NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Esketamine for treatment-resistant depression [ID1414]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Esketamine for treatment-resistant depression [ID1414]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

Pre-technical engagement documents

1. **Company submission** from **Janssen**

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. SANE

4. **Expert personal perspectives** from:
   a. Professor Hamish McAllister-Williams – clinical expert, nominated by Janssen
   b. [redacted] – patient expert, nominated by SANE
   c. Mr Peter Pratt – commissioning expert, nominated by NHS England

5. **Evidence Review Group report** prepared by **Kleijnen Systematic Reviews**

6. **Evidence Review Group – factual accuracy check**

Post-technical engagement documents

7. **Technical engagement response** from **Janssen**
   a) Company response
   b) Company response – additional evidence

8. **Technical engagement responses from experts:**
   a. Mr Peter Pratt – commissioning expert, nominated by NHS England
   b. Professor Navneet Kapur – Guideline lead, nominated by National Guideline Alliance

   Technical engagement responses from consultees and commentators

   There were no technical engagement responses from consultees and commentators

9. **Evidence Review Group critique of company response to technical**

engagement prepared by **Kleijnen Systematic Reviews**

10. Final Technical Report

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Esketamine for treatment-resistant depression (ID1414)

Document B

Company evidence submission

July 2019

File name	Version	Contains confidential information	Date
ID1414 TRD_esketamine Document B_CIC	**1.0**	**Yes**	**05th of July 2019**

Contents

Tables and figures

Abbreviations

5-HT	5-hydroxytryptamine
AAP	Atypical antipsychotic
AC	Active comparator
AD	Antidepressant
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ANCOVA	Analysis of covariance
APA	The American Psychiatric Association
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
Atyp AP	Atypical antipsychotic
Aug	Augmentation
AV	Atrioventricular
BAP	British Association for Psychopharmacology
BDNF	Brain-derived neurotrophic factor
BL	Baseline
BMI	Body Mass Index
BNF	British National Formulary
BPIC-SS	Bladder Pain/Interstitial Cystitis Symptom Score
BPRS+	4-item positive symptom subscale of the Brief Psychiatric Rating Scale
CADSS	Clinician-Administered Dissociated States Scale
CBT	Cognitive behavioural therapy
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEP	Cost-effectiveness plane
CFB	Change from baseline
CG	Clinical guideline
CGADR	Clinical Global Assessment of Discharge Readiness
CGI-S	Clinical Global Impression – Severity
CHMP	Committee on Human Medicinal Products
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CrI	Credible interval
CSR	Clinical study report
C-SSRS	Columbia – Suicide Severity Rating Scale
CYP3A4	Cytochrome P450 3A4 enzyme
DA	Dopamine
DB	Double-blind
DBP	Diastolic blood pressure
DBS	Deep brain stimulation
DC	Discontinued
DCAE	Discontinued due to adverse event
DIC	Deviance information criterion
Diff.	Difference

DNA	Deoxyribonucleic acid
DSM-2/3/4/5	Diagnostic and Statistical Manual of Mental Disorders – 2/3/4/5
EAMS	Early Access to Medicine Scheme
ECG	Electrocardiogram
eCRF	Electronic case report form
ECT	Electroconvulsive therapy
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-VAS	EuroQol – Visual Analogue Scale
EQ-5D	EuroQol-5 Dimension
EQ-5D-5L	EuroQol-5 Dimension-5 Level
ESK-NS	Esketamine nasal spray
ESK-NS + OAD	Esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant
ESK-NS-56 + OAD	Esketamine nasal spray (56 mg [fixed dose]) plus a newly initiated oral antidepressant
ESK-NS-84 + OAD	Esketamine nasal spray (84 mg [fixed dose]) plus a newly initiated oral antidepressant
FAS	Full analysis set
FDA	US Food and Drug Administration
FE	Fixed effect
Freq	Frequency
F/U	Follow-up
GABA	Gamma-amino butyric acid
GAD-7	Generalised Anxiety Disorder – 7-item scale
GAF	Global Assessment of Functioning
GCP	Good Clinical Practice
GP	General practitioner
HAM-D	Hamilton Depression Rating Scale
HAM-D-17	Hamilton Depression Rating Scale 17-item
HbA1c	Glycated haemoglobin
HCP	Healthcare professionals
HCRU	Healthcare resource use
HE	Health Economic
HR	Hazard ratio
HRQoL	Health-related quality of life
HRSD(-17)	Hamilton Rating Scale for Depression (17-item)
HRU	Healthcare resource use
HRUQ	Healthcare Resource Use Questionnaire
HSI	Health status index
HSUV	Health state utility value
HTA	Health technology assessment
HVLT-R	Hopkins Verbal Learning Test – Revised
ICER	Incremental cost-effectiveness ratio
ICF	Informed consent form
IDMC	Independent data monitoring committee
IDS-C_{30}	Inventory of Depressive Symptomatology-Clinician-rated, 30-item scale
IND	Induction
IR	Immediate release

IWRS	Interactive web response system
LOCF	Last observation carried forward
LS	Least squares
LY	Life years
LYG	Life years gained
MA	Maintenance phase
MADRS	Montgomery-Asberg Depression Rating Scale
MAIC	Matching adjusted indirect comparison
MAOI	Monoamine oxidase inhibitor
MA_TEP	Maintenance phase transferred-entry placebo
MCI	Mild cognitive impairment
MCID	Minimum clinically important difference
MDD	Major depressive disorder
MDE	Major depressive episode
Med	Medication
MedDRA	Medical Dictionary for Regulatory Activities
MGH-ATRQ	Massachusetts General Hospital Antidepressant Treatment Response Questionnaire
MGH-Female RLHQ	Massachusetts General Hospital – Female Reproductive Lifecycle and Hormones Questionnaire
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	Myocardial infarction
MINI	Mini-International Neuropsychiatric Interview
MMRM	Mixed-effects model using repeated measures
MMSE	Mini-Mental State Examination
MOAA/S	Modified Observer's Assessment of Alertness/Sedation Scale
MP	Maintenance phase
MRU	Medical resource use
n	Number
NA	Not applicable
NE	Not estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute of Health Research
NMA	Network meta-analysis
NMDA	N-methyl-D-aspartate
NNT	Number needed to treat
Nortrip	Nortriptyline
NS	Nasal spray
OAD	Oral antidepressant
OAD + PBO-NS	Newly initiated oral antidepressant plus placebo nasal spray
OC	Observed cases
OCD	Obsessive compulsive disorder
OL	Open-label
ONS	Office for National Statistics
OP	Optimisation phase
OP_TEP	Optimisation phase transferred-entry placebo
OR	Odds ratio
PAQ	Patient Adherence Questionnaire

PBO	Placebo
PCA	Prescription cost analysis
PHQ-9	Patient Health Questionnaire – 9 questions
PI	Principal Investigator
PIM	Promising Innovative Medicine
PRIMA	Preliminary Independent Model Advice
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PWC-20	Physician Withdrawal Checklist – 20-item
QALY	Quality-adjusted life year
QIDS	Quick Inventory of Depressive Symptomatology
QoL	Quality of life
RCT	Randomised controlled trial
RE	Random effect
RNA	Ribonucleic acid
RR	Relative risk
rTMS	Transcranial magnetic stimulation
RWE	Real-world evidence
SARI	Serotonin antagonist and reuptake inhibitors
SAS	Safety analysis set
SBP	Systolic blood pressure
SD	Standard deviation
SDS	Sheehan Disability Scale
SE	Standard error
SIQA	Site-Independent Qualification Assessment
SLaM	South London and Maudsley
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SNRI	Serotonin–norepinephrine reuptake inhibitor
SOC	System Organ Class
SSRI	Selective serotonin reuptake inhibitor
STOP-BANG	Snoring, Tiredness, Observed Apnoea, Blood Pressure, Body Mass Index Age, Neck Circumference, and Gender Questionnaire
TA	Technology appraisal
TCA	Tricyclic antidepressant
TEAE	Treatment-emergent adverse event
TeCA	Mirtazapine
TRD	Treatment-resistant depression
TSH	Thyroid-stimulating hormone
Tx	Treatment
UK	United Kingdom
ULN	Upper limit of normal
UPSIT	University of Pennsylvania Smell Identification Test
US	United States
VNS	Vagal nerve stimulation
w	Week

WHO	World Health Organization
wk	Week
WTP	Willingness to pay
XR	Extended release
y	Year(s)

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

This submission covers the technology's full (anticipated) marketing authorisation for the following anticipated indication:

The treatment of adults with treatment-resistant Major Depressive Disorder who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode.

The final scope for esketamine nasal spray (referred to as ESK-NS in this document) for treatment-resistant depression (TRD) was issued by NICE in May 2019. The decision problem for this technology appraisal is an evaluation of the clinical and cost-effectiveness of ESK-NS for the treatment of patients with TRD (Table 1).

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with treatment-resistant depression.	The population would be more appropriately defined as: "Adults with treatment resistant MDD who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode."	The proposed wording reflects the expected marketing authorisation of the intervention.
Intervention	ESK-NS in addition to established clinical management	ESK-NS co-administered with a newly initiated oral antidepressant (OAD).	The proposed wording reflects the expected marketing authorisation of the intervention
Comparator(s)	• SSRIs • TCAs • MAOI • SNRIs • Vortioxetine • Combination or augmentation treatments (with lithium or an antipsychotic) • ECT • Best supportive care	As per the scope, plus the tetracyclic antidepressant (OAD) mirtazapine. Figure 5 shows the most relevant comparators.	Mirtazapine is currently not included in the final scope. Mirtazapine should be included as a comparator as two retrospective database analyses conducted by 1) King's College London, using secondary data from the South London and Maudsley (SLaM) Trust, and 2) IQVIA, using *Longitudinal Patient Data,* a primary care prescription data set, which show that mirtazapine is amongst the five most frequently prescribed treatments for TRD (1, 2). NICE stated in their early scientific advice in 2013 (7) and at the NICE Scoping Workshop for ESK-NS in TRD held on 17th September 2018 that RWE will determine which comparators are the most relevant ones. Figure 5 shows the most frequently used OAD therapies for TRD in the UK. Of the list of comparators in the final scope, it shows that SSRIs, TCAs, SNRIs, and mirtazapine are the most relevant comparators.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	• Response to treatment (including response rate and time to response) • Relapse (including relapse rate and time from remission to relapse) • Severity of depression • Cognitive dysfunction • Remission of symptoms • Anxiety • Sleep quality • Hospitalisation • Functioning and associated disability • Mortality • Adverse effects of treatment (including adverse effects of treatment discontinuation) • HRQoL	As per the scope, with the addition of the impact of ESK-NS on indirect costs and carer health related quality of life (HRQoL).	TRD-associated disability has been associated with substantial indirect costs. In a systematic literature review, Johnston et al 2019 (3) found that increasing treatment resistance was associated with higher costs, reduced HRQoL and decreased health status. In addition, McCrone et al 2018 (4) showed that 80% of the total UK society burden of TRD was due to lost productivity and carer burden. NICE CG90 states that “depression incurs significant non-healthcare costs such as social service costs, direct costs to patients and their families, and lost productivity costs due to morbidity or premature mortality” (5). Consideration of the wider indirect cost impact is in line with NICE social values which state that: “Decisions about whether to recommend interventions should not be based on evidence of their relative costs and benefits alone. NICE must consider other factors when developing its guidance, including the need to distribute health resources in the fairest way within society as a whole” (6). Additionally, the feedback from NICE at the early scientific advice meeting was that “Workplace productivity and occupational functioning should not currently be included in the base case of the economic model however such data could be presented as supporting evidence” (7).

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Subgroups to be considered	If evidence allows the following subgroups will be considered by severity of the condition in people with treatment-resistant depression. In addition, the clinical and cost effectiveness of ESK-NS may be considered in different positions in the treatment pathway.	No subgroup analyses based on level of severity at baseline or ESK-NS in different positions in the treatment pathway.	There is insufficient comparative evidence to evaluate the effectiveness of ESK-NS by level of severity or positioning in the treatment pathway. Therefore, ESK-NS plus OAD has been considered in the full label population, as per the clinical trials and anticipated license indication.
Special considerations including issues related to equity or equality	-	• In relation to equality, Janssen would like to highlight geographic access as a key consideration. • Additionally, there may be an equality consideration for patients aged ≥65 years.	See Section B.1.4.

Abbreviations: ECT, electroconvulsive therapy; HRQoL, health-related quality of life; MAOI, monoamine oxidase inhibitor; MDD, major depressive disorder; NICE, National Institute for Health and Care Excellence; OAD, oral antidepressant; RWE, real-world evidence; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitor; TCAs, tricyclic antidepressants; TRD, treatment-resistant depression.

B.1.2 Description of the technology being appraised

A draft summary of product characteristics (SmPC) for information for use regarding ESK-NS is listed in Appendix C.

ESK-NS is a first-in-class OAD with a novel mechanism of action, which is distinctively different to that of other widely used OAD (e.g. selective serotonin reuptake inhibitors [SSRIs], serotonin–norepinephrine reuptake inhibitor [SNRIs], tricyclic antidepressants [TCAs], and monoamine oxidase inhibitors [MAOIs]). Whereas other OADs target reuptake/breakdown of monoamine neurotransmitters (serotonin, norepinephrine, and dopamine) or their respective receptor pharmacodynamics, ESK-NS exerts its action via transient NMDA receptor blockade or modulation.

Details of the technology being appraised in the submission, including the method of administration, dosing and related costs, are provided in Table 2.

Table 2. Technology being appraised

UK approved name and brand name	UK approved name: Esketamine nasal spray Brand name: SPRAVATO®
Mechanism of action	ESK-NS has a novel mechanism of action that is hypothesised to alter the underlying pathophysiological process of depression (see Section B.2.12.2). ESK-NS exerts its action by transient NMDA receptor blockade or modulation. This increases the presynaptic release of glutamate and stimulates AMPA receptors on glutamatergic neurons. This release of glutamate in turn leads to a release of BDNF, hence restoring synaptic function and connectivity. In this way, ESK-NS improves the synaptic function that is critical in the sustained reduction of depressive symptoms (8). ESK-NS is formulated for nasal administration to provide a non-invasive, patient-acceptable, rapidly absorbed and readily bioavailable route of delivery. Nasal spray provides direct route to the brain avoiding the blood brain barrier and leading to rapid onset of action (9). Compared with racemic ketamine (a mixture of R-ketamine and esketamine), esketamine has a higher potency towards the NMDA receptor, which allows a lower dose in less volume, which in turn facilitates intranasal delivery from a single use drug-device combination product (10).
Marketing authorisation/CE mark status	A regulatory submission was made to the EMA in October 2018. CHMP positive opinion is expected in September 2019 with marketing authorisation anticipated to be granted by the European Commission in November 2019.
Indications and any restriction(s) as described in the	The anticipated indication is as follows: • ESK-NS is indicated for treatment resistant major depressive disorder in adults who have not responded to at least two different treatments

summary of product characteristics (SmPC)	with antidepressants in the current moderate to severe depressive episode). • ESK-NS must be co-administered with a newly initiated OAD therapy.
Method of administration and dosage	ESK-NS comes as a single-use device that delivers a total of 28 mg of esketamine in two sprays (one spray per nostril). ESK-NS is self-administered and is to be used under the supervision of a healthcare professional. One device (for a 28 mg dose), two devices (for a 56 mg dose), or three devices (for an 84 mg dose), are to be used, with a five-minute interval between each nasal spray self-administration. The ESK-NS device includes abuse-deterrent features in its design. These features include a single-use application, minimal residual volume after use, an indicator feature that shows if a device is used or unused, and a minimum required force of 60 N to pull the device apart. The number of devices supplied per pack will be limited to 1, 2, or 3 devices to deliver the prescribed dose of 28, 56, or 84 mg esketamine, respectively. Drug administration of ESK-NS will occur in a controlled environment under the supervision of a health care professional. This controlled distribution model is intended to limit diversion. During clinical development trials of ESK-NS, the percentage of nasal spray kits that were not returned from the clinical sites was 0.004% (5 of 141,561 kits). **Induction phase dosing:** • In weeks 1–4, patients start on 56 mg (<65 years) or 28 mg (≥65 years) on Day 1. Subsequent doses are 56 or 84 mg twice a week. Dose adjustments should be made based on efficacy and tolerability. • Evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine need for continued treatment. **Maintenance phase dosing:** • It is recommended to maintain the dose the patient receives at the end of the induction phase in the maintenance phase. o In weeks 5-8, 56 mg or 84 mg once weekly. o From Week 9, 56 mg or 84 mg every 2 weeks or once weekly. • The need for continued treatment should be re-examined periodically. After depressive symptoms improve, treatment is recommended for at least 6 months. Further detail concerning the method of administration and dosage of ESK-NS can be found in the (draft) SmPC (Appendix C) and in the diagram provided in Appendix L.
Additional tests or investigations	During and after ESK-NS administration at each treatment session, patients should be observed for sedation and dissociation until the patient is stable based on clinical judgment. In the SUSTAIN-2 trial, approximately 60% of individuals were ready to leave after 1 hour, with approximately 95% ready to leave after 90 minutes. The suitability for treatment with ESK-NS should be assessed by a specialist in mental health.
List price and average cost of a course of treatment	£163 per 28 mg device. The average cost per person treated for TRD with ESK-NS over the average course of therapy is estimated to be around £10,554.25
Patient access scheme (if applicable)	Not applicable.

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF, Brain-Derived Neurotropic Factor; CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; MDD, major depressive disorder; NMDA, N-methyl-D-aspartate; OAD, oral antidepressant.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Background

TRD, which is defined as major depressive disorder (MDD) that has not responded to at least two different treatments with OADs in the current moderate to severe depressive episode, is a common form of mental illness affecting more than 130,000 patients in England (1, 11, 12). TRD is life-threatening; at least 30% of patients with TRD attempt suicide at least once during their lifetime (13) – severely impacting not only themselves, but also their carers, the healthcare system, and broader society. It can develop at any age, but disproportionally effects people of working age. The total estimated UK societal burden of TRD is £3.9 billion, the majority of which (80%) is due to carer burden and lost productivity (4). There is currently no European Medicines Agency (EMA) approved pharmacological treatment specifically for TRD. Despite numerous available pharmacological therapies, including several different OAD drug classes, there is a serious need for new treatment options as many patients currently fail to achieve the treatment goal of remission or even a sufficient response.

Clinical trials in depression, and mental health generally, are notoriously associated with high placebo rates which makes it challenging to ascertain the true relative treatment effect of the active drug over placebo (14). A number of theories for the high placebo rates have been proposed, including expectancy of the treatment effect, outcome measurement, the therapeutic setting, and intensity of interaction resulting in a treatment effect (15). This challenge, amongst others, of conducting trials in depression, has led to limited new investment and innovation in the disease area.

ESK-NS is the first breakthrough in depression treatment in over 30 years. ESK-NS is a novel product developed by Janssen for TRD. While several definitions of TRD are used in clinical practice, world health authorities, including the FDA and the EMA, define patients with TRD as individuals with MDD, commonly referred to as ‘moderate to severe depression’, who have not responded to at least two different antidepressant treatments given at an adequate dose and for an adequate duration

in the current episode of depression (16, 17). This is aligned to the definition of TRD used in the clinical development program for ESK-NS.

Promising data from the Phase 2 trials have led to FDA breakthrough designation status for ESK-NS in TRD (November 2013) and its future indication in MDD with imminent risk for suicide (August 2016). In the UK, ESK-NS has been awarded Promising Innovative Medicine (PIM) designation through the Early Access to Medicine Scheme (EAMS) for treatment of symptoms of MDD in adults at imminent risk for suicide (October 2018). ESK-NS provides a new therapeutic option for people with moderate-severe TRD, which tackles the significant impact that mental health, as the leading cause of disability in the UK, has on national income and productivity, and which has been identified and prioritised by the UK Government and the National Health Service (NHS) in *The NHS Long Term Plan* (12).

In May 2019, ESK-NS was granted a new and specific ATC code under the antidepressant category (N06AX27) by the World Health Organization (WHO). This decision reflects the recognition of ESK-NS as a new therapeutic class of antidepressant.

A European marketing authorisation application for ESK-NS in TRD was submitted in October 2018 and is currently under review by the EMA. Marketing authorisation is expected in November 2019.

B.1.3.2 Health condition

MDD is a severely debilitating and potentially life-threatening psychiatric disorder. MDD is characterised by recurrent episodes of persistent low mood and/or loss of interest or pleasure in (almost) all activities (18). Accompanying psychophysiological symptoms may include profound sleep disturbance, fatigue, change in appetite/weight, agitation or slowness of speech/action, diminished concentration, decreased libido, inability to enjoy life, and feelings of worthlessness. In severe cases, MDD can lead to suicidal ideation, suicide attempts, and death by suicide. MDD causes clinically significant distress as well as impairment in a person's ability to function socially, occupationally, and in other important areas of life including maintaining relationships and caring for themselves and others. The presence of concurrent physical and mental health problems delays recovery from both (19).

Depression increases mortality risk by 50% (20) and doubles the risk of coronary heart disease in adults (21). Around 3% of the UK population, about 2 million people, are affected by MDD at any given time (22).

TRD is a debilitating subtype of MDD, which has failed to respond to at least two different OADs during their current depressive episode (3, 22). About 87% of patients with TRD do not achieve remission with currently available OADs (23) equating to over 130,000 people in the UK suffering from TRD. As per NICE Early Scientific advice given to Janssen for ESK-NS in 2013 (7), many patients end up cycling through several more treatment options (7) leading to further treatment resistance and chronicity of the disease over time. The limitations of currently available MDD drugs used to treat TRD leaves a large unmet need for efficacious and safe treatments for patients.

B.1.3.3 Diagnosis and symptomatology

MDD is diagnosed through clinical assessment. The assessment is against criteria set out in the 5th edition of Diagnostic and Statistics Manual for Mental Disorders (DSM-5) (18). Five or more symptoms must have been present within the same 2-week period and must represent a change from previous functioning. Symptoms must include either one of depressed mood or anhedonia (inability to feel pleasure) occurring most of the day, nearly every day as indicated by subjective reports or observations by others. Other symptoms, which must also occur nearly every day, can include: significant weight loss or gain or increase/decrease in appetite; insomnia/hypersomnia; psychomotor agitation/retardation; fatigue/loss of energy; feelings of worthlessness or excessive/inappropriate guilt; diminished ability to think/concentrate or indecisiveness; recurrent thoughts of death, suicidal ideation (with or without a specific plan), or suicide attempt. Symptoms must cause clinically significant distress or impaired functioning (social, occupational or other important areas).

The diagnosis cannot be made if the symptoms or depressive episodes can be attributable to the physiological effects of a substance or to another medical condition, or which can be better explained by other psychiatric conditions such as schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional

disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders. Specifically, the individual must never have experienced a manic or hypomanic episode.

Clinical manifestations that have significant interpersonal variability can be separated into psychological, physical, and social, as shown in Table 3. To summarise the symptomatology, patients with MDD, and TRD especially, suffer from a depressive syndrome which is characterised by the following combination of symptoms: depressive mood, impaired ability to feel joy, decreased impulsion, increased exhaustion, sleeping problems, anorexia or increased appetite with corresponding weight change, decreased ability to concentrate and brooding. In many cases, patients feel weary of life or have suicidal ideation to the point of suicidal actions (24, 25).

Table 3. Symptoms of MDD and TRD

Psychological Symptoms	Physical Symptoms	Social Symptoms
• Continuous low mood or sadness • Feeling hopeless and helpless • Having low self-esteem • Feeling tearful • Feeling guilt-ridden • Feeling irritable and intolerant of others • Having no motivation or interest in things • Finding it difficult to make decisions • Not getting any enjoyment out of life • Feeling anxious or worried • Having suicidal thoughts or thoughts of harm • Anhedonia	• Moving or speaking more slowly than usual • Change in appetite or weight (usually decreased, but sometimes increased) • Constipation • Unexplained aches and pains • Lack of energy/ fatigue • Lack of interest in sex (loss of libido) • Changes to the menstrual cycle in women • Disturbed sleep (for example, finding it hard to fall asleep at night or waking up very early in the morning) • Agitation or slowing of movements	• Withdrawal from social activities • Not doing well at work • Taking part in fewer social activities and avoiding contact with friends • Neglecting hobbies and interests • Having difficulty in home and family life • Irritability

Abbreviations: MDD, major depressive disorder; TRD, treatment-resistant depression.
Source: Adapted from American Psychiatric Association 2016 (18) and NICE CG90 (5).

A number of scoring systems have been developed to measure disease activity, although most have been used primarily in clinical trials. In clinical practice, semi-structured interviews are usually used to diagnose and monitor the level of depressive symptoms. Scoring systems are rarely used in NHS clinical practice.

In the ESK-NS clinical trials, the clinician reported Montgomery-Asberg Depression Rating Scale (MADRS) and the patient reported outcome Patient Health Questionnaire (PHQ-9) are used to measure the severity of depressive episodes in patients with mood disorders. The feedback from NICE early scientific advice was that “the MADRS score is appropriate to measure outcomes in the ESK-NS clinical trials” (7). The MADRS consists of 10 items each scored from 0 (symptom is not present or is normal) to 6 (severe or continuous presence of the symptom). The domains measured included sadness, inner tension, sleep, appetite, concentration, and suicidal thoughts. The PHQ-9 is a 9-item scale and each item is rated on a 4-point scale (0 = Not at all, 1 = Several Days, 2 = More than half the days, and 3 = Nearly every day). A higher score indicates greater severity of depression, which counts for both scales.

B.1.3.4 Aetiology

As TRD is a subset of MDD that occurs following the initial onset of MDD, it is important to understand the factors contributing to MDD as well as those influencing TRD. Table 4 shows there are several non-modifiable, medical, and environmental risk factors for the development of MDD. These interacting factors can be categorised into internalising factors (genetics, neuroticism, low-self-esteem, early-onset anxiety disorder, past history of major depression), externalising factors (genetics, substance misuse, and conduct disorder) and adversity factors (trauma, stressful life events in past year, parental loss, low parental warmth, history of divorce, marital problems, low social support, low education) (26). As such, given the multitude of factors as well complex pathophysiology, no single theory conclusively explains the aetiology of MDD.

Table 4. Key non-modifiable, medical, environmental, and medication based risk factors for MDD/TRD.

Non-modifiable risk factor	
Early age at onset of depression Genetic changes Hyperactivity in certain brain areas Reduced levels of neurotransmitters	Increased age Female gender Reduced levels of GABA in the brain Genetic risk factors
Medical risk factors	
Cardiovascular comorbidity eg hypertension Metabolic comorbidity eg cancer, diabetes and high BMI	Chronicity of preceding MDD episode (s) High rate of MDD episode recurrence Presence of psychiatric co-morbidities Wrong diagnosis, including failure to recognize MDD subtypes Presence of personality disorders, anxiety disorders or melancholia Suicidal ideation Young MDD onset
Medication risk factors	
Certain medications (blood pressure medication, sleeping pills)	Wrong medication or wrong doses
Environmental risk factors	
Lower education levels or lower social class Factors during pregnancy e.g. stress, smoking, alcohol, cannabis, being malnourished, low birth weight Early trauma Diet quality High stress levels Ethnic minority status Stressful life events such as job loss, bereavement, assault, relationship breakdown Lower levels of interpersonal or economic resources Lifestyle factors such as smoking and obesity can lead to more severe MDD	Lower levels of interpersonal or economic resources Lower functional status and QoL High levels of stress Poorer social support and a lack of family networks Ethnic minority status

Abbreviations: GABA, gamma-amino butyric acid; MDD, major depressive disorder; QoL, quality of life; TRD, treatment-resistant depression;
Sources: (24, 27-33).

B.1.3.5 Pathophysiology

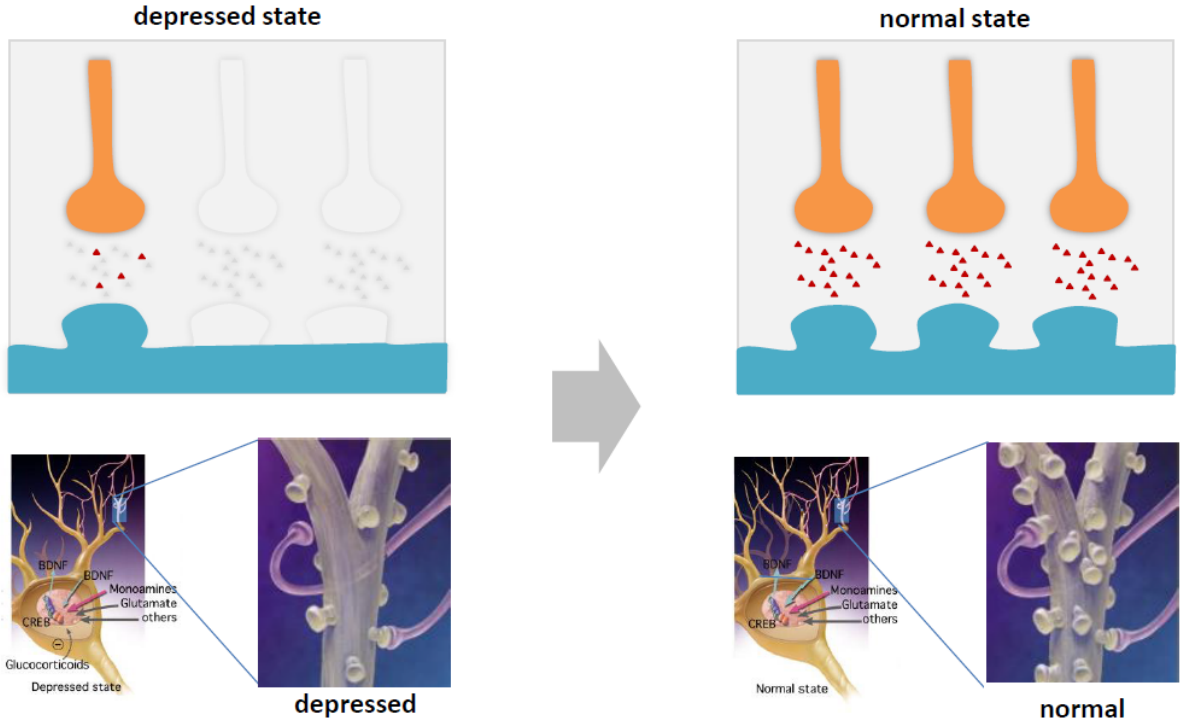
Several hypotheses exist which aim to explain the biochemical changes observed in MDD. These hypotheses are based on studies investigating the neurotransmitters serotonin, norepinephrine, and dopamine, psychosocial stress and stress hormones, neurocircuitry, neurotrophic factors, and circadian rhythms (34). The many theories of depression and the relatively low response rate of all available OADs suggest that depression is a clinically and etiologically heterogeneous disorder. As theories of depression apply to only some types of depressed patients but not others, and because depressive pathophysiology may vary considerably across the course of

illness, the current extant knowledge argues against a unified hypothesis of depression (34).

Primarily, the neurotransmitters serotonin, noradrenaline, and dopamine are the starting points of the currently available pharmacological therapeutic approaches regarding the presumed neurobiological basis of MDD. These neurotransmitters all target the monoaminergic receptor systems (34, 35). Based upon the slow onset of effect of up to six weeks, coupled with the high number of patients who do not respond to OADs, it is clear that the pharmacotherapeutic regulation of neurotransmission via these monoaminergic substances does not address the key unmet medical needs of depression. These unmet needs require treatments with high effectiveness, rapid onset of action, and sustained response. This has led to research focusing on other neuronal pathways, with considerable attention being given to glutamatergic neurotransmission.

ESK-NS is a glutamate receptor modulator with a new mechanism of action in the treatment of TRD that differs from that of the currently approved OADs. Glutamate receptor modulators are a new class of antidepressants that work differently than current OADs and are expected to fill the aforementioned unmet need. This new mode of action is thought to release neuro-growth factors and rapidly restore synaptic functions and connectivity. Synaptic function is critical in the coordinated, appropriate flow of information throughout the nervous system to adjust behaviour to environmental stimuli and to control body functions, memories, and emotions. Dysfunction of the synapses is thought to play a key role in the development of depression. By restoring the dysfunction of synapses, the underlying cause of depression can be treated (Figure 1) (8).

Figure 1. Synaptic dysfunction in depression and the hypothesised working mechanism of glutamate receptor modulators (e.g., esketamine) in restoring the synapses

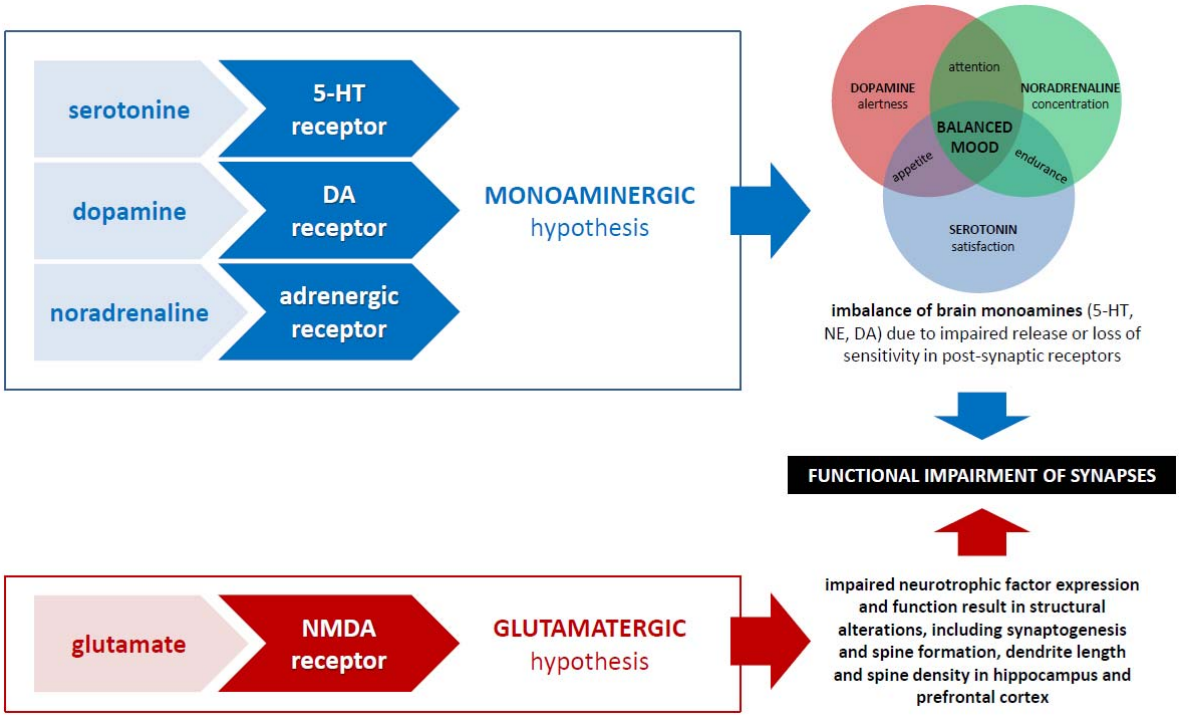


Source: Duman and Aghajanian (36).

Currently available OADs are based on modulating the monoaminergic system and often take four to six weeks before a full response to treatment is exerted, which is a severe limitation, given the need for urgent relief of depressive and suicidal crises. In addition, low rates of response and remission are also experienced by many patients taking OADs, especially after multiple lines of therapy.

It is hypothesised that the combination of monoaminergic and glutamatergic therapies has a complementary treatment effect on depressive symptoms to restore the functional impairment of synapses in the short- and longer-terms, Figure 2.

Figure 2. The differences and complementarity in working mechanism between conventional oral monoaminergic antidepressants and ESK-NS's glutamatergic mechanism of action



Abbreviations: 5-HT, 5-hydroxytryptamine; DA, dopamine; NE, noradrenaline; NMDA, N-methyl-D-aspartate.

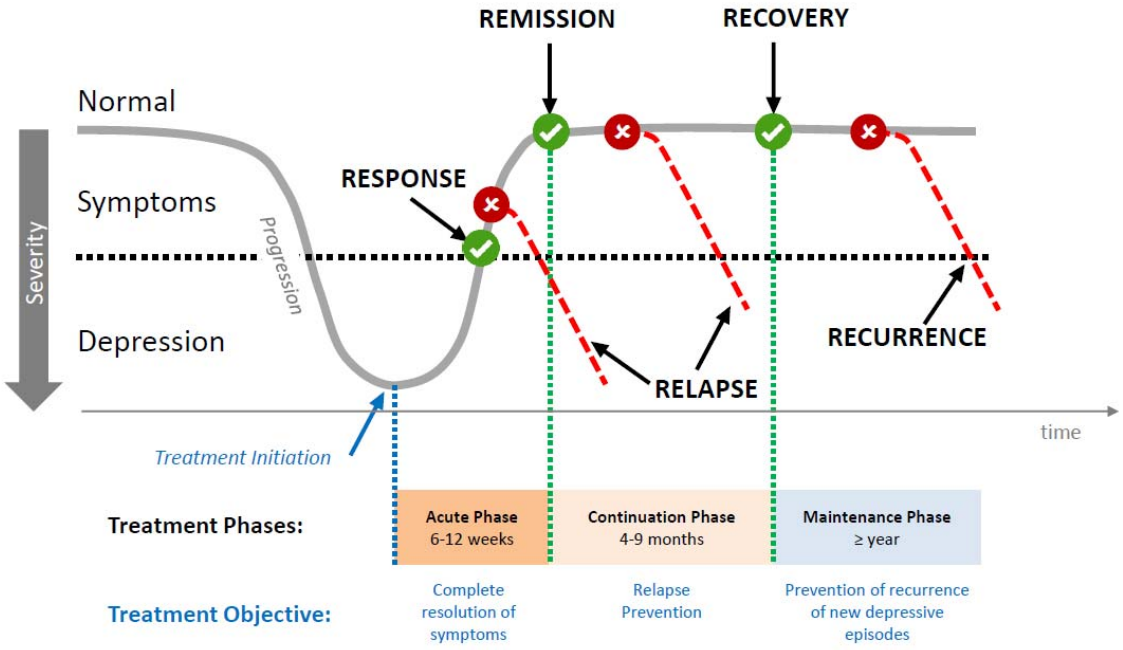
TRD imposes a considerable health and economic burden on patients, families (including dependents and carers) the health service and wider society. Episodes of depression in patients with TRD are typically three times longer than in patients with non-treatment resistant MDD (37) and are associated with increased all-cause mortality (38), mainly due to a seven times increased risk of suicide relative to MDD (39). The impact of TRD on patient health-related quality of life (HRQoL) is profound; patients with TRD have around 35% greater reductions in HRQoL compared with non-treatment resistant MDD, and report impairment in HRQoL in the range of metastatic cancer or acquired blindness (40). Compared to patients with non-treatment resistant MDD, patients with TRD utilise more medical resources, have 50% lower labour force participation and a 20% increase in work activity impairment (3, 40, 41).

B.1.3.5.1 Treatment phases and duration

Figure 3 shows the different treatment phases and objectives of antidepressant treatment. The acute treatment phase ranges between four to eight and sometimes

12 weeks, and the goal of remission is the treatment objective in this phase. After treatment success in the acute phase, the continuation phase focuses on relapse prevention and further stabilising remission, which can take up to nine months (42). A patient that has been stable in remission (absence of symptoms) for 4-9 months can be considered 'in recovery', and clinical guidelines recommend continuing treatment until that point. Once recovery is reached, the maintenance treatment phase aims to prevent recurrence of a new depressive episode. For a small proportion of patients who are at high risk of relapse, it is recommended treatment is continued for up to 2 years after they have reached remission. OADs are used to prevent recurrence in the recurrence-prevention phase (5, 43).

Figure 3. Natural history and management for MDD adapted from Qaseem et al 2016 (25) and Kupfer et al 1991 (44)



Abbreviations: MDD, major depressive disorder.

B.1.3.6 Clinical guidelines

There are no UK or European clinical guidelines specific to TRD. In the UK, the most relevant clinical guidelines for the treatment of MDD and TRD include the NICE Clinical Guidelines on the recognition and management of depression in adults (CG90) and the British Association for Psychopharmacology (BAP) evidence-based

guidelines for treating depressive disorders with antidepressants (5, 45). The specific relevant details of each guideline are provided in Sections B.1.3.6.1 and B.1.3.6.2.

NICE have also published one technology appraisal of relevance, TA367: Vortioxetine for treating major depressive episodes (46), which is described briefly in Section B.1.3.6.4.

The American Psychiatric Association (APA) Practice Guidelines for the treatment of patients with MDD (42) has been included for its description of the duration of the relapse prevention phase, which is important for guidance on treatment duration; relevant information is described briefly in Section B.1.3.6.3.

B.1.3.6.1 NICE Clinical Guidelines on Depression in Adults: recognition and management (CG90) – 2009 (5)

NICE CG90 includes recommendations for mild to moderate and moderate to severe depression including TRD. MDD is considered moderate to severe depression, and thus the relevant sections covering moderate to severe depression from CG90 are described here. For first-line management of MDD, NICE depression guidelines (NICE CG90) recommend OAD – typically a SSRI, which is considered to be as effective as any other OAD, with a favourable benefit/risk ratio.

Treatment is assessed:

- After one week of starting OAD in those aged younger than 30 years or those who are considered to have an increased risk for suicide, and frequently thereafter until risk is no longer clinically important.
- After two weeks for people started on antidepressants who are not considered to be at increased risk of suicide and ≥30 years.
- After two weeks to assess tolerability and adherence.
- After four weeks on a therapeutic dose to assess tolerability and response, with a switch recommended to another OAD for inadequate response or patient preference/tolerability. Subsequent assessments are every two to four weeks in the first three months and then at longer intervals if response is good.

For relapse prevention, patients who respond to treatment should continue to take their OAD at the effective dose for at least six months after remission. For those at

high risk of relapse, OAD should be continued at the effective dose for at least two years, with a re-evaluation to assess if maintenance treatment needs to continue thereafter.

If people with depression have not responded to an initial SSRI after 4–6 weeks, NICE CG90 recommends increasing the dose, switching to a different SSRI, or a better tolerated newer generation OADs such as venlafaxine. Based on a network meta-analysis (NMA) conducted by Cipriani et al (47), the Guideline Development Group in NICE CG90 concluded that there was insufficient evidence to indicate a difference in efficacy and tolerability between individual OADs and therefore no specific OAD treatment recommendations were made. The same conclusion was reached in NICE TA367 (48). The meta-analysis has recently been updated with data from nine additional OADs, which again found few differences between antidepressants when all data were considered (49).

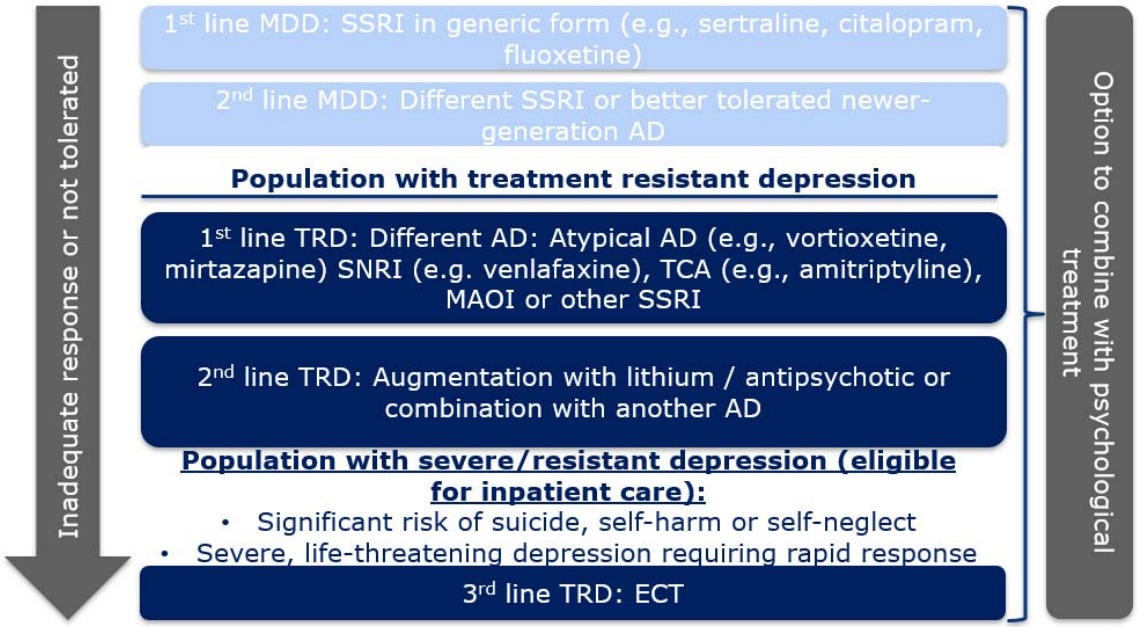
The first treatment after no response to a second OAD is considered first-line TRD. After no response to a second OAD, NICE CG90 recommends a switch to an OAD of a different pharmacological class that may be less well tolerated, for example an SNRI, a TCA or a MAOI should be given. NICE CG90 recommends considering augmentation with lithium or antipsychotics, and combination with another OAD if the person with depression is prepared to tolerate the increased side effect burden.

For a person whose depression has not responded to either pharmacological or psychological interventions, NICE recommends combining pharmacological treatments with cognitive behaviour therapy (CBT) in all treatment lines. Additionally, NICE CG90 recommends that patients whose depression has inadequate or incomplete response to two or more interventions should be referred to mental health professionals.

Regarding non-pharmacological physical/somatic therapies, electroconvulsive therapy (ECT) is the only intervention recommended without additional audit/governance requirements. ECT should be considered to achieve rapid and short-term improvement of severe symptoms after an adequate trial of other treatment options has proven ineffective and/or when the condition is potentially life-threatening. Transcranial magnetic stimulation (rTMS) and Vagus Nerve Stimulation

(VNS) have highly restrictive availability due to requirements for clinical governance/audit or additional research governance due to variable clinical response or inadequate supportive data respectively. Finally, current treatment for patients with severe depressive symptoms can sometimes include hospitalisation due to the ineffectiveness of other existing therapies (5).

Figure 4. Current MDD and TRD treatment pathway derived from NICE CG90



Abbreviations: AD, antidepressant; ECT, electroconvulsive therapy; MAOI, monoamine oxidase inhibitor; OAD, oral antidepressant; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

B.1.3.6.2 British Association of Psychopharmacology (BAP) evidence-based guidelines on treating depressive disorders with antidepressants – 2008, updated 2015 (45)

The BAP guidelines not only recommend a SSRI as first-line treatment in moderate-to-severe depression, they specifically advise selection of OADs based on individual patient requirements. In the absence of these requirements, evidence-based selection should favour a SSRI or newer antidepressant based on tolerability and safety in overdose. In more severely ill patients where maximising efficacy is an overriding factor, clomipramine (TCA), venlafaxine (≥150mg) (SNRI), escitalopram (20mg) (SSRI), sertraline (SSRI), amitriptyline (TCA) or mirtazapine (TeCA) should be used in preference to other OADs.

B.1.3.6.3 American Psychiatry Association (APA) Practice Guidelines for the Treatment of Patients with Major Depressive Disorder – Third Edition (42)

The APA MDD guidelines recommend, to reduce the risk of relapse, that patients who have been treated successfully with antidepressant medications in the acute phase, should continue treatment with these agents for 4–9 months. Consequently, the APA guidelines provide a range for the treatment duration of OADs, which is broadly consistent with the NICE CG90 recommendation of continuing OAD treatment for at least six months after remission (5).

B.1.3.6.4 TA367: Vortioxetine for treating major depressive episodes (8)

NICE has appraised and recommended vortioxetine for the treatment of third line MDD in TA367. Despite a clinical evidence base in first and second line MDD, NICE recommended vortioxetine in adults with major depressive episodes whose condition has responded inadequately to two OADs within the current depressive episode.

B.1.3.7 Current clinical pathway of care

The current recommended treatment pathway for MDD and TRD is described in NICE CG90 and the BAP guidelines, however the pathway in real-life NHS clinical practice differs to that described within the guidelines. In clinical guidelines, referral to mental health professionals is recommended for patients whose depression has inadequate or incomplete response to two or more interventions (see Section B.1.3.6). In clinical practice however, only an estimated 10% of patients with TRD are referred to specialist mental health services (generally those deemed to be at risk of suicide), despite significant functional impairment and lack of treatment response. Waiting times for specialist mental healthcare services are often considerable, prolonging patient suffering (12, 50, 51). This results in most patients with TRD cycling through OAD therapies in a primary care setting for long periods (7), with no improvements in their health state putting them at risk of crisis and hospitalisation, an issue that was highlighted during the NICE early scientific advice meeting (7). A substantial proportion of patients with MDD (10% to 30%) (1, 23, 40) do not respond or remit on currently marketed monoaminergic-based OADs such as SSRIs and SNRIs, which leaves them in a depressive state and at potential risk of

self-harm, as well as having a negative impact on their personal and working lives (37-39, 41).

B.1.3.7.1 Antidepressant treatments in clinical practice

There is currently no licenced treatment option for TRD in the UK. Consequently, there is no established consensus among health care professionals (HCPs) on which treatment strategy should be adopted for patients who have not responded to at least two OAD treatments of adequate dose and duration. As a result, the recommendations in NICE CG90 to switch to another OAD of a different pharmacological class for the treatment of patients with TRD are not always followed in clinical practice. This is the same for subsequent treatment options such as augmentation with lithium or antipsychotics or another OAD. In a study of five primary care practices in England, no more than 19% of patients were treated with OADs in accordance with guidelines and only 41% reported continuing with treatment over six months of therapy (52).

Historically, in the absence of an effective pharmacological therapy, switching or optimising OADs, as well as augmentation with antipsychotics/lithium are used in the TRD population, as recommended in the NICE CG90 and BAP depression guidelines (see Section B.1.3.6). The evidence on augmentation and combination antidepressant treatments specifically in the TRD population is sparse (see Section B.2.9).

Expert opinion from seven UK healthcare professionals, including general practitioners (GPs) and consultant psychiatrists, confirmed that in clinical practice in England, patients with TRD are currently treated with the options described in the clinical guidelines, but that there was no consensus on the sequence in which treatments (and their various combinations) were administered, because "*there is no clear differentiation of one treatment versus the other in terms of efficacy and safety*" (1, 2, 50, 53).

Overall, the current treatment strategies are suboptimal in TRD, and response and remission rates of currently available OADs are <20% and <15% respectively (23). Even when patients with TRD respond or remit to OADs, it usually takes between 4 to 6 weeks to achieve the optimal treatment effect (23, 54, 55), and during this time

patients may already experience AEs and continue to suffer from their symptoms. For patients with TRD responding to OAD, the durability of their response or remission is less than that observed in non-TRD MDD. There is a 60–70% risk of patients experiencing relapse within six months – twice the rate observed in those with non-TRD-MDD (23). This stark statistic underscores the need for a treatment with a rapid onset of action, which can increase response and remission, and sustain remission. Given the current limitations of existing treatment options for patients with TRD, many patients end up cycling through numerous different treatment options (7) unable to achieve a sufficient response or attain the treatment aim of remission.

Currently available non-pharmacologic treatment options for later lines of TRD (e.g., ECT) also have considerable limitations in terms of long-term efficacy, safety and acceptability to patients. ECT has an estimated short-term response rate of 60–80%, making it more effective than OAD therapies (56). However, evidence suggests that the efficacy is not sustained in the long term (57). ECT is not recommended for TRD maintenance due to the lack of clear long-term efficacy, requirement for anaesthesia and significant side effects (57, 58). The latter include brain damage, severe confusion and considerable cognitive impairment (acute confusion, anterograde amnesia and retrograde amnesia) (57). The use of these therapies in the NHS clinical practice are therefore relatively limited (≤2% based on data from SLaM) (1).

Table 5. Summary of currently used treatments in patients with TRD and their limitations (5, 45, 54, 55, 57, 59-61)

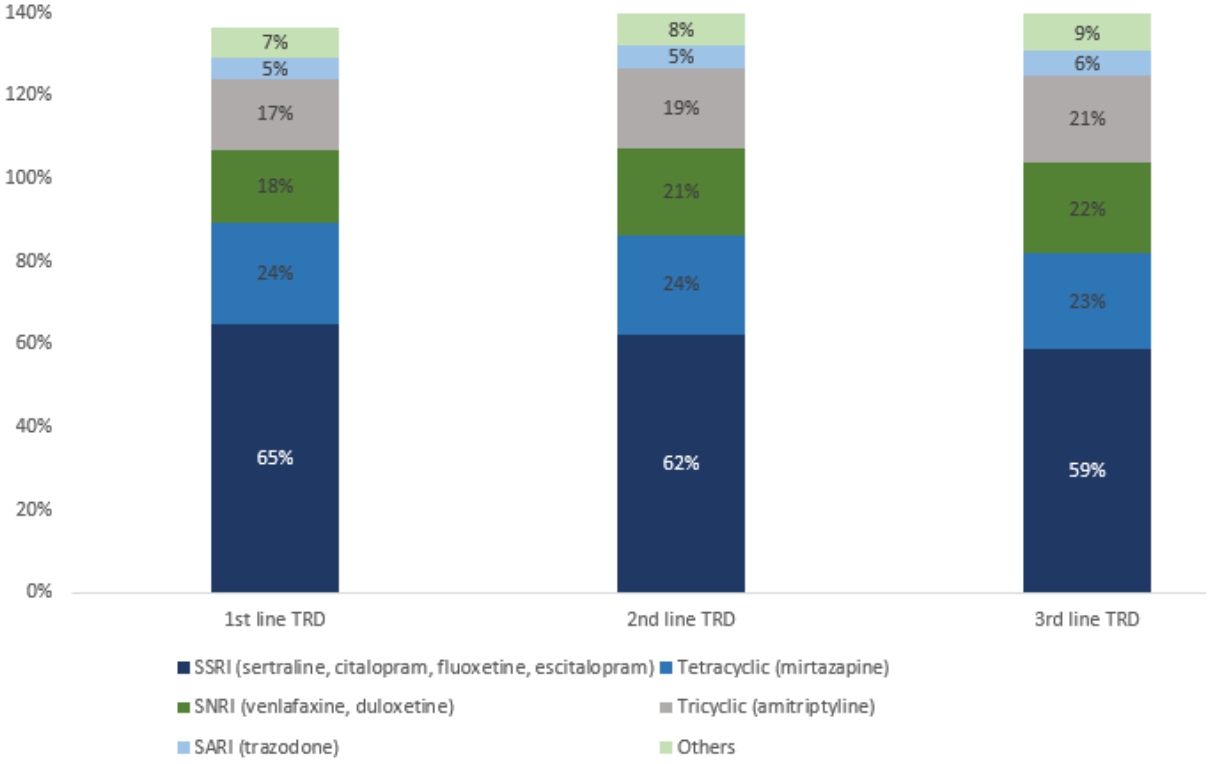
Existing treatment option	Examples	Limitations
SSRI antidepressants	Citalopram, escitalopram, fluoxetine, paroxetine, sertraline, vilazodone	Delayed onset of action; Low response and remission rates; Poor treatment adherence; Requires active monitoring Safety profile
SNRI antidepressants	Duloxetine, venlafaxine	
Other antidepressants	Vortioxetine	Delayed onset of action; Low response and remission rates Not studied in TRD
MAOIs	Phenelzine, tranylcypromine	Delayed onset of action; Low response and remission rates; Active monitoring due to AE profile and risk of overdosing
TCAs and TeCAs	Amitriptyline, desipramine, doxepine, imipramine,	Delayed onset of action;

Existing treatment option	Examples	Limitations
	mianserin, nortriptyline, mirtazapine	High dropout rates (low tolerability); Active monitoring due to risk of overdosing
Adjunctive / augmentative agent	Lithium	Low response and remission rates; Active monitoring due to AE profile and risk of overdosing; Many contraindications
Adjunctive / Augmentative Atypical Antipsychotics	Aripiprazole, olanzapine, quetiapine, risperidone	Low response and remission rates; Active monitoring due to AE profile
Non-pharmacological therapies	ECT	Requirement for anaesthesia; Significant side effects; Lack of clear long-term efficacy, hence needs to be followed by continuation pharmacotherapy

Abbreviations: AE, adverse event; ECT, electroconvulsive therapy; MAOI, monoamine oxidase inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TeCA, tetracyclic antidepressant; TRD, treatment resistant depression.

As NICE stated in the early scientific advice (7) and at the NICE Scoping Workshop: "Real World Evidence (RWE) will determine which comparators are the most relevant ones". Of the list of comparators included in the final scope, SSRIs, TCAs, SNRIs, and mirtazapine are the most frequently used and therefore the most relevant comparators. Data from the IQVIA Longitudinal Patient Database for the date range 1st April 2007 to 31st March 2018 (2) were analysed to identify the most prescribed antidepressants by line of treatment, as shown in Figure 5. About 62% of patients prescribed first-line TRD treatment were prescribed an SSRI, approximately 24% were prescribed mirtazapine and 18% were prescribed a SNRI. The high rate of amitriptyline prescribing is likely explained by its use to also treat pain and sleep disturbance. Because of the different treatments being co-prescribed and used in combination therapies, the totals in the figure are >100%.

Figure 5. Most frequently used antidepressant therapies in 1st, 2nd and 3rd line TRD in UK (based on IQVIA database)



Abbreviations: SARI, serotonin antagonist and reuptake inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TRD, treatment resistant depression.
Note: values exceeding 100% are explained by co-prescribing.

B.1.3.7.2 Patient perspective

The manifestation of MDD/TRD is heterogenous, varying greatly in terms of combination of symptoms, course of illness and severity. Despite the heterogenous nature of the condition, there is likely to be a considerable burden on a patient's quality of life. Symptoms can last for months, or even years, and can be seriously debilitating. They manifest through impaired capacity, and inability to work to the point of complete inability to move, which (62) substantially interference with the patient's vocation, social integration, and relationships (18). This is particularly the case for patients with TRD, for whom symptoms persist longer than with MDD due to the lack of efficacy of OAD therapies, often leading to worsening outcomes (63).

Evidence shows that, compared with MDD, TRD has a greater impact on multiple outcomes at the patient level, such as a higher risk of suicide, hospitalisation, lower labour force participation, medical resource utilisation, and societal costs (40). Additionally, TRD has an indirect impact on morbidity and mortality, through the

development of concomitant and co-morbid psychological and physical conditions (64-67).

As well as impacting a person's quality of life, non-response to treatment elevates the already increased risk of suicide in patients with MDD. Multicentre European studies have consistently reported that patients with TRD compared with the MDD group are at a significantly higher risk for suicide (33, 68). In one study, 50% of patients who experience treatment resistance exhibit severe suicidality compared with 11% of patients who do respond to a treatment (69).

In a focus group held in March 2019 (70), patients with TRD indicated that *"the limitations in effective treatment options result in the clinicians offering similar treatments over and over again, and that is not helping, and even more discouraging [for the patients]"*. In addition, these patients mentioned that it feels like their disease is 'endless' as they have no hope that additional treatment(s) will be effective making them anxious to start another treatment. The disease is characterised by patients feeling embarrassed and stigmatised about their disease and living isolated lives, with *"no quality of life"* as a result.

There is a large unmet need for a safe, well-tolerated treatment with a rapid onset of action and durable efficacy. Introducing a treatment which achieves a rapid reduction of depressive symptoms whilst reducing the need of care could significantly reduce the burden of TRD for patients, their carers and the economy.

B.1.3.8 Future clinical pathway of care

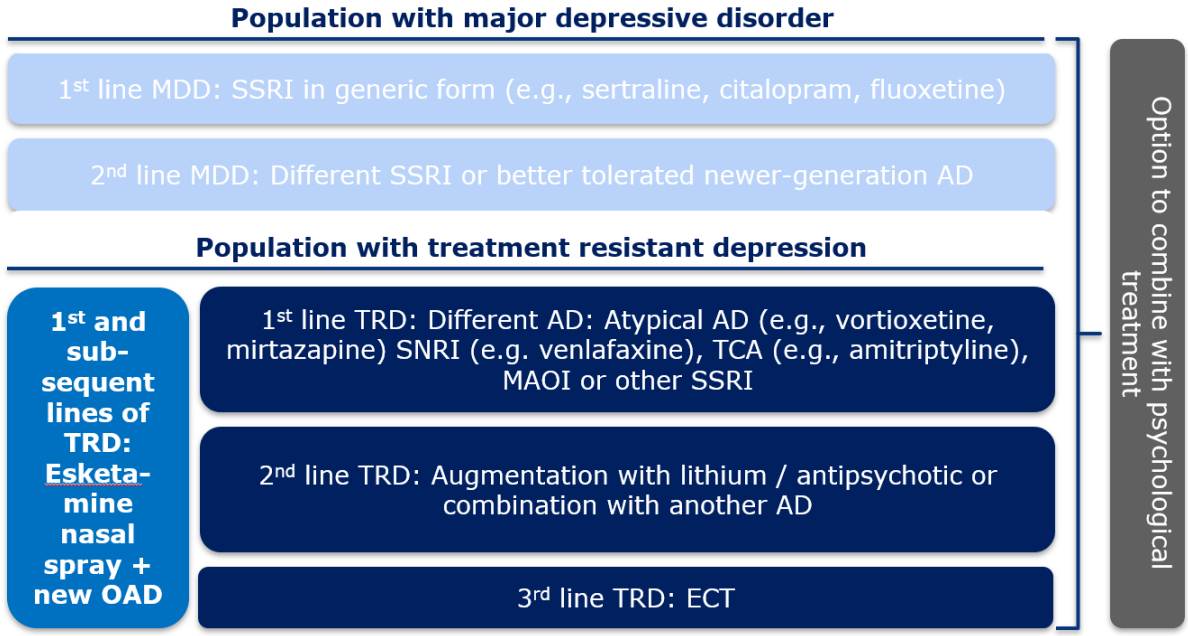
ESK-NS is the first antidepressant with a new mechanism of action in the field of depression in over 30 years and will be the first fast-acting OAD indicated specifically for patients with TRD. Whilst almost all the commonly used OADs are monoaminergic, ESK-NS has a novel mechanism of action, that exerts its action by transient NMDA receptor blockade or modulation, which is hypothesised to alter the underlying pathophysiological process of depression. This unique mechanism of action results in a rapid onset of action (within 24 hours), and in combination with a newly initiated OAD, 20% greater response and remission rates for the short-term, and 50% lower relapse rates for the long-term in comparison with currently available

OADs used in the TRD population (71, 72). This gives patients with TRD the opportunity to break the current cycle of ineffective treatments.

ESK-NS must be co-administered with a newly initiated OAD. It is hypothesised that a combination of two treatments with different mechanisms of action (monoaminergic and glutamatergic) will have a complementary positive treatment effect.

ESK-NS plus a newly initiated OAD is anticipated to be used in all TRD treatment lines in patients with moderate to severe depressive symptoms. This has been confirmed by seven UK clinicians through an advisory board (50) and validated by clinicians who attended the NICE Scoping Workshop. The anticipated positioning of ESK-NS is also reflected in the list of comparators included in the final NICE scope. This would result in the positioning of ESK-NS plus OAD in the MDD and TRD treatment pathway as depicted in Figure 6.

Figure 6. Future MDD and TRD treatment pathway as discussed at NICE Scoping Workshop



Abbreviations: AD, antidepressant; ECT, electroconvulsive therapy; MAOI, monoamine oxidase inhibitor; MDD, major depressive disorder; NICE, The National Institute for Health and Care Excellence; OAD, oral antidepressant; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TRD, Treatment-resistant depression.

During and after ESK-NS administration at each treatment session, patients should be monitored for sedation and dissociation until the patient is stable and ready to leave the clinic based upon clinical judgment. While ESK-NS could potentially be used in all lines of TRD treatment, the suitability should be addressed by a specialist

in mental health and the setting needs to be appropriate to allow for the required observation and monitoring period.

The availability of ESK-NS is expected to reduce the number of patients with TRD who continuously cycle through different OADs in primary care and prevent patients with TRD ending up in a crisis. Additionally, it is expected to diminish the need for combination and augmentation strategies in addition to invasive non-pharmacological treatments that are associated with an increased side effect burden in later lines.

Undoubtedly, TRD has a significant burden of disease; the diminished chance of reaching remission, together with the increased likelihood of recurrence result in cycles of depression which severely limit a person's quality of life as well as that of their family and friends, which can last over a lifetime. ESK-NS thus affords patients, the majority of who are of working age, the opportunity to function both socially and occupationally again and to reduce the significant burden that TRD imposes not only on the healthcare system, but also on society in general.

B.1.4 Equality considerations

In relation to equality, Janssen would like to highlight geographic access as a key consideration. ESK-NS will require observation by a healthcare professional during and post-self-administration with additional restrictions for driving (not permitted until the next day after a restful sleep). Additionally, some patients with TRD may not be able to drive due to the nature of their condition. It will be important to ensure that access to healthcare support will not inappropriately discriminate against individuals for whom geography may pose a challenge.

Additionally, there may be an equality consideration for the population of adults aged ≥65 years given different outcomes in TRANSFORM-3 compared to TRANSFORM-2. A separate trial (TRANSFORM-3) was conducted in this older population due to the different dosing, comorbidities, number of previous failures, time until response and treatment received in clinical practice. For improved tolerability, the starting dose was 28 mg in the TRANSFORM-3 trial (adults ≥65 years), whereas the starting dose was 56 mg in the pivotal TRANSFORM-2 trial. The dosing recommendations in the label is expected to reflect these different starting doses. The Phase 2 dose-

response study SYNAPSE showed that the 56 mg dose is the lowest efficacious dose. Initially in the TRANSFORM-3 trial, investigators were cautious with the approach used in the elderly, resulting in under-dosing of many patients. Additionally, a duration of treatment exceeding 4 weeks may be required for ESK-NS to reach its full treatment effect in this population. Lastly, there is unlikely to be any comparative effectiveness evidence against other treatments in this population.

A pre-specified subgroup analysis of the TRANSFORM-3 trial showed that there was meaningful symptom improvement for patients in the subgroup aged 65–74 years, similar to the magnitude of the efficacy results reported in the younger adult population included in TRANSFORM-2. The small number of patients in the ≥75 years of age subgroup (n=22) means that the apparent lack of efficacy in this latter age group must be interpreted with caution. Given the similar relative treatment effect in adults 18–64 years and 65–74 years, and a relatively small number (n=22) of patients were ≥75 years, data from TRANSFORM-2 should be considered representative of the full licensed population.

B.2 Clinical effectiveness

Context

The challenges of developing an effective pharmacological intervention for patients who have failed to achieve a response to at least two different OADs are borne out by the failure of numerous clinical trials to show statistically significant improvements of active treatments over placebo in depression more broadly (73), hence there are currently no approved pharmacological treatments for TRD specifically.

ESK-NS clinical programme

ESK-NS is the first antidepressant with a new mechanism of action in the field of depression in over 30 years and will be the first fast-acting antidepressant indicated specifically for patients with TRD. ESK-NS plus a newly initiated OAD is anticipated to be used in all TRD treatment lines in patients with moderate to severe depressive symptoms.

- The clinical trial programme for ESK-NS consists of six Phase 3 clinical trials: three acute treatment 4-week studies –TRANSFORM-1, TRANSFORM-2, TRANSFORM-3, and three maintenance studies – SUSTAIN-1, SUSTAIN-2, and SUSTAIN-3.

The focus of this submission is on the TRANSFORM-2 and SUSTAIN-1 trials. The other four trials are supportive.

TRANSFORM-2:

- A randomised, double-blind, short-term trial in adults (aged 18–64 years) with TRD comparing the efficacy and safety of flexibly-dosed ESK-NS plus a newly initiated OAD versus a newly initiated OAD plus PBO-NS.
- Consisted of phases: a 4-week screening/prospective observational phase with an optional up to 3-week period to taper the current antidepressant medication; a 4-week double-blind induction phase with intranasal treatment sessions twice weekly; and a 24-week posttreatment follow-up phase.

- The primary endpoint was the change in clinician-administered MADRS total score (independent, remote rater) from baseline (Day 1 prior to randomisation) to the end of the 4-week double-blind induction phase.
- Key secondary endpoints included: proportion of patients showing onset of MADRS response by Day 2 (24 hours) that was maintained to the end of induction, change in SDS total score from baseline to the end of induction, change in PHQ-9 total score from baseline to the end of induction, proportion of responders and patients in remission (MADRS) at the end of induction.

SUSTAIN-1:

- A randomised, double-blind, long-term trial in adults (aged 18–64 years) with TRD who had achieved stable remission or stable response that compared the maintenance of efficacy of continued flexibly-dosed ESK-NS plus OAD treatment with that of OAD plus PBO-NS.
- Consisted of an open-label induction phase (4 weeks; direct-entry patients only); an optimisation phase (12 weeks; both direct-entry and transferred-entry patients); and a double-blind maintenance phase (variable duration; both direct-entry and transferred-entry patients).
- The primary endpoint was the time between patient randomisation into the maintenance phase and the first documentation (earliest date) of a relapse event (based on MADRS). Patients were eligible to enter the maintenance phase if they were in stable remission (based on MADRS) at the end of the optimisation phase following treatment with ESK-NS plus an OAD.
- The key secondary endpoint was the time between patient randomisation and first documentation of a relapse (based on MADRS) during the maintenance phase among patients in stable response (based on MADRS) at the end of the optimisation phase.

The TRANSFORM-1, TRANSFORM-3, SUSTAIN-2, and SUSTAIN-3 trials are supporting trials in this submission and have not been included in the economic model.

B.2.1 Identification and selection of relevant studies

Full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised are provided in Appendix D.

Systematic literature reviews (SLRs) were conducted to identify RCT evidence reporting on the efficacy and safety of ESK-NS and relevant comparator treatments for:

- Acute management of patients with TRD
- Ongoing maintenance treatment of patients with TRD.

Searches for acute management studies were conducted on 14 July 2017 and updated on 10 May 2019.

Searches for maintenance treatment studies were conducted on 1 February 2017 and updated on 23 May 2019.

B.2.1.1 Acute treatment SLR

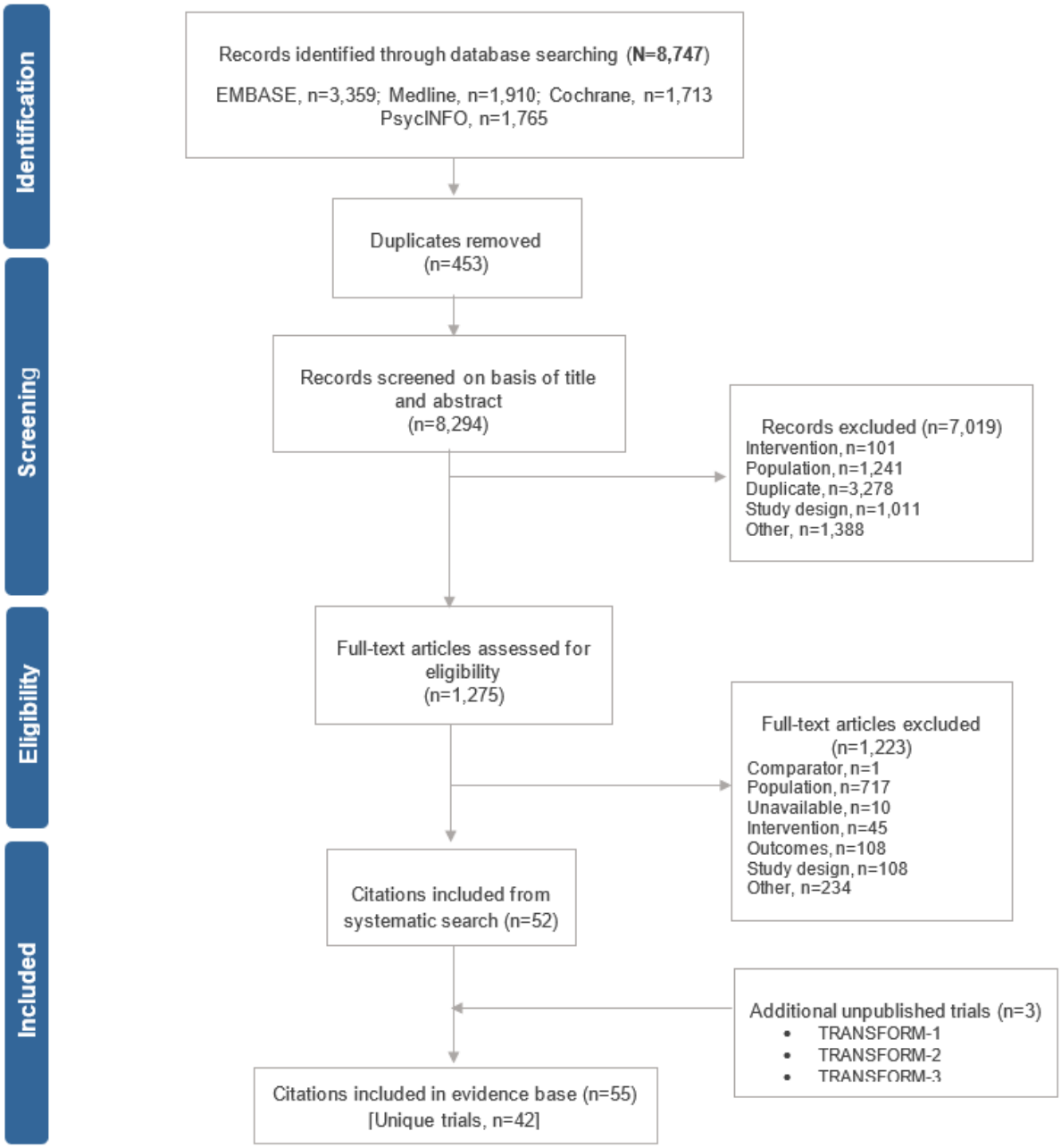
Searches of Embase, Medline, Psychinfo, and Cochrane databases using Ovid were conducted on 14 July 2017 (and updated on 10 May 2019). The US National Institutes of Health Clinical Trial Registry (http://www.clinicaltrials.gov) was also searched to identify any completed clinical trials that met the study selection criteria and had results available, but which had not yet been published.

Studies of interest included RCTs investigating relevant treatments for depression and which enrolled adult patients (≥18 years) with TRD (defined as unipolar MDD with failure to respond to two or more antidepressant treatment regimens).

The original search identified a total of 55 citations (including 3 unpublished Janssen-sponsored studies – TRANSFORM-1 (74, 75), TRANSFORM-2 (76, 77) and TRANSFORM-3 (78, 79)) reporting on 42 unique trials. A further 13 citations reporting on 13 unique trials were identified in the updated search.

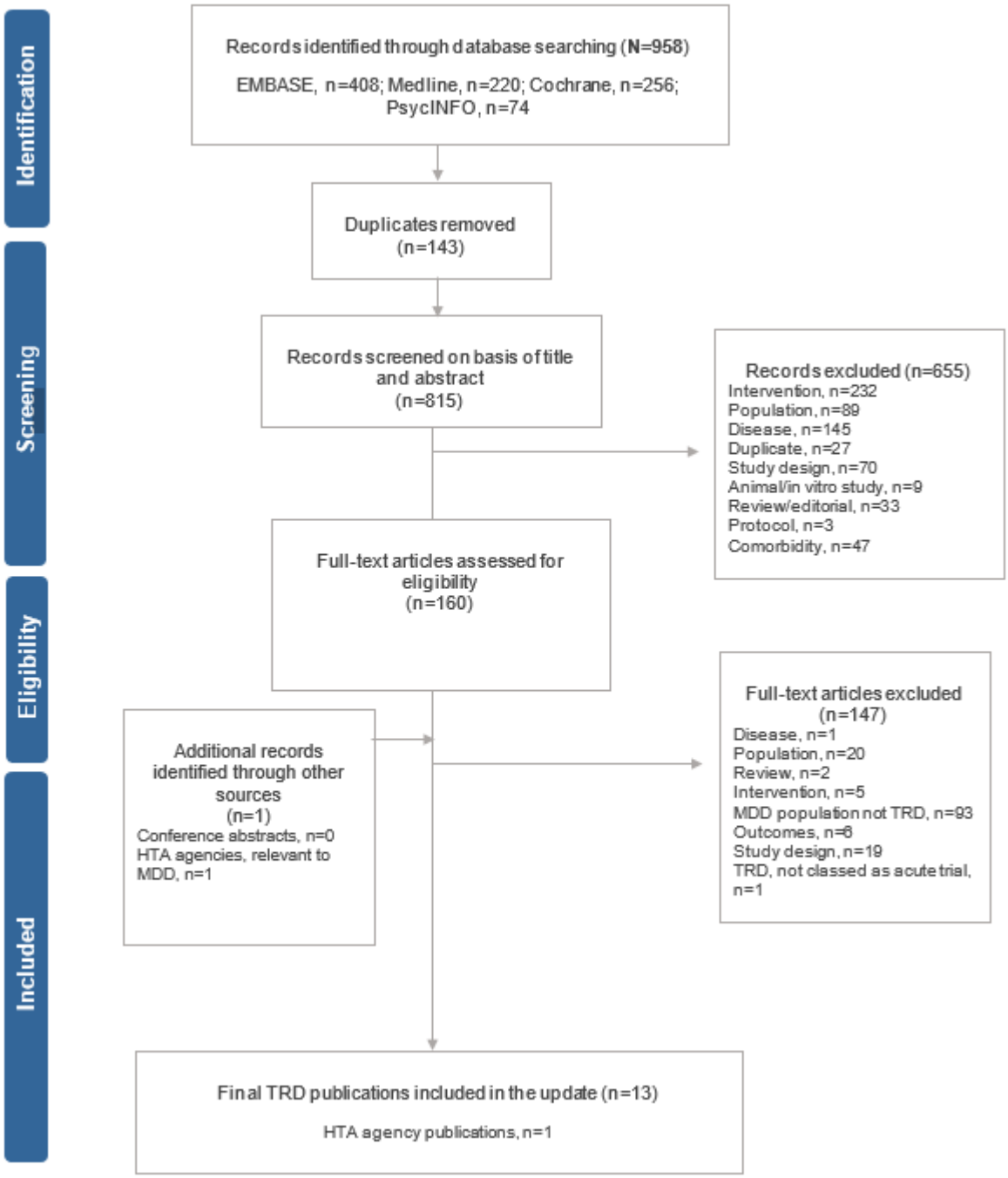
PRISMA flow diagrams detailing studies that were included and excluded at each stage of screening are provided in Figure 7 for the original SLR and Figure 8 for the SLR update. Full lists of included and excluded studies are provided in Appendix D.

Figure 7. PRISMA diagram – acute management of patients with TRD (Original SLR; 14 July 2017)



Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review; TRD, treatment-resistant depression.

Figure 8: PRISMA diagram – acute management of patients with TRD (SLR update – 10 May 2019)



Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review; TRD, treatment-resistant depression.

B.2.1.2 Maintenance treatment SLR

Searches of Embase, Medline, and the Cochrane Central Register of Controlled Trials were conducted on 1 February 2017 (and updated on 23 May 2019) The Clinical Trial Registry (http://www.clinicaltrials.gov), and the EU Clinical Trial Registry

(http://www.clinicalregister.eu) were searched to identify any completed or ongoing clinical trials that met the study selection criteria and had results available but which had not yet been published. Hand searches of conference proceedings for the previous two years were also performed.

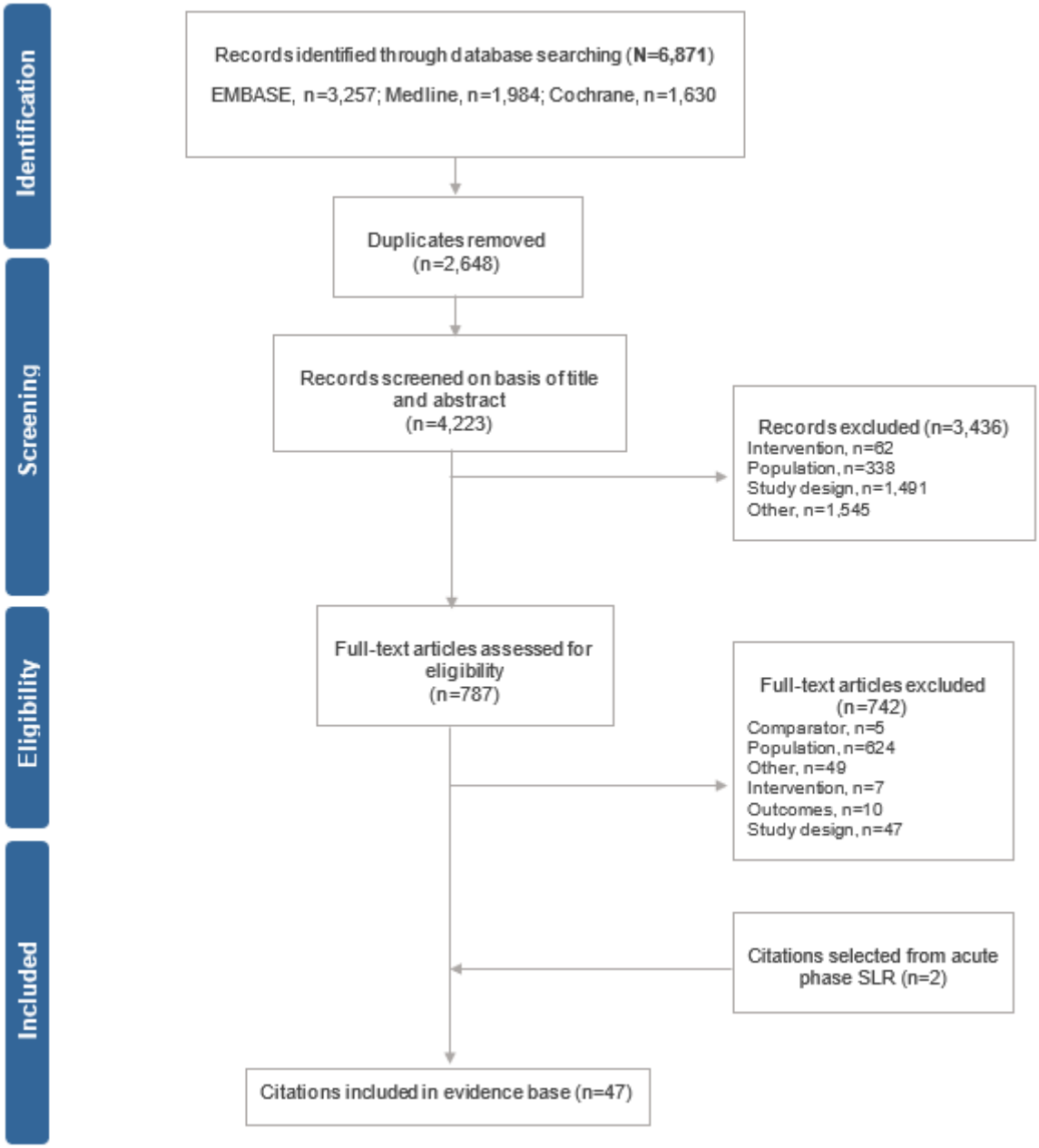
Studies of interest included RCTs investigating relevant treatments for depression and which enrolled adult patients (≥18 years) with TRD (defined as unipolar MDD with failure to respond to two or more antidepressant treatment regimens) who received long-term/maintenance (≥4 weeks) or relapse prevention treatment.

In order to supplement the evidence base for maintenance treatments, the evidence obtained from the related SLR of acute phase treatments for TRD was extended to screen for possible extension or follow-up phases. Four trials were identified with extended follow-up phases after acute treatment, outcomes for which were available for three trials. One trial (Shelton 2001 (80)) had already been included in the maintenance phase SLR; therefore, only two additional citations were incorporated into the overall evidence base, one of which was the Janssen-sponsored SUSTAIN-1 study (81, 82).

In total, 45 publications were identified in the 1 February 2017 search. Five studies that enrolled adult patients (≥18 years old) with MDD at imminent risk of suicide were subsequently deemed irrelevant to the decision problem and not considered further. A further 2 relevant studies were identified in the 23 May 2019 update.

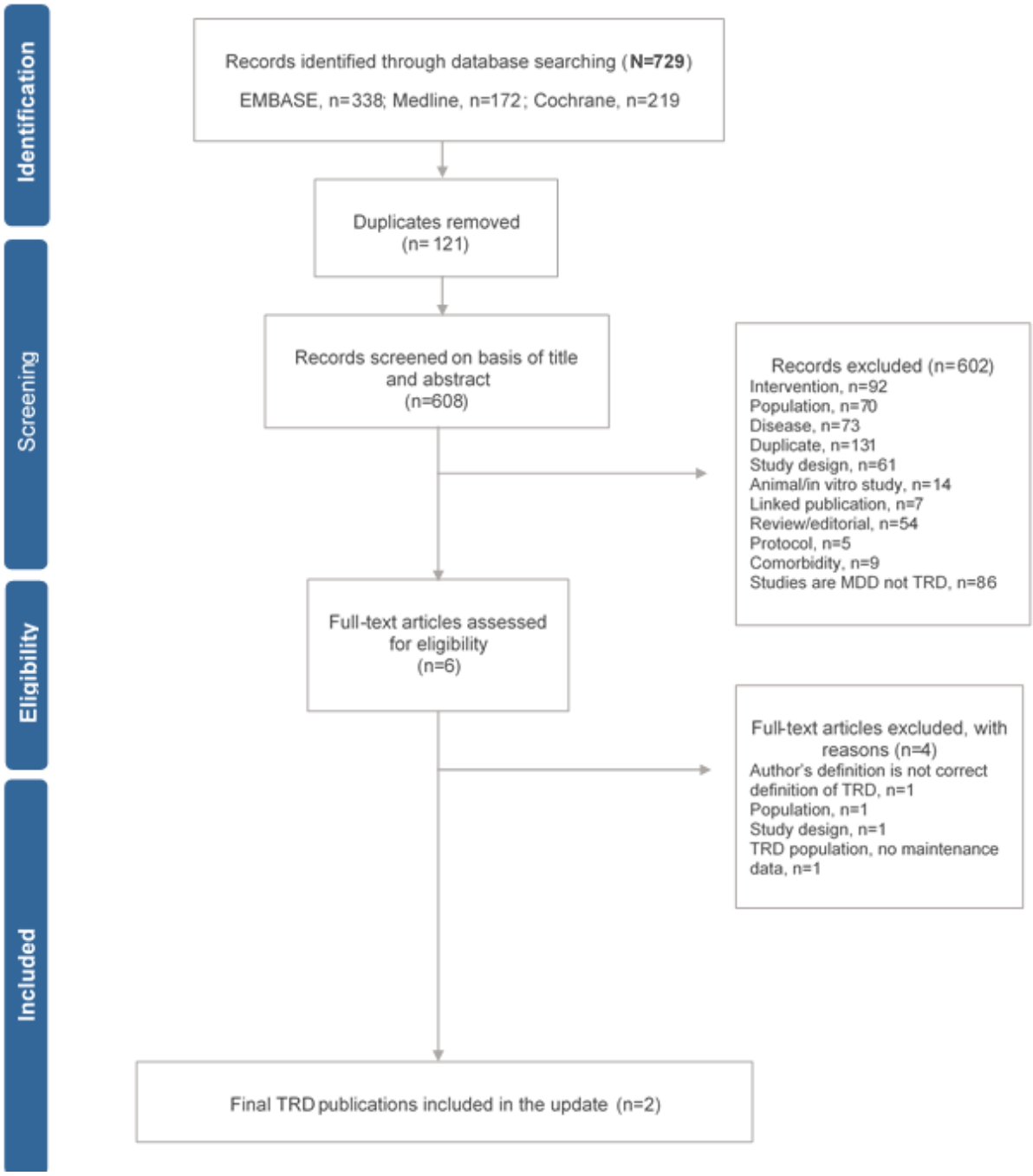
PRISMA flow diagrams detailing studies that were included and excluded at each stage are provided in Figure 9 for the original (February 2017) SLR and Figure 10 for the May 2019 update. Full lists of included and excluded studies are provided in Appendix D.

Figure 9: PRISMA diagram – clinical SLR for maintenance treatment (initial February 2017 search)



Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

Figure 10: PRISMA diagram – clinical SLR for maintenance treatment (May 2019 update)



Abbreviations: MDD, major depressive disorder; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review; TRD, treatment-resistant depression.

B.2.1.3 Clinical trials in the field of depression in perspective

In mental health and depression trials specifically, many trials fail to show a statistically significant efficacy outcome of the active drug compared with placebo. Of the randomised, placebo-controlled studies of OADs, approximately 50% have failed to show statistical superiority over placebo on change from baseline to endpoint (73).

This demonstrates the challenge of conducting a successful trial in the field of depression, mainly caused by the high placebo effect of clinical trial participants. This challenge is also acknowledged by the CHMP (17). It is important to note that the ESK-NS Phase 3 trials did not compare to an inactive comparator (placebo) alone; it is one of the first trials in the field of depression including an active comparator (AC) arm, which consisted of a newly initiated OAD plus PBO-NS.

B.2.1.4 The treatment effect of the active comparator arm in the ESK-NS trials compared with the treatment of OADs observed in other clinical trials and NHS clinical practice

The AC arm in the TRANSFORM-2 trial is unlikely to reflect the true treatment effect of a newly initiated OAD seen in clinical practice. The AC arm of the TRANSFORM-2 trial consists of a newly initiated SSRI/SNRI, in addition to a PBO-NS and intense HCP contact to administer the placebo device. This was to ensure double-blinding of the randomised clinical trial; however, it clearly differs from current NHS clinical practice.

As shown in Table 6, the current NHS clinical practice when an OAD is prescribed is characterised by less frequent and shorter duration visits to HCPs than future clinical practice after initiation of ESK-NS + OAD. Table 6 also shows the future practice of visits after initiation of ESK-NS treatment, which is aligned to TRANSFORM-2.

Table 6. Current and future clinical treatment pathway for TRD (50, 53, 83)

Treatment phase	Existing clinical practice when OAD is prescribed	Future clinical practice for ESK-NS + OAD
Acute treatment phase Aim: complete resolution of TRD symptoms	• Initiation of OAD • First visit on average 3–4 weeks after switching to a new OAD • On average, four visits in the first 3 months after switch to a new OAD • Visit of 20–30 minutes, usually with GP, to assess treatment effect, and consider continuation or change in treatment	• Initiation of ESK-NS + OAD • Eight visits in first 4 weeks • At visit eight (at 4 weeks), there will be time with a prescriber (psychiatrist) to assess treatment response, and consider continuation or change in treatment On average 1 hour and 10 minutes per visit: • 10 minutes self-administration (under supervision of nurse). Blood pressure will be measured before first self-administration • 1 hour observation (by healthcare assistant) where blood pressure is measured 1–3 times

Treatment phase	Existing clinical practice when OAD is prescribed	Future clinical practice for ESK-NS + OAD
Relapse prevention treatment phase Aim: preventing relapse of MDD episode	• One visit every 4–12 weeks • Visit of 10–30 minutes, usually with GP, to assess treatment effect, and consider continuation or change in treatment	Weeks 5–8: • Weekly visits Weeks 8 onwards: • Fortnightly or weekly visits On average 1 hour and 20 minutes per visit: • 10 minutes self-administration (under supervision of nurse). Blood pressure will be measured before first self-administration • 1 hour observation (by healthcare assistant) where blood pressure is measured 1–3 times The need for continued treatment will be evaluated periodically
	After the depressive symptoms resolve, treatment for at least 6 months is recommended for consolidation of the anti-depressive response	After depressive symptoms improve, treatment is recommended for at least 6 months
Recurrence prevention Aim: prevent new episode of MDD	• Prevention of MDD recurrence is with an OAD following entry into a 'recovery' state	• Prevention of MDD recurrence is with an OAD following entry into a 'recovery' state • For patients at high risk of recurrence, ESK-NS treatment may be extended to up to 2 years based on clinical judgement

Abbreviations: GP, general practitioner; MDD, major depressive disorder; OAD, oral antidepressant; TRD, Treatment-resistant depression.

The AC arm of the TRANSFORM-2 trial is very different to AC arms in other studies. The change in MADRS total score from baseline to the end of induction among patients in the active comparator arm of TRANSFORM-2 was more than twice that observed in equivalent studies in which patients with TRD were treated with a newly initiated OAD (84, 85). Response and remission rates were 52.0% and 31.0%, respectively, among patients in the active comparator arm of TRANSFORM-2 compared with 16.8% and 13.7%, respectively, among patients with TRD in the STAR*D study, some of whom were receiving combination/augmentation therapies (23). The systematic literature review of clinical studies in TRD showed there is no other trial conducted with a similarly high number of follow-up visits (eight visits in four weeks) and a placebo nasal spray in the AC arm. The presence of these two aspects are known to contribute to a therapeutic response. It has been shown that follow-up visit assessments in OAD treatment trials translate into a significant therapeutic effect, representing about 40% of the response to placebo.

The reasons for the high response in the OAD + PBO-NS arm of TRANSFORM-2 were discussed during an advisory board with seven UK clinical psychiatric experts, noted in the literature (Rutherford 2013 (15)), and also discussed by the FDA and EMA during their review of the ESK-NS regulatory dossier. Based on available evidence, it was concluded that the main reasons for the high TRANSFORM-2 treatment effect included:

- Use of a nasal spray delivery system leading to patient expectation of 'something novel'.
- High patient expectation of benefit due to the portrayal in the media of esketamine as a 'promising' new treatment option for depression.
- High frequency and intensity of patient-health care professional interaction due to twice-weekly visits (of considerable length).
- Treatment effect of the newly initiated OAD, an active drug which is the first line standard of care for TRD.

While considerable care was taken to minimise other contributors to a placebo response in the Phase 3 studies (e.g., remote rater assessments were implemented to minimise MADRS rater drift and placebo nasal spray included as a bittering agent), an impact of placebo response on the comparator arm is likely to remain. For example, there were cases of patients given the PBO-NS device who reported the adverse event of dissociation, which should be unique to the active ingredient of ESK-NS. Quantification of the impact of expectation on placebo response has been evaluated in recent studies. Additionally, quantification of the impact of additional visits in MDD trials has been undertaken by Posternak and Zimmerman (2007) (86).

The use of ESK-NS in real world clinical practice will require the same number of physician visits as observed in TRANSFORM-2. Therefore, adjustment for visit effect for the ESK-NS + OAD arm is not appropriate. Conversely, in clinical practice, patients with TRD on OADs do not receive the same intensive therapeutic contact as was the case in TRANSFORM-2, which amounted to eight clinic visits during the 4-week acute treatment period (see Table 6). See Section B.2.3.7 for full details regarding the adjustment methodology.

B.2.2 List of relevant clinical effectiveness evidence

The clinical trial programme for ESK-NS consists of six Phase 3 clinical trials: three acute treatment 4-week studies –TRANSFORM-1, TRANSFORM-2, TRANSFORM-3, and three maintenance studies – SUSTAIN-1, SUSTAIN-2, and SUSTAIN-3.

The focus of the submission from this section onwards is on the TRANSFORM-2 and SUSTAIN-1 trials, since these:

- Evaluate the efficacy of flexible dosing (56 mg/84 mg) of ESK-NS, which is in line with its anticipated licence and use in clinical practice.
- Provide evidence for ESK-NS of direct relevance to the NICE scope in terms of population, intervention, and outcomes.
- Provide data used to inform the NMA and economic model.

The rationale for not including the TRANSFORM-1, TRANSFORM-3, SUSTAIN-2, and SUSTAIN-3 trials in the economic model is below.

TRANSFORM-2 was a randomised, double-blind, short-term trial in adults (aged 18–64 years) with TRD that compared the efficacy and safety of flexibly-dosed ESK-NS plus a newly initiated OAD versus a newly initiated OAD plus PBO-NS. SUSTAIN-1 was a randomised, double-blind, long-term trial in adults (aged 18–64 years) with TRD who had achieved stable remission or stable response that compared the maintenance of efficacy of continued flexibly-dosed ESK-NS plus OAD treatment with that of OAD plus PBO-NS. The use of a newly-initiated OAD (instead of one to which patients had previously not responded) was thought to provide patients a greater likelihood of achieving sustained improvement following discontinuation of ESK-NS. Furthermore, initiating a new OAD, instead of continuing a failed medication to which the patient had demonstrated no clinically meaningful response, ensured that all patients (in all the Phase 3 studies) received a clinically optimised OAD treatment, consistent with international clinical treatment recommendations for MDD to replace an ineffective therapy with a different agent.

The TRANSFORM-1, TRANSFORM-3, SUSTAIN-2, and SUSTAIN-3 trials are regarded as supporting trials in this submission and have not been included in the base case economic model, since:

- In TRANSFORM-1, with the exception of the first dose (56 mg for all patients) ESK-NS was administered at fixed doses of either 56 mg or 84 mg which is not reflective of the anticipated esketamine licence.
- TRANSFORM-3 enrolled only patients with TRD aged ≥65 years, who, for tolerability reasons, were started on an initial dose of 28 mg ESK-NS which is below the minimum effective dose of 56 mg[a].
- SUSTAIN-2 was a non-comparative study, primarily designed to assess long-term safety (with minimal efficacy data).
- SUSTAIN-3 is ongoing. Only interim safety data are available (see Section B.2.10).

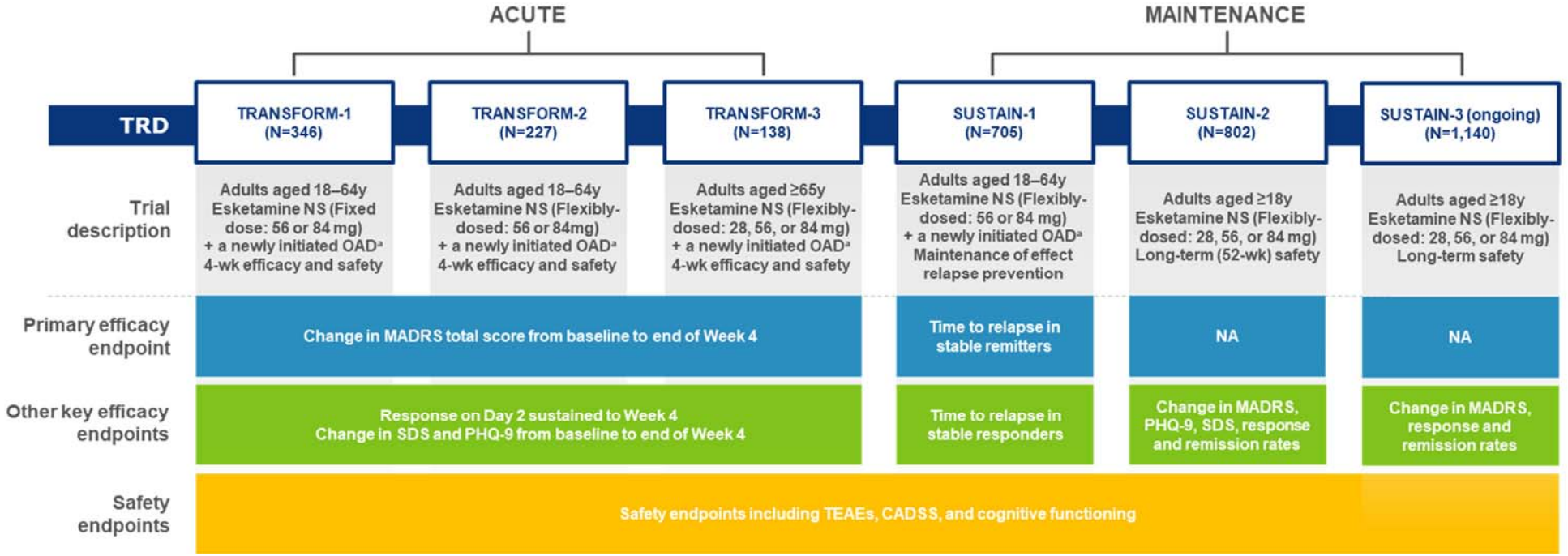
Brief summaries of methods and key efficacy results for each of the TRANSFORM-1, TRANSFORM-3, and SUSTAIN-2 supporting trials are provided in the submission (Section B.2.7). Full details (complete methods and results) of each of these supporting trials are provided in Appendix M (methods) and Appendix N (results).

Figure 11 presents an overview of the six trials comprising the Phase 3 esketamine clinical trial programme. A top line summary of the six trials, highlighting how the pivotal trials, TRANSFORM-2 and SUSTAIN-1, inform the NICE decision problem and model, is provided in Table 7.

A crucial difference in the design of the ESK-NS clinical trial programme compared with that of traditional OADs was the request from the FDA that the ESK-NS programme comprise both short-term (acute treatment) and long-term (maintenance treatment) studies. Unlike OADs, which typically have the same dosing regimen for short-term and long-term use, for ESK-NS, it was uncertain whether long-term treatment would be necessary as it was hypothesised that the antidepressant effect following short-term ESK-NS treatment could be maintained with an OAD alone. The maintenance study, SUSTAIN-1, however, showed this to not be the case: patients who discontinued ESK-NS demonstrated a significantly greater relapse rate than those who remained on ESK-NS (see B.2.6.2).

[a] Note that TRANSFORM-2 is representative of the entire TRD patient population in line with the findings of the TRANSFORM-3 65-74 years subgroup analysis data, Section B.1.4

Figure 11. Esketamine Phase 3 clinical trial programme



Abbreviations: CADSS, Clinician-Administered Dissociated States Scale; MADRS, Montgomery-Asberg Depression Rating Scale; NA, not applicable; NS, nasal spray; OAD, oral antidepressant; PHQ-9, Patient Health Questionnaire – 9 questions; SDS, Sheehan Disability Scale; TEAE, treatment-emergent adverse event; TRD, treatment-resistant depression; wk, week; y, years.

[a] Each trial (except for SUSTAIN-2 and SUSTAIN-3) featured a control arm in which patients received a newly initiated OAD plus placebo nasal spray.

Note that in SUSTAIN-2 and SUSTAIN-3, patients were incentivised to stay on treatment. These studies are therefore not appropriate to inform treatment duration.

Table 7. Clinical effectiveness evidence for ESK-NS

Trial no. (acronym)	TRANSFORM-1 (ESKETINTRD3001)	TRANSFORM-2 (ESKETINTRD3002)	TRANSFORM-3 (ESKETINTRD3005)	SUSTAIN-1 (ESKETINTRD3003)	SUSTAIN-2 (ESKETINTRD3004)	SUSTAIN-3 (ongoing) (ESKETINTRD3008)
Primary sources	CSR (74), study protocol (75)	CSR (76), study protocol (77), manuscript (71)	CSR (78), study protocol (79)	CSR (81), study protocol (82), manuscript (72)	CSR (87), study protocol (88)	CSR (89)
Additional sources	Posters (90, 91)	Posters (90, 92, 93)	Poster (94)	Posters (95, 96)	Posters (95, 97)	NA
Relevance of study to this submission	Supporting	**Pivotal**	Supporting	**Pivotal**	Supporting	Supporting (ongoing; interim data only)
Study design	Randomised, double-blind, parallel-group, active-controlled, multicentre, Phase 3				Open-label, multicentre, long-term, Phase 3	
Population	Adults (aged 18–64 years) with recurrent or single-episode TRD[a]		Adults (aged ≥65 years) with recurrent or single-episode TRD[a]	Adults (aged 18–64 years) with recurrent or single-episode TRD. Patients either directly entered the study or transferred from TRANSFORM-1/2 (having completed double-blind induction phase and demonstrated treatment response at end of 4-week double-blind induction phase of these transfer studies)	Adults (aged ≥18 years) with recurrent or single-episode TRD	
Intervention(s)	Fixed dose ESK-NS (56 mg OR 84 mg) twice weekly for 4 weeks (starting dose for all patients: 56 mg) PLUS newly initiated OAD	Flexibly-dosed ESK-NS (56 mg/84 mg) twice weekly for 4 weeks (starting dose for all patients: 56 mg) PLUS newly initiated OAD	Flexibly-dosed ESK-NS (28 mg/56 mg/84 mg) twice weekly for 4 weeks (starting dose for all patients: 28 mg) PLUS newly initiated OAD	Flexibly-dosed ESK-NS (**SUSTAIN-1:** 56 mg/84 mg; **SUSTAIN-2/3:** 28 mg/56 mg/84 mg in patients aged ≥65 years) twice weekly, weekly, or every other week (depending on efficacy and tolerability) until relapse or study termination PLUS newly initiated OAD		

Trial no. (acronym)	TRANSFORM-1 (ESKETINTRD3001)		TRANSFORM-2 (ESKETINTRD3002)	TRANSFORM-3 (ESKETINTRD3005)	SUSTAIN-1 (ESKETINTRD3003)	SUSTAIN-2 (ESKETINTRD3004)	SUSTAIN-3 (ongoing) (ESKETINTRD3008)
Comparator(s)	Newly initiated OAD plus PBO-NS twice weekly for 4 weeks				Newly initiated OAD plus PBO-NS twice weekly, weekly, or every other week (depending on efficacy and tolerability) until relapse or study termination	NA	
Indicate if trial supports application for marketing authorisation	**Yes**	✓	✓	✓	✓	✓	✓
	No						
Indicate if trial used in the economic model	**Yes**		✓		✓		
	No	✓		✓		✓	✓
Rationale for use/non-use in the model	ESK-NS was administered as a fixed dose which is not in line with the anticipated licence		ESK-NS was administered via flexible dosing in line with the anticipated licence[a]	Enrolled patients aged ≥65 years, who, for tolerability reasons, were started on an initial dose of 28 mg ESK-NS which is below the minimum effective dose of 56 mg[a]	ESK-NS was administered via flexible dosing in line with the anticipated licence	A non-comparative study primarily designed to assess long-term safety (with minimal efficacy data)	An ongoing, non-comparative study primarily designed to assess long-term safety (with minimal efficacy data). Only interim data are available

Trial no. (acronym)	TRANSFORM-1 (ESKETINTRD3001)	TRANSFORM-2 (ESKETINTRD3002)	TRANSFORM-3 (ESKETINTRD3005)	SUSTAIN-1 (ESKETINTRD3003)	SUSTAIN-2 (ESKETINTRD3004)	SUSTAIN-3 (ongoing) (ESKETINTRD3008)
Reported outcomes specified in the decision problem[b]	• Response (MADRS) • Severity of depression (MADRS, CGI-S, PHQ-9) • Remission (MADRS) • Anxiety (GAD-7) • Functioning and associated disability (SDS) • Mortality (Safety outcome) • Adverse effects of treatment (including adverse effects of treatment discontinuation) • Health-related quality of life (EQ-5D)	• **Response (MADRS**) • Severity of depression (MADRS, CGI-S, PHQ-9) • **Remission (MADRS**) • Anxiety (GAD-7) • Functioning and associated disability (SDS) • Mortality (Safety outcome) • **Adverse effects of treatment (including adverse effects of treatment discontinuation)** • **Health-related quality of life (EQ-5D)**	• Response (MADRS) • Severity of depression (MADRS, CGI-S, PHQ-9) • Remission (MADRS) • Anxiety (GAD-7) • Functioning and associated disability (SDS) • Mortality (Safety outcome) • Adverse effects of treatment (including adverse effects of treatment discontinuation) • Health-related quality of life (EQ-5D)	• **Relapse (MADRS)** • Severity of depression (MADRS, CGI-S, PHQ-9) • Remission (MADRS) • Anxiety (GAD-7) • Functioning and associated disability (SDS) • Mortality (Safety outcome) • **Adverse effects of treatment (including adverse effects of treatment discontinuation)** • Health-related quality of life (EQ-5D)	• Response (MADRS, PHQ-9) • Severity of depression (MADRS, CGI-S, PHQ-9) • Remission (MADRS, PHQ-9) • Anxiety (GAD-7) • Functioning and associated disability (SDS) • Mortality (Safety outcome) • Adverse effects of treatment (including adverse effects of treatment discontinuation) • Health-related quality of life (EQ-5D)	• Response (MADRS) • Severity of depression (MADRS, CGI-S) • Remission (MADRS) • Mortality (Safety outcome) • Adverse effects of treatment

Abbreviations: CGI-S, Clinical Global Impression – Severity; CSR, clinical study report; EQ-5D, EuroQol-5 Dimension; GAD-7, Generalised Anxiety Disorder – 7-item scale; MADRS, Montgomery-Asberg Depression Rating Scale; NA, not applicable; OAD, oral antidepressant; PHQ-9, Patient Health Questionnaire – 9 questions; SDS, Sheehan Disability Scale; TRD, treatment-resistant depression.

[a] Regarding the differences in patient age in TRANSFORM-2 versus TRANSFORM-3, Janssen believe TRANSFORM-2 to be wholly representative of the entire TRD patient population in line with the findings of the subgroup analysis described in Section B.1.4.

[b] Outcomes marked in bold are used in the model.

B.2.3 Summary of methodology of the pivotal trials – TRANSFORM-2 and SUSTAIN-1

B.2.3.1 Overview of TRANSFORM-2 and SUSTAIN-1 trials

TRANSFORM-2 was a randomised, double-blind, multicentre, active-controlled study in adult patients with TRD. The primary objective was to evaluate the efficacy of ESK + newly initiated OAD compared with a newly initiated OAD + PBO NS. The change in the depressive symptoms is evaluated based on the MADRS score after four weeks to prove efficacy in the context of the acute phase.

SUSTAIN-1 used a randomised withdrawal design to assess, in a blinded fashion among patients who had achieved stable remission after 16 weeks of treatment with ESK-NS, the time to relapse between patients randomised to continue treatment with ESK NS + OAD and those randomised to discontinue ESK-NS and switch to PBO-NS and continue on an OAD. SUSTAIN-1 also evaluated the time from randomisation to relapse in the maintenance phase for patients in stable response (not in remission) after 16 weeks.

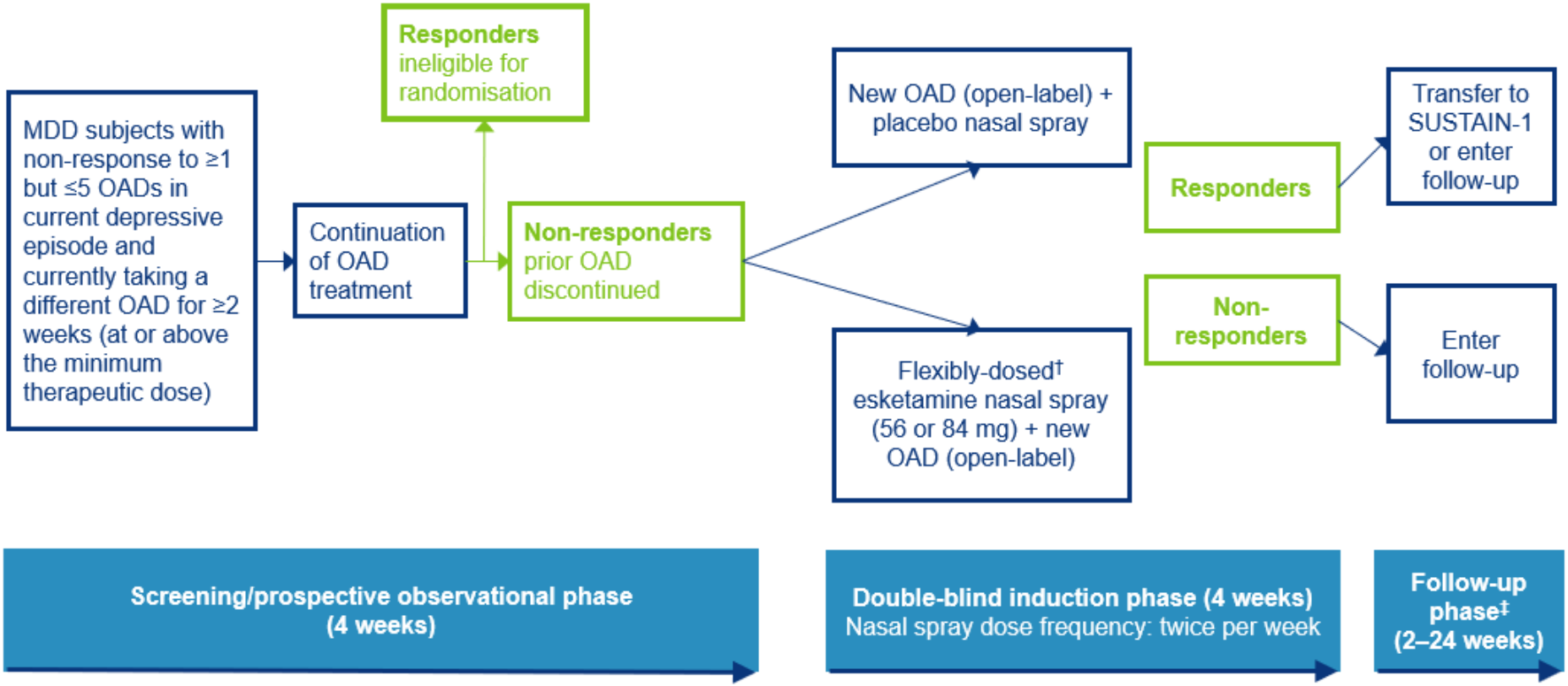
B.2.3.2 Trial design schematics

Schematics illustrating the designs of the pivotal trials, TRANSFORM-2 and SUSTAIN-1, are presented in Figure 12 and Figure 13, respectively.

TRANSFORM-2 consisted of a 4-week screening/prospective observational phase, an optional 3-week period to taper the current OAD medication, a 4-week double-blind induction phase during which nasal spray treatment sessions occurred twice weekly, and a 24-week post-treatment follow-up phase.

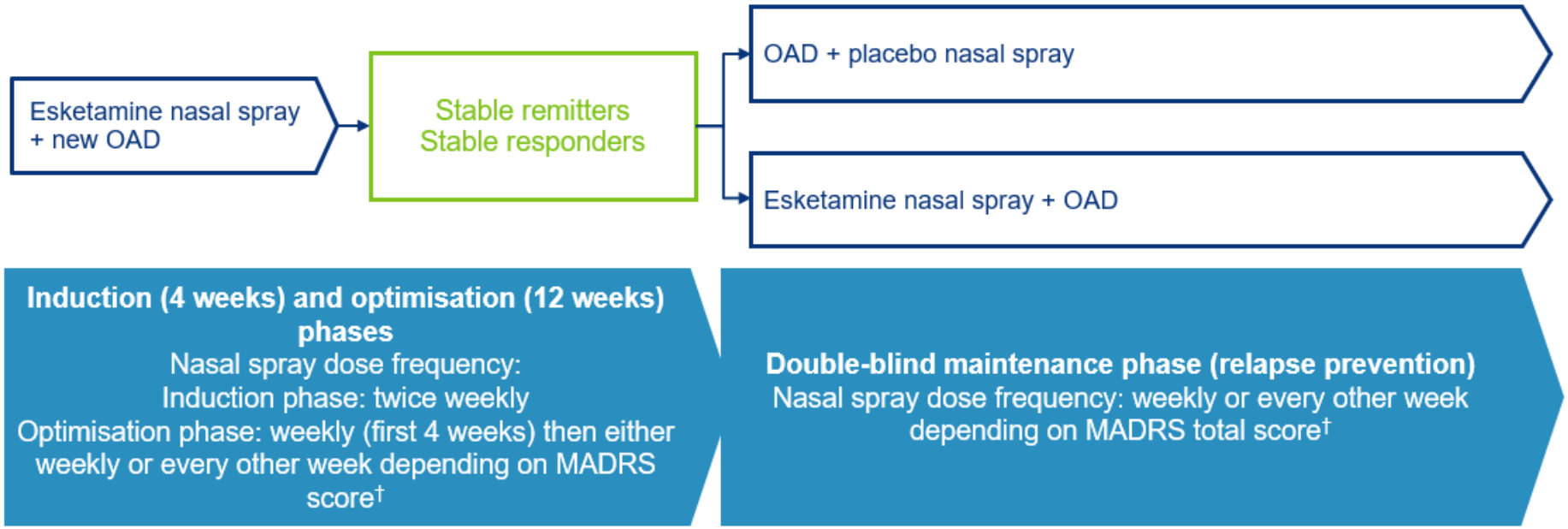
SUSTAIN-1 consisted of an open-label induction phase (4 weeks; direct-entry patients only), an optimisation phase (12 weeks; both direct-entry and transferred-entry patients), and a double-blind maintenance phase (variable duration; both direct-entry and transferred-entry patients from short-term ESK-NS trials).

Figure 12. Trial design for TRANSFORM-2



Abbreviations: MDD, major depressive disorder; OAD, oral antidepressant.
† On Day 1 of the induction phase, all patients randomised to receive esketamine nasal spray started with a dose of 56 mg. Thereafter, esketamine could be dosed flexibly (56 or 84 mg) based on efficacy and tolerability up until Day 15 (or Day 18 if the Day 15 treatment session did not occur). Beyond Day 15, the esketamine nasal spray dose was to remain unchanged. Further details on esketamine and OAD dose titrations are provided in Appendix M.
Note: Patients who withdrew early from the double-blind induction phase and received at least one dose of nasal spray study medication had an early withdrawal visit and then proceeded to the follow-up phase.
‡ From the follow-up phase, patients could also transfer to SUSTAIN-3 (ongoing). Non-responders remained double-blinded on their nasal spray treatment.

Figure 13. Trial design for SUSTAIN-1



Abbreviations: MADRS, Montgomery-Asberg Depression Rating Scale; OAD, oral antidepressant; TRD, treatment-resistant depression.
† See Appendix M for further details on esketamine nasal spray dosing frequency.
SUSTAIN-1 was a randomised, double-blind, long-term trial in adults (aged 18–64 years) with TRD who had achieved stable remission or stable response that compared the maintenance of efficacy of continued flexibly-dosed esketamine nasal spray plus OAD treatment with that of OAD plus placebo nasal spray. The study ended upon 84 relapses occurring. An interim analysis was performed at 30 relapses. Efficacy analyses included direct-entry patient as well as patients transferred from TRANSFORM-1 and TRANSFORM-2 who were on esketamine nasal spray plus OAD and during these studies. Patients who were on OAD plus placebo nasal spray during TRANSFORM-1 and TRANSFORM-2 could also enter the study but these patients were only considered in safety analyses.

B.2.3.3 Comparative summary of trial methodology

A comparative summary of the methodologies of the pivotal trials, TRANSFORM-2 and SUSTAIN-1, is presented in Table 8.

Table 8. Comparative summary of pivotal trial methodologies

Trial no. (acronym)	ESKETINTRD3002 (TRANSFORM-2)	ESKETINTRD3003 (SUSTAIN-1)
Study objective	• To evaluate the efficacy of flexibly-dosed ESK-NS (56 mg/84 mg) plus a newly initiated OAD (ESK-NS + OAD) versus a newly initiated OAD plus PBO-NS (OAD + PBO-NS) for the treatment of TRD in adults aged 18–64 years • To evaluate the safety and tolerability of each treatment regimen	• To evaluate the efficacy of flexibly-dosed ESK-NS (56 mg/84 mg) plus a newly initiated OAD (ESK-NS + OAD) versus a newly initiated OAD + PBO-NS in delaying relapse of depressive symptoms in adults aged 18–64 years with TRD who are in stable remission following an induction (4 weeks) and optimisation (12 weeks) course of ESK-NS plus an OAD • To evaluate the safety and tolerability of each treatment regimen
Study location	Patients were enrolled at secondary care sites in Czech Republic (6 sites), Germany (9 sites), Poland (7 sites), Spain (7 sites), and the US (10 sites).	Patients were enrolled at secondary care sites in Belgium (4 sites), Brazil (13 sites), Canada (2 sites), Czech Republic (11 sites), Estonia (1 site), France (5 sites), Germany (4 sites), Hungary (12 sites), Italy (4 sites), Mexico (6 sites), Poland (15 sites), Slovakia (3 sites), Spain (10 sites), Sweden (4 sites), Turkey (16 sites), and the US (54 sites).
Study period	7 August 2015 (date first patient signed informed consent) to 6 November 2017 (date of last observation for last patient recorded as part of the database).	6 October 2015 (date first patient signed informed consent) to 15 February 2018.
Number of patients enrolled	N=227	N=705
Trial design	Randomised, double-blind, parallel-group, active-controlled, multicentre, Phase 3.	
Study phases	• Screening/prospective observational phase: 4 weeks • Antidepressant taper period: ≤3 weeks (optional) • Double-blind induction phase: 4 weeks • Follow-up phase: ≤24 weeks (only for those patients ineligible or unwilling to participate in subsequent long-term study SUSTAIN-1 following double-blind induction phase)	**Direct-entry patients only:** • Screening/prospective observational phase, with an optional taper of ≤3 weeks for OAD(s): 4 weeks • Open-label induction phase: 4 weeks **Direct-entry and transferred-entry (from TRANSFORM-1/2) responder[a] patients:** • Optimisation phase: 12 weeks (open-label for direct-entry patients, double-blind for transferred-entry patients)

Trial no. (acronym)	ESKETINTRD3002 (TRANSFORM-2)	ESKETINTRD3003 (SUSTAIN-1)
		• Maintenance phase: variable duration (until relapse or study termination) • Follow-up phase: 2 weeks
Method of randomisation	Randomisation was achieved centrally via an IWRS, balanced using randomly permuted blocks (block size of four), and stratified by country and class of OAD (SNRI or SSRI) initiated in the double-blind induction phase.	Randomisation was implemented only in the maintenance phase and was achieved centrally via an IWRS, balanced using randomly permuted blocks (block size of four), stratified by country.
Method of blinding	• Investigators and site personnel were not provided with the IWRS randomisation codes and remained blinded to treatment assignments until all patients had completed the study. • The ESK and PBO nasal spray devices were indistinguishable. A bittering agent (denatonium benzoate) was added to the placebo solution to simulate the taste of the nasal spray solution containing active drug. • Throughout TRANSFORM-2, and during the double-blind maintenance phase of SUSTAIN-1, the same number of nasal spray devices (three) were given to patients to self-administer regardless of what dose of ESK-NS (56 mg/84 mg) or treatment (esketamine versus placebo) they were taking (see Appendix M for further details concerning blinding). • In SUSTAIN-1, transferred-entry patients who achieved stable remission[b] or stable response[c] at the end of the optimisation phase after treatment with an OAD plus PBO-NS continued to receive the same treatment to maintain the blinding for the ongoing short-term studies.	
Esketamine treatment	Beginning from the double-blind induction phase, patients (N=227) were randomised 1:1 to receive either: • ESK-NS (flexible dosing: 56 mg or 84 mg) twice weekly for 4 weeks (n=116), or • PBO-NS twice weekly for 4 weeks (n=111) (See Appendix M for further details on administration and dose titration of esketamine)	**Open-label induction phase (direct-entry patients only):** • ESK-NS (flexible dosing: 56 mg or 84 mg) twice weekly for 4 weeks (n=437) **Optimisation phase (direct-entry and transferred-entry patients):** • Patients continued to receive the same nasal spray treatment (esketamine or placebo) from the induction phase; therefore, direct-entry (n=273) and transferred-entry patients (n=268) continued to receive open-label and double-blind nasal spray treatment, respectively. • No changes to the nasal spray dose were permitted during the optimisation phase but the frequency of nasal spray medication sessions was reduced to once per week for the first 4 weeks, then once per week or once every other week, depending on the severity of depressive symptoms[d]. **Double-blind maintenance phase:** Patients in stable remission[b] (n=176) were randomised 1:1 to either: • Continue with ESK-NS (same dose) and the same OAD (n=90), or • Continue with the same OAD but switch to PBO-NS (n=86)

Trial no. (acronym)	ESKETINTRD3002 (TRANSFORM-2)	ESKETINTRD3003 (SUSTAIN-1)
		Patients with stable response[c] (but who were not in stable remission[b]) (n=124) were randomised 1:1 to either: • Continue with ESK-NS (same dose) and the same OAD (n=62), or • Continue with the same OAD but switch to PBO-NS (n=59) Transferred-entry patients who achieved stable remission[b] or stable response[c] after treatment with an OAD plus PBO-NS in the optimisation phase (n=55) continued to receive the same treatment in the maintenance phase to maintain the blinding of the ongoing short-term studies. For all patients, the frequency of nasal spray treatment sessions was individualised to once weekly or once every other week based on the severity of depression.[d] A patient could only switch the frequency of their treatment a maximum of three times. (See Appendix M for further details on administration and dose titration of esketamine).
OAD treatment	On Day 1 of induction (**TRANSFORM-2** patients and direct-entry **SUSTAIN-1** patients), or, beginning from the optimisation phase of **SUSTAIN-1** (transferred-entry patients) treatment in all patients was initiated, open-label, on one of four OADs from two classes: an SSRI (escitalopram or sertraline), or an SNRI (duloxetine or venlafaxine XR). Dosing of the OAD was according to local prescribing guidelines with protocol-specified titration to the maximally tolerated dose (see Appendix M for further details on OAD administration and dose titration).	
Permitted and disallowed concomitant medications	Pre-study non-antidepressant medications administered up to 30 days before the start of the screening/prospective observational phase were recorded. All antidepressant treatments, including adjunctive treatments for MDD, taken during the current depressive episode (including those taken >30 days prior to the start of the screening/prospective observational phase) were recorded. The following medications/therapies were permitted for use during the trial: • Benzodiazepine/non-benzodiazepine sleeping medications (prohibited within 12 hours prior to nasal spray dose of study medication/cognition testing; no dose increases beyond the equivalent of 6 mg/day of lorazepam or new benzodiazepine medications were permitted during the induction phase) • Benztropine (prohibited if use was continuous, prohibited within 12 hours prior to cognition testing) • Cough/cold preparations (nasal spray-administered preparations were not to be used from 1 hour prior to nasal spray dose of study medication) • Diphenhydramine (prohibited within 12 hours prior to nasal spray dose of study medication) • Thyroid hormone supplements (for treating thyroid conditions only; patients must have been on a stable dose for ≥6 weeks prior to the first dose of nasal spray study medication)	

Trial no. (acronym)	ESKETINTRD3002 (TRANSFORM-2)	ESKETINTRD3003 (SUSTAIN-1)
	• Psychotherapy (including CBT) provided it had been ongoing for 6 months prior to the start of the screening/prospective observational phase and will remain unchanged until the end of the last treatment phase • New psychotherapy (except for new CBT, which was prohibited) was permitted during the study • Prescribed psychostimulants for indications other than MDD with dosing restrictions on nasal spray treatment session days The following medications were disallowed from 1 week (or 5 half-lives, whichever is longer) prior to the first dose and until after the last dose of nasal spray study medication: amantadine, anorexiants, anticholinesterase inhibitors, anticonvulsants, antidepressants (other than those initiated during induction), antipsychotics, chloral hydrate, melatonin, valerian, clonidine, oral corticosteroids, CYP3A4 inhibitors/inducers, dextromethorphan, ketanserin, lithium, memantine, methyldopa, metyrosine, opioids, psychostimulants, reserpine, scopolamine, St. John's Wort, thyroid hormone/thyroxine prescribed for depression, warfarin. Therapies including ECT, deep brain stimulation, transcranial magnetic stimulation, newly initiated CBT (≤3 months prior to the screening/prospective observational phase), and VNS were prohibited from study entry to the end of the last treatment phase.	
Pre-planned subgroups	• Gender; race (White, Black, Other); country; number of previous treatment failures[l] in current episode (based on MGH-ATRQ); class of OAD study medication (SNRI or SSRI) • Functional impairment based on baseline SDS total score: not impaired (0–3), mild (4–11), moderate (12–19), marked (20–26), extreme (27–30) • Age group (18–44 years, 45–64 years) • Region (North America, Europe, Other) • Baseline MADRS total score (≤/> median) (**TRANSFORM-2 only**) • Consented protocol (pre-/post-protocol amendment 4) (**SUSTAIN-1 only**)[m] • Study entry route (direct-entry, transferred-entry) (**SUSTAIN-1 only**) • OAD (duloxetine, escitalopram, sertraline, venlafaxine XR) (**SUSTAIN-1 only**)	

Abbreviations: CBT, cognitive behavioural therapy; CYP3A4, cytochrome P450 3A4 enzyme; ECT, electroconvulsive therapy; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; IWRS, interactive web response system; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; MGH-ATRQ, Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; SDS, Sheehan Disability Scale; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TRD, treatment-resistant depression; VNS, vagal nerve stimulation; XR, extended release.

[a] Response was defined as a ≥50% reduction from baseline in the MADRS total score.

[b] Stable remission was defined as a MADRS total score of ≤12 for at least three of the last four weeks of the optimisation phase with one excursion of the MADRS total score >12 or one missing MADRS assessment permitted at Week 13 or 14 of the optimisation phase only. The MADRS total score at Weeks 15 and 16 was required to be ≤12.

[c] Stable response was defined as a ≥50% reduction in the MADRS total score from baseline in each of the last two weeks of the optimisation phase without meeting the criteria for stable remission.

[d] Severity of depressive symptoms assessed using the MADRS score.

[e] Treatment failure was defined as non-response to an OAD taken for ≥6 weeks at the minimum therapeutic dose with a lack of clinically meaningful improvement.

[f] See Appendix M for details of protocol amendment 4.

B.2.3.4 Eligibility criteria

Eligibility criteria for enrolment in the pivotal trials, TRANSFORM-2 and SUSTAIN-1, are presented in Table 9. For inclusion in TRANSFORM-2 and/or SUSTAIN-1, patients had to:

- Be aged 18–64 years, inclusive.
- Have failed to respond to ≥1 but ≤5 OADs in the current episode of depression.

The patient populations enrolled in TRANSFORM-2 and SUSTAIN-1 were generally reflective of UK clinical practice, as outlined in Section B.2.13.2.3

Table 9. Eligibility criteria for TRANSFORM-2 and SUSTAIN-1

Inclusion/exclusion criteria	
Patient age	18–64 years, inclusive.
Diagnostic and treatment history criteria	**At the start of the screening/prospective observational phase:** • Patient meets DSM-5 diagnostic criteria for single-episode MDD (the duration must be ≥2 years) or recurrent MDD, without psychotic features, based on clinical assessment and confirmed by the MINI • IDS-C_{30} total score of ≥34 • Non-response (≤25% improvement) to ≥1 but ≤5 OADs in the current episode of depression, taken at or above the minimum therapeutic dose, assessed using the MGH-ATRQ and confirmed by documented medical history and pharmacy/prescription records • Currently taking, and not responding to, a different OAD for at least the previous 2 weeks, at or above the minimum therapeutic dose o Adherent to current OAD treatment (without adjustment in dosage) throughout the screening/prospective observational phase, as documented on the PAQ (missing ≥4 days of treatment in the prior 2-week period was considered inadequate adherence) **During the screening/prospective observational phase:** • Patient's current major depressive episode, depression symptom severity (Week 1 MADRS total score ≥28 required), and OAD treatment response in the current depressive episode confirmed using a SIQA **At the end of the screening/prospective observational phase:** • Non-response to current OAD treatment, defined as ≤25% improvement in the MADRS total score from Week 1–4 of the screening/prospective observational phase and a MADRS total score of ≥28 at Week 2 and Week 4

Inclusion/exclusion criteria	
	• **SUSTAIN-1 only:** Transferred-entry patients were required to have completed the double-blind induction phase of one of the **TRANSFORM-1** or **TRANSFORM-2** studies and demonstrated treatment response (≥50% reduction in MADRS total score from baseline) at the end of the 4-week double-blind induction phase.
General inclusion criteria	• Current major depressive episode, and OAD treatment response in the current episode, confirmed using a SIQA • Patient medically stable based on physical exam, medical history, vital signs (including blood pressure), pulse oximetry, and 12-lead ECG performed during the screening/prospective observational phase • Patient medically stable based on clinical laboratory tests performed during the screening/prospective observational phase o Patients with thyroid disease/disorder treated with thyroid hormones must have been on a stable dose of thyroid hormones for 3 months prior to the start of the screening/prospective observational phase and must have TSH within the normal range • Patient comfortable with self-administration of nasal spray medication and able to follow the administration instructions provided • Use of birth control where applicable • Willing and able to adhere to trial prohibitions and restrictions • Willing to participate in the study and signed an ICF
General exclusion criteria	• The patient's depressive symptoms have previously demonstrated non-response to: o Esketamine or ketamine in the current major depressive episode, per clinical judgement, or o All of the OAD treatment options available in the respective country for the induction phase (duloxetine, escitalopram, sertraline, and venlafaxine XR) in the current major depressive episode (based on MGH-ATRQ), or o An adequate course of treatment with ECT (≥7 unilateral/bilateral treatments) in the current major depressive episode • Current or prior history of any of the following: o Implant for VNS or has received DBS in the current episode of depression o DSM-5 diagnosis of a psychotic disorder or MDD with psychosis, bipolar or related disorders (confirmed by the MINI), comorbid OCD, intellectual disability[a], autism spectrum disorder; borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder o Suicidal/homicidal ideation/intent within 6 months prior to screening per the investigator's clinical judgements and/or based on C-SSRS, or a history of suicidal behaviour in the 12 months prior to screening o Moderate/severe substance or alcohol abuse according to DSM-5 criteria o Seizures o UPSIT total score ≤18 at screening o Cardiovascular-related conditions (cerebrovascular disease, aneurysmal vascular disease, coronary artery disease with MI/unstable angina/revascularisation procedure within 12 months prior to screening, valvular heart disease, heart failure, ECG abnormalities at screening or on Day 1) o Uncontrolled hypertension or ongoing evidence of uncontrolled hypertension during screening (supine SBP >140 mmHg or DBP >90 mmHg) o Pulmonary insufficiency or $Sp0_2$ <93% at screening or prior to first nasal spray treatment session o Liver cirrhosis or ALT/AST ≥2 × ULN or total bilirubin >1.5 × ULN at screening

Inclusion/exclusion criteria	
	o Positive test result(s) for drugs of abuse at screening or prior to the first nasal spray treatment session o Uncontrolled diabetes mellitus/secondary diabetes (HbA1c >9%) at screening or history of diabetic ketoacidosis, hyperglycaemic coma, or severe hypoglycaemia with loss of consciousness within 3 months prior to screening o Untreated glaucoma o Any anatomical/medical condition that may impede delivery/absorption of nasal spray study drug o Malignancy in previous 5 years o Hypersensitivity to esketamine/ketamine or all of the available OAD treatment options for the induction phase o Patient has taken any of the prohibited therapies listed in Table 8 that would not permit dosing on Day 1 o Patient is taking a total daily dose of benzodiazepines greater than the equivalent dose of 6 mg/day of lorazepam at screening o Score of ≥5 on the STOP-BANG questionnaire o Patient has received an investigational drug/used an invasive investigational medical device in the prior 60 days or has participated in ≥2 MDD/other psychiatric condition clinical interventional studies in the previous 12 months o Pregnant, breast-feeding, or planning to become pregnant o AIDS diagnosis o Any condition/situation/circumstance for which the investigator deems participation in the study would not be in the best interest of the patient or that could prevent/limit/confound the protocol-specified assessments o Major surgery in the 12 weeks prior to screening o Patient is an employee of the investigator/study site or family member of the employee

Abbreviations: AIDS, acquired immunodeficiency syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase; C-SSRS, Columbia – Suicide Severity Rating Scale; DBP, diastolic blood pressure; DBS, deep brain stimulation; DSM-5, Diagnostic and Statistical Manual of Mental Disorders – 5; ECG, electrocardiogram; ECT, electroconvulsive therapy; HbA1c, glycated haemoglobin; ICF, informed consent form; IDS-C_{30}, Inventory of Depressive Symptomatology-Clinician-rated, 30-item scale; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; MGH-ATRQ, Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; MI, myocardial infarction; MINI, Mini-International Neuropsychiatric Interview; OAD, oral antidepressant; OCD, obsessive compulsive disorder; PAQ, Patient Adherence Questionnaire; SBP, systolic blood pressure; SIQA, Site-Independent Qualification Assessment; STOP-BANG, Snoring, Tiredness, Observed Apnoea, Blood Pressure, Body Mass Index Age, Neck Circumference, and Gender Questionnaire; TSH, thyroid-stimulating hormone; ULN, upper limit of normal; UPSIT, University of Pennsylvania Smell Identification Test; VNS, vagal nerve stimulation; XR, extended release.

[a] DSM-5 diagnostic code 319.

B.2.3.5 Outcomes

Outcomes were measured for severity of depressive symptoms, functional impairment and disability, overall severity of illness, level of anxiety symptoms, health-related quality of life and health utility using different instruments and scoring systems (for further details see Table 10).

A key component of the efficacy outcomes for clinical remission, clinical response and clinical relapse is the MADRS score. The MADRS score is a clinician-rated questionnaire and calculated as the sum of scores on 10 items. The questionnaire includes questions on the following symptoms 1. Apparent sadness 2. Reported sadness 3. Inner tension 4. Reduced sleep 5. Reduced appetite 6. Concentration difficulties 7. Lassitude 8. Inability to feel 9. Pessimistic thoughts 10. Suicidal thoughts. Scores of 0 to 6 points indicate normal/symptom absents, a score of 9 to 17 indicates mild depression, a score of 18 to 34 points indicates moderate depression, and a score >34 points indicates severe depression (98).

Adverse events were also recorded as safety endpoints.

A brief overview of each of the endpoints and how they are interpreted is provided in Table 10. A more comprehensive overview of the TRANSFORM-2 and SUSTAIN-1 trial endpoints is provided in Appendix M.

Table 10. Endpoints measured in TRANSFORM-2 and SUSTAIN-1

Endpoint	Explanation of measure
MADRS	The MADRS is a commonly used clinician-rated scale designed to measure depression severity and detect changes due to antidepressant treatment (99). On the basis of MADRS, in TRANSFORM-2 and SUSTAIN-1: • **Response** was defined as a ≥50% reduction from baseline in MADRS total score. • **Remission** was defined as a MADRS total score of ≤12.[a] • **Onset of clinical response by Day 2 maintained to Day 28** was defined as the onset of clinical response (≥50% reduction from baseline in MADRS total score) by Day 2 (24 hours) that was maintained to Day 28 with only one excursion (non-response) on Days 8, 15, or 22 (the MADRS total score must have still shown a ≥25% improvement from baseline at the time of the excursion). Patients who discontinued before Day 28 for any reason were considered non-responders. • **Onset of clinical response by Day 8 maintained to Day 28** was defined as the onset of clinical response (≥50% reduction from baseline in MADRS total score) by Day 8 that was maintained to Day 28 with only one excursion (non-response) on Days 15 or 22 (the MADRS total score must have still shown a ≥25% improvement from baseline at the time of the excursion). Patients who discontinued before Day 28 for any reason were considered non-responders. • **Stable response** was defined as a ≥50% reduction in the MADRS total score from baseline in each of the last two weeks of the optimisation phase without meeting the criteria for stable remission.

Endpoint	Explanation of measure
	• **Stable remission** was defined as a MADRS total score of ≤12 for at least three of the last four weeks of the optimisation phase with one excursion of the MADRS total score >12 or one missing MADRS assessment permitted at Week 13 or 14 of the optimisation phase only. The MADRS total score at Weeks 15 and 16 was required to be ≤12. • **Relapse** was defined as a MADRS total score of ≥22 for two consecutive assessments separated by 5–15 days and/or hospitalisation for worsening depression or any other clinically relevant event determined per clinical judgment to be suggestive of a relapse of depressive illness such as suicide attempt, completed suicide, or hospitalisation for suicide prevention.
SDS	The SDS is a patient-reported outcome measure and is a 5-item questionnaire which is widely used and accepted for assessment of functional impairment and associated disability (100). On the basis of SDS, in TRANSFORM-2 and SUSTAIN-1: • **Response** was defined as scores ≤4 for each item and ≤12 for SDS total score. • **Remission** was defined as scores ≤2 for each item and ≤6 for SDS total score.
PHQ-9	The PHQ-9 is a validated, 9-item, patient-reported outcome measure used to assess depressive symptoms (101-103). On the basis of PHQ-9, in TRANSFORM-2 and SUSTAIN-1: • **Response** was defined as a ≥50% reduction from baseline in PHQ-9 total score. • **Remission** was defined as a PHQ-9 total score of ≤4.
CGI-S	The CGI-S, endorsed by the EMA as an appropriate secondary efficacy outcome in clinical trials in depression (17), provides an overall clinician-determined summary measure of the severity of the patient's illness
GAD-7	The GAD-7 is a brief and validated measure of overall anxiety (104, 105).
EQ-5D-5L	The EQ-5D-5L is a standardised instrument used as a measure of health outcome, primarily designed for self-completion by respondents. It consists of the EQ-5D-5L descriptive system and the EQ-VAS.

Abbreviations: CGI-S, Clinical Global Impression – Severity; EQ-VAS, EuroQol – Visual Analogue Scale; EQ-5D-5L, EuroQol-5 Dimension-5 Level; GAD-7, Generalised Anxiety Disorder – 7-item scale; MADRS, Montgomery-Asberg Depression Rating Scale; PHQ-9, Patient Health Questionnaire – 9 questions; SDS, Sheehan Disability Scale.

[a] Although MADRS total score ≤10 is the more commonly used definition for remission (106), a definition of ≤12 was pre-specified for the ESK-NS trials (and has been used in multiple published clinical studies (107, 108)) since MADRS was to be assessed via remote raters. The Sponsor selected a definition of MADRS total score ≤12 based on data from a Phase 0 study suggesting that remote MADRS raters scored slightly higher (by an average of 2 points) than face-to-face raters when patients demonstrated lower overall symptom severity (i.e., MADRS total score <15).

B.2.3.6 Trial endpoints

The primary and secondary efficacy endpoints of TRANSFORM-2 and SUSTAIN-1 are outlined in Table 11.

Table 11. Primary and secondary efficacy endpoints in TRANSFORM-2 and SUSTAIN-1

	TRANSFORM-2	SUSTAIN-1
Primary efficacy endpoint	**MADRS total score:** Change in the 10-item clinician-administered MADRS total score (independent, remote rater) from baseline (Day 1 prior to randomisation) to the end of the 4-week double-blind induction phase.	**Relapse:** The time between patient randomisation into the maintenance phase and the first documentation (earliest date) of a relapse event (based on MADRS[a]) during the maintenance phase among patients in stable remission (based on MADRS[b]) at the end of the optimisation phase following treatment with ESK-NS plus an OAD.

	TRANSFORM-2	SUSTAIN-1
Secondary and other efficacy endpoints	• Proportion of patients showing onset of response (based on MADRS[c]) by Day 2 (24 hours) that was maintained to the end of induction • Change in SDS total score from baseline to the end of induction • Change in PHQ-9 total score from baseline to the end of induction • Proportion of responders (based on MADRS[c]) at the end of induction • Proportion of patients in remission (based on MADRS[e]) at the end of induction • Proportion of patients showing onset of clinical response (based on MADRS[c]) by Day 8 of induction that was maintained to the end of induction • Change from baseline to the end of induction in the following: o CGI-S o GAD-7 o EQ-5D-5L	• The time between patient randomisation and the first documentation (earliest date) of a relapse (based on MADRS[a]) during the maintenance phase among patients in stable response (based on MADRS[d]) at the end of the optimisation phase • Change from baseline (of the maintenance phase) to the end of the maintenance phase in the following: o Depressive symptoms (MADRS and PHQ-9) o Severity of illness (CGI-S) o Symptoms of anxiety (GAD-7) o HRQoL (EQ-5D-5L) o Functioning and associated disability (SDS) • Response and remission rates over time based on MADRS,[c,e] PHQ-9,[f,g] and SDS[h,i]
Safety outcomes	Monitoring of TEAEs, clinical laboratory tests, vital signs/physical examinations, ECG, pulse oximetry, Nasal Symptom Questionnaire; C-SSRS, CADSS, BPRS+, MOAA/S, CGADR, PWC-20, BPIC-SS, HVLT-R, UPSIT, Smell Threshold Test.	

Abbreviations: BPIC-SS, Bladder Pain/Interstitial Cystitis Symptom Score; BPRS+, 4-item positive symptom subscale of the Brief Psychiatric Rating Scale; CADSS, Clinician-Administered Dissociated States Scale; CGADR, Clinical Global Assessment of Discharge Readiness; CGI-S, Clinical Global Impression – Severity; C-SSRS, Columbia – Suicide Severity Rating Scale; ECG, electrocardiogram; EQ-5D-5L, EuroQol-5 Dimension-5 Level; GAD-7, Generalised Anxiety Disorder – 7-item scale; HVLT-R, Hopkins Verbal Learning Test – Revised; MADRS, Montgomery-Asberg Depression Rating Scale; MOAA/S, Modified Observer's Assessment of Alertness/Sedation Scale; OAD, oral antidepressant; PHQ-9, Patient Health Questionnaire – 9 questions; PWC-20, Physician Withdrawal Checklist – 20-item; SDS, Sheehan Disability Scale; TEAE, treatment-emergent adverse event; UPSIT, University of Pennsylvania Smell Identification Test.

[a] Relapse was defined as a MADRS total score of ≥22 for two consecutive assessments separated by 5–15 days and/or hospitalisation for worsening depression or any other clinically relevant event determined per clinical judgment to be suggestive of a relapse of depressive illness such as suicide attempt, completed suicide, or hospitalisation for suicide prevention.

[b] Stable remission was defined as a MADRS total score of ≤12 for at least three of the last four weeks of the optimisation phase with one excursion of the MADRS total score >12 or one missing MADRS assessment permitted at Week 13 or 14 of the optimisation phase only. The MADRS total score at Weeks 15 and 16 was required to be ≤12.

[c] Response was defined as a ≥50% reduction from baseline in the MADRS total score.

[d] Stable response was defined as a ≥50% reduction in the MADRS total score from baseline in each of the last two weeks of the optimisation phase without meeting the criteria for stable remission.

[e] Remission was defined as a MADRS total score of ≤12.

[f] Response using PHQ-9 was defined as a ≥50% reduction from baseline in the PHQ-9.

[g] Remission was defined as a PHQ-9 total score of ≤4.

[h] Response using SDS was defined as scores ≤4 for each item and ≤12 for SDS total score.

[i] Remission using SDS was defined as scores ≤2 for each item and ≤6 for SDS total score. Post hoc adjustment to account for the therapeutic effect of additional clinical visits in TRANSFORM-2

B.2.3.7 Post hoc adjustment to account for the therapeutic effect of additional clinical visits in TRANSFORM-2

Efficacy estimates (response and remission) for the OAD + PBO-NS arm of the TRANSFORM-2 trial were high compared with other studies in TRD (see Section D.1.3.2 in Appendix D). One of the main reasons is the high number of visits (n=8) during the TRANSFORM-2 acute treatment phase. Eight visits are considerably more than the one or two visits that a patient with TRD would get in the first four weeks after switching to a newly initiated OAD.

Quantification of the impact of additional visits in MDD trials has been undertaken by Posternak and Zimmerman (2007) (86). In this study, follow-up visits were shown to account for 40% of the placebo treatment effect (86). This was used as the basis of the *post-hoc* adjustment of the TRANSFORM-2 OAD + PBO-NS treatment effect to approximate the treatment effect of OADs in NHS clinical practice.

The study showed that each clinic visit was associated with a Hamilton Depression Rating Scale (HAM-D) reduction (improvement) of 0.67–0.86 points, two additional visits were associated with twice the therapeutic effect of one, and the therapeutic impact of visits was cumulative and proportional. For the *post-hoc* adjustment of TRANSFORM-2 OAD + PBO-NS treatment effect, the most conservative value from the Posternak and Zimmerman study of 0.67 HAM-D points per additional clinic visit was used.

In TRANSFORM-2, depressive symptoms were evaluated using the MADRS. Absolute HAM-D score improvements of 10, 20, and 25 points have been found to correspond to improvements of 12, 26, and 34 points in MADRS score, respectively (109).

In the *post-hoc* adjustment of TRANSFORM-2 results, a therapeutic improvement effect of 0.67 HAM-D points per follow-up clinic visit was converted to MADRS using a 1-point improvement on HAM-D being equivalent to ~1.2 points improvement on MADRS. Both values are conservative, corresponding to the lower bound of the plausible ranges suggested. By combining these values, it was estimated that each follow-up visit would be associated with an improvement of 0.804 points in MADRS score. In clinical practice, it is unlikely that patients with TRD prescribed a new OAD

would visit an HCP for treatment administration (although patients may still have one or two visits during the induction period for general disease management; see Table 6). To be conservative in the *post-hoc* adjustment, it was estimated that patients with TRD switched to a new OAD would have two clinic visits over a 4-week period (induction phase). In TRANSFORM-2, there were eight clinic visits for patients in the OAD + PBO-NS arm during the induction phase. The treatment effect observed for the OAD + PBO-NS arm of TRANSFORM-2 was therefore adjusted to account for the therapeutic effect of six additional clinic visits versus clinical practice (i.e., six extra physician visits would not occur in clinical practice for patients on an OAD treatment). Six extra visits translated to a 4.824-point improvement in MADRS score (0.804 MADRS points per visit × six visits). Therefore, the adjustment applied was as follows:

$$MADRS_{Adjusted} = MADRS_{original} + 4.824.$$

This equation was applied at the individual level (i.e., the observed MADRS scores at the end of the acute phase for individual patients were adjusted), and then the efficacy estimates (response and remission) were recalculated.

The OAD efficacy estimates resulting from applying the suggested treatment effect adjustment largely aligned (but were still higher) with efficacy data observed in other OAD trials enrolling patients with TRD:

- In the OAD + PBO-NS arm of TRANSFORM-2, the unadjusted response rate was 52%, and the unadjusted remission rate was 31%. After applying the treatment effect adjustment (assuming six additional clinic visits), the response rate was 34% and the remission rate was 18% (Section B.2.6.1.3).
- From the literature, response and remission rates for OADs (in particular SSRI/SNRIs – which were the type of OADs used in TRANSFORM-2) are much lower (less than half) than those observed in the (unadjusted) OAD + PBO-NS arm of TRANSFORM-2 (see Appendix D). Even with the Posternak adjustment of the OAD + PBO-NS arm results, they are still higher than those observed in other trials, meaning the TRANSFORM-2 trial still likely underestimates the true value of ESK-NS for the treatment of TRD.

B.2.3.8 Baseline characteristics and demographics

B.2.3.8.1 TRANSFORM-2

Demographic and baseline characteristics of patients enrolled in the full analysis set of TRANSFORM-2 are presented in Table 12. (See Section B.2.4 for definitions of patient populations and how they were used in statistical analyses).

In general, treatment groups were similar with respect to baseline characteristics.

All patients had non-response to at least two OADs prior to randomisation, with non-response being confirmed prospectively during the screening/prospective observational phase for at least one of these OADs.

Prior to randomisation, most patients (57.9%) had non-response to two OADs (assessed using the MGH-ATRQ), with 27.2%, 7.0%, and 4.4% having a history of non-response to three, four, or five or more OADs, respectively.

Table 12. Baseline characteristics and demographics of patients enrolled in TRANSFORM-2 (full analysis set)

Characteristic	ESK-NS + OAD (N=114)	OAD + PBO-NS (N=109)	Total (N=223)
Age, mean years (SD)	44.9 (12.58)	46.4 (11.14)	45.7 (11.89)
Age category, n (%)			
18–44 years	54 (47.4)	40 (36.7)	94 (42.2)
45–64 years	60 (52.6)	69 (63.3)	129 (57.8)
65–74 years	NA	NA	NA
≥74 years	NA	NA	NA
Sex, n (%)			
Male	39 (34.2)	46 (42.2)	85 (38.1)
Female	75 (65.8)	63 (57.8)	138 (61.9)
Race, n (%)			
American Indian or Alaskan Native	NA	NA	NA
Asian	1 (0.9)	1 (0.9)	2 (0.9)
Black or African American	6 (5.3)	5 (4.6)	11 (4.9)
White	106 (93.0)	102 (93.6)	208 (93.3)
Multiple	1 (0.9)	1 (0.9)	2 (0.9)
Not reported	NA	NA	NA
Other	NA	NA	NA
Unknown	NA	NA	NA
Ethnicity, n (%)			
Hispanic or Latino	5 (4.4)	7 (6.4)	12 (5.4)
Not Hispanic or Latino	108 (94.7)	99 (90.8)	207 (92.8)
Not reported	0	1 (0.9)	1 (0.4)
Unknown	1 (0.9)	2 (1.8)	3 (1.3)
Weight (kg), mean (SD)	79.30 (20.14)	82.67 (19.47)	80.95 (19.84)

Characteristic	ESK-NS + OAD (N=114)	OAD + PBO-NS (N=109)	Total (N=223)
Height (cm), mean (SD)	169.23 (10.18)	169.81 (9.95)	169.51 (10.05)
BMI (kg/m^2), mean (SD)	27.5 (5.84)	28.6 (6.24)	28.1 (6.05)
BMI category (kg/m^2), n (%)			
Underweight (<18.5)	1 (0.9)	2 (1.8)	3 (1.3)
Normal (18.5–≤25)	41 (36.0)	28 (25.7)	69 (30.9)
Overweight (25–≤30)	41 (36.0)	36 (33.0)	77 (34.5)
Obese (30–≤40)	28 (24.6)	39 (35.8)	67 (30.0)
Morbidly obese (≥40)	3 (2.6)	4 (3.7)	7 (3.1)
Employment status, n (%)[a]			
Any type of employment	68 (59.6)	63 (57.8)	131 (58.7)
Any type of unemployment	34 (29.8)	35 (32.1)	69 (30.9)
Other	12 (10.5)	11 (10.1)	23 (10.3)
Hypertension status, n (%)[b]			
Yes	18 (15.8)	27 (24.8)	45 (20.2)
No	96 (84.2)	82 (75.2)	178 (79.8)
Region, n (%)			
Europe	69 (60.5)	65 (59.6)	134 (60.1)
North America	45 (39.5)	44 (40.4)	89 (39.9)
Other	NA	NA	NA
Class of OAD, n (%)			
SNRI	77 (67.5)	75 (68.8)	152 (68.2)
SSRI	37 (32.5)	34 (31.2)	71 (31.8)
OAD, n (%)			
Duloxetine	60 (52.6)	61 (56.0)	121 (54.3)
Escitalopram	21 (18.4)	17 (15.6)	38 (17.0)
Sertraline	16 (14.0)	16 (14.7)	32 (14.3)
Venlafaxine XR	17 (14.9)	15 (13.8)	32 (14.3)
Age when diagnosed with MDD, mean years (SD)	32.1 (12.53)	35.3 (13.04)	33.7 (12.86)
MADRS total score, mean (SD)	37.0 (5.69)	37.3 (5.66)	37.1 (5.67)
Screening IDS-C_{30} total score, mean (SD)	46.0 (6.26)	45.7 (5.89)	45.9 (6.07)
CGI-S, mean (SD)	5.1 (0.68)[c]	5.1 (0.67)	5.1 (0.67)
CGI-S category, n (%)			
Mildly ill	0	0	0
Moderately ill	21 (18.4)	19 (17.4)	40 (17.9)
Markedly ill	64 (56.1)	63 (57.8)	127 (57.0)
Severely ill	27 (23.7)	26 (23.9)	53 (23.8)
Among the most extremely ill patients	1 (0.9)	1 (0.9)	2 (0.9)
Not assessed	1 (0.9)	0	1 (0.4)
PHQ-9 total score, mean (SD)	20.2 (3.63)	20.4 (3.74)	20.3 (3.68)
Screening C-SSRS lifetime, n (%)[d]			
No event	65 (57.0)	61 (56.0)	126 (56.5)
Suicidal ideation	40 (35.1)	34 (31.2)	74 (33.2)
Suicidal behaviour	9 (7.9)	14 (12.8)	23 (10.3)
Screening C-SSRS past 6 or 12 months, n (%)[d]			
No event	77 (67.5)	74 (67.9)	151 (67.7)

Characteristic	ESK-NS + OAD (N=114)	OAD + PBO-NS (N=109)	Total (N=223)
Suicidal ideation (past 6 months)	37 (32.5)	34 (31.2)	71 (31.8)
Suicidal behaviour (past 12 months)[e]	0	1 (0.9)	1 (0.4)
Duration of current episode, mean weeks (SD)	111.4 (124.28)	118.0 (187.37)	114.6 (157.96)
Number of previous antidepressant medications prior to randomisation, n (%)[f,g]			
2	66 (57.9)	70 (64.2)	136 (61.0)
3	31 (27.2)	22 (20.2)	53 (23.8)
4	8 (7.0)	12 (11.0)	20 (9.0)
≥5	5 (4.4)	4 (3.7)	9 (4.0)
Number of major depressive episodes including current episode, n (%)			
1	15 (13.2)	14 (12.8)	29 (13.0)
2–5	81 (71.1)	78 (71.6)	159 (71.3)
6–10	16 (14.0)	15 (13.8)	31 (13.9)
>10	2 (1.8)	2 (1.8)	4 (1.8)
Family history of depression, n (%)			
Yes	51 (44.7)	56 (51.4)	107 (48.0)
No	63 (55.3)	53 (48.6)	116 (52.0)
Family history of anxiety disorder, n (%)			
Yes	10 (8.8)	16 (14.7)	27 (11.7)
No	104 (91.2)	93 (85.3)	197 (88.3)
Family history of bipolar disorder, n (%)			
Yes	8 (7.0)	11 (10.1)	19 (8.5)
No	106 (93.0)	98 (89.9)	204 (91.5)
Family history of schizophrenia, n (%)			
Yes	6 (5.3)	4 (3.7)	10 (4.5)
No	108 (94.7)	105 (96.3)	213 (95.5)
Family history of alcohol abuse, n (%)			
Yes	18 (15.8)	20 (18.3)	38 (17.0)
No	96 (84.2)	89 (81.7)	185 (83.0)
Family history of substance abuse, n (%)			
Yes	8 (7.0)	4 (3.7)	12 (5.4)
No	106 (93.0)	105 (96.3)	211 (94.6)

Abbreviations: BMI, Body Mass Index; CGI-S, Clinical Global Impression – Severity; C-SSRS, Columbia – Suicide Severity Rating Scale; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; ESK-NS-56 + OAD, esketamine nasal spray (56 mg [fixed dose]) plus a newly initiated oral antidepressant; ESK-NS-84 + OAD, esketamine nasal spray (84 mg [fixed dose]) plus a newly initiated oral antidepressant; IDS-C_{30}, Inventory of Depressive Symptomatology-Clinician-rated, 30-item scale; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; MGH-ATRQ, Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; PHQ-9, Patient Health Questionnaire – 9 questions; SD, standard deviation; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; XR, extended release.

[a] Any type of employment included: any category containing "employed," sheltered work, housewife or dependent husband, and student. Any type of unemployment included: any category containing "unemployed." Other included: retired and no information available.

[b] Hypertension status was classified as "Yes" if hypertension was recorded in the patient's medical history.

[c] N=113.

[d] C-SSRS category: No event = 0; Suicidal ideation = 1, 2, 3, 4, 5; Suicidal behaviour = 6, 7, 8, 9, 10.

[e] Due to a data collection error, one patient in TRANSFORM-2 reported suicidal behaviour in the 12 months prior to screening. The suicidal behaviour for this patient actually occurred more than 12 months prior to screening.

[f] Referring to the number of antidepressant medications with non-response (defined as ≤25% improvement in MGH-ATRQ) taken for ≥6 weeks during the current episode.

[g] All of the five patients not accounted for in this baseline measure were determined to have failed at least two OADs based on other data in the database.

B.2.3.8.2 SUSTAIN-1

Demographic and baseline characteristics of patients in the all enrolled analysis set and full (stable remitters/stable responders) analysis sets of SUSTAIN-1 (induction phase) are presented in Table 13. Table 14 presents the number of MDD episodes (including the current episode) experienced by patients who are stable remitters and stable responders.

At screening, most patients (89.0%) had documented non-response to two or more OADs taken for at least six weeks, assessed using the MGH-ATRQ.

Table 13. Baseline (IND) characteristics and demographics of patients enrolled in SUSTAIN-1 (All enrolled analysis set; full analysis set)

Characteristic	All enrolled analysis set (N=705)	Full (stable remitters[a]) analysis set			Full (stable responders[b]) analysis set		
		ESK-NS + OAD (N=90)	OAD + PBO-NS (N=86)	Total (N=176)	ESK-NS + OAD (N=62)	OAD + PBO-NS (N=59)	Total (N=121)
Age, mean years (SD)	46.1 (11.10)	45.4 (12.12)	46.2 (11.16)	45.8 (11.64)	47.2 (11.00)	46.7 (9.76)	47.0 (10.37)
Age category, n (%)							
18–44 years	292 (41.4)	38 (42.2)	37 (43.0)	75 (42.6)	23 (37.1)	24 (40.7)	47 (38.8)
45–64 years	413 (58.6)	52 (57.8)	49 (57.0)	101 (57.4)	39 (62.9)	35 (59.3)	74 (61.2)
Sex, n (%)							
Male	248 (35.2)	32 (35.6)	27 (31.4)	59 (33.5)	24 (38.7)	17 (28.8)	41 (33.9)
Female	457 (64.8)	58 (64.4)	59 (68.6)	117 (66.5)	38 (61.3)	42 (71.2)	80 (66.1)
Race, n (%)							
American Indian or Alaskan Native	1 (0.1)	0	1 (1.2)	1 (0.6)	0	0	0
Asian	3 (0.4)	0	0	0	0	1 (1.7)	1 (0.8)
Black or African American	31 (4.4)	4 (4.4)	6 (7.0)	10 (5.7)	2 (3.2)	1 (1.7)	3 (2.5)
White	635 (90.1)	80 (88.9)	76 (88.4)	156 (88.6)	57 (91.9)	55 (93.2)	112 (92.6)
Multiple	4 (0.6)	1 (1.1)	0	1 (0.6)	0	1 (1.7)	1 (0.8)
Not reported	9 (1.3)	3 (3.3)	2 (2.3)	5 (2.8)	0	0	0
Other	22 (3.1)	0	0	0	3 (4.8)	1 (1.7)	4 (3.3)
Ethnicity, n (%)							
Hispanic or Latino	94 (13.3)	14 (15.6)	12 (14.0)	26 (14.8)	8 (12.9)	9 (15.3)	17 (14.0)
Not Hispanic or Latino	600 (85.1)	73 (81.1)	72 (83.7)	145 (82.4)	54 (87.1)	50 (84.7)	104 (86.0)
Not reported	10 (1.4)	3 (3.3)	2 (2.3)	5 (2.8)	0	0	0
Unknown	1 (0.1)	0	0	0	0	0	0
Weight (kg), mean (SD)	81.61 (19.41)	82.78 (19.55)	84.21 (20.78)	83.48 (20.12)	83.30 (21.15)	81.26 (20.38)	82.31 (20.72)
Height (cm), mean (SD)	168.88 (10.19)	169.05 (11.33)	168.60 (9.67)	168.83 (10.53)	169.60 (9.43)	168.83 (8.85)	169.23 (9.12)
BMI (kg/m^2), mean (SD)	28.6 (6.23)	28.9 (5.75)	29.5 (6.26)	29.2 (6.00)	28.8 (6.42)	28.5 (6.55)	28.6 (6.46)
BMI category (kg/m^2), n (%)							
Underweight (<18.5)	6 (0.9)	2 (2.2)	0	2 (1.1)	1 (1.6)	1 (1.7)	2 (1.7)
Normal (18.5–≤25)	195 (27.7)	19 (21.1)	18 (20.9)	37 (21.0)	17 (27.4)	20 (33.9)	37 (30.6)
Overweight (25–≤30)	259 (36.7)	32 (35.6)	33 (38.4)	65 (36.9)	23 (37.1)	17 (28.8)	40 (33.1)
Obese (30–≤40)	212 (30.1)	33 (36.7)	30 (34.9)	63 (35.8)	19 (30.6)	18 (30.5)	37 (30.6)
Morbidly obese (≥40)	33 (4.7)	4 (4.4)	5 (5.8)	9 (5.1)	2 (3.2)	3 (5.1)	5 (4.1)
Employment status, n (%)[c]							

Characteristic	All enrolled analysis set (N=705)	Full (stable remitters[a]) analysis set			Full (stable responders[b]) analysis set		
		ESK-NS + OAD (N=90)	OAD + PBO-NS (N=86)	Total (N=176)	ESK-NS + OAD (N=62)	OAD + PBO-NS (N=59)	Total (N=121)
Any type of employment	448 (63.5)	57 (63.3)	54 (62.8)	111 (63.1)	43 (69.4)	40 (67.8)	83 (68.6)
Any type of unemployment	180 (25.5)	23 (25.6)	19 (22.1)	42 (23.9)	13 (21.0)	14 (23.7)	27 (22.3)
Other	77 (10.9)	10 (11.1)	13 (15.1)	23 (13.1)	6 (9.7)	5 (8.5)	11 (9.1)
Hypertension status, n (%)[d]							
Yes	147 (20.9)	23 (25.6)	19 (22.1)	42 (23.9)	11 (17.7)	9 (15.3)	20 (16.5)
No	558 (79.1)	67 (74.4)	67 (77.9)	134 (76.1)	51 (82.3)	50 (84.7)	101 (83.5)
Region, n (%)							
Europe	411 (58.3)	52 (57.8)	50 (58.1)	102 (58.0)	34 (54.8)	35 (59.3)	69 (57.0)
North America	195 (27.7)	22 (24.4)	20 (23.3)	42 (23.9)	18 (29.0)	16 (27.1)	34 (28.1)
Other	99 (14.0)	16 (17.8)	16 (18.6)	32 (18.2)	10 (16.1)	8 (13.6)	18 (14.9)
Class of OAD, n (%)							
SNRI	440 (62.9)[e]	62 (68.9)	58 (67.4)	120 (68.2)	35 (56.5)	36 (61.0)	71 (58.7)
SSRI	259 (37.1)[e]	28 (31.1)	28 (32.6)	56 (31.8)	27 (43.5)	23 (39.0)	50 (41.3)
OAD, n (%)							
Duloxetine	323 (46.2)[e]	47 (52.2)	38 (44.2)	85 (48.3)	27 (43.5)	30 (50.8)	57 (47.1)
Escitalopram	128 (18.3)[e]	13 (14.4)	14 (16.3)	27 (15.3)	17 (27.4)	10 (16.9)	27 (22.3)
Sertraline	130 (18.6)[e]	15 (16.7)	14 (16.3)	29 (16.5)	10 (16.1)	13 (22.)	23 (19.0)
Venlafaxine XR	118 (16.9)[e]	15 (16.7)	20 (23.3)	35 (19.9)	8 (12.9)	6 (10.2)	14 (11.6)
Age when diagnosed with MDD, mean years (SD)	32.7 (11.70)	32.5 (11.42)	33.4 (11.41)	32.9 (11.39)	36.2 (13.25)	34.0 (10.54)	35.1 (12.01)
MADRS total score, mean (SD)	37.9 (5.50)	37.4 (5.20)	37.6 (4.66)	37.5 (4.93)	40.1 (5.56)	38.9 (4.92)	39.5 (5.27)
Screening IDS-C_{30} total score, mean (SD)	47.2 (7.26)	46.9 (6.24)	47.7 (7.77)	47.3 (7.02)	47.9 (7.75)	48.6 (7.46)	48.2 (7.59)
CGI-S, mean (SD)	5.1 (0.66)	5.1 (0.69)	5.1 (0.71)	5.1 (0.70)	5.3 (0.72)	5.1 (0.64)	5.2 (0.68)
CGI-S category, n (%)							
Normal, not at all ill	0	0	0	0	0	0	0
Borderline mentally ill	0	0	0	0	0	0	0
Mildly ill	2 (0.3)	0	1 (1.2)	1 (0.6)	0	0	0
Moderately ill	98 (13.9)	18 (20.0)	13 (15.1)	31 (17.6)	9 (14.5)	9 (15.3)	18 (14.9)
Markedly ill	412 (58.4)	47 (52.2)	51 (59.3)	98 (55.7)	29 (46.8)	35 (59.3)	64 (52.9)
Severely ill	187 (26.5)	25 (27.8)	19 (22.1)	44 (25.0)	23 (37.1)	15 (25.4)	38 (31.4)
Among the most extremely ill patients	6 (0.9)	0	2 (2.3)	2 (1.1)	1 (1.6)	0	1 (0.8)
PHQ-9 total score, mean (SD)	19.9 (4.18)	19.2 (4.16)	19.8 (3.43)	19.5 (3.82)	20.5 (4.12)	20.4 (4.15)	20.4 (4.12)
Screening C-SSRS lifetime, n (%)[f]							
No event	407 (57.7)	64 (71.1)	62 (72.1)	126 (71.6)	36 (58.1)	39 (66.1)	75 (62.0)

Characteristic	All enrolled analysis set (N=705)	Full (stable remitters[a]) analysis set			Full (stable responders[b]) analysis set		
		ESK-NS + OAD (N=90)	OAD + PBO-NS (N=86)	Total (N=176)	ESK-NS + OAD (N=62)	OAD + PBO-NS (N=59)	Total (N=121)
Suicidal ideation	193 (27.4)	19 (21.1)	17 (19.8)	36 (20.5)	16 (25.8)	11 (18.6)	27 (22.3)
Suicidal behaviour	105 (14.9)	7 (7.8)	7 (8.1)	14 (8.0)	10 (16.1)	9 (15.3)	19 (15.7)
Screening C-SSRS past 6 or 12 months, n (%)[f]							
No event	499 (70.8)	72 (80.0)	72 (83.7)	144 (81.8)	42 (67.7)	45 (76.3)	87 (71.9)
Suicidal ideation (past 6 months)	205 (29.1)	18 (20.0)	14 (16.3)	32 (18.2)	20 (32.3)	14 (23.7)	34 (28.1)
Suicidal behaviour (past 12 months)	1 (0.1)	0	0	0	0	0	0
Duration of current episode, mean weeks (SD)	132.2 (209.18)	112.2 (171.30)	110.5 (147.41)	111.4 (159.62)	121.6 (193.85)	141.8 (254.43)	131.4 (224.71)
Number of previous antidepressant medications prior to study entry, n (%)[g]							
2	248 (57.7)[h]	60 (66.7)	53 (61.6)	113 (64.2)	34 (54.8)	31 (52.5)	65 (53.7)
3	111 (25.8)[h]	16 (17.8)	20 (23.3)	36 (20.5)	21 (33.9)	20 (33.9)	41 (33.9)
4	39 (9.1)[h]	8 (8.9)	7 (8.1)	15 (8.5)	5 (8.1)	3 (5.1)	8 (6.6)
≥5	20 (4.7)[h]	3 (3.3)	1 (1.2)	4 (2.3)	1 (1.6)	4 (6.8)	5 (4.1)
Number of major depressive episodes including current episode, n (%)							
1	83 (11.8)[i]	10 (11.1)	9 (10.5)	19 (10.8)	7 (11.3)	6 (10.2)	13 (10.7)
2–5	454 (64.5)[i]	62 (68.9)	60 (69.8)	122 (69.3)	41 (66.1)	42 (71.2)	83 (68.6)
6–10	122 (17.3)[i]	8 (8.9)	12 (14.0)	20 (11.4)	8 (12.9)	9 (15.3)	17 (14.0)
>10	45 (6.4)[i]	10 (11.1)	5 (5.8)	15 (8.5)	6 (9.7)	2 (3.4)	8 (6.6)
Family history of depression, n (%)							
Yes	318 (45.1)	39 (43.3)	36 (41.9)	75 (42.6)	30 (48.4)	21 (35.6)	51 (42.1)
No	387 (54.9)	51 (56.7)	50 (58.1)	101 (57.4)	32 (51.6)	38 (64.4)	70 (57.9)
Family history of anxiety disorder, n (%)							
Yes	64 (9.1)	5 (5.6)	4 (4.7)	9 (5.1)	5 (8.1)	1 (1.7)	6 (5.0)
No	641 (90.9)	85 (94.4)	82 (95.3)	167 (94.9)	57 (91.9)	58 (98.3)	115 (95.0)
Family history of bipolar disorder, n (%)							
Yes	46 (6.5)	7 (7.8)	5 (5.8)	12 (6.8)	4 (6.5)	2 (3.4)	6 (5.0)
No	659 (93.5)	83 (92.2)	81 (94.2)	164 (93.2)	58 (93.5)	57 (96.6)	115 (95.0)
Family history of schizophrenia, n (%)							
Yes	28 (4.0)	4 (4.4)	1 (1.2)	5 (2.8)	1 (1.6)	3 (5.1)	4 (3.3)
No	677 (96.0)	86 (95.6)	85 (98.8)	171 (97.2)	61 (98.4)	56 (94.9)	117 (96.7)
Family history of alcohol abuse, n (%)							
Yes	95 (13.5)	7 (7.8)	9 (10.5)	16 (9.1)	6 (9.7)	12 (20.3)	18 (14.9)
No	610 (86.5)	83 (92.2)	77 (89.5)	160 (90.9)	56 (90.3)	47 (79.7)	103 (85.1)

Characteristic	All enrolled analysis set (N=705)	Full (stable remitters[a]) analysis set			Full (stable responders[b]) analysis set		
		ESK-NS + OAD (N=90)	OAD + PBO-NS (N=86)	Total (N=176)	ESK-NS + OAD (N=62)	OAD + PBO-NS (N=59)	Total (N=121)
Family history of substance abuse, n (%)							
Yes	29 (4.1)	2 (2.2)	6 (7.0)	8 (4.5)	5 (8.1)	0	5 (4.1)
No	676 (95.9)	88 (97.8)	80 (93.0)	168 (95.5)	57 (91.9)	59 (100.0)	116 (95.9)

Abbreviations: BMI, Body Mass Index; CGI-S, Clinical Global Impression – Severity; C-SSRS, Columbia – Suicide Severity Rating Scale; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; IDS-C_{30}, Inventory of Depressive Symptomatology-Clinician-rated, 30-item scale; IND, induction; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; MGH-ATRQ, Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; PHQ-9, Patient Health Questionnaire – 9 questions; SD, standard deviation; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; XR, extended release.

[a] Stable remission was defined as a MADRS total score ≤12 for at least three of the last four weeks of the optimisation phase, with one excursion of a MADRS total score >12 or one missing MADRS assessment permitted at Week 13 or Week 14 of the optimisation phase only.

[b] Stable response was defined as a ≥50% reduction in the MADRS total score from baseline (Day 1 of the induction phase, prior to the first nasal spray dose) in each of the last two weeks of the optimisation phase, but without meeting criteria for stable remission.

[c] Any type of employment included: any category containing “employed,” sheltered work, housewife or dependent husband, and student. Any type of unemployment included: any category containing “unemployed.” Other included: retired and no information available.

[d] Hypertension status was classified as “Yes” if hypertension was recorded in the patient’s medical history.

[e] N=699.

[f] C-SSRS category: No event = 0; Suicidal ideation = 1, 2, 3, 4, 5; Suicidal behaviour = 6, 7, 8, 9, 10.

[g] Referring to the number of antidepressant medications with non-response (defined as ≤25% improvement in MGH-ATRQ) taken for ≥6 weeks during the current episode. Patients not accounted for in this baseline measure were determined to have failed at least two OADs based on other data in the database.

[h] N=430 (Full [IND] analysis set).

[i] N=704.

Table 14. Number of prior MDD episodes among stable remitter and stable responder patients (N=297)

Number of prior MDD episodes (including current episode)	n (%)	Cumulative, n (%)
1	32 (10.77)	32 (10.77)
≤2	73 (24.58)	105 (35.35)
≤3	57 (19.19)	162 (54.55)
≤4	36 (12.12)	198 (66.67)
≤5	39 (13.13)	237 (79.80)
≤6+	60 (20.20)	297 (100.0)

Abbreviations: MDD, major depressive disorder.

B.2.4 Statistical analysis and definitions of patient populations in the pivotal trials – TRANSFORM-2 and SUSTAIN-1

B.2.4.1 Definitions of patient population analysis sets

Definitions of, and patient numbers comprising, the patient population analysis sets of TRANSFORM-2 and SUSTAIN-1 are provided in Table 15 and Table 16, respectively. For SUSTAIN-1, only the key patient population sets, referred to most frequently in B.2.6.2, are defined in Table 16. For a complete tabulated summary of all SUSTAIN-1 patient population sets, please see Appendix M.

In general, efficacy outcomes were analysed using the full analysis set or modified full analysis set, and safety outcomes were analysed using the safety analysis set.

Table 15. Definitions of patient population analysis sets – TRANSFORM-2

Analysis set	Definition	ESK-NS + OAD (N=116)	OAD + PBO-NS (N=111)	Total (N=227)
All randomised analysis set, n (%)	All patients who were randomised (i.e., patients who reported a randomisation date, or were assigned a randomisation number) regardless of whether treatment was received. This analysis set was used in the calculation of overall study completion/withdrawal rates.	116 (100.0)	111 (100.0)	227 (100.0)
Full analysis set, n (%)	All randomised patients who received at least one dose of nasal spray study medication and one dose of OAD medication during the double-blind induction phase. Double-blind induction phase efficacy analyses were based on the full analysis set.	114 (98.3)	109 (98.2)	223 (98.2)

Analysis set	Definition	ESK-NS + OAD (N=116)	OAD + PBO-NS (N=111)	Total (N=227)
Safety analysis set, n (%)	All randomised patients who received at least one dose of nasal spray study medication or one dose of OAD medication during the double-blind induction phase. Analyses of change from baseline included only patients who had both baseline and at least one post-baseline observation during that phase. Screen failures and randomised patients who received no double-blind study medication were excluded from the safety analysis set. Patients who received an incorrect treatment were analysed under the planned treatment.	115 (99.1)	109 (98.2)	224 (98.7)
Follow-up analysis set, n (%)	All patients who entered the follow-up phase. This analysis set was used to summarise all efficacy and safety evaluations during the follow-up phase.	34 (29.3)	52 (46.8)	86 (37.9)

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray.

Table 16. Definitions of the key patient population analysis sets – SUSTAIN-1

Analysis set	Definition	ESK-NS + OAD	OAD + PBO-NS	Total
All enrolled analysis set	All transferred-entry and direct-entry patients who were not screen failures.	NA	NA	705
Full (stable remitters) analysis set	All patients who were in stable remission at the end of the optimisation phase and who had received at least one dose of nasal spray study drug and one dose of OAD during the maintenance phase. (Stable remission defined as a MADRS total score of ≤12 for at least three of the last four weeks of the optimisation phase with one excursion of the MADRS total score >12 or one missing MADRS assessment permitted at Week 13 or 14 of the optimisation phase).	90	86	176
Full (stable responders) analysis set	All patients who were stable responders (but not stable remitters) at the end of the optimisation phase and who had received at least one dose of nasal spray study drug and one dose of OAD during the maintenance phase. (Stable response defined as a ≥50% reduction in the MADRS total score from baseline in each of the last two weeks of the optimisation phase without meeting the criteria for stable remission).	62	59	121

Abbreviations: AE, adverse event; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; IND, induction; MA, maintenance phase; MADRS, Montgomery-Asberg Depression Rating Scale; MA_TEP, maintenance phase transferred-entry placebo; NA, not applicable; OAD, oral antidepressant; OP, optimisation phase; OP_TEP, optimisation phase transferred-entry placebo; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray.

B.2.4.2 Statistical analysis

B.2.4.2.1 TRANSFORM-2:

A summary of the TRANSFORM-2 statistical analysis plan is provided in Table 17.

- The hypothesis was that switching from a failed OAD to ESK-NS plus a newly initiated OAD would be superior to switching to a newly initiated OAD treatment (active comparator) plus PBO-NS in improving depressive symptoms in adult patients with TRD.

B.2.4.2.2 SUSTAIN-1

A summary of the SUSTAIN-1 statistical analysis plan is provided in Table 17.

- The hypothesis was that ESK-NS plus an OAD is more effective than treatment with an OAD plus PBO-NS in delaying relapse of depressive symptoms in patients with TRD in stable remission.
- SUSTAIN-1 was implemented as a random withdrawal design to perform analyses on time to relapse (i.e. survival analyses). As such, the follow-up duration was different between patients, depending on their inclusion date and time remaining until study termination. The study was not set up to analyse patient's outcomes at fixed timepoints. For this reason, response and remission rates over time were not measured at a fixed date but at the endpoint, which corresponds to the last record available for the patients. This can be viewed as analysis of covariance (ANCOVA) based on last observation carried forward (LOCF) at the longest observed follow-up per patient.

Table 17. Summary of statistical analyses

	TRANSFORM-2	SUSTAIN-1
Sample size, power calculation	The maximum sample size planned was calculated assuming a treatment difference for the double-blind induction phase of 6.5 points in MADRS total score between ESK-NS + OAD and the OAD + PBO-NS arms, an SD of 12, a one-sided significance level of 0.025, and a drop-out rate of 25%. The treatment difference and SD used in this calculation were based on results of Panel A of the ESKETINTRD2003 study and on clinical judgment. About 98 patients were required to be randomised to each treatment group to achieve 90% power using a fixed design assuming no interim analysis.	The maximum number of relapses (in patients with stable remission) required was 84, which would provide 90% power to detect a hazard ratio of 0.493 at the one-sided significance level of 0.025 for a fixed-sample design to detect superiority of ESK-NS plus an OAD over OAD plus PBO-NS in delaying relapse of depressive symptoms in patients with TRD who were in stable remission. Calculation of sample size assumed that the time to the first relapse follows an exponential distribution, with a median time of 6 months for an OAD plus PBO-NS and 12.17 months for ESK-NS plus an OAD (corresponding 6-month relapse rates: 50% for OAD plus PBO-NS and 28.95% for ESK-NS plus an OAD). Accounting for assumptions made for accrual period and rate, maximum study duration, and dropout rate, a total of approximately 211 patients in stable remission needed to be randomised (1:1) to obtain 84 relapses.
Interim analysis for sample size re-estimation or stopping for futility	An interim analysis was planned to re-estimate sample size or to stop the study due to futility. Due to recruitment dynamics, a sample size re-estimation was not recommended after the study started, and the interim analysis was removed from the planned analyses in the second protocol amendment.	To evaluate the assumptions used in the sample size calculation, relapse rates were to be monitored sequentially during the maintenance phase. In particular, a two-stage group sequential design was adopted, with one interim analysis to be performed when at least 33 relapse events had occurred in stable remitters with at least 30 relapses from patients treated with ESK-NS plus an OAD in the optimisation phase. If 33 relapses were reported in stable remitters and the notification was not triggered by the IWRS system, further determination of the timing of the interim analysis was to be made at every third relapse reported in stable remitters. Making this assessment at every third relapse helped to maintain the blind for transferred-entry patients. Early termination of the maintenance phase for efficacy was to be based on interim analysis results. At the interim analysis, if the study was not stopped for efficacy, then a sample size re-estimation was to be performed to ensure a conditional power at stage 2 of at least 90% with a minimum number of relapses after interim to be 29 and a maximum number of relapses after interim to be 54 (with 30 relapses having occurred before the interim analysis).

	TRANSFORM-2	SUSTAIN-1
		The interim analysis was conducted according to a separate statistical analysis plan. The IDMC reviewed the interim analysis results and made a recommendation to either stop the study for efficacy or provide the sample size adjustment based on the rules defined in the interim analysis statistical analysis plan. Changes to sample size were communicated to the IWRS vendor. None of the esketamine team members or staff members at the investigational sites conducting the clinical study was informed of the results of the interim analysis or of any adjustments that were made to the sample size; however, the clinical supplies group was to be informed of the decision made at the interim analysis so that only the required amount of study medication could be packaged.
Statistical testing sequence and levels of significance	A fixed sequence, serial gatekeeping procedure was applied to adjust for multiplicity and to strongly control type I error across the primary and the three key secondary efficacy endpoints. Testing of the endpoints was performed sequentially in the following order: change in MADRS total score, onset of clinical response by Day 2 (24 hours), change in SDS total score, and change in PHQ-9 total score. Testing of the endpoints was performed sequentially in the order indicated above and were considered statistically significant at the one-sided 0.025 level only if the endpoint was individually significant at the one-sided 0.025 level and previous endpoints in the hierarchy were significant at the one-sided 0.025 level.	A two-stage group sequential design, with one interim analysis was adopted as described above. In either case of stopping at the interim analysis or continuing with sample size re-estimation, control of overall type I error would thereby be maintained. At the time of the interim analysis, time to relapse was to be evaluated and compared between ESK-NS plus an OAD and an OAD plus PBO-NS. The Wang-Tsiatis boundary with shape parameter Δ=0.1 was used for detection of early efficacy. As 31 relapses were included in the interim analysis instead of 30 (as planned; see above), the interim efficacy analysis was performed at a significance level of 0.0097 (two-sided) rather than 0.0086. If the result of the interim analysis was significant (i.e., Z_{IA} ≥2.586, where a positive Z_{IA} favours ESK-NS plus an OAD in delaying relapse compared with an OAD plus PBO-NS) the study was to be terminated and ESK-NS plus an OAD declared superior to an OAD plus PBO-NS in delaying relapse. Otherwise, the study was to continue and be stopped once the number of relapses determined by the sample size re-estimation occurred during the maintenance phase. The final efficacy analysis was performed at a significance level of 0.046 (two-sided). If the result of the final efficacy analysis was significant (Z_f ≥1.998), ESK-NS plus an OAD would be declared superior to an OAD plus PBO-NS in delaying relapse.

	TRANSFORM-2	SUSTAIN-1
Hypothesis objective	The hypothesis for TRANSFORM-2 was that, in adult patients with TRD, switching from a failed OAD to ESK-NS plus a newly initiated OAD would be superior to switching to a newly initiated OAD treatment (active comparator) plus PBO-NS in improving depressive symptoms.	ESK-NS plus an OAD is more effective than treatment with an OAD plus PBO-NS in delaying relapse of depressive symptoms in patients with TRD in stable remission.
Statistical analysis (primary outcome)	The primary estimand, the main clinical quantity of interest to be estimated in the study, was defined by the following four components: • Population: patients with TRD. • Endpoint: change from baseline to Day 28 in the MADRS total score. • Measure of Intervention: the effect of the initially randomised treatment together with the OAD that would have been observed had all patients remained on their randomised treatment throughout the double-blind induction phase. • Summary measure: difference in treatment means. The primary analysis was based on the full analysis set and the MADRS total scores collected during the double-blind induction phase. Two approaches were used to analyse the primary endpoint, dependent on the regulatory needs of specific regions: ANCOVA (EU) and MMRM (non-EU). ***ANCOVA*** Change from baseline in MADRS total score at Day 28 of the double-blind induction phase was analysed based on LOCF data. The model included factors for treatment, country, and class of OAD (SNRI or SSRI), and baseline MADRS total score as a covariate. Comparison of the ESK-NS plus an OAD arm versus the OAD plus a PBO-NS arm was performed using the appropriate contrast. In addition, descriptive statistics of actual values and changes from baseline were provided for observed case and LOCF data during the double-blind phase and for observed case data during the follow-up phase.	The primary estimand, the main clinical quantity of interest to be estimated in the study, was defined by the following four components: • Population: patients with TRD in stable remission on esketamine at the end of the optimisation phase. • Variable: time to relapse during the maintenance phase, while on their initially randomised treatment. • Intercurrent Event: the intercurrent event of treatment discontinuation is captured through the variable definition. • Summary measure: Kaplan-Meier estimate of the survival function. The primary analysis was based on the full (stable remitters) analysis set and relapse (based on MADRS total score, defined in Table 10) collected during the maintenance phase. The treatment groups were compared using the weighted log-rank test. Time to relapse was summarised (number of events, number of censored patients and quartiles of time to relapse). The cumulative distribution function of the time to relapse was estimated by the Kaplan-Meier method.

	TRANSFORM-2	SUSTAIN-1
	MMRM Change from baseline in MADRS total score at Day 28 of the double-blind induction phase was analysed based on observed data. The model included baseline MADRS total score as a covariate, and treatment, class of OAD (SNRI or SSRI), day, day-by-treatment interaction, and country as fixed effects. The within-patient covariance between visits was estimated via an unstructured variance-covariance matrix. Comparison of ESK-NS plus an OAD arm(s) versus the OAD plus PBO-NS arm was performed using the appropriate contrast. Means (±SE), mean changes (±SE) from baseline, and least square mean changes (±SE) from baseline were presented graphically. In addition, to explore the course of treatment effect over time ANCOVA (LOCF and observed data) and MMRM (observed data) analyses were performed at each scheduled assessment time point.	
Statistical analysis (key secondary outcomes)	• Analysis of the proportion of patients showing onset of clinical response by Day 2 (24 hours) that was maintained for the duration of the double-blind induction phase in the ESK-NS plus an OAD arm versus the OAD plus PBO-NS arm was planned using a Cochran-Mantel-Haenszel chi square test adjusting for country and class of antidepressant (SSRI or SNRI). • Change from baseline in SDS total score and change from baseline in PHQ-9 total score at Day 28 in the double-blind induction phase were analysed using the same models described for the primary efficacy analysis.	• For time to relapse in stable responders (who were not stable remitters), time to relapse was summarised and the cumulative distribution function of time to relapse was estimated by the Kaplan-Meier method. The difference in time to relapse between treatment groups was evaluated using a two-sided log-rank test and the hazard ratio and 95% CI were estimated based on the Cox proportional hazards model with treatment as a factor. • For MADRS, PHQ-9, CGI-S, GAD-7, and SDS, change from baseline (for the maintenance phase) at each visit, including observed case and LOCF data, were analysed using the ANCOVA model with factors for treatment and country and baseline score as covariates. The proportion of patients with response and remission based on MADRS, PHQ-9 or SDS were summarised over time.
Data management, patient withdrawals	**Imputation for missing timepoints:** For endpoints using ANCOVA, the LOCF method was applied to the MADRS total score, SDS total score, PHQ-9 total score, and CGI-S for the double-blind induction phase. The last post-baseline observation during the double-blind induction phase was carried forward as the endpoint	**Imputation for missing timepoints:** For the MADRS, CGI-S, PHQ-9, GAD-7 and SDS, both observed case and LOCF values were determined for the induction, optimisation and maintenance phases. The last post-baseline observation during each phase was carried forward as the “Endpoint.” In addition to the observed

	TRANSFORM-2	SUSTAIN-1
	for that phase. In addition to the observed cases and the endpoint assessments, the LOCF values were created for intermediate post-baseline timepoints as well.	cases and endpoint assessment, the LOCF values were created for intermediate post baseline timepoints.
	Imputation for missing items: For MADRS total score, if two or more items were missing, no imputation was performed, and the total score was left missing. Otherwise, the total score was calculated as a sum of the non-missing items multiplied by the ratio of the maximum number of items (i.e., 10) to the number of non-missing items. For all other scales where multiple items were summed to create a total, if any item of the scale was missing at a visit, the total score for that scale at that visit was left blank.	
Subgroup analyses	See Section B.2.6.1.6	See Section B.2.6.2.4

Abbreviations: ANCOVA, analysis of covariance; CGI-S, Clinical Global Impression – Severity; CI, confidence interval; GAD-7, Generalised Anxiety Disorder – 7-item scale; IDMC, independent data monitoring committee; IWRS, Interactive Web Response System; LOCF, last observation carried forward; MADRS, Montgomery-Asberg Depression Rating Scale; MMRM, Mixed-Effects Model using Repeated Measures; OAD, oral antidepressant; PHQ-9, Patient Health Questionnaire – 9 questions; SD, standard deviation; SDS, Sheehan Disability Scale; SE, standard error; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TRD, treatment-resistant depression.

B.2.4.3 Rationale for use of observed case versus LOCF datasets in analyses based on TRANSFORM-1/2/3

In the submission, data has been reported using a mixed effects model using repeated measures (MMRM) based on observed case (OC) analysis. For completeness, clinical outcomes have also been reported using analysis of covariance (ANCOVA) model using change from baseline to Day 28 based on last observation carried forward (LOCF). There a number of reasons for choosing a MMRM OC approach to reporting data, which are outlined below.

Traditionally, analyses of mean changes from baseline in clinical trials have relied on LOCF ANCOVA approach. A LOCF ANCOVA approach is viewed as a conservative approach resulting in an underestimation of treatment effects. Increasingly, MMRM OC is seen as a superior approach due to the inherent restrictive assumption with ANCOVA LOCF, which is that patients can never drop out of a trial due to a lack of efficacy and that patients' responses remain constant from the last observed value to the end-point of the trial (110).

In contrast, a MMRM OC approach uses data collected from all patients (those who drop out as well as those who complete the study) to predict mean longitudinal outcomes for the treatment group. In other words, the MMRM OC uses the actual data from all patients to predict what would have happened had patients stayed in the trial, assuming the data observed until the time of dropout is a useful predictor of the data that was not observed (110). Moreover, in neurological and psychiatric drug products, following an extensive analysis of 48 clinical data sets, MMRM OC has been shown to be a better method at controlling for Type 1 error rates and minimising biases when compared with LOCF ANCOVA (111). The case for MMRM OC models is made stronger compared with LOCF when the numbers of patients is sufficiently large, and the proportion of missing data is small, as is the case with the ESK-NS trials; in the TRANSFORM-2 study 86.7% of patients completed the study (112).

In the NMA, the choice of MMRM OC for the main analysis of acute data was applied both for the comparison versus OAD monotherapy (based only on TRANSFORM-2 study data) and for the comparison versus the majority of the other comparators

(based on the NMA). This ensured consistency across approaches (results for ESK-NS + OAD remain the same whatever the comparator, only the comparator data change).

When considering the economic model, the approach of using data from the acute study (TRANSFORM-2) using MMRM OC and Kaplan Meier estimates for loss of response and relapse for the continuation and maintenance phases (SUSTAIN-1) are conceptually consistent with each other. In both approaches, drop-out patients are represented by the patients who are still observed in the trial thereby ensuring consistency of data handling throughout the model.

Given the above reasons, the MMRM OC analysis is the preferred method in reporting of clinical results, for the data used in the NMA, and for estimation of transition probabilities in the economic model.

B.2.4.4 Participant flow

Full details of participant flow in the TRANSFORM-2 and SUSTAIN-1 trials, including CONSORT diagrams and details of completions/withdrawals, are provided in Appendix D.

B.2.4.4.1 TRANSFORM-2

A total of 435 patients were screened for TRANSFORM-2 of which 227 patients met the inclusion criteria and were randomised to treatment during the double-blind induction phase with either:

- ESK-NS (flexibly-dosed: 56 or 84 mg) plus a newly initiated OAD (ESK-NS + OAD; n=116), or
- A newly initiated OAD + PBO-NS (n=111).

Of the 227 patients randomly assigned to treatment, 197 (86.8%) patients completed the 28 day double-blind induction phase, and 30 (13.2%) patients withdrew. A total of 86 patients entered the follow-up phase of which 43 (50.0%) completed the follow-up phase and 43 (50.0%) withdrew. A total of 161 (70.9%) patients completed the whole trial. In total, 118 patients continued into SUSTAIN-1. A total of 23 patients, 12 in the ESK-NS + PBO arm and 11 in the OAD + PBO-NS arm, discontinued from the study

without entering the follow-up phase or transferring into SUSTAIN-1 (see CONSORT diagram in Appendix D).

B.2.4.4.2 SUSTAIN-1

A total of 1,097 patients were screened for SUSTAIN-1 of which 705 were enrolled:

- 437 direct-entry patients
- 268 transferred-entry patients from either TRANSFORM-1 or TRANSFORM-2.

Transferred-entry patients who were on an OAD plus PBO-NS were not included in efficacy analyses but were included in safety analyses.

Of the patients who directly entered the open-label induction phase of SUSTAIN-1 and transferred-entry patients on ESK-NS plus an OAD, 455 met the criteria for response and started the optimisation phase. Of the 455 patients who entered the optimisation phase, 175 met the criteria for stable remission and 124 met the criteria for stable response at the end of the optimisation phase and were therefore eligible to be randomised to receive treatment with either ESK-NS (flexibly-dosed: 56 or 84 mg) plus an OAD (ESK-NS + OAD) or OAD + PBO-NS during the maintenance phase. The numbers of patients who completed or withdrew from SUSTAIN-1 by trial phase are provided in Appendix D.

B.2.5 Quality assessment of the pivotal trials – TRANSFORM-2 and SUSTAIN-1

Quality assessments for TRANSFORM-2 and SUSTAIN-1 are presented in Table 18. Quality assessments for the supporting trials, TRANSFORM-1/3 and SUSTAIN-2/3, are provided in Appendix D.

TRANSFORM-2 and SUSTAIN-1 (as well as the supporting studies, TRANSFORM-1/3) were large, randomised, multinational, double-blind, active-controlled, well-conducted, and methodologically robust Phase 3 studies. The study protocol and amendments were approved by an independent ethics committee or institutional review board, and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

An Independent Data Monitoring Committee was established to monitor data on an ongoing basis to ensure the continuing safety of the study patients.

Randomisation to study drugs was achieved via a central IWRS, the ESK-NS and PBO-NS devices were identical, and a bittering agent was added to the placebo solution to simulate the taste of the nasal spray solution containing esketamine. Given the dissociative effects associated with ESK-NS and to minimise the impact of this potentially leading to unblinding, remote, independent raters were used to conduct the primary efficacy measure, the MADRS.

Table 18. Quality assessment results for TRANSFORM-2 and SUSTAIN-1

Trial number (acronym)	TRANSFORM-2 (ESKETINTRD3002)	SUSTAIN-1 (ESKETINTRD3003)
Was randomisation carried out appropriately?	Yes. Patients were randomised in a 1:1 ratio based on a computer-generated randomisation schedule prepared before the study by or under the supervision of the sponsor.	Yes. At the start of the maintenance phase patients were randomised in a 1:1 ratio based on a computer-generated randomisation schedule prepared before the study under the supervision of the sponsor.
Was the concealment of treatment allocation adequate?	Yes. IWRS was used to assign a unique treatment code, which dictated the treatment assignment and matching medication kits for the patient.	Yes. An IWRS was used to assign a unique treatment code, which dictated the treatment assignment and matching medication kits for the patient.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Demographics and disease characteristics were balanced between the groups. Randomisation was balanced by using randomly permuted blocks (block size=4) and was stratified by country and class of OAD (SNRI or SSRI) initiated in the double-blind induction phase.	Yes. Demographics and disease characteristics were balanced between the groups. Both randomisations were balanced by using randomly permuted blocks (block size=4) and were stratified by country.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes. This was a double-blind study. The IWRS was used to manage study agent inventory while ensuring that no one at the site had to be unblinded. The investigator was not provided with the treatment randomisation codes. The investigators and the site personnel were blinded to the treatment assignment until all patients completed study participation through the follow-up phase. To maintain the blinding of intranasal study medication, the esketamine and placebo intranasal devices were indistinguishable (via use of a bittering agent added to the placebo solution to simulate the taste of the intranasal solution with active drug). To ensure an unbiased efficacy evaluation, independent, remote (by phone), blinded MADRS raters were used to assess the antidepressant treatment response.	Yes. This was a double-blind study. The IWRS was used to manage study agent inventory while ensuring that no one at the site had to be unblinded. The investigator was not provided with the unique treatment randomisation codes. The blind was not to be broken until all patients completed the study and the database was finalised. To maintain the blinding of intranasal study medication, the esketamine and placebo intranasal devices were indistinguishable (via use of a bittering agent added to the placebo solution to simulate the taste of the intranasal solution with active drug). To ensure an unbiased efficacy evaluation, independent, remote (by phone), blinded MADRS raters were used to assess the antidepressant treatment response.
Were there any unexpected imbalances in drop-outs between groups?	No. The overall drop-outs were generally well-balanced between treatment arms.	No. The overall drop-outs during the randomised maintenance phase were generally well-balanced between treatment arms and the primary reasons for treatment discontinuation were also well-balanced between treatment arms.
Is there any evidence to suggest that the authors	No. Based on the clinical study report all outcomes are reported in detail.	No. Based on the clinical study report all outcomes are reported in detail.

Trial number (acronym)	TRANSFORM-2 (ESKETINTRD3002)	SUSTAIN-1 (ESKETINTRD3003)
measured more outcomes than they reported?		
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Efficacy analyses in the double-blind induction phase were performed on the FAS, defined as all randomised patients who received at least 1 dose of intranasal study medication and 1 dose of OAD medication. The safety analysis set was defined as all randomised patients who received at least 1 dose of intranasal study medication or 1 dose of OAD medication. For the MADRS, if 2 or more items were missing, no imputation was performed and the total score was left missing. For all other scales where multiple items were summed to create a total, if any item of the scale was missing at a visit, the total score for that scale at that visit was left blank.	Yes. There were 2 FAS defined for the maintenance phase: - Full (stable remitters): used to perform primary and secondary efficacy evaluations on randomised patients who were in stable remission at the end of the optimisation phase and who received at least 1 dose of intranasal study drug and 1 dose of OAD during the maintenance phase. - Full (stable responders): used to perform secondary efficacy evaluations on randomised patients who were stable responders (who were not stable remitters) at the end of the optimisation phase and who received at least 1 dose of intranasal study drug and 1 dose of OAD during the maintenance phase. For the MADRS, if 2 or more items were missing, no imputation was performed, and the total score was left missing. For all other scales where multiple items were summed to create a total, if any item of the scale was missing at a visit, the total score for that scale at that visit was considered missing.

Abbreviations: FAS, full analysis set; IWRS, interactive web response system, MADRS, Montgomery-Asberg Depression Rating Scale; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

B.2.6 Clinical effectiveness results of the pivotal trials – TRANSFORM-2 and SUSTAIN-1

The two pivotal trials, TRANSFORM-2 and SUSTAIN-1, met their primary objectives related to short-term depression symptom control (TRANSFORM-2) and longer-term relapse prevention (SUSTAIN-1). These highly significant results were achieved despite using an active comparator arm consisting of a newly initiated OAD with a PBO-NS added, rather than a true placebo. Moreover, the composition of the comparator arm, with the inclusion of the PBO-NS and high intensity follow-up contact for blinding is likely to have resulted in a higher treatment effect in the active comparator arm than is typically observed in other TRD trials investigating OADs or in clinical practice. The active comparator arm is therefore not fully reflective of how OAD treatment would be given in clinical practice in the NHS. Expert clinical opinion supports the assertion that the responses observed in the active comparator arm are much higher than would be expected in the TRD patient population.
These factors are discussed in more detail in Section B.2.13.2.

B.2.6.1 TRANSFORM-2, the acute treatment study

Key Results

Results for the primary efficacy endpoint were statistically significant for the mean change in MADRS total score from baseline to Day 28. The secondary endpoints of onset of clinical response by Day 2, and improvements in response and remission at day 28 also favoured ESK-NS + OAD compared with PBO-NS + OAD. Patient reported outcomes were also improved (PHQ-9 and EQ-5D).

Mean changed in MADRS total score

- TRANSFORM-2 met its primary endpoint, for which patients treated with ESK-NS + OAD experienced statistically significant and clinically meaningful improvements in depressive symptoms: mean change in MADRS total score from baseline to the end of induction –21.4 versus –17.0 in OAD + PBO-NS arm (p=0.010).

- Change in MADRS total score from baseline to Day 2 was statistically significantly greater in patients treated with ESK-NS + OAD versus OAD + PBO-NS (Unadjusted LS mean treatment difference: –3.3; p=0.004; MMRM).

Clinical response and remission

- Based on clinician-assessed MADRS, higher response (≥50% reduction from baseline in MADRS total score) and remission (MADRS total score of ≤12) rates were achieved among patients in the ESK-NS + OAD arm (69.3% and 52.5%, respectively) versus the OAD + PBO-NS arm (52.0% and 31.0%, respectively).
  - Adjusting (*post-hoc*) for the high treatment effect observed in the OAD + PBO-NS arm resulted in a response rate of 31.0% and remission rate of 18.0% among patients in the OAD + PBO-NS arm.

HRQoL

- Patient-reported measures showed significant improvements in functional impairment and disability (SDS) and depressive symptom severity (PHQ-9) with ESK-NS + OAD (nominal 1-sided p≤0.003) versus OAD + PBO-NS.
- Associated improvements in HRQoL were experienced by patients in the ESK-NS + OAD arm, as shown by the increase from baseline to the end of induction (Day 28) in mean EQ-5D-5L HSI versus OAD + PBO-NS (0.310 versus 0.235, respectively).

The above short-term outcomes translate into improvements in patient social and occupational functioning, which will likely have a positive impact on their family and friends.

B.2.6.1.1 Treatment exposure

Between Day 8 and Day 25 of the induction phase, on any given ESK-NS administration day, 28–37% of patients were receiving ESK-NS 56 mg and 63–72% were receiving ESK-NS 84 mg. (Note that beyond Day 15 [or Day 18 if the Day 15 treatment session did not occur], no further ESK-NS dose changes were permitted [see Appendix M for further details]).

B.2.6.1.2 Primary efficacy outcome: Change in MADRS total score from baseline to the end of induction

TRANSFORM-2 met its primary endpoint of a statistically significant improvement in depressive symptoms, as assessed by MADRS, with ESK-NS + OAD versus OAD + PBO-NS. The improvement observed was considered clinically meaningful and likely translates into considerable improvements in patient's lives.

Change in MADRS total score from baseline to the end of the double-blind, 4-week induction phase significantly favoured ESK-NS + OAD over OAD + PBO-NS (Table 19; observed cases and LOCF).

- The unadjusted difference in mean MADRS total scores between the ESK-NS + OAD and OAD + PBO-NS arms exceeded the minimum clinically important difference (MCID) for MADRS (defined as a difference of 1.6–1.9 in scores (113)) at every time point during the induction phase.
- The significantly greater reduction from baseline in MADRS in the ESK-NS+ OAD versus the OAD + PBO-NS arm translated into more patients in the ESK-NS + OAD versus the OAD + PBO-NS arm achieving response and/or remission, as shown in Section B.2.6.1.3.

Table 19. MADRS total score: Change from baseline to the end of induction (unadjusted, observed cases MMRM and LOCF ANCOVA; full analysis set)

	ESK-NS + OAD N=114	OAD + PBO-NS N=109
Baseline (observed cases)		
N	114	109
Mean (SD)	37.0 (5.69)	37.3 (5.66)
Day 28 (observed cases)		
N	101	100
Mean (SD)	15.5 (10.67)	20.6 (12.70)
Change from baseline to Day 28 (observed cases)		
N	101	109
Mean (SD)	–21.4 (12.32)	–17.0 (13.88)
MMRM (observed cases)[a]		
Difference in LS means (SE)	–4.0 (1.69)	-
95% CI	–7.31; –0.64	-
1-sided p-value	0.010	-
Baseline (LOCF)		
N	114	109
Mean (SD)	37.0 (5.69)	37.3 (5.66)
Endpoint of induction (LOCF)		
N	112	109

	ESK-NS + OAD N=114	OAD + PBO-NS N=109
Mean (SD)	17.4 (12.18)	21.0 (12.86)
Change from baseline to endpoint of induction (LOCF)		
N	112	109
Mean (SD)	–19.6 (13.58)	–16.3 (14.24)
ANCOVA (LOCF)[b]		
Difference in LS means (SE)	–3.5 (1.63)	-
95% CI	–6.67; –0.26	-
1-sided p-value	0.017	-

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; LOCF, last observation carried forward; LS, least squares; MADRS, Montgomery-Asberg Depression Rating Scale; MMRM, mixed-effects model using repeated measures; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; SD, standard deviation; SE, standard error; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a] Change from baseline was the response variable and fixed effect model terms for treatment, day, country, class of OAD (SNRI or SSRI), treatment-by-day, and baseline MADRS value were covariates.

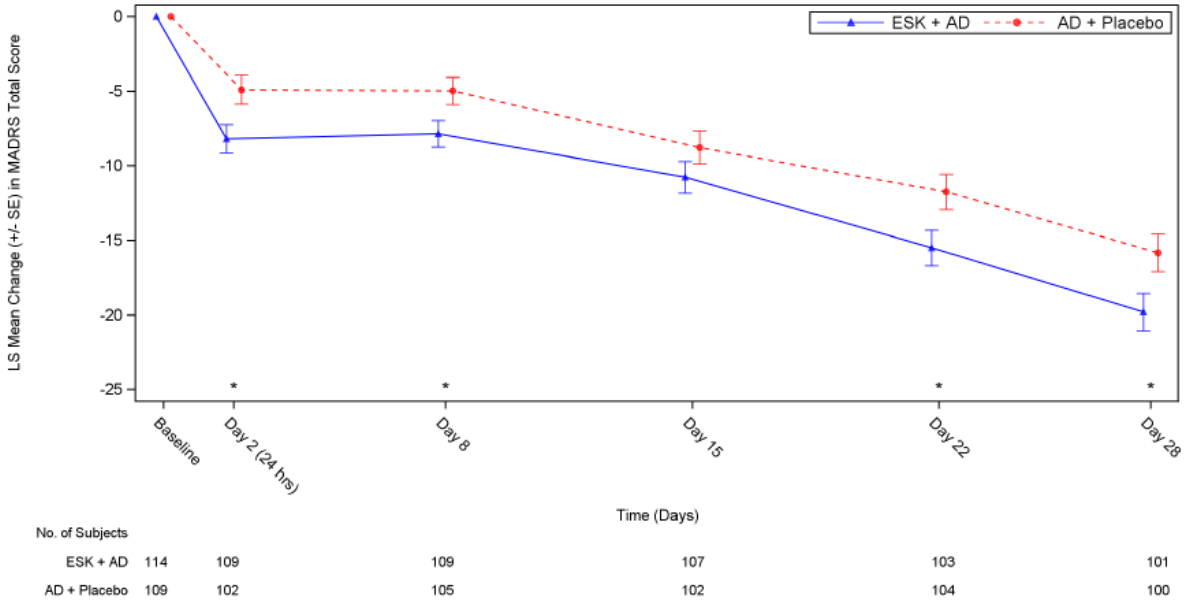
[b] Change from baseline was the response variable and treatment, country, class of OAD (SNRI or SSRI), and baseline MADRS value were covariates.

B.2.6.1.2.1 Least squares mean change in MADRS total score over time

Changes in unadjusted MADRS total score (LS mean) from baseline over time significantly favoured ESK-NS + OAD over OAD + PBO-NS at Day 2 (–3.3), Day 8 (–2.9), Day 22 (–3.8), and Day 28 (–4.0) (MMRM; 1-sided p<0.020) (Figure 14).

ANCOVA analysis of the primary efficacy outcome was consistent with the MMRM analysis (see Appendix N).

Figure 14. LS mean (SE) changes in MADRS total score over time (observed cases MMRM; full analysis set)



Abbreviations: AD, antidepressant; ESK, esketamine; LS, least squares; MADRS, Montgomery-Asberg Depression Rating Scale; MMRM, mixed-effects model using repeated measures; SE, standard error.
Note: Change from baseline was the response variable and fixed effect model terms for treatment, day, country, class of OAD (SNRI or SSRI), treatment-by-day, and baseline MADRS value were covariates.
* 1-sided p<0.020.

B.2.6.1.3 Response and remission rates based on MADRS and SDS (directly relevant to HE model)

Based on both physician-reported MADRS and patient-reported Sheehan Disability Scale (SDS) total scores, the proportions of responders and remitters in the ESK-NS + OAD and OAD + PBO-NS arms generally increased over time during the induction phase, and favoured ESK-NS + OAD at all time points (Figure 15, [MADRS Day 28 values]; see Appendix N).

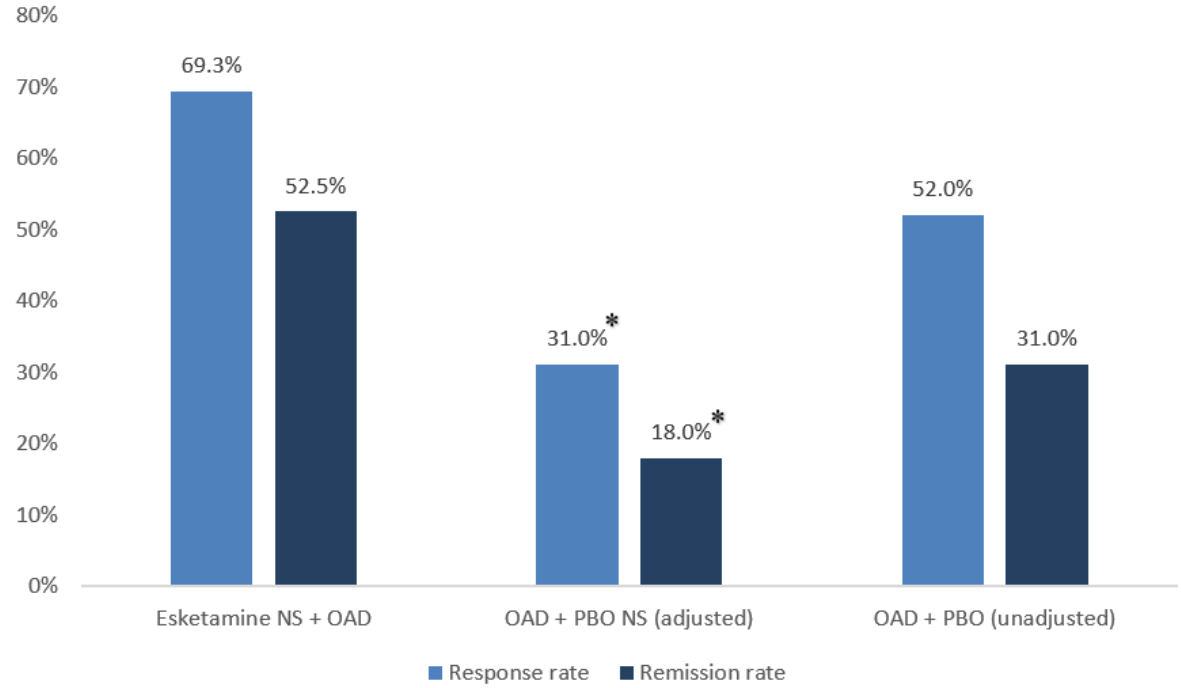
Note that Figure 15 also presents adjusted response and remission rates for the OAD + PBO-NS arm based on a *post-hoc* analysis conducted to investigate the comparability of the placebo rates observed in TRANSFORM-2 to those observed in other trials as well as in clinical practice (further detail is provided in Section B.2.3.7).

Based on MADRS, higher response (≥50% reduction from baseline in MADRS total score) and remission (MADRS total score of ≤12) rates were achieved among patients treated with ESK-NS plus OAD (69.3% and 52.5%, respectively) versus OAD + PBO NS (31.0% and 18.0% after adjustment for treatment effect, conducted

post hoc, and 52.0% and 31.0% unadjusted data from TRANSFORM-2, respectively) at four weeks.

From a patient perspective, improved response and remission rates likely translate into greater improvements in mood, appetite, sleep, and concentration, as well as higher numbers of patients taking care of themselves, their relatives and friends, and resuming work/normal lives.

Figure 15. Day 28 response and remission rates based on MADRS (observed cases)



Abbreviations: Esketamine NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; MADRS, Montgomery-Asberg Depression Rating Scale; OAD + PBO (-NS), newly initiated oral antidepressant plus placebo nasal spray.
Response based on MADRS was defined as a ≥50% reduction from baseline in MADRS total score.
Remission based on MADRS was defined as a MADRS total score of ≤12.
* Adjusted results based on a post hoc analysis of response and remission rates in the OAD + PBO-NS arm of TRANSFORM-2. See Section B.2.3.7 for further details.

B.2.6.1.3.1 Number needed to treat to achieve response and remission

The NNT (95% CI) to achieve response and remission, respectively, based on unadjusted MADRS total score at Day 28 was 6 (1.3; 10.2) and 5 (1.8; 7.5).

After adjusting (*post-hoc*) for the high treatment effect in the OAD + PBO-NS arm (see Section B.2.3.7), the NNT (95% CI) reduced to 3 (3; 5) for both response and remission (Table 20).

Table 20. NNT to achieve response and remission (based on post hoc adjusted data)

Outcome	ESK-NS + OAD			OAD + PBO-NS			Risk difference		NNT
	Positive outcome (N)	Negative outcome (N)	Probability positive outcome	Positive outcome (N)	Negative outcome (N)	Probability positive outcome	Estimate (95% CI)	SE	Estimate (95% CI)
Remission	53	48	0.525	18	82	0.180	0.345 (0.222; 0.468)	0.063	3 (3; 5)
Response	70	31	0.693	34	66	0.340	0.353 (0.224; 0.482)	0.066	3 (3; 5)

Abbreviations: CI, confidence interval; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; NNT, number needed to treat; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; SE, standard error.

B.2.6.1.4 Key secondary efficacy outcomes relevant to HE model and/or scope

The key secondary efficacy outcomes in TRANSFORM-2 were all in favour of ESK-NS + OAD over OAD + PBO-NS as shown in Table 21 and as detailed in the following sections.

Table 21. Summary of key secondary efficacy outcomes

	ESK-NS + OAD N=114	OAD + PBO-NS N=109
Achieved onset of clinical response by Day 2, n (%)	9 (7.9)	5 (4.6)
Change from baseline to Day 28 in SDS (observed cases)		
N	86	85
Mean (SD)	–13.6 (8.31)	–9.4 (8.43)
Change from baseline to endpoint in SDS (LOCF)		
N	95	89
Mean (SD)	–12.5 (8.85)	–9.3 (8.39)
Change from baseline to Day 28 in PHQ-9 (observed cases)		
N	104	100
Mean (SD)	–13.0 (6.42)	–10.2 (7.80)
Change from baseline to endpoint in PHQ-9 (LOCF)		
N	111	105
Mean (SD)	–12.2 (6.87)	–10.1 (7.87)

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; LOCF, last observation carried forward; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; PHQ-9, Patient Health Questionnaire – 9 questions; SD, standard deviation; SDS, Sheehan Disability Scale.
Note that as per the predefined hierarchical testing procedure, since the first of the key secondary efficacy outcomes (onset of clinical response by Day 2 [maintained to Day 28]) did not demonstrate a statistically significant difference between the trial arms, the subsequent key outcomes could not be formally evaluated.

B.2.6.1.4.1 Onset of clinical response by Day 2 (24 hours) maintained to Day 28 (based on MADRS total score)

The onset of clinical response (≥50% reduction from baseline in MADRS total score) was numerically more rapid in the ESK-NS + OAD arm than the OAD + PBO-NS arm

as measured by the proportions of patients with onset by Day 2 (24 hours) that was maintained to Day 28 (one excursion allowed) (Table 22).

- The odds of achieving onset of clinical response by Day 2 (maintained to Day 28) with ESK-NS + OAD were 1.79 times larger than for OAD + PBO-NS, although the result was not statistically significant (p=0.161).
  - Note, however, that the change in MADRS total score from baseline to Day 2 was statistically significantly greater in patients treated with ESK-NS + OAD versus the comparator arm (LS mean treatment difference: –3.3; p=0.004; MMRM).
- As a result of the non-statistically significant result and based on the predefined testing sequence of key secondary endpoints, SDS total score and PHQ-9 total score could not be formally evaluated (results presented in subsequent subsections).

Table 22. Onset of clinical response by Day 2 maintained to Day 28 (full analysis set)

	ESK-NS + OAD N=114	OAD + PBO-NS N=109
Achieved onset of clinical response by Day 2, n (%)	9 (7.9)	5 (4.6)
Generalised Cochran-Mantel-Haenszel test[a]		
1-sided p-value	0.161	-
OR (95% CI)	1.79 (0.57; 5.67)	-

Abbreviations: CI, confidence interval; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; OAD, oral antidepressant; OR, odds ratio; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
[a] Adjusted for region and class of OAD (SNRI or SSRI).

B.2.6.1.4.2 Change in SDS total score from baseline to the end of induction

Improvements in functional impairment and associated disability, as assessed by SDS, favoured the ESK-NS + OAD arm over OAD + PBO-NS (Table 23).

- Based on MMRM, the mean (SD) change in SDS total score from baseline to Day 28 was –13.6 (8.31) in the ESK-NS + OAD arm and –9.4 (8.43) in the OAD + PBO-NS arm; LS mean (95% CI) difference was –4.0 (–6.28; –1.64).
- The SDS result was nominally significant (1-sided p<0.001), although the outcome could not be formally evaluated because the predefined hierarchical testing procedure was terminated after the first key secondary endpoint (onset of clinical response by Day 2 [maintained to Day 28]).

- Greater improvements in SDS translates into reduced impact of depressive symptoms on work, social, and family functioning.

Table 23. SDS total score: Change from baseline to Day 28 (observed cases MMRM and LOCF ANCOVA; full analysis set)

	ESK-NS + OAD N=114	OAD + PBO-NS N=109
Baseline		
N	111	104
Mean (SD)	24.0 (4.07)	24.2 (4.38)
Day 28 (observed cases)		
N	86	86
Mean (SD)	10.1 (7.71)	14.8 (9.07)
Change from baseline to Day 28 (observed cases)		
N	86	85
Mean (SD)	–13.6 (8.31)	–9.4 (8.43)
MMRM (observed cases)[a]		
Difference in LS means (SE)	–4.0 (1.17)	
95% CI	–6.28; –1.64)	
1-sided p-value[b]	<0.001	
Endpoint of induction (LOCF)		
N	95	90
Mean (SD)	11.2 (8.28)	14.8 (8.93)
Change from baseline to endpoint of induction (LOCF)		
N	95	89
Mean (SD)	–12.5 (8.85)	–9.3 (8.39)
ANCOVA (LOCF)[c]		
Difference in LS means (SE)	–3.5 (1.19)	-
95% CI	–5.85; –1.16	-
1-sided p-value[b]	0.002	-

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; LOCF, last observation carried forward; LS, least squares; MMRM, mixed-effects model using repeated measures; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; SD, standard deviation; SDS, Sheehan Disability Scale; SE, standard error; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a] Change from baseline was the response variable and fixed effect model terms for treatment, day, country, class of OAD (SNRI or SSRI), treatment-by-day, and baseline SDS value were covariates.

[b] Nominal p-value; could not be formally tested due to termination of hierarchical testing sequence after the key secondary outcome of onset of clinical response by Day 2.

[c] Change from baseline was the response variable and treatment, country, class of OAD (SNRI or SSRI), and baseline SDS value were covariates.

B.2.6.1.4.3 Change in PHQ-9 total score from baseline to the end of induction

Improvements in depressive symptoms, as assessed by patient-reported PHQ-9, favoured the ESK-NS + OAD arm over OAD + PBO-NS (Table 24).

- Based on MMRM, the mean (SD) change in PHQ-9 total score from baseline to the end of induction was –13.0 (6.42) in the ESK-NS + OAD arm and –10.2 (7.80) in the OAD + PBO-NS arm; LS mean (SE; 95% CI) treatment difference was –2.4 (0.88; nominal p=0.003).
- The PHQ-9 result was nominally significant (1-sided p=0.003), although the outcome could not be formally evaluated.
- Greater improvements in PHQ-9 translates into improvements in mood and the ability to feel pleasure, energy, appetite, sleep, and concentration.

Table 24. PHQ-9 total score: Change from baseline to Day 28 (observed cases MMRM and LOCF ANCOVA; full analysis set)

	ESK-NS + OAD N=114	OAD + PBO-NS N=109
Baseline		
N	114	109
Mean (SD)	20.2 (3.63)	20.4 (3.74)
Day 28 (observed cases)		
N	104	100
Mean (SD)	7.3 (5.74)	10.2 (7.68)
Change from baseline to Day 28 (observed cases)		
N	104	100
Mean (SD)	–13 (6.42)	–10.2 (7.80)
MMRM (observed cases)[a]		
Difference in LS means (SE)	–2.4 (0.88)	-
95% CI	–4.18; –0.69	-
1-sided p-value	0.003	-
End of induction (LOCF)		
N	111	105
Mean (SD)	8.0 (6.24)	10.2 (7.64)
Change from baseline to the end of induction (LOCF)		
N	111	105
Mean (SD)	–12.2 (6.87)	–10.1 (7.87)
ANCOVA (LOCF)[c]		
Difference in LS means (SE)	–2.2 (0.89)	-
95% CI	–3.93; –0.40	-
1-sided p-value[b]	0.008	-

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; LOCF, last observation carried forward; LS, least squares; MMRM, mixed-effects model using repeated measures; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; SD, standard deviation; SE, standard error; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
[a] Change from baseline was the response variable and fixed effect model terms for treatment, day, country, class of OAD (SNRI or SSRI), treatment-by-day, and baseline PHQ-9 value were covariates.
[b] Nominal p-value; could not be formally tested due to termination of hierarchical testing sequence after the key secondary outcome of onset of clinical response by Day 2.
[c] Change from baseline was the response variable and treatment, country, class of OAD (SNRI or SSRI), and baseline PHQ-9 value were covariates.

B.2.6.1.5 Other secondary efficacy outcomes relevant to HE model and/or scope

B.2.6.1.5.1 Onset of response by Day 8, change from baseline in CGI-S and GAD-7

Other secondary efficacy outcomes included onset of clinical response by Day 8, and change from baseline in Clinical Global Impression – Severity (CGI-S) and Generalised Anxiety Disorder – 7-item scale (GAD-7) (Table 25).

Table 25. Other secondary efficacy outcomes (clinical response by Day 8, CGI-S and GAD-7)

	ESK-NS + OAD N=114	OAD + PBO-NS N=109
Onset of clinical response by Day 8		
N	114	109
Clinical response by Day 8, n (%)	12 (10.5)	7 (6.4)
Generalised Cochran-Mantel-Haenszel test[a]		
1-sided p-value[b]	0.137	-
OR (95% CI)	1.74 (0.65; 4.70)	-
Change in CGI-S from baseline to Day 28 (observed cases)		
N	101	97
Mean (SD) change	–2.1 (1.33)	–1.6 (1.38)
MMRM[e]		
Difference in LS means (SE)	–0.4 (0.17)	-
95% CI	–0.72; –0.04	-
1-sided p-value[b]	0.015	-
Change in CGI-S from baseline to endpoint of induction (LOCF)		
N	111	109
Median (range) change	–2.0 (–5; 1)	–2.0 (–5; 1)
ANCOVA[c]		
1-sided p-value[b]	0.017	-
OR (95% CI)	2.8 (1.14; 7.68)	-
Change in GAD-7 from baseline to Day 28 (observed cases)		
N	110	102
Mean (SD) change	–7.9 (6.12)	–6.8 (5.75)
ANCOVA[d]		
Difference in LS means (SE)	–1.0 (0.67)	-
95% CI	–2.35; 0.28	-
1-sided p-value[b]	0.061	-
Change in GAD-7 from baseline to endpoint of induction (LOCF)		
N	110	102
Mean (SD) change	–7.9 (6.12)	–6.8 (5.75)
ANCOVA[d]		
Difference in LS means (SE)	–1.0 (0.67)	-
95% CI	–2.35; 0.28	-
1-sided p-value[b]	0.061	-

Abbreviations: ANCOVA, analysis of covariance; CGI-S, Clinical Global Impression – Severity; CI, confidence interval; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; GAD-7, Generalised Anxiety Disorder – 7-item scale; LOCF, last observation carried forward; LS, least squares; MADRS, Montgomery-Asberg Depression Rating Scale; MMRM, mixed-effects model using repeated measures; OAD, oral antidepressant; OR, odds ratio; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; SD, standard deviation; SDS, Sheehan Disability Scale; SE, standard error; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
[a] Adjusted for region and class of OAD (SNRI or SSRI).
[b] p-value is descriptive and not inferential as this endpoint was not part of the predefined hierarchical testing sequence used to control for type I error.
[c] Change from baseline was the response variable and treatment, country, class of OAD (SNRI or SSRI), and baseline CGI-S value (unranked) were covariates.
[d] Change from baseline was the response variable and treatment, country, class of OAD (SNRI or SSRI), and baseline GAD-7 value were covariates.
[e] Change from baseline was the response variable and the fixed effect model terms for treatment, day, country, class of OAD (SNRI or SSRI), treatment-by-day, and baseline CGI-S values were covariates.

B.2.6.1.5.2 EQ-5D-5L

- In both the ESK-NS + OAD and the OAD + PBO-NS arms, the percentages of patients reporting problems (levels 2–5) in each of the five dimensions of EuroQol-5 Dimension-5 Level (EQ-5D-5L) decreased from baseline to Day 28.
  - Improvements in Domain 3 of EQ-5D-5L (usual activities) were statistically significantly greater among patients in the ESK-NS + OAD versus the OAD + PBO-NS arms at both Day 15 and Day 28 ($p \leq 0.0461$; see Appendix N).
- ESK-NS + OAD treatment resulted in a greater improvement in HRQoL versus OAD + PBO-NS, as shown by the increase from baseline in mean (SD) health status index (HSI) score to Day 28: 0.310 (0.2191) versus 0.235 (0.2525), respectively (Table 26).
- Mean EQ-5D-5L sum and EuroQol – Visual Analogue Scale (EQ-VAS) scores also improved from baseline to Day 28 in both trial arms.
  - The mean (SD) increase (improvement) in EQ-VAS from baseline to the end of induction was 29.1 (26.32) among patients in the ESK-NS + OAD arm versus 20.9 (26.60) among patients in the OAD + PBO-NS arm.
- Compared with OAD + PBO-NS, ESK-NS + OAD treatment resulted in greater improvements in overall health. ESK-NS + OAD treatment resulted in more patients being able to care for themselves, improved mobility, experience less pain/discomfort and reduced depression/anxiety, and a statistically significantly higher number of patients being able to resume their normal activities, compared with patients treated with OAD + PBO-NS.

Table 26. EQ-5D-5L HSI score: Change from baseline to Day 28 (observed cases and LOCF, full analysis set)

	ESK-NS + OAD N=114	OAD + PBO-NS N=109
Baseline		
N	114	109
Mean (SD)	0.530 (0.2081)	0.501 (0.2143)
Day 28 (observed cases)		
N	104	100
Mean (SD)	0.843 (0.1407)	0.732 (0.2325)
Change from baseline to Day 28 (observed cases)		
N	104	100
Mean (SD) change	0.310 (0.2191)	0.235 (0.2525)
End of induction (LOCF)		
N	111	105
Mean (SD)	0.817 (0.1777)	0.735 (0.2296)
Change from baseline to end of induction (LOCF)		
N	111	105
Mean (SD) change	0.288 (0.2317)	0.231 (0.2506)

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; HSI, health status index; LOCF, last observation carried forward; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; SD, standard deviation.

B.2.6.1.6 Subgroup analyses

Pre-planned subgroup analyses were performed on the subgroups listed in Table 8 (results presented in Appendix E) in which there were five or more patients (patient gender, age group, region, baseline MADRS total score, number of previous treatment failures in the current episode of depression; functional impairment [SDS], race, class of OAD [SNRI or SSRI], and country). Each subgroup analysis consisted of an MMRM (OC) of the treatment difference (95% CI) in the mean change in MADRS total score from baseline to the end of induction.

Patient demographics and disease characteristics for subgroups were not defined.

A summary of the results of the subgroup analyses, including a forest plot representation of the subgroup analyses, is provided in Appendix E.

- Results of the subgroup analyses were generally consistent with the full analysis set, favouring ESK-NS + OAD treatment over OAD + PBO-NS for reducing MADRS scores during induction (LS mean difference in change in MADRS total score <0 favouring ESK-NS + OAD).

- Exceptions (LS mean difference in change in MADRS total score >0) were in patients classified as having moderate functional impairment (SDS score: 12–19; n=32), patients of black ethnic origin (n=11), and patients located in Poland (n=38).
- Subgroup analyses show that the effect of ESK-NS was the same, irrespective of the OAD it was combined with. As NICE indicated at the early scientific advice meeting, “this would support the case for the generalisability of the trial results” (7).
- The number of patients in some subgroups were small, generating wide confidence intervals that crossed the boundary of equivalence in some cases, and therefore the results should be interpreted with caution.

B.2.6.1.7 Conclusion: TRANSFORM-2, the acute treatment study

- TRANSFORM-2 met its primary endpoint showing statistically significant and clinically meaningful improvements in depressive symptoms, based on change in MADRS total score from baseline to the end of induction.
- Treating patients with TRD (aged 18–64 years) with flexibly-dosed ESK-NS (plus newly initiated OAD) in the acute induction phase resulted in higher response and remission rates compared with the active comparator arm (comprising a newly initiated OAD plus PBO-NS).
- ESK-NS also resulted in nominally significant improvements in functional impairment and disability (SDS) and depressive symptom severity (PHQ-9), and associated improvements in HRQoL (EQ-5D-5L HSI and EQ-VAS) versus OAD + PBO-NS.
- The superiority of ESK-NS + OAD over OAD + PBO-NS was demonstrated despite the treatment effect in the OAD + PBO-NS arm being much higher than that observed in similar trials and in clinical practice (see Section B.2.13).

The TRANSFORM-2 data shows that treatment with ESK-NS + OAD translates into improvements in patient social and occupational functioning and therefore quality of life, which will likely have an additional positive impact on carers.

B.2.6.2 SUSTAIN-1, the relapse prevention study

Key Results

For patients with TRD who experienced remission or response after ESK-NS + OAD treatment, continuation of ESK-NS + OAD resulted in clinically meaningful superiority in delaying relapse compared with OAD + PBO-NS.

Relapse

- Only 26.7% of patients in stable remission at randomisation on ESK-NS + OAD experienced a relapse during the maintenance phase, compared with 45.3% of those who continued on the same OAD but switched to PBO-NS from ESK-NS (primary endpoint, p=0.003).
- Only 25.8% of patients in stable response at randomisation who continued ESK-NS + OAD experienced a relapse event compared with 57.6% of those who were switched to OAD + PBO-NS (p<0.001).

Other relevant endpoints

- Ongoing ESK-NS + OAD treatment also significantly delayed worsening of symptom severity and functional impairment during the maintenance phase, based on mean changes over time in MADRS, SDS, and PHQ-9 total scores (in both stable remitter and responder patients; p≤0.025).

HRQoL

- In a consistent manner, stable remitters and stable responders continuing ESK-NS + OAD experienced smaller deterioration in HRQoL (EQ-5D-5L HSI) over the duration of the maintenance phase, compared with those who continued their OAD but switched to PBO-NS.

Overall, the results of SUSTAIN-2 show that maintenance treatment with ESK-NS + OAD is associated with sustained improvement in patient social and occupational functioning and quality of life.

B.2.6.2.1 Treatment exposure

On Day 1 of the maintenance phase, 44.4% of stable remitter patients who were randomised to continued ESK-NS treatment were receiving the 56 mg dose, and 55.6% were receiving the 84 mg dose.

B.2.6.2.2 Primary efficacy outcome: Time to relapse during the maintenance phase in stable remitters

SUSTAIN-1 met its primary endpoint: for patients in stable remission after 16 weeks of ESK-NS + OAD treatment, continued treatment with ESK-NS + OAD demonstrated clinically meaningful and statistically significant (2-sided p=0.003 log-rank test) superiority to treatment with OAD + PBO-NS, as measured by delayed time to relapse.

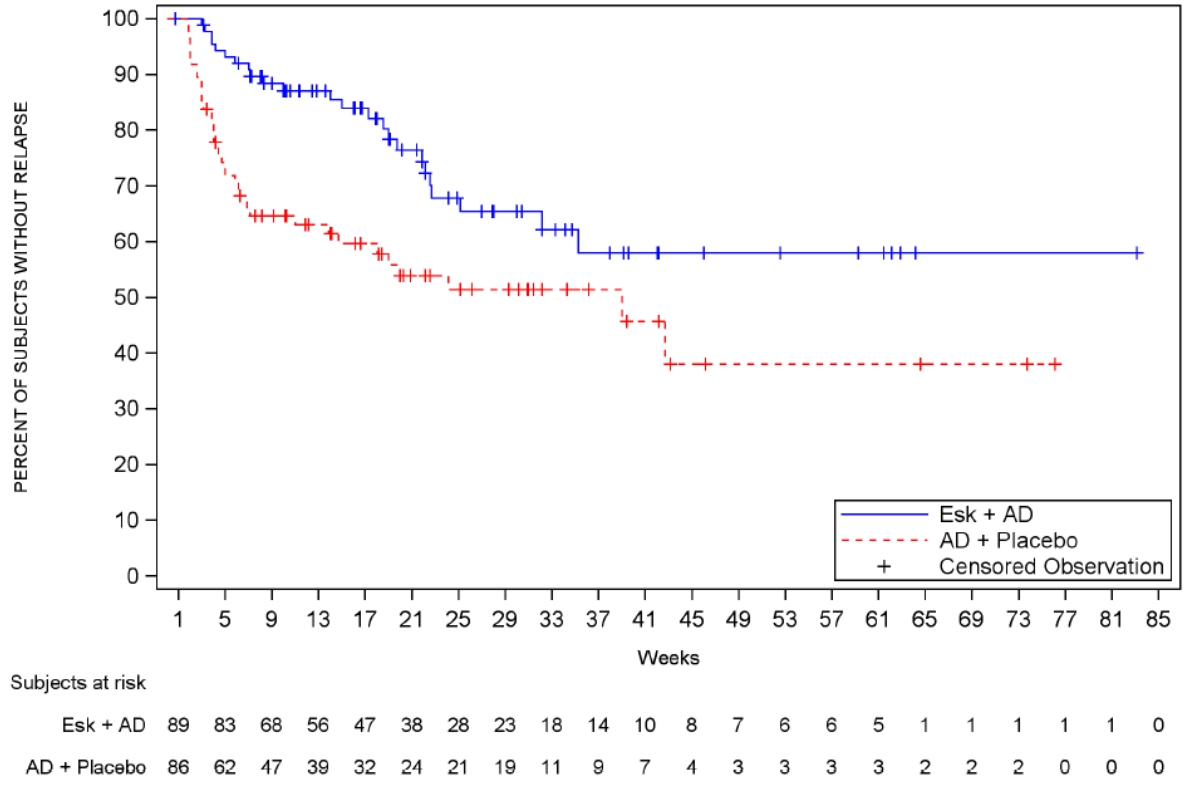
- 45.3% of stable remitters who were switched to OAD + PBO-NS experienced a relapse event during the maintenance phase compared with only 26.7% of patients who remained on ESK-NS + OAD. Stable remitters continuing ESK-NS + OAD treatment experienced a 51% reduction in the risk of relapse compared with patients switched to OAD + PBO-NS (HR: 0.49; 95% CI: 0.29; 0.84).
- Based on Kaplan-Meier estimates, median time to relapse (time point at which the cumulative survival function equals 50%) was not reached (not estimable) in the ESK-NS + OAD arm but was 273.0 days for OAD + PBO-NS (Table 27; Figure 16).
- The most common reason for relapse was MADRS total score ≥22 for two consecutive assessments (see Appendix N).

Table 27. Time to relapse and proportions of patients remaining relapse-free (full [stable remitters] analysis set)

	ESK-NS + OAD N=90	OAD + PBO-NS N=86
Time to relapse (days)[a]		
Patients assessed, n (%)	90	86
Patients censored, n (%)	66 (73.3)	47 (54.7)
Relapses, n (%)	24 (26.7)	39 (45.3)
25th percentile (95% CI)	153.0 (105.0; 225.0)	33.0 (22.0; 48.0)
Median (95% CI)	NE	273.0 (97.0; NE)
75th percentile (95% CI)	NE	NE
HR (95% CI)[b]	0.49 (0.29; 0.84)	-
2-sided p-value[c]	0.003	-

Abbreviations: CI, confidence interval; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; HR, hazard ratio; NE, not estimable; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray.
[a] Based on Kaplan-Meier product limit estimates.
[b] HRs and CIs are weighted estimates based on Wassmer (2006) (114) and calculated using R.
[c] Based on the final test statistic which is a weighted combination of the log-rank test statistics calculated on the interim full analysis set and on the full analysis set in stable remitters.

Figure 16. Cumulative proportion of patients who remained relapse-free (full [stable remitters] analysis set)



Abbreviations: AD, oral antidepressant; Esk, esketamine nasal spray.

B.2.6.2.3 Secondary efficacy outcomes relevant to HE model and/or scope

B.2.6.2.3.1 Time to relapse during the maintenance phase in stable responders (who were not remitters)

In patients in stable response (but not in remission) after 16 weeks of ESK-NS + OAD treatment, continued treatment with ESK-NS + OAD demonstrated clinically meaningful and statistically significant superiority to treatment with OAD + PBO-NS in delaying time to relapse (2-sided p<0.001 log-rank test).

- 57.6% of stable responders who were switched to OAD + PBO-NS experienced a relapse event during the maintenance phase compared with only 25.8% of patients who remained on ESK-NS + OAD.
- Stable responders continuing ESK-NS + OAD experienced a 70% reduction in the risk of relapse compared with those switched to OAD + PBO-NS (HR: 0.30; 95% CI: 0.16; 0.55).
- Based on Kaplan-Meier estimates, median time to relapse (time point at which the cumulative survival function equals 50%) was 88.0 days for OAD + PBO-

NS versus 635.0 days for ESK-NS + OAD (Table 28; Figure 17). Of note, the median time to relapse was only reached because the last patient remaining at risk had relapsed at 635 days in the ESK-NS+OAD arm.

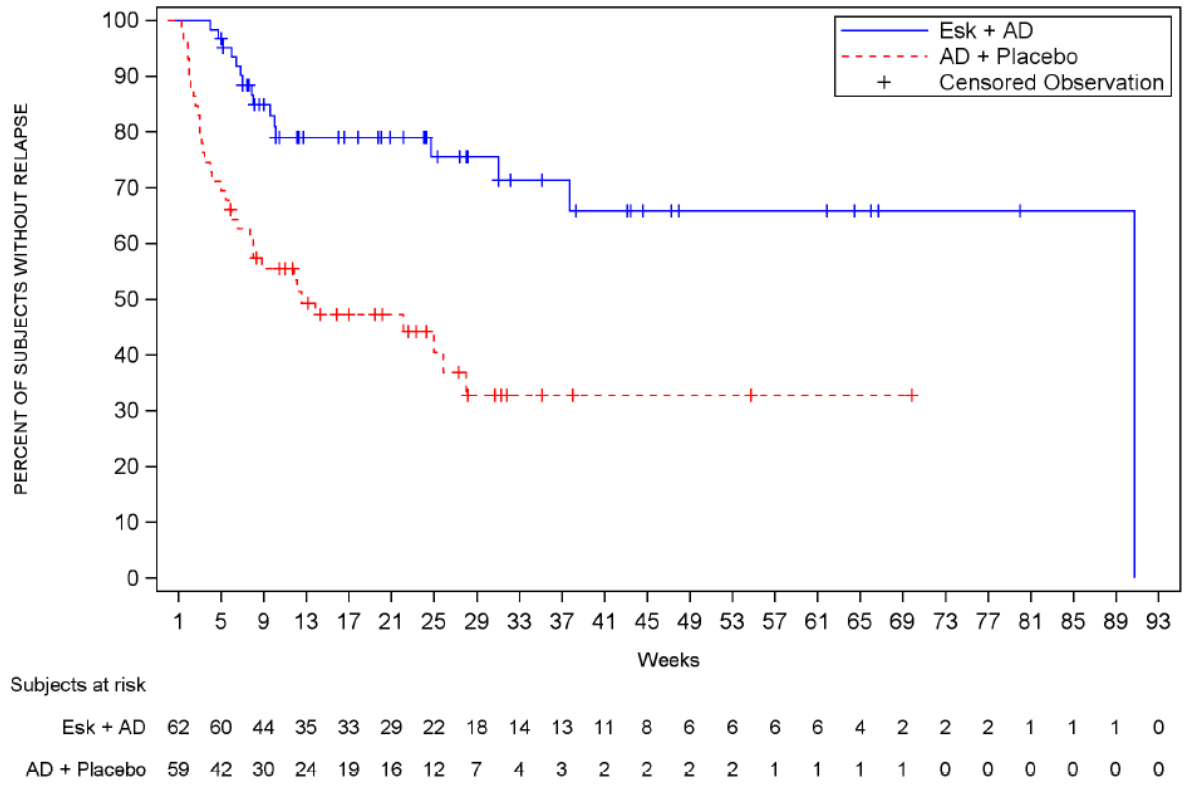
- The most common reason for relapse was MADRS total score ≥22 for two consecutive assessments (see Appendix N).

Table 28. Time to relapse and proportions of patients remaining relapse-free (full [stable responders] analysis set)

	ESK-NS + OAD N=62	OAD + PBO-NS N=59
Time to relapse (days)[a]		
Patients assessed, n (%)	62 (100.0)	59 (100.0)
Patients censored, n (%)	46 (74.2)	25 (42.4)
Relapses, n (%)	16 (25.8)	34 (57.6)
25th percentile (95% CI)	217.0 (56.0; 635.0)	24.0 (17.0; 46.0)
Median (95% CI)	635.0 (264.0; 635.0)	88.0 (46.0; 196.0)
75th percentile (95% CI)	635.0 (NE)	NE
HR (95% CI)[b]	0.30 (0.16; 0.55)	
2-sided p-value[c]	<0.001	

Abbreviations: CI, confidence interval; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; HR, hazard ratio; NE, not estimable; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray.
[a] Based on Kaplan-Meier product limit estimates.
[b] Regression analysis of survival data based on Cox proportional hazards model with treatment as a factor.
[c] Log-rank test.

Figure 17. Cumulative proportion of patients who remained relapse-free (full [stable responders] analysis set)



Abbreviations: AD, antidepressant; Esk, esketamine.

B.2.6.2.3.2 Change in MADRS, PHQ-9, and SDS total scores over the duration of the maintenance phase

- ESK-NS + OAD treatment significantly delayed worsening of symptoms during the maintenance phase versus OAD + PBO-NS based on mean changes over time in physician-reported MADRS, and patient-reported PHQ-9 and SDS total scores (in both remitter and responder patients; p≤0.025) (see Table 29).
- Overall, these results translate into improved maintenance of energy levels, appetite, mood, sleep, concentration, and social/occupational functioning with ongoing ESK-NS + OAD versus OAD + PBO-NS treatment.

B.2.6.2.3.3 Change in CGI-S and GAD-7 over the duration of the maintenance phase

Other secondary efficacy outcomes included change in CGI-S and GAD-7 over the duration of the maintenance phase, the results for which are presented in Table 29.

Table 29. Other secondary efficacy outcomes in SUSTAIN-1

	Full (stable remitters) analysis set N=176		Full (stable responders) analysis set N=121	
	ESK-NS + OAD N=90	OAD + PBO-NS N=86	ESK-NS + OAD N=62	OAD + PBO-NS N=59
Change in MADRS total score over the duration of the maintenance phase, LOCF				
N	89	86	62	59
Mean (SD) change	7.5 (11.59)	12.5 (13.63)	4.4 (11.38)	11.4 (12.00)
ANCOVA[a]				
Difference in LS means (SE)	–5.2 (1.82)	-	–7.4 (1.95)	-
95% CI	–8.7; –1.58	-	–11.30; –3.55	-
2-sided p-value[b]	0.005	-	<0.001	-
Change in PHQ-9 total score over the duration of the maintenance phase, LOCF				
N	89	86	61	58
Mean (SD) change	3.3 (5.58)	5.9 (7.09)	1.7 (5.02)	4.7 (5.48)
ANCOVA[a]				
Difference in LS means (SE)	–2.4 (0.90)	-	–3.0 (0.93)	-
95% CI	–4.20; –0.65	-	–4.87; –1.18	-
2-sided p-value[b]	0.008	-	0.002	-
Change in SDS total score over the duration of the maintenance phase, LOCF				
N	82	77	58	53
Mean (SD) change	4.7 (7.34)	7.2 (10.44)	2.2 (6.63)	6.8 (7.64)
ANCOVA[a]				
Difference in LS means (SE)	–2.9 (1.30)	-	–4.7 (1.31)	-
95% CI	–5.51; –0.38	-	–7.30; –2.10	-
2-sided p-value[b]	0.025	-	<0.001	-
Change in CGI-S total score over the duration of the maintenance phase, LOCF				
N	89	86	62	58
Median (range) change	0.0 (–3; 4)	1.0 (–2; 5)	0.0 (–2; 4)	1.0 (–3; 5)
ANCOVA[a]				
2-sided p-value	0.055	-	0.002	-
Change in GAD-7 total score over the duration of the maintenance phase, LOCF				
N	89	86	61	58
Mean (SD) change	2.2 (4.45)	4.0 (5.93)	1.4 (3.76)	2.6 (4.26)
ANCOVA[a]				
Difference in LS means (SE)	–1.7 (0.72)	-	–1.1 (0.72)	-
95% CI	–3.12; –0.28	-	–2.56; 0.31	-
2-sided p-value[b]	0.020	-	0.123	-

Abbreviations: ANCOVA; analysis of covariance; CGI-S, Clinical Global Impression – Severity; CI, confidence interval; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; GAD-7, Generalised Anxiety Disorder – 7-item scale; LOCF, last observation carried forward; LS, least squares; MADRS, Montgomery-Asberg Depression Rating Scale; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; PHQ-9, Patient Health Questionnaire – 9 questions; SD, standard deviation; SDS, Sheehan Disability Scale; SE, standard error.

[a] Change from baseline was the response variable and treatment, country, and baseline value were covariates.

[b] p-value is descriptive and not inferential as there was no multiplicity adjustment to control for type I error for this endpoint.

B.2.6.2.3.4 Response and remission rates over the duration of the maintenance phase based on MADRS, PHQ-9, and SDS

Based on MADRS, PHQ-9 and SDS definitions, the proportions of patients in stable remission and stable response, who had maintained their remitter/responder status by the end of the maintenance phase, were consistently higher among ESK-NS + OAD patients than OAD + PBO-NS (Table 30). Overall, the results of SUSTAIN-1 indicate sustained improvements in the physician-reported symptoms of depression (mood, tension, sleep, appetite, concentration, lassitude, and empathy) as well as in patient-reported depressive symptoms and functional impairment/disability.

Table 30. Response and remission rates over the duration of the maintenance phase based on MADRS, PHQ-9, and SDS (LOCF)

	Full (stable remitters) analysis set N=176		Full (stable responders) analysis set N=121	
	ESK-NS + OAD N=90	OAD + PBO-NS N=86	ESK-NS + OAD N=62	OAD + PBO-NS N=59
Response/remission based on MADRS, n/N (%)				
Responder at beginning of MA	90/90 (100.0)	86/86 (100.0)	62/62 (100.0)	59/59 (100.0)
Responder at end of MA	67/89 (75.3)	48/86 (55.8)	41/62 (66.1)	20/59 (33.9)
Remitter at beginning of MA	90/90 (100.0)	85/86 (98.8)	37/62 (59.7)	38/59 (64.4)
Remitter at end of MA	58/89 (65.2)	36/86 (41.9)	29/62 (46.8)	15/59 (25.4)
Response/remission based on PHQ-9, n/N (%)				
Responder at beginning of MA	88/90 (97.8)	86/86 (100.0)	60/62 (96.8)	56/59 (94.9)
Responder at end of MA	72/89 (80.9)	57/86 (66.3)	48/61 (78.7)	40/58 (69.0)
Remitter at beginning of MA	83/90 (92.2)	76/86 (88.4)	25/62 (40.3)	32/59 (54.2)
Remitter at end of MA	51/89 (57.3)	38/86 (44.2)	23/61 (37.7)	12/58 (20.7)
Response/remission based on SDS, n/N (%)				
Responder at beginning of MA	84/89 (94.4)	74/84 (88.1)	45/60 (75.0)	48/57 (84.2)
Responder at end of MA	58/83 (69.9)	43/78 (55.1)	42/60 (70.0)	23/53 (43.4)
Remitter at beginning of MA	72/89 (80.9)	63/84 (75.0)	28/60 (46.7)	30/57 (52.6)
Remitter at end of MA	48/83 (57.8)	30/78 (38.5)	25/60 (41.7)	11/53 (20.8)

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; LOCF, last observation carried forward; MA, maintenance phase; MADRS, Montgomery-Asberg Depression Rating Scale; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; PHQ-9, Patient Health Questionnaire – 9 questions; SDS, Sheehan Disability Scale.

B.2.6.2.3.5 EQ-5D-5L

- In both stable remitters and stable responders, those in the ESK-NS + OAD arm experienced smaller reductions in HRQoL (EQ-5D-5L HSI) compared with those in the OAD + PBO-NS arm over the duration of the maintenance phase (Table 31).

- Mean changes in EQ-5D-5L sum and EQ-VAS scores also favoured the ESK-NS + OAD over the OAD + PBO-NS arm in both the stable remitter and stable responder patient populations.

Table 31. EQ-5D HSI score: Change over the duration of the maintenance phase

	Full (stable remitters) analysis set N=176		Full (stable responders) analysis set N=121	
	ESK-NS + OAD N=90	**OAD + PBO-NS N=86**	**ESK-NS + OAD N=62**	**OAD + PBO-NS N=59**
Baseline (of maintenance phase)				
N	90	86	62	59
Mean (SD)	0.925 (0.0440)	0.918 (0.0422)	0.877 (0.0664)	0.875 (0.0796)
End of maintenance phase				
N	88	86	61	58
Mean (SD)	0.857 (0.1275)	0.822 (0.1442)	0.855 (0.0880)	0.802 (0.1292)
Change from baseline				
N	88	86	61	58
Mean (SD)	–0.067 (0.1180)	–0.096 (0.1484)	–0.023 (0.0753)	–0.073 (0.1383)

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; HSI, health status index; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; SD, standard deviation.

B.2.6.2.4 Subgroup analyses

Pre-planned subgroup analyses were performed on the subgroups listed in Table 8 (results presented in Appendix E) in which there were five or more patients (patient gender, race, age group, region, country, number of previous treatment failures in the current episode of depression, functional impairment [SDS at baseline of the induction phase], class of OAD [SNRI or SSRI], stable remission definition in protocol amendment 4 [yes/no; see Appendix M], revised stable responder definition in protocol amendment 4 [yes/no; see Appendix M], entry source [direct-entry/transferred-entry from TRANSFORM-1/2], and OAD). Each subgroup analysis consisted of a Cox regression of the time to relapse (days) during the maintenance phase among patients in stable remission receiving treatment with either ESK-NS + OAD or OAD + PBO-NS.

Patient demographics and disease characteristics for subgroups were not defined.

A forest plot representation of the subgroup analyses is provided in Appendix E.

- Results of the subgroup analyses were generally consistent with those observed in the full (stable remitters) analysis set, favouring ESK-NS + OAD treatment over OAD + PBO-NS in delaying the time to relapse in patients in remission (HR<1, favouring ESK-NS + OAD).
- In the majority of cases, subgroups were not identified that predicted a shorter or longer time to relapse, versus OAD + PBO-NS.
- Exceptions (HR>1) were in patients located in the Czech Republic (n=28), and in patients classified at induction phase baseline as having extreme functional impairment (SDS score: 27–30; n=47).
- The numbers of patients in some subgroups was small, generating wide confidence intervals that crossed the boundary of equivalence in some cases (HR=1); the results should therefore be interpreted with caution.

B.2.6.3 Conclusion: SUSTAIN-1, the relapse prevention study

- In SUSTAIN-1, maintenance treatment with ESK-NS + OAD significantly reduced relapse rates in patients with TRD aged 18–64 years.
  - Relapse rates were lower both in patients in stable remission and those in stable response who, at randomisation, continued ESK-NS + OAD compared with those who, at randomisation, continued the same OAD but switched to PBO-NS from ESK-NS.
- Ongoing ESK-NS + OAD treatment also significantly delayed worsening of symptom severity and functional impairment during the maintenance phase, based on mean changes over time in MADRS, SDS, and PHQ-9 total scores (in both stable remitter and responder patients).
- In a consistent manner, continuing ESK-NS + OAD treatment was associated with smaller deterioration in HRQoL (EQ-5D-5L HSI) over the duration of the maintenance phase, compared with those who continued their OAD but switched to PBO-NS.
- Importantly, as the patients in the comparator arm of SUSTAIN-1 had previously achieved stable remission with ESK-NS + OAD, the long-term treatment effect in the active comparator arm might not provide a true efficacy estimate of OADs in the maintenance phase of treatment as described further in Section B.2.13.2.7.

Overall, the SUSTAIN-1 data show that maintenance treatment with ESK-NS + OAD is associated with sustained improvement in patient social and occupational functioning and quality of life, which will have a positive impact on not only the patients themselves, but also their family, friends and carers.

B.2.7 Clinical effectiveness methods and results of supporting trials – TRANSFORM-1/3 and SUSTAIN-2

Supporting evidence is derived from two further Phase 3 trials in the acute setting (TRANSFORM-1 and TRANSFORM-3) and one Phase 3 trial in the maintenance phase (SUSTAIN-2). These studies are considered as non-pivotal to the decision problem, based on the dosing posology, population, or study design employed.

- Overall, the results of the supporting trials support those of the pivotal trials, demonstrating that ESK-NS plus a newly initiated OAD helps patients with TRD improve depression symptoms, function and quality of life which are then sustained in the long term.

B.2.7.1 TRANSFORM-1

TRANSFORM-1 was a 4-week, randomised, double-blind, active-controlled, multicentre, Phase 3 trial that enrolled adult patients (aged 18–64 years) with recurrent or single-episode TRD (non-response to ≥1 but ≤5 OADs in the current episode of depression). Beginning from the 4-week induction phase, enrolled patients (N=346) were randomised 1:1:1 to receive:

- ESK-NS (56 mg [fixed dose[2]]) plus a newly initiated OAD twice weekly for 4 weeks (n=117)
- ESK-NS (84 mg [fixed dose]) plus a newly initiated OAD twice weekly for 4 weeks[3] (n=116)
- A newly initiated OAD plus PBO-NS twice weekly for 4 weeks (OAD + PBO-NS; n=113).

The primary efficacy outcome in TRANSFORM-1 was the change in MADRS total score from baseline to the end of induction.

A summary of the TRANSFORM-1 data is presented in Table 32.

[2] Not in line with the anticipated licensed dosing for esketamine nasal spray which is for flexible dosing of esketamine nasal spray.
[3] Patients randomised to receive the 84 mg esketamine dose were started at Day 1 on 56 mg before increasing to 84 mg at Day 4.

Complete details of TRANSFORM-1 methodology and results are provided in Appendix M and Appendix N, respectively.

Table 32. Summary of TRANSFORM-1 results

Endpoint	ESK-NS-56 + OAD N=115	ESK-NS-84 + OAD N=114	OAD + PBO-NS N=113
MADRS			
Mean (SD) CFB to Day 28 (OC)	–19.0 (13.86) (n=111)	–18.8 (14.12) (n=98)	–14.8 (15.07) (n=108)
Diff in LS means vs OAD + PBO-NS (95% CI; 1-sided p-value; MMRM)[a]	–4.1 (–7.67, –0.49; p=0.013)	–3.2 (–6.88, 0.45; p=0.044)	-
Mean (SD) CFB to the endpoint of induction (LOCF)	–18.3 (14.21) (n=115)	–17.4 (14.25) (n=113)	–14.3 (15.00) (n=113)
Diff in LS means vs OAD + PBO-NS (95% CI; 1-sided p-value; ANCOVA)[b]	–4.1 (–7.53, –0.60; p=0.011)	–2.0 (–5.52, 1.42; p=0.125)	-
Achieved onset of clinical response by Day 2 (24 hours), n/N (%)	12/115 (10.4)	10/114 (8.8)	2/113 (1.8)
Diff in response rate vs OAD + PBO-NS (1-sided p-value)[c]	8.90 (p=0.010)	6.76 (p=0.041)	-
OR (95% CI)	6.47 (1.38; 60.45)	5.34 (1.09; 50.91)	-
Achieved onset of clinical response by Day 8, n/N (%)	15/115 (13.0)	13/114 (11.4)	4/113 (3.5)
1-sided p-value vs OAD + PBO-NS[d]	p=0.005	p=0.009	-
OR (95% CI)	3.98 (1.28; 12.31)	3.83 (1.18; 12.44)	-
Responder (based on MADRS) at Day 28, n/N (%) (OC)	60/111 (54.1)	52/98 (53.1)	42/108 (38.9)
Responder (based on MADRS) at endpoint of induction, n/N (%) (LOCF)	61/115 (53.0)	54/113 (47.8)	42/113 (37.2)
Remitter (based on MADRS) at Day 28, n/N (%) (OC)	40/111 (36.0)	38/98 (38.8)	33/108 (30.6)
Remitter (based on MADRS) at endpoint of induction, n/N (%) (LOCF)	40/115 (34.8)	40/113 (35.4)	33/113 (29.2)
SDS			
Mean (SD) CFB to Day 28 (OC)	–11.0 (9.32) (n=88)	–11.1 (10.04) (n=87)	–8.4 (9.70) (n=90)
Diff in LS means vs OAD + PBO-NS (95% CI; 1-sided p-value; MMRM)[a]	–2.5 (–5.25, 0.20; p=0.036)	–2.2 (–4.91; 0.53; p=0.059)	-
Mean (SD) CFB to the endpoint of induction (LOCF)	–10.7 (9.39) (n=91)	–10.2 (10.00) (n=99)	–8.1 (9.57) (n=95)
Diff in LS means vs OAD + PBO-NS (95% CI; 1-sided p-value; ANCOVA)[b]	–2.7 (–5.33, –0.01; p=0.025)	–1.7 (–4.35, 0.85; p=0.095)	-
Responder (based on SDS) at Day 28, n/N (%)	36/90 (40.0)	35/87 (40.2)	35/92 (38.0)
Remitter (based on SDS) at Day 28, n/N (%)	29/90 (32.2)	26/87 (29.9)	19/92 (20.7)
PHQ-9			
Mean (SD) CFB to Day 28 (OC)	–11.0 (8.07) (n=110)	–11.7 (7.74) (n=99)	–9.1 (8.35) (n=108)
Diff in LS means vs OAD + PBO-NS (95% CI; 1-sided p-value; MMRM)[a]	–2.3 (–4.34, –0.31; p=0.012)	–2.2 (–4.26, –0.20; p=0.016)	-

Endpoint	ESK-NS-56 + OAD N=115	ESK-NS-84 + OAD N=114	OAD + PBO-NS N=113
Mean (SD) CFB to the endpoint of induction (LOCF)	–10.9 (8.26) (n=113)	–10.9 (7.81) (n=112)	–8.9 (8.37) (n=113)
Diff in LS means vs OAD + PBO-NS (95% CI; 1-sided p-value; ANCOVA)[b]	–2.5 (–4.53, –0.54; p=0.007)	–1.9 (–3.87, 0.08; p=0.031)	-
CGI-S			
Median (range) CFB to Day 28 (OC)	–2.0 (–5; 1) (n=109)	–2.0 (-5; 1) (n=98)	–1.0 (– 6; 3) (n=108)
1-sided p-value vs OAD + PBO-NS (ANCOVA)[b]	p=0.003	p=0.004	
Median (range) CFB to endpoint of induction (LOCF)	–2.0 (–5; 1) (n=115)	–2.0 (–5; 1) (n=113)	–1.0 (–6; 3) (n=113)
1-sided p-value vs OAD + PBO-NS (ANCOVA)[b]	p=0.006	p=0.021	-
OR (95% CrI) for improved CGI-S at endpoint of induction	3.2 (1.28; 8.14)	2.5 (1.01; 6.54)	-
GAD-7			
Mean (SD) CFB to Day 28 (OC)	–7.4 (5.93) (n=111)	–7.7 (5.72) (n=109)	–6.0 (6.01) (n=111)
Diff in LS means vs OAD + PBO-NS (95% CI; 1-sided p-value; ANCOVA)[b]	–1.5 (–2.81, –0.18; p=0.013)	–1.4 (–2.77, –0.12; p=0.016)	-
Mean (SD) CFB to endpoint of induction (LOCF)	–7.4 (5.94) (n=111)	–7.7 (5.72) (n=109)	–6.0 (6.01) (n=111)
Diff in LS means vs OAD + PBO-NS (95% CI; 1-sided p-value; ANCOVA)[b]	–1.5 (–2.84, –0.20; p=0.012)	–1.4 (–2.77, –0.12; p=0.016)	-
EQ-5D-5L			
Mean (SD) change in HSI from baseline to Day 28 (OC)	0.229 (0.2503) (n=109)	0.264 (0.2458) (n=99)	0.190 (0.2486) (n=108)
Mean (SD) change in HSI from baseline to endpoint of induction (LOCF)	0.224 (0.2481) (n=113)	0.243 (0.2395) (n=112)	0.181 (0.2495) (n=113)

Abbreviations: ANCOVA; analysis of covariance; CGI-S, Clinical Global Impression – Severity; CI, confidence interval; CrI, credible interval; EQ-5D-5L, EuroQol-5 Dimension-5 Level; ESK-NS-56 + OAD, esketamine nasal spray (56 mg [fixed dose]) plus a newly initiated oral antidepressant; ESK-NS-84 + OAD, esketamine nasal spray (84 mg [fixed dose]) plus a newly initiated oral antidepressant; GAD-7, Generalised Anxiety Disorder – 7-item scale; HSI, health status index; LS, least squares; MADRS, Montgomery-Asberg Depression Rating Scale; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; OR, odds ratio; PHQ-9, Patient Health Questionnaire – 9 questions; SD, standard deviation; SDS, Sheehan Disability Scale; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a] Change from baseline was the response variable and the fixed effect model terms for treatment (ESK-NS-56 + OAD, ESK-NS-84 + OAD, and OAD + PBO-NS), day, region, class of OAD (SNRI or SSRI), treatment-by-day, and baseline value were covariates.

[b] Change from baseline was the response variable and treatment, region, class of OAD (SNRI or SSRI), and baseline value were covariates.

[c] Fisher's exact test for mean score difference between treatments. Results are weighted estimates.

[d] Generalised Cochran-Mantel-Haenszel test for mean score difference between treatments adjusting for region and class of OAD (SNRI or SSRI).

B.2.7.2 TRANSFORM-3

TRANSFORM-3 was a 4-week, randomised, double-blind, active-controlled, multicentre, Phase 3 trial that enrolled adult patients (aged ≥65 years) with recurrent or single-episode TRD (non-response to ≥1 but ≤8 OADs in the current episode of

depression). Beginning from the 4-week induction phase, enrolled patients (N=138) were randomised 1:1 to receive:

- ESK-NS (flexibly-dosed: 28 mg, 56 mg, or 84 mg) plus a newly initiated OAD twice weekly for 4 weeks (n=72), or
- A newly initiated OAD + PBO-NS twice weekly for 4 weeks (n=66).

The primary efficacy outcome in TRANSFORM-3 was the change in MADRS total score from baseline to the end of induction. The primary and secondary efficacy results are presented in Table 33.

Complete details of TRANSFORM-3 methodology and results are provided in Appendix M and Appendix N, respectively.

Table 33. Summary of TRANSFORM-3 results

Endpoint	ESK-NS + OAD N=72	OAD + PBO-NS N=65
MADRS		
Mean (SD) CFB to Day 28 (OC) Diff in LS means vs PBO (95% CI; 1-sided p-value; MMRM)[a]	–10.0 (12.74) (n=63) –3.6 (–7.20, –0.07; p=0.029)	–6.3 (8.86) (n=60) -
Mean (SD) CFB to endpoint of induction (LOCF) Diff in LS means vs OAD + PBO-NS (95% CI; 1-sided p-value; ANCOVA)[b]	–9.3 (12.28) (n=71) –3.6 (–7.16, –0.03; p=0.026)	–5.6 (9.11) (n=64) -
Responder (based on MADRS) at Day 28, n/N (%) (OC)	17/63 (27.0)	8/60 (13.3)
Responder (based on MADRS) at endpoint of induction, n/N (%) (LOCF)	17/71 (23.9)	8/64 (12.5)
Remitter (based on MADRS) at Day 28, n/N (%) (OC)	11/63 (17.5)	4/60 (6.7)
Remitter (based on MADRS) at endpoint of induction, n/N (%) (LOCF)	11/71 (15.5)	4/64 (6.3)
SDS		
Mean (SD) CFB to Day 28 (OC) Diff in LS means vs OAD + PBO-NS (95% CI; 1-sided p-value; MMRM)[a]	–7.9 (n=29) –4.6 (–8.21, –0.94; p=0.007)	–3.4 (n=32) -
Mean (SD) CFB to the endpoint of induction (LOCF) Diff in LS means vs OAD + PBO-NS (95% CI; 1-sided p-value; ANCOVA)[b]	–6.7 (n=35) –2.8 (–6.39, 0.75; p=0.060)	–3.8 (n=36) -
Responder (based on SDS) at Day 28 of induction, n/N (%)	15/44 (34.1)	10/44 (22.7)
Remitter (based on SDS) at Day 28 of induction, n/N (%)	7/44 (15.9)	2/44 (4.5)
PHQ-9		
Mean (SD) CFB to Day 28 (OC) Diff in LS means vs OAD + PBO-NS (95% CI; 1-sided p-value; MMRM)[a]	–6.7 (n=64) –2.8 (–5.08, –0.48; p=0.009)	–3.9 (n=57) -
Mean (SD) CFB to the endpoint of induction (LOCF) Diff in LS means vs OAD + PBO-NS (95% CI; 1-sided p-value; ANCOVA)[a]	–6.7 (n=69) –2.7 (–5.02, –0.45; p=0.010)	–3.9 (n=61) -

Endpoint	ESK-NS + OAD N=72	OAD + PBO-NS N=65
CGI-S		
Median (range) CFB to Day 28 (OC) 1-sided p-value vs OAD + PBO-NS (ANCOVA)[b]	–1.0 (–4; 1) (n=64) 0.002	0.0 (–4, 1) (n=60) -
Median (range) CFB to endpoint of induction (LOCF) 1-sided p-value vs OAD + PBO-NS[e,f] OR (95% CrI) for improved CGI-S at endpoint of induction[g]	–1.0 (–4; 1) (n=71) <0.001 5.3 (1.85; 15.85)	0.0 (–4; 3) (n=65) - -
EQ-5D-5L		
Mean (SD) change in HSI from baseline to Day 28 (OC)	0.086 (0.2674) (n=65)	0.041 (0.2074) (n=59)
Mean (SD) change in HSI from baseline to end of induction (LOCF)	0.081 (0.2624) (n=70)	0.026 (0.2235) (n=64)

Abbreviations: ANCOVA, analysis of covariance; CFB, change from baseline; CGI-S, Clinical Global Impression – Severity; CI, confidence interval; CrI, credible interval; Diff, difference; EQ-5D-5L, EuroQol-5 Dimension-5 Level; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; HSI, health status index; LS, least squares; MADRS, Montgomery-Asberg Depression Rating Scale; MMRM, mixed-effects model using repeated measures; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; OC, observed cases; OR, odds ratio; PHQ-9, Patient Health Questionnaire – 9 questions; SD, standard deviation; SDS, Sheehan Disability Scale; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a] Change from baseline was the response variable and the fixed effect model terms for treatment (ESK-NS + OAD, OAD + PBO-NS), day, region, class of OAD (SNRI or SSRI), treatment-by-day, and baseline value were covariates.

[b] Change from baseline was the response variable and treatment (ESK-NS + OAD, OAD + PBO-NS), region, class of OAD (SNRI or SSRI), and baseline value were covariates.

Subgroup analysis by patient age group

A pre-specified subgroup analysis of TRANSFORM-3 patients by age group was conducted to assess the relative treatment efficacy of ESK-NS by age group (65–74 years versus ≥75 years).

- Among ESK-NS-treated patients, the change from baseline to Day 28 of induction in MADRS total score was –13.4 for patients aged 65–74 years and –5.8 for patients aged ≥75. For patients aged 65–74 years, the LS mean difference (95% CI) versus PBO-NS was –5.4 (–9.65, –1.24) and for patients aged ≥75, the LS mean difference (95% CI) was 2.0 (–8.45, 12.48).

The results showed that the response to ESK-NS treatment among patients aged 65–74 years was similar in magnitude to that observed in the younger patients (aged 18–64 years) enrolled in TRANSFORM-2. TRANSFORM-3 patients aged ≥75 years, on the other hand, exhibited a smaller mean treatment response, although it is important to note there were only 22 patients in this subgroup so the results should be interpreted with caution.

Given the similar relative treatment effects observed in adults aged 18–64 years (TRANSFORM-2) and adults aged 65–74 years (TRANSFORM-3), the data from TRANSFORM-2 alone can be considered representative of the full TRD population.

B.2.7.3 SUSTAIN-2

SUSTAIN-2 was a long-term (1-year), open-label, multicentre, Phase 3 safety trial that also reported efficacy data for ESK-NS. Enrolled patients were adults (aged ≥18 years; N=802) with recurrent or single-episode TRD (non-response to ≥2 OADs in the current episode of depression).

Patients received treatment with ESK-NS (flexibly-dosed: 28 mg [patients aged ≥65 years only], 56 mg, or 84 mg) plus a newly initiated OAD. Treatment frequency was twice weekly for 4 weeks during the induction phase (where applicable – see Appendix M for further details), reducing to once weekly for the first 4 weeks of the optimisation/maintenance phase, and thereafter individualised to once weekly or every other week depending on depression severity.

Efficacy outcomes assessed in SUSTAIN-2 included change over time in: MADRS, PHQ-9, CGI-S, GAD-7, EQ-5D-5L, and SDS, and response and remission rates over time based on MADRS and PHQ-9.

Complete details of SUSTAIN-2 methodology and a tabulated summary of results are provided in Appendix M and Appendix N, respectively.

- Overall, treatment with ESK-NS + OAD resulted in improvements during the 4-week induction phase in measures of depressive symptoms, their severity, and associated disability (MADRS, PHQ-9, SDS, CGI-S, GAD-7, and EQ-5D-5L), which were maintained over the duration of the 48-week optimisation/maintenance phase.
- Based on MADRS, 78.4% of patients achieved responder status by the end of the 4-week induction phase and 47.2% of patients achieved remission. At the end of the optimisation/maintenance phase, 76.5% of patients were responders and 58.2% were remitters.

B.2.7.4 Conclusion: TRANSFORM-1/3 and SUSTAIN-2 supporting studies

Across TRANSFORM-1 and TRANSFORM-3:

- Higher response and remission rates (MADRS, SDS) were achieved with ESK-NS + OAD versus OAD + PBO-NS.
- Improvements in patient-reported functional impairment and disability (SDS) and depressive symptom severity (PHQ-9) over the course of induction favoured the ESK-NS arms over OAD + PBO-NS.

In SUSTAIN-2, a non-comparative long-term study, ESK-NS + OAD resulted in improvements during the 4-week induction phase in depressive symptom severity, functional impairment and associated disability (MADRS, PHQ-9, SDS), which were maintained over the 48-week optimisation/maintenance phase. Interpretation of the clinical significance of the findings of the supporting studies is provided in Section B.2.13.

Overall, the results of the supporting trials, TRANSFORM-1/3 and SUSTAIN 2 corroborate those of the pivotal trials, demonstrating that treatment with ESK-NS plus a newly initiated OAD helps patients with TRD to improve depression symptoms, functioning, and quality of life, which are sustained in the long term.

B.2.8 Meta-analysis

No other trials besides TRANSFORM-1/2/3 and SUSTAIN-1/2 report on the short- and long-term (respectively) efficacy and safety of ESK-NS plus a newly initiated OAD for the treatment of patients with TRD. A meta-analysis of TRANSFORM-1 and TRANSFORM-2 results was not possible due to the mismatch in fixed versus flexible ESK-NS dosing between the two trials. Similarly, a meta-analysis of TRANSFORM-3 and TRANSFORM-2 results was not possible given the mismatch in ESK-NS dosing as well as the discrepancy in patient population mean ages. A meta-analysis of SUSTAIN-1 and SUSTAIN-2 results was also not possible due to differences in ESK-NS dosing, patient population mean ages, study outcomes, and the fact that SUSTAIN-2 did not have a PBO-NS active comparator arm.

B.2.9 Indirect and mixed treatment comparisons

A Bayesian NMA was conducted to assess the relative clinical efficacy of ESK-NS plus a newly initiated OAD versus the comparators identified in the NICE scope. Clinical trial heterogeneity in terms of overall study design, inclusion criteria, and patient population meant treatment comparisons could not be undertaken (in either acute or maintenance treatment settings).

Only by relaxing the criteria for inclusion in the NMA (see Section B.2.9.1) could limited acute treatment comparisons between ESK-NS and various comparators be made. The lack of long-term efficacy data for TRD treatments meant maintenance treatment comparisons were still not possible, even when observational studies were taken into consideration.

Simulating data to support evidence network generation was also explored, as was a matching adjusted treatment comparison (MAIC). Neither of these approaches were deemed appropriate to inform the cost-effectiveness analysis (CEA). Further details are provided in Appendix D (simulated data) and Appendix O (MAIC report).

Given that the acute treatment comparisons were not robust, they were only used to inform scenario analyses in the CEA, with the base case using an in-trial analysis of TRANSFORM-2 and comparing ESK-NS plus OAD with OAD alone. Accordingly, only a brief overview of the NMA methods and results is presented in Form B with full details provided in Appendix D.

B.2.9.1 Methodology

A summary of indirect comparisons considered in the NMA is presented in Table 34.

Table 34. Summary of the feasibility of indirect comparison for switch SSRI/SNRI and ESK-NS for each outcome

Comparator	CFB MADRS (4-6 week)	Response (4-6 week)	Response (4-8 week)	Remission (4-6 week)	Remission (4-8 week)	Discontinuations due to AEs (any follow-up)
Switch ECT	×	✓	✓	×	×	✓
Switch SSRI (fluoxetine) + AAP (olanzapine)	✓	×	✓	×	✓	✓
Switch AAP	✓	×	✓	×	✓	✓

Comparator	CFB MADRS (4-6 week)	Response (4-6 week)	Response (4-8 week)	Remission (4-6 week)	Remission (4-8 week)	Discontinuations due to AEs (any follow-up)
Switch tetracyclic (mirtazapine)	×	×	✓	×	✓	✓
Switch tricyclic antidepressant	×	×	×	×	×	✓
Augmentation tricyclic (nortriptyline) ± PBO	✓	×	✓	×	✓	✓
Augmentation SSRI/SNRI + lithium	✓	×	✓	×	✓	✓
Augmentation SSRI/SNRI + AAP	✓	×	✓	×	✓	✓
Augmentation SSRI/SNRI ± PBO	✓	×	✓	×	✓	✓

Abbreviations: AAP, atypical antipsychotic; AE, adverse event; CFB, change from baseline; ECT, electroconvulsive therapy; MADRS, Montgomery-Asberg Depression Rating Scale; PBO, placebo; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

A total of 19 trials, including TRANSFORM-2 (see Appendix D), reporting on comparators/outcomes of relevance to the NICE scope, were compatible for inclusion in a best-case scenario evidence network (see Section D.1.3.1.2 in Appendix D) which presents the connectivity of the trials but does not consider the reporting of specific outcomes within the trials. All 19 trials were identified during the initial acute treatment SLR.

Outcomes reported across the trials of the best-case scenario evidence network included:

- Change from baseline in MADRS total score (“CFB MADRS score”),
- Response rates based on MADRS (“MADRS response”),
- Remission rates based on MADRS (“MADRS remission”), and
- Discontinuations due to adverse events (AE)s.

Since key studies connecting to TRANSFORM-2 in the best-case scenario evidence network did not report MADRS response and remission rates at 4–6 weeks, evidence networks for these outcomes – key drivers of the cost-effectiveness analysis (CEA) – were not feasible. Only when the scope of the comparison was broadened to include 8-week data were evidence networks feasible as follows:

- CFB MADRS:

  - Base case (includes 3–4 week CFB data only, no variance imputation)
- MADRS response:
  - Base case (includes 4-week MADRS response data) **– not feasible**
  - Scenario 1 (includes MADRS or HAM-D response data at 4–6 weeks)
  - Scenario 2 (includes MADRS or HAM-D response data at 4–8 weeks)
- MADRS remission:
  - Base case (includes 4-week MADRS remission data) **– not feasible**
  - Scenario 1 (includes MADRS or HAM-D remission data at 4–8 weeks)
- Discontinuations due to AEs

B.2.9.2 Results

A robust NMA based on response and remission base case criteria (4-week MADRS response/remission data) was not possible. Overall, based on the relaxed criteria NMAs (MADRS response Scenario 1 and 2, and MADRS remission Scenario 1), ORs were consistently in favour of ESK-NS over every comparator in each outcome for which sufficient data were available to support NMA: change from baseline in MADRS total scores, and response and remission rates based on MADRS. The ORs were consistently in favour of ESK-NS, even when conservatively comparing over different induction period lengths. Patients were more likely to discontinue treatment with ESK-NS due to AEs relative to all comparators (AEs associated with ESK-NS typically occurred shortly after dosing, when patients were under the supervision of a healthcare professional, were transient, resolving on the same day, and reduced in frequency with repeated dosing).

Response and remission scenario analyses using adjusted OAD + PBO-NS data (to account for the therapeutic effect of frequent clinic visits) – as per the methodology described by Posternak and Zimmerman (86) (see Appendix D) – further increased the odds that ESK-NS plus OAD was superior over every comparator.

Table 35 and Table 36 present the ORs of achieving remission and response, respectively, based on both unadjusted and adjusted TRANSFORM-2 data.

NMA results, including outcome-specific evidence networks, details concerning fixed- versus random-effect model selection, and model fit statistics for the analyses undertaken are presented in Appendix D.

Table 35. NMA results – OR (95% CrI) for achieving remission

ESK-NS plus newly initiated OAD versus:	OR (95% CrI)	
	Unadjusted TRANSFORM-2 OAD+PBO-NS data	Adjusted TRANSFORM-2 OAD data
Newly initiated OAD	2.48 (1.39, 4.42)	5.13 (2.71, 9.90)
Switch tetracyclic (mirtazapine)	3.48 (1.40, 8.62)	7.21 (2.77, 18.78)
Aug tricyclic (nortrip) ± PBO	1.81 (0.68, 4.88)	3.76 (1.35, 10.64)
Aug SSRI/SNRI + lithium	1.89 (0.71, 5.11)	3.92 (1.42, 10.98)
Aug SSRI/SNRI + AAP	1.38 (0.54, 3.64)	2.89 (1.08, 7.83)
Switch SSRI + AAP	1.84 (0.77, 4.44)	3.83 (1.53, 9.67)
Aug SSRI/SNRI ± PBO	2.73 (1.05, 7.28)	5.69 (2.09, 15.63)

Abbreviations: AAP, atypical antipsychotic; Aug, augmentation; CrI, credible interval; nortrip, nortriptyline; OR, odds ratio; PBO, placebo; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Table 36. NMA results – OR (95% CrI) for achieving response

ESK-NS plus newly initiated OAD versus:	OR (95% CrI)	
	Unadjusted TRANSFORM-2 OAD+PBO-NS data	Adjusted TRANSFORM-2 OAD data
Newly initiated OAD	2.10 (1.19, 3.76)	4.44 (2.49, 8.10)
Switch tetracyclic (mirtazapine)	2.83 (1.15, 6.93)	6.00 (2.41, 14.89)
Aug tricyclic (nortrip) ± PBO	1.93 (0.83, 4.61)	4.09 (1.74, 9.81)
Aug SSRI/SNRI + lithium	3.66 (1.54, 9.01)	7.67 (3.24, 18.9)
Aug SSRI/SNRI + AAP	2.42 (1.04, 5.77)	5.06 (2.19, 12.08)
Switch SSRI + AAP	2.28 (1.07, 4.94)	4.81 (2.24, 10.58)
Aug SSRI/SNRI ± PBO	4.63 (1.96, 11.18)	9.68 (4.12, 23.52)
Aug tricyclic (nortrip) ± lithium	3.58 (0.40, 40.57)	7.57 (0.82, 86.06)
Switch ECT	1.24 (0.03, 21.90)	2.64 (0.07, 46.85)

Abbreviations: AAP, atypical antipsychotic; Aug, augmentation; CrI, credible interval; nortrip, nortriptyline; OR, odds ratio; PBO, placebo; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

B.2.9.3 Uncertainties in the indirect and mixed treatment comparisons

Given the lack of studies providing MADRS-based, 4-week efficacy data in patients with TRD treated with interventions of relevance to the NICE scope, a robust NMA was not possible. The NMA conducted with relaxed criteria (that is, 4–8 week efficacy timepoints and HAM-D scores converted to MADRS) is associated with limitations and uncertainties meaning that the results should be interpreted with caution. The main factors contributing to uncertainty in the NMA included:

- Combining 4–8 week time-points since the trial data in TRD suggests that relative treatment effects are not constant from 4 weeks onwards but change over time.

- Combining two different scales (MADRS and HAM-D) compounded with the variability in response/remission definitions across the trials (e.g., remission based on MADRS was inconsistently defined as ≤12, ≤10, and ≤8).
- Systematic differences in common comparator treatment arms – the inclusion of TRANSFORM-2 relied on a switch SSRI/SNRI ± placebo node. Trial arms connecting via this node, however, were mostly 'switch SSRI.' Only a single trial in addition to TRANSFORM-2 was 'switch SSRI/SNRI.'

B.2.10 Adverse reactions

For the purposes of marketing authorisation, the safety profile for ESK-NS has been well characterised based on 1,045 patient-years of treatment across the TRANSFORM-1/2/3 and SUSTAIN-1/2 Phase 3 trials (as well as a Phase 2 dose-finding study ESKETINTRD2003). Interim data are also available from the ongoing SUSTAIN-3 Phase 3 trial.

These studies demonstrate that ESK-NS is well tolerated with manageable risks.

When taken in the proposed therapeutic dose range for ESK-NS for TRD (28–84 mg), most TEAEs in the ESK-NS + OAD arm occurred shortly after dosing, when patients were under the supervision of a healthcare professional, were transient, resolved on the same day, and attenuated in frequency with repeated dosing. In clinical practice, most AEs will be managed within the post-administration observation period mandated by the (draft) SmPC, which states that "…at each treatment session, patients should be monitored under the supervision of a healthcare professional to assess when the patient is considered stable based on clinical judgement."

Low incidence of TEAEs leading to treatment discontinuation reflects the manageable safety profile – in TRANSFORM-2, 7.0% of patients in the ESK-NS + OAD arm [0.9% in the OAD + PBO-NS arm] had nasal spray treatment withdrawn due to TEAEs.

In the pivotal acute treatment trial, TRANSFORM-2, the most commonly reported TEAEs (incidence: ≥10% of patients) with ESK-NS + OAD included dissociation, nausea, vertigo, dysgeusia, dizziness, headache, somnolence, vision blurred, paraesthesia, and anxiety. Only three patients experienced a SAE during the study (two in the ESK-NS + OAD arm and one in the OAD + PBO-NS arm), none of which were possibly, probably, or very likely related to treatment.

Longer-term exposure in the open-label maintenance trial, SUSTAIN-2 (up to 1 year), and in the ongoing open-label maintenance trial, SUSTAIN-3 (mean 13.7 months), yielded no new safety issues.

Among the 1,861 patients treated with ESK-NS across the six Phase 2 and 3 studies, a total of seven deaths have been reported, three of which were completed suicides. Based on the severity of patients' underlying illness, and the lack of a consistent pattern, the suicides were considered unrelated to ESK-NS treatment.

Overall, it is anticipated that ESK-NS will have an acceptable, recognisable, and manageable safety profile when used in clinical practice.

For the purposes of the marketing authorisation application, the clinical development programme for ESK-NS in TRD (Phases I, II, and III) has provided safety data from more than 2,300 healthy patients and patients. The main safety analysis set for marketing authorisation consists of 1,045 patient-years of exposure to ESK-NS from six Phase 3 studies (TRANSFORM-1/2/3, SUSTAIN-1/2/3[4]) and one Phase 2 study (ESKETINTRD2003; (115)).

The AE data presented in Section B.2.10.1 are taken from TRANSFORM-2 and SUSTAIN-1 since these are the Phase 3 studies of most relevance to the decision problem and were used to inform the economic model. Safety data for the other ESK-NS Phase 3 trials were similar with that of TRANSFORM-2 and SUSTAIN-1.

The safety overview provided in Section B.2.10.3 includes reference to the broader safety set used to support marketing authorisation, including SUSTAIN-2, as well to the ongoing SUSTAIN-3 study, both of which are dedicated open-label, long-term, safety studies. The Phase 2 study (ESKETINTRD2003) is included in the overview since it contributes to the overall safety profile for marketing authorisation; however, given the availability of Phase 3 studies and subsequent use of these studies to inform economic modelling, the Phase 2 study has not been reported in Section B.2.2 nor in further detail elsewhere in the submission.

[4] Based on interim data from SUSTAIN-3 which is ongoing.

B.2.10.1 Studies identified in Section 2.2

B.2.10.1.1 TRANSFORM-2

An overall summary of AEs reported during the double-blind induction and follow-up phases of TRANSFORM-2 is presented in Table 37. A summary of AEs reported in at least 5% of patients in either trial arm during the induction phase is presented in Table 38. Note that unless otherwise stated, all AEs were treatment-emergent.

Table 37. Overall summary of AEs reported during the induction (safety analysis set) and follow-up (follow-up analysis set) phases of TRANSFORM-2

	ESK-NS + OAD	OAD + PBO-NS
Induction phase, n (%)	**N=115**	**N=109**
AE	98 (85.2)	66 (60.6)
AE possibly related to nasal spray drug[a]	90 (78.3)	39 (35.8)
AE possibly related to OAD[a]	39 (33.9)	26 (23.9)
AE leading to death	1 (0.9)	0
≥1 serious AE	1 (0.9)	1 (0.9)
AE leading to nasal spray drug being withdrawn[b]	8 (7.0)	1 (0.9)
AE leading to OAD being withdrawn[b]	4 (3.5)	0
Follow-up phase, n (%)	**N=34**	**N=52**
AE	9 (26.5)	12 (23.1)
AE possibly related to nasal spray drug[a]	0	1 (1.9)
AE possibly related to OAD[a]	1 (2.9)	3 (5.8)
AE leading to death	0	0
≥1 serious AE	1 (2.9)	0
AE leading to OAD being withdrawn[b]	0	0

Abbreviations: AE, adverse event; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; MedDRA, Medical Dictionary for Regulatory Activities; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray.
[a] Study drug relationships of possible, probable, and very likely were included in this category.
[b] An AE that started in the double-blind induction phase and resulted in discontinuation in the follow-up phase was counted as treatment-emergent in the double-blind induction phase.
Note: Incidence was based on the number of patients experiencing ≥1 AE, not the number of events.
Note: AEs were coded using MedDRA version 20.0.

Table 38. AEs reported in ≥5% of patients (safety analysis set) during the induction phase of TRANSFORM-2

	ESK-NS + OAD (N=115)	OAD + PBO-NS (N=109)
Total number of patients with an AE, n (%)	98 (85.2)	66 (60.6)
Nervous system disorders, n (%)	72 (62.6)	39 (35.8)
Dysgeusia	28 (24.3)	13 (11.9)
Dizziness	24 (20.9)	5 (4.6)
Headache	23 (20.0)	19 (17.4)
Somnolence	15 (13.0)	7 (6.4)
Paraesthesia	13 (11.3)	1 (0.9)
Dizziness postural	8 (7.0)	1 (0.9)

	ESK-NS + OAD (N=115)	OAD + PBO-NS (N=109)
Hypoaesthesia	8 (7.0)	1 (0.9)
Psychiatric disorders, n (%)	55 (47.8)	21 (19.3)
Dissociation[a]	30 (26.1)	4 (3.7)
Anxiety	12 (10.4)	5 (4.6)
Insomnia	11 (9.6)	5 (4.6)
Gastrointestinal disorders, n (%)	52 (42.5)	26 (23.9)
Nausea	30 (26.1)	7 (6.4)
Vomiting	11 (9.6)	2 (1.8)
Diarrhoea	10 (8.7)	10 (9.2)
Dry mouth	9 (7.8)	3 (2.8)
Hypoaesthesia oral	9 (7.8)	1 (0.9)
Paraesthesia oral	9 (7.8)	1 (0.9)
Ear and labyrinth disorders, n (%)	34 (29.6)	6 (5.5)
Vertigo	30 (26.1)	3 (2.8)
General disorders and administration site conditions, n (%)	30 (26.1)	13 (11.9)
Feeling drunk	9 (7.8)	1 (0.9)
Fatigue	5 (4.3)	6 (5.5)
Respiratory, thoracic and mediastinal disorders, n (%)	24 (20.9)	15 (13.8)
Throat irritation	9 (7.8)	5 (4.6)
Nasal discomfort	8 (7.0)	2 (1.8)
Eye disorders, n (%)	18 (15.7)	3 (2.8)
Vision blurred	14 (12.2)	3 (2.8)
Investigations, n (%)	14 (12.2)	4 (3.7)
Blood pressure increased	11 (9.6)	0

Abbreviations: AE, adverse event; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; MedDRA, Medical Dictionary for Regulatory Activities; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray.

[redacted]

Note: Incidence was based on the number of patients experiencing ≥1 AE, not the number of events.
Note: AEs were coded using MedDRA version 20.0.

B.2.10.1.2 SUSTAIN-1

An overall summary of AEs reported during the induction, optimisation, and maintenance phases of SUSTAIN-1 is presented in Table 39. A summary of AEs reported in at least 5% of patients during each phase of SUSTAIN-1 is presented in Table 40.

Note that during the induction and optimisation phases of SUSTAIN-1, all patients received ESK-NS plus an OAD. It was only at the beginning of the maintenance phase that patients were randomised 1:1 to either continue ESK-NS + OAD or switch (double-blind) to OAD + PBO-NS.

Table 39. Overall summary of AEs reported during the induction, optimisation, maintenance (safety analysis set), and follow-up phases (follow-up analysis set) of SUSTAIN-1

	Induction phase	Optimisation phase	Maintenance phase		Follow-up phase	
	ESK-NS + OAD (N=437)	ESK-NS + OAD (N=455)	ESK-NS + OAD (N=152)	OAD + PBO-NS (N=145)	ESK-NS + OAD during any phase (N=481)	OAD + PBO-NS for all phases (N=64)
AE, n (%)	336 (76.9)	335 (73.6)	125 (82.2)	66 (45.5)	53 (11.0)	5 (7.8)
AE possibly related to nasal spray drug, n (%)[a]	301 (68.9)	281 (61.8)	106 (69.7)	37 (25.5)	7 (1.5)	0
AE possibly related to OAD, n (%)[a]	71 (16.2)	61 (13.4)	13 (8.6)	9 (6.2)	3 (0.6)	0
AE leading to death, n (%)	0	0	0	0	0	0
≥1 serious AE, n (%)	13 (3.0)	11 (2.4)	4 (2.6)	1 (0.7)	3 (0.6)	0
AE leading to nasal spray drug being withdrawn, n (%)	22 (5.0)	5 (1.1)	4 (2.6)	3 (2.1)	NA[b]	NA[b]
AE leading to OAD being withdrawn, n (%)[c]	8 (1.8)	2 (0.4)	3 (2.0)	0	0[c]	0[c]

Abbreviations: AE, adverse event; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; MedDRA, Medical Dictionary for Regulatory Activities; NA, not applicable; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray.
[a] Study drug relationships of possible, probable, and very likely were included in this category.
[b] Patients did not receive nasal spray during the follow-up phase.
[c] An AE that started in the induction phase and resulted in discontinuation in a subsequent phase was counted as treatment-emergent in the induction phase.
Note: Incidence was based on the number of patients experiencing ≥1 AE, not the number of events.
Note: AEs were coded using MedDRA version 20.0.

Table 40. AEs reported in ≥5% of patients by SUSTAIN-1 study phase

	ESK-NS + OAD	OAD + PBO-NS
Induction phase (Safety [IND] analysis set)	**N=437**	**NA**
Total number of patients with an AE, n (%)	336 (76.9)	-
Nervous system disorders, n (%)	248 (56.8)	-
Dizziness	97 (22.2)	-
Dysgeusia	90 (20.6)	-
Somnolence	65 (14.9)	-
Headache	60 (13.7)	-
Paraesthesia	48 (11.0)	-
Sedation	44 (10.1)	-
Dizziness postural	33 (7.6)	-
Hypoaesthesia	30 (6.9)	-
Psychiatric disorders, n (%)	163 (37.3)	-
Dissociation	82 (18.8)	-
Anxiety	31 (7.1)	-
Gastrointestinal disorders, n (%)	150 (34.3)	-
Nausea	94 (21.5)	-
Hypoaesthesia oral	32 (7.3)	-
Vomiting	29 (6.6)	-
Ear and labyrinth disorders, n (%)	108 (24.7)	-
Vertigo	99 (22.7)	-
Respiratory, thoracic and mediastinal disorders, n (%)	88 (20.1)	-
Nasal discomfort	29 (6.6)	-
Throat irritation	26 (5.9)	-
Eye disorders, n (%)	63 (14.4)	-
Vision blurred	45 (10.3)	-
Investigations, n (%)	42 (9.6)	-
Blood pressure increased	34 (7.8)	-
Optimisation phase (Safety [OP] analysis set)	**N=455**	**NA**
Total number of patients with an AE, n (%)	335 (73.6)	-
Nervous system disorders, n (%)	212 (46.6)	-
Dysgeusia	79 (17.4)	-
Somnolence	63 (13.8)	-
Dizziness	61 (13.4)	-
Headache	57 (12.5)	-
Dizziness postural	26 (5.7)	
Hypoaesthesia	24 (5.3)	-
Paraesthesia	24 (5.3)	-
Psychiatric disorders, n (%)	136 (29.9)	-
Dissociation	73 (16.0)	-
Gastrointestinal disorders, n (%)	116 (25.5)	-
Nausea	48 (10.5)	-
Hypoaesthesia oral	34 (7.5)	-
Ear and labyrinth disorders, n (%)	101 (22.2)	-
Vertigo	91 (20.0)	-
Respiratory, thoracic and mediastinal disorders, n (%)	73 (16.0)	-
Nasal discomfort	26 (5.7)	-
Investigations, n (%)	47 (10.3)	-

	ESK-NS + OAD	OAD + PBO-NS
Blood pressure increased	26 (5.7)	-
Eye disorders, n (%)	46 (10.1)	-
Vision blurred	30 (6.6)	-
Maintenance phase (Safety [MA] analysis set)	**N=152**	**N=145**
Total number of patients with an AE, n (%)	125 (82.2)	66 (45.5)
Nervous system disorders, n (%)	83 (54.6)	30 (20.7)
Dysgeusia	41 (27.0)	10 (6.9)
Somnolence	32 (21.1)	3 (2.1)
Dizziness	31 (20.4)	7 (4.8)
Headache	27 (17.8)	14 (9.7)
Paraesthesia	11 (7.2)	0
Dizziness postural	10 (6.6)	3 (2.1)
Sedation	10 (6.6)	1 (0.7)
Hypoaesthesia	9 (5.9)	0
Psychiatric disorders, n (%)	60 (39.5)	15 (10.3)
Dissociation	35 (23.0)	0
Anxiety	12 (7.9)	5 (3.4)
Confusional state	9 (5.9)	0
Gastrointestinal disorders, n (%)	53 (34.9)	11 (7.6)
Nausea	25 (16.4)	1 (0.7)
Hypoaesthesia oral	20 (13.2)	0
Vomiting	10 (6.6)	1 (0.7)
Paraesthesia oral	8 (5.3)	1 (0.7)
Ear and labyrinth disorders, n (%)	43 (28.3)	9 (6.2)
Vertigo	38 (25.0)	8 (5.5)
Eye disorders, n (%)	32 (21.1)	1 (0.7)
Vision blurred	24 (15.8)	1 (0.7)
Diplopia	9 (5.9)	0
Infections and infestations, n (%)	32 (21.1)	25 (17.2)
Viral upper respiratory tract infection	11 (7.2)	12 (8.3)
Respiratory, thoracic and mediastinal disorders, n (%)	29 (19.1)	11 (7.6)
Nasal discomfort	11 (7.2)	4 (2.8)
Throat irritation	8 (5.3)	1 (0.7)
Investigations, n (%)	19 (12.5)	10 (6.9)
Blood pressure increased	10 (6.6)	5 (3.4)

Abbreviations: AE, adverse event; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; IND, induction; MA, maintenance phase; MedDRA, Medical Dictionary for Regulatory Activities; NA, not applicable; OP, optimisation phase; OAD + PBO-NS, newly initiated oral antidepressant placebo nasal spray.
Note: Incidence was based on the number of patients experiencing ≥1 AE, not the number of events.
Note: AEs were coded using MedDRA version 20.0.

B.2.10.2 Additional studies

There are no additional studies beside those identified/discussed in Section B.2.2 and in the safety overview in B.2.10.3 that provide safety data for ESK-NS.

B.2.10.3 Safety overview

Based on the overall clinical trial programme for ESK-NS and evidence submitted for marketing authorisation, key safety observations for ESK-NS are outlined below.

Overall safety profile

- Over the proposed ESK-NS therapeutic dose range for use in TRD (28, 56, or 84 mg), most AEs occurred shortly after dosing, when patients were under the supervision of a healthcare professional. In clinical practice, most AEs will be managed within the post-administration observation period mandated by the (draft) SmPC, which states that "…at each treatment session, patients should be monitored under the supervision of a healthcare professional to assess when the patient is considered stable based on clinical judgement."
- Reported AEs were transient, resolved on the same day (within the observation period), were consistent with the findings from Phase 1 and Phase 2a esketamine intravenous studies and expected based on the pharmacological profile. Furthermore, the frequency of AEs reported reduced with repeated doses of ESK-NS. No new safety concerns associated with ESK-NS were identified in the Phase 2 and 3 studies (ESKETINTRD2003, TRANSFORM-1/2/3, SUSTAIN-1/2/3).
- In the long-term open-label safety study, SUSTAIN-2, in which ESK-NS was administered continuously to patients for up to 1 year, no new AEs were reported. Similarly, an interim analysis from the ongoing open-label safety study, SUSTAIN-3 (See Section B.2.11 for further details), revealed no unexpected safety findings after a mean treatment exposure of 13.7 months, with a safety and tolerability profile that is consistent with the previous Phase 3 clinical studies.

Common AEs

- Among the completed Phase 2 and 3 ESK-NS trials, the most commonly observed AEs in patients with TRD treated with ESK-NS + OAD arm (incidence ≥10% and higher than that reported in the corresponding OAD + PBO-NS arm) were dissociation, dizziness, nausea, sedation, headache, vertigo, dysgeusia, hypoaesthesia, blood pressure increased, anxiety, and vomiting.

Serious AEs

- In the completed Phase 3 studies, serious AEs were reported at low rates in the ESK-NS + OAD arm (≤6.9%) and OAD + PBO-NS arm (≤3.1%) arms (where applicable).
- The most frequent serious AEs in ESK-NS-treated patients across the completed Phase 3 studies were in the MedDRA SOC psychiatric disorders and were associated with the patient's underlying disease state.

Specific AEs

Nasal tolerability

- Nasal tolerability of ESK-NS was acceptable, and objective evaluations showed no impact on sense of smell.

Changes in blood pressure

- There is a well-established link between ketamine exposure and haemodynamic changes (elevated blood pressure and pulse rate) (116).
- Transient increases in blood pressure were observed following administration of ESK-NS, peaking at 40 minutes post-dose (consistent with peak plasma elevations), and returning to (or close to) pre-treatment levels within 1.5 hours post-dose.
- Blood pressure increases did not appreciably attenuate with continued ESK-NS use; however, they seldom required intervention and were not associated with any adverse clinical outcomes.
- Few patients discontinued ESK-NS treatment owing to increased blood pressure.

Cognition

- During Phase I testing, a single 84 mg dose of ESK-NS given to healthy patients was associated with an early transient decline in cognitive function.
- In the acute treatment trials (TRANSFORM-1/2/3), treatment with ESK-NS did not influence any aspect of cognition evaluated in adult patients with TRD and was not associated with any systematic changes in cognition in elderly patients.

- In SUSTAIN-2, overall group mean performance on multiple cognitive domains, including visual learning and memory as well as spatial memory/executive function, either improved or remained stable post-baseline in adult patients.
- In the subset of elderly patients (≥65 years) enrolled in SUSTAIN-2, a slowing of reaction time was observed starting at Week 20 through to the end of the study; however, this appeared to represent an isolated observation related to processing speed and not a broad attentional impairment.
- Performance on all other cognitive tests remained stable in elderly patients in SUSTAIN-2.

Dissociation/perceptual changes

- Administration of subanaesthetic doses of ketamine are associated with transient, dose-related dissociation/perceptual changes (117).
- Consistent with the observation of peak plasma esketamine levels at approximately 40 minutes after dose administration, dissociative/perceptual changes captured using the Clinician-Administered Dissociated States Scale (CADSS) had an onset shortly after the start of the dose, peaked by 40 minutes post-dose, and typically resolved within 1.5 hours.
- Reported AEs associated with these symptoms were mostly transient, resolved on the day of dosing, generally attenuated with repeated dosing, and only infrequently were severe (<4%) or resulted in ESK-NS discontinuation (0.4%).
- Dissociative symptoms/perceptual changes and dizziness/vertigo attenuated with subsequent ESK-NS treatments.

Suicidal ideation and behaviour

- There is no evidence to suggest that ESK-NS is associated with increased risk of suicidal ideation and behaviour.
- Across the 346 patients treated with ESK-NS in the three Phase 3 acute treatment trials (TRANSFORM-1/2/3), the overall incidence of specific AEs of suicidal ideation and intentional self-injury was 0.6% and 0.3%, respectively.
- In a meta-analysis of controlled studies of antidepressant drugs (N=10,927 patients), the reported rates of suicidal ideation and suicide attempt/intentional self-injury were 0.39% and 0.38%, respectively (118).

Potential for abuse

- While the potential for abuse, misuse, and diversion exists for ESK-NS due to its similar pharmacologic profile to ketamine, there were no reports of overdose, drug abuse, or confirmed diversion of drug product across the clinical development programme.
- Product labelling for ESK-NS, and several features of the single-use disposable nasal spray and limited pack sizes, together with administration under the supervision of a healthcare professional, and legal controls (e.g. restrictions on storage, delivery of the product directly to the site of care) will mitigate the risk for abuse and misuse of this product.

Specific AEs that were absent

- Notably absent in the clinical studies with ESK-NS were respiratory depression, QT interval prolongation (a measure of cardiac repolarisation/electrophysiology), development of psychotic-like symptoms or mania, interstitial or ulcerative cystitis, treatment-emergent hepatotoxicity, and clinically significant body weight gain, all of which in the literature had been found to be associated with either ketamine exposure or OAD use (119-122).

Discontinuations

- Discontinuation of ESK-NS treatment due to AEs was uncommon across all clinical studies and tended to be highest early in the course of treatment. In SUSTAIN-2, where ESK-NS treatment was administered for up to 1 year, <10% of patients experienced AEs necessitating discontinuation of ESK-NS. In the interim analysis of SUSTAIN-3, where ESK-NS treatment was administered for a mean of 13.7 months up to 1 year, 4.1% of patients experienced AEs necessitating discontinuation of ESK-NS.

Deaths

- A total of seven deaths were reported among the 1,861 patients treated with ESK-NS across the six Phase 2 and 3 studies (i.e. including interim safety data from SUSTAIN-3), three of which were completed suicides. Based on the severity of patients' underlying illness, and the lack of a consistent pattern, the suicides were considered unrelated to ESK-NS treatment.

- The overall mortality rate and rate of completed suicide in ESK-NS-treated patients was comparable with those reported in a meta-analysis of 70 controlled studies of OADs (118).

Conclusion

Pivotal safety data supporting the marketing authorisation application is available from 1,045 patient-years of exposure to ESK-NS over the course of six Phase 2 and III studies. Over the proposed ESK-NS therapeutic dose range for use in TRD (28, 56, or 84 mg), ESK-NS is well tolerated with most AEs occurring shortly after dosing (when patients are still under the supervision of a healthcare professional) and resolving on the same day.

B.2.11 Ongoing studies

A long-term safety study of ESK-NS in patients with TRD (ESKETINTRD3008 [SUSTAIN-3]) is ongoing, from which an interim safety analysis is available (Data cut-off 31 December 2018) (89).

The study is a multicentre, long-term extension study to evaluate the safety, tolerability, and efficacy of flexibly-dosed ESK-NS in patients with TRD. The study population includes adult and elderly men and women who previously participated in completed or ongoing trials, including TRANSFORM-1/2/3, SUSTAIN-1/2. The interim analysis provides data from 1,140 patients treated for a mean of 13.7 months. As described in Section B.2.10.3, the interim analysis has revealed no unexpected safety findings, with a safety and tolerability profile that is consistent with the previous Phase 3 clinical studies.

SUSTAIN-3 is expected to complete in Q3 2021, when final safety and efficacy data will be available.

B.2.12 Innovation

ESK-NS represents a step-change in the management of patients with TRD. If recommended by NICE, ESK-NS will become the first new mode of action antidepressant in England in 30 years and the first antidepressant treatment available that is specifically indicated for patients with TRD.

The positive impact of ESK-NS treatment on outcomes of patients with TRD will potentially enable patients to return to work or other normal activities of daily living. This will in turn have a positive impact on the patient's families, friends and carers, boosting their productivity to incur a wider societal benefit.

B.2.12.1 ESK-NS is recognised as an innovative, breakthrough therapy

ESK-NS has received two breakthrough therapy designations from the FDA in the US – in November 2013 for TRD, and in August 2016 for the indication of MDD with imminent risk for suicide. ESK-NS also received a Promising Innovative Medicine (PIM) designation from the MHRA in October 2018 based on the upcoming indication for the treatment of symptoms of MDD in adults at imminent risk for suicide. A PIM designation is granted to medicines that are not yet licensed but for which there is a clear unmet medical need and a positive signal of safety and efficacy. Additionally, in May 2019, ESK-NS was granted a new and specific ATC code under the antidepressant category (N06AX27) by WHO. This decision reflects the recognition of ESK-NS as a new therapeutic class of antidepressant.

B.2.12.2 ESK-NS has a novel mode of action

Traditional OADs are mostly monoaminergic, directly modulating dopamine, epinephrine/norepinephrine, serotonin, and/or melatonin neurotransmitter systems in the body or brain. By contrast, ESK-NS offers a novel mode of action, targeting NMDA receptors and increasing the release of glutamate, in turn leading to a release of BDNF and restoration of synaptic function (8). Glutamatergic modulators such as esketamine are increasingly viewed as the next generation of novel therapeutics for the treatment of mood disorders (123).

Esketamine is the S-enantiomer and more potent form of ketamine meaning a relatively lower dose (than if racemic ketamine were administered) is required to exert a given effect, potentially translating into fewer side effects.

B.2.12.3 ESK-NS has a rapid onset of action

In the last 15 years, there has been a paradigm shift in the treatment of MDD owing to the realisation that achieving response and remission early in the disease process correlates with a lower risk of relapse and better overall outcomes (124). Failure to achieve early and complete remission, on the other hand, is associated with an increased risk of relapse, sustained risk of suicide, and comorbidities (23, 125).

Whereas traditional OADs typically require two weeks or longer to produce an initial response and four to six weeks for a full response (23, 126), ESK-NS has a rapid onset, with some patients achieving clinical response in as little as 24 hours after their first dose (see Section B.2.6.1.4.1).

B.2.12.4 ESK-NS offers a non-invasive, convenient route of administration

Administered as a nasal spray (in a fixed-dose, single-use device), ESK-NS treatment is convenient to use and non-invasive. The fact it is administered intranasally likely also contributes to its rapid onset of action since it bypasses the blood brain barrier (9). The convenience of ESK-NS contrasts greatly with that of comparator treatments such as ECT, for example, which requires a general anaesthetic.

B.2.12.5 ESK-NS achieves high response and remission rates in previously non-responding patients

In patients with TRD who, by definition, have failed to respond to standard-of-care treatment, ESK-NS achieves high rates of treatment response and remission (Section B.2.6.1.5), with the treatment effect sustained long-term (Section B.2.6.2.2). ESK-NS thus addresses an unmet need for an effective treatment option for patients with TRD, as was confirmed by early scientific advice received from NICE in 2013 (7). Furthermore, ESK-NS achieves its superior therapeutic effect with a safety profile that is manageable and comparable to that of the standard of care.

B.2.12.6 ESK-NS impacts carers and has a significant wider societal impact

The impact of ESK-NS treatment on outcomes of patients with TRD will also have an impact on the patient's families by reducing the need and burden for informal care. Additionally, it will enable patients to return to work and/or normal daily activities of living, thereby improving productivity and inferring a positive wider societal impact. These significant benefits are not currently captured within the quality-adjusted life year (QALY) framework and therefore are considerably underestimated in this submission.

B.2.13 Interpretation of clinical effectiveness and safety evidence

The totality of evidence from the ESK-NS Phase 3 studies shows that ESK-NS provides clinically meaningful, rapid, and sustained improvement in depressive symptoms for patients. The efficacy results, combined with a well-characterised safety profile and comprehensive risk mitigation programme, highlight the potential for ESK-NS to improve the treatment landscape for patients suffering from TRD.

Data from TRANSFORM-2 and SUSTAIN-1 show that ESK-NS, in combination with a newly initiated OAD, provides statistically significant, clinically meaningful, rapid, and sustained improvement of depressive symptoms in patients with TRD versus a newly initiated OAD plus PBO-NS. The new mode of action combined with the unique route of administration means ESK-NS acts more quickly (≤24 hours) compared with currently available OADs. Combined with a newly initiated OAD, ESK-NS induces about 20% (unadjusted) to 35% (adjusted) higher response and remission levels at 4 weeks after treatment adjustment and reduces the risk of relapse by 50% in the long-term. It also improves quality of life in the short- and long-term compared with an active comparator, a newly initiated OAD plus PBO-NS, while providing a favourable benefit/risk profile.

B.2.13.1 Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology

People with MDD who have not shown clinically meaningful improvement after at least two different OADs within a single episode are regarded as having TRD, and because they have been considered as unresponsive to previous treatments, are considered difficult to treat. The challenges of developing an effective

pharmacological intervention for this condition are evident through the failure of numerous clinical trials to show statistically significant improvements of active treatments over placebo in depression more broadly (73), and the fact that there is currently no approved pharmacological treatments for TRD specifically.

Flexibly-dosed ESK-NS plus a newly initiated OAD has been shown to be highly effective in treating this condition in two pivotal Phase 3 clinical trials, which compared with an active comparator arm consisting of a newly initiated OAD plus PBO-NS:

- in the acute, induction phase of treatment, in TRANSFORM-2.
- in the longer-term, maintenance phase of treatment, in SUSTAIN-1.

Efficacy in the acute induction treatment phase

A key aim of treatment in the short-term is to achieve a response to treatment, through a reduction in symptom severity and functional impairment as rapidly as possible, and ideally to achieve remission from these symptoms. Response and remission are commonly measured by MADRS, a clinician-rated measure of depressive symptom severity.

TRANSFORM-2 met its primary endpoint, with a statistically significant and clinically meaningful improvement in the severity of depressive symptoms, as shown by the change in MADRS total score from baseline to the end of induction. The onset of clinical response was also more rapid with mean change in MADRS total score from baseline being observed by Day 2. The study also showed a statistically significant and clinically meaningful improvement in MADRS-based response and remission rates with ESK-NS + OAD versus the active comparator arm of OAD + PBO-NS.

These improved clinical outcomes enable a considerably higher number of patients to care for themselves and their relatives and friends again, go back to work, and return to normal life.

Additional patient-reported measures showed nominally significant improvements in functional impairment and disability (SDS) and depressive symptom severity (PHQ-9) with ESK-NS + OAD versus the active comparator arm.

Associated improvements in HRQoL were experienced by patients in the ESK-NS + OAD arm, as shown by the increase from baseline to the end of induction (Day 28) in mean EQ-5D-5L HSI versus OAD + PBO-NS. Compared to OAD + PBO-NS, ESK-NS + OAD treatment resulted in more patients being able to care for themselves, who are more mobile, experience less pain and depression or anxiety, and pick up their usual activities compared with OAD + PBO-NS.

The demonstrated superiority of ESK-NS + OAD over OAD + PBO-NS in TRANSFORM-2 is remarkable given the treatment effect of OAD + PBO-NS in the trial was found to be higher than that observed in other TRD/MDD trials (84, 85) as well as in clinical practice, as is described further in B.2.13.2.4. Adjustment of the OAD + PBO-NS treatment effect in line with the findings of a 2007 study by Posternak and Zimmerman (86) further highlighted the superiority of ESK-NS + OAD over OAD + PBO-NS (see Figure 15).

Efficacy in the maintenance treatment phase

The key aim of longer-term, maintenance treatment is to avoid a relapse once a patient achieves a response or goes into remission following their induction therapy. The rationale behind the design of the SUSTAIN-1 trial was to determine whether continued ESK-NS treatment was needed to sustain response/remission, or whether the initial response to ESK-NS could be maintained with an OAD alone after discontinuation of ESK-NS. In SUSTAIN-1, ESK-NS significantly reduced relapse rates in stable responders and stable remitters.

Ongoing ESK-NS + OAD treatment also significantly delayed worsening of symptom severity and functional impairment during the maintenance phase, based on mean changes over time in MADRS, SDS, and PHQ-9 total scores (in both stable remitter and responder patients). In a consistent manner, stable remitters and stable responders continuing ESK-NS + OAD experienced smaller deterioration in HRQoL (EQ-5D-5L HSI) over the duration of the maintenance phase, compared with those who continued on their OAD but switched to PBO-NS.

Supporting efficacy evidence

The evidence base is further enhanced by data from two Phase 3 trials in the acute setting and one Phase 3 trial in the maintenance phase. These studies are considered as supportive but non-pivotal to the decision problem, based on the

dosing posology, population or study design employed, and as described previously in Section B.2.2. However, results were all in favour of ESK-NS + OAD.

Safety

For the purposes of marketing authorisation, the safety profile for ESK-NS has been well characterised based on 1,045 patient-years of treatment across the TRANSFORM-1/2/3 and SUSTAIN-1/2/3 Phase 3 trials (as well as a Phase 2 dose-finding study ESKETINTRD2003).

These studies demonstrate that ESK-NS is well tolerated with manageable risks. When taken in the proposed therapeutic dose range for the treatment of TRD (56–84 mg), most treatment-emergent adverse events (TEAEs) with ESK-NS occurred shortly after dosing, when patients were under the supervision of a healthcare professional, were transient, and resolved on the same day. In clinical practice, most AEs will be managed within the post-administration observation period mandated by the (draft) SmPC, which states that "…at each treatment session, patients should be monitored under the supervision of a healthcare professional to assess when the patient is considered stable based on clinical judgement." The low incidence of TEAEs leading to treatment discontinuation reflects the manageable safety profile – in TRANSFORM-2, 7.0% of patients in the ESK-NS + OAD arm [0.9% in the OAD + PBO-NS arm] had nasal spray treatment withdrawn due to TEAEs.

Longer-term exposure to ESK-NS in the maintenance trials (SUSTAIN-1/2/3) yielded no new safety issues than those identified in the acute treatment trials.

Overall, it is anticipated that ESK-NS will have an acceptable, recognisable, and manageable safety profile when used in clinical practice.

Indirect treatment comparisons

Indirect treatment comparisons were attempted to assess the relative efficacy of ESK-NS versus relevant comparator therapies for acute and maintenance treatment. Due to considerable heterogeneity between trials considered for inclusion in NMA, only limited acute treatment analyses could be run, and only when criteria for inclusion in the evidence network were relaxed. Overall, based on the relaxed criteria NMAs, ORs were consistently in favour of ESK-NS over every comparator in each outcome for which sufficient data were available to support NMA: change from

baseline in MADRS total scores, and response and remission rates based on MADRS. The indirect treatment comparisons were not considered robust and are therefore only used in scenario analyses in the CEA.

Conclusion

Overall, the body of evidence demonstrates that, in patients with TRD, ESK-NS plus a newly initiated OAD provides statistically significant and clinically meaningful improvements in depressive symptoms and relapse prevention when compared with an active comparator arm consisting of a newly initiated OAD plus PBO-NS. ESK-NS addresses a large unmet need for a safe, well-tolerated treatment with a rapid onset of action and durable efficacy for TRD. For patients who describe their disease as 'endless' and that they have no quality of life as a result, ESK-NS offers the first new opportunity and hope in depression in over 30 years.

B.2.13.2 Strengths and limitations of the clinical evidence base for the technology

B.2.13.2.1 TRANSFORM-2 and SUSTAIN-1 were methodologically robust

TRANSFORM-2 and SUSTAIN-1 (as well as the supporting studies, TRANSFORM-1/3) were large, randomised, multinational, double-blind, active-controlled, well-conducted, and methodologically robust Phase 3 studies. In TRANSFORM-2, non-response to at least one OAD was assessed prospectively during a screening/observation phase prior to randomisation. Randomisation to ESK-NS + OAD versus PBO-NS arms was achieved via a central IWRS, the ESK-NS and PBO-NS devices were identical, and a bittering agent was added to the placebo solution to simulate the taste of the nasal spray solution containing esketamine. Given the dissociative effects associated with ESK-NS and to minimise the impact of their potentially leading to unblinding, independent remote raters were used to conduct the primary efficacy measure, the MADRS. The MADRS is a widely-used tool in clinical trials in depression and is regarded by the EMA as "acceptable" for use as a primary efficacy outcome to measure symptomatic improvement in this setting (17). NICE early scientific advice also confirmed the appropriateness of MADRS use in the TRANSFORM-2 and SUSTAIN-1 trials (7).

A range of other recognised and validated tools, both investigator/clinician reported and patient-reported, including SDS, PHQ-9, CGI-S, GAD-7 and EQ-5D were also used to capture key aspects of the disease, including depressive symptom severity, functional impairment, anxiety and HRQoL (see Table 10).

B.2.13.2.2 TRANSFORM-2 and SUSTAIN-1 provide efficacy and safety data of direct relevance to the anticipated licence for ESK-NS

TRANSFORM-2 and SUSTAIN-1 provide key pivotal efficacy and safety data for flexibly-dosed ESK-NS from a total of 932 patients with TRD treated as per the recommended flexible dosing posology in the (draft) SmPC and in line with its anticipated use in clinical practice.

B.2.13.2.3 Patient characteristics were reflective of the UK TRD population

Patients enrolled in TRANSFORM-2 and SUSTAIN-1 (as well as the supporting studies, TRANSFORM-1/3 and SUSTAIN-2) were broadly reflective of patients with TRD seen in UK clinical practice – most patients (~60%) were female, mean baseline MADRS total score corresponded to severe depression with many patients having a history of suicidal ideation/behaviour, and the mean duration of the current episode of depression was prolonged (~120 weeks) (Appendix P).

Neither TRANSFORM-2 or SUSTAIN-1 enrolled any patients in the UK. (One UK patient was enrolled in the supporting trial, TRANSFORM-3, and 12 UK patients were enrolled in the long-term safety study, SUSTAIN-2). Although subgroup analyses conducted on the primary outcomes in TRANSFORM-2 and SUSTAIN-1 did suggest minor effects of patient region, country, and/or ethnicity on ESK-NS treatment response, drawing conclusions from these results is cautioned due to the small numbers of patients in these subgroups and the resulting wide confidence intervals.

B.2.13.2.4 Superiority of ESK-NS was demonstrated despite OAD treatment effect in the active comparator arm being higher than in other OAD TRD trials and in clinical practice

In mental health and depression trials specifically, many trials have failed to show a statistically significant efficacy outcome of the active drug compared with placebo. Of

the randomised, placebo-controlled studies conducted in support of an anti-depressant claim approximately 50% have failed to show statistical superiority over placebo on change from baseline to endpoint in the Hamilton Depression Rating Scale (73). This shows the challenge of conducting a successful trial in the field of depression, mainly due to the high placebo effect of clinical trial participants. This challenge is also acknowledged by the CHMP (17).

It is important, therefore, to reiterate that the statistically significant benefits of ESK-NS demonstrated in TRANSFORM-2 and SUSTAIN-1 (as well as those of TRANSFORM-1/3) were achieved despite using an active comparator arm consisting of a newly initiated OAD with a PBO-NS added. Moreover, the composition of the comparator arm, with the inclusion of this PBO-NS and high intensity follow-up contact, likely resulted in a high treatment effect for the active comparator arm, higher than that observed in other OAD TRD trials as well as in clinical practice. The active comparator arm as designed for the blinding is not fully reflective of how OAD treatment would be given in clinical practice in the NHS (see Table 6).

The expected absolute treatment response for ESK-NS + OAD in clinical practice is likely to match that observed in the trials since the higher number of clinic visits and nasal spray as the mode of delivery will still apply when ESK-NS is administered in clinical practice. Due to the higher treatment response of the active comparator in TRANSFORM-2, the relative treatment effect of ESK-NS plus OAD as measured in TRANSFORM-2 would not reflect the relative treatment effect when compared with an OAD in normal NHS clinical practice.

As such, it is extremely likely that the relative treatment effect of flexibly-dosed ESK-NS predicted by the ESK-NS trials are highly conservative, impacted by unusually high response rates in the active comparator arm, and therefore lower than expected to be observed in clinical practice. Expert clinical input and evidence from the literature provides compelling evidence that this is the case.

B.2.13.2.5 TRANSFORM-2 results were subject to strict hierarchical statistical testing

In the pivotal TRANSFORM-2 study (as was the case in TRANSFORM-1), to adjust for multiplicity and to control for type I error, a hierarchical testing procedure was used in the statistical analyses of the primary and three key secondary efficacy outcomes. Accordingly, while the primary efficacy endpoint was met in the TRANSFORM-2 study, the first of the three key secondary efficacy outcomes – onset of clinical response by Day 2 (24 hours) maintained to Day 28 – was not statistically significant. As a result, the two subsequent key secondary efficacy outcomes (change in SDS and PHQ-9 total scores from baseline to the end of induction) could not be formally tested. However, these outcomes were both shown to be nominally significant for improvements ESK-NS + OAD versus the active comparator arm. Similarly, in the supporting TRANSFORM-1 study, failure to meet the primary endpoint precluded formal evaluation of the downstream endpoints; however, the key secondary efficacy endpoints reached nominal significance for the 56 mg ESK-NS dose. Although the hierarchical testing procedure wasn't employed for TRANSFORM-3, most of the secondary efficacy endpoints reached statistical significance, even though the primary efficacy endpoint was not met.

In mental health and depression trials specifically, failure to achieve a statistically significant result is not uncommon. An analysis of 81 placebo-controlled MDD trials conducted over a 25-year period found that approximately half (53%) have failed to show statistical superiority over placebo on change from baseline to endpoint in the Hamilton Depression Rating Scale (73).

Consequently, TRANSFORM-2, having demonstrated statistical significance versus an active comparator (OAD + PBO-NS) in its primary efficacy endpoint, serves to highlight the efficacy of ESK-NS (plus a newly initiated) for the treatment of TRD.

B.2.13.2.6 Strict criteria defining onset of clinical response by Day 2 limited the ability of TRANSFORM-2 to demonstrate the rapid onset of action of ESK-NS

TRANSFORM-2 failed to demonstrate a significant difference in the rates of onset of MADRS-based clinical response at Day 2 (maintained to Day 28) between ESK-NS

+ OAD and OAD + PBO-NS-treated patients. However, in addition to the high relative treatment effect in the OAD + PBO-NS arm described earlier (see Section B.2.13.2.4), TRANSFORM-2 (and TRANSFORM-1) set very strict criteria defining onset of clinical response by Day 2 (based on guidance received by the FDA). Patients needed to demonstrate a ≥50% improvement in MADRS total score within 24 hours of taking the first dose (double-blind) of ESK-NS that was maintained to Day 28 of the induction phase with only one excursion allowed on either Days 8, 15, or 22. Given the fluctuation of symptoms in TRD, fulfilling these criteria presented a significant challenge.

The use of remote MADRS raters likely also reduced the sensitivity of the tool since raters did not know their patients or their baseline condition, and, in not being able to see their patients, were unable to judge effect or change in effect during the rating process.

Despite the failure of TRANSFORM-2 to show a significant difference between arms in the rate of onset of MADRS-based clinical response at Day 2, the change in MADRS total score from baseline to Day 2 (24 hours) was statistically significantly greater in patients treated with ESK-NS + OAD versus the comparator arm (LS mean treatment difference: –3.6; p=0.004).

B.2.13.2.7 Patients in the active comparator arm of SUSTAIN-1 are possibly affected by a "carry-over" effect of prior ESK-NS treatment

Patients in remission who were randomised to receive ongoing treatment with ESK-NS + OAD during the maintenance phase of SUSTAIN-1 represent the best data source to inform the long-term efficacy of ESK-NS + OAD in delaying disease relapse.

There are limitations, however, when considering SUSTAIN-1 as the source of comparative efficacy for OADs in the longer term, due to the design of this study. SUSTAIN-1 used a randomised blinded withdrawal design in patients who had achieved stable remission after 16 weeks of treatment with ESK-NS + OAD (end of the optimisation phase). The difference in time to relapse between patients randomised to continue treatment with ESK-NS + OAD and those randomised to discontinue this treatment and switch to OAD + PBO-NS was then assessed. As the

patients in the comparator arm previously achieved stable remission with ESK-NS + OAD due to the design of the study, the long-term treatment effect in the active comparator arm likely does not provide a true efficacy estimate of OADs in the maintenance phase of treatment because of a potential “carry-over” effect of prior ESK-NS treatment.

For this reason, in the economic analysis, it was necessary to derive long-term OAD efficacy data from the STAR*D trial (23) – the largest study available that examines the durability of OAD-induced treatment response. This study is described further in Section B.3.

B.2.13.2.8 Supporting evidence

The supporting acute phase trials, TRANSFORM-1 and TRANSFORM-3 both failed to meet their primary endpoints; potential explanations for both are provided below. It should be reiterated that neither study is considered as pivotal to the decision problem, based on anticipated posology and population treated.

For TRANSFORM-1, the use of the hierarchical testing procedure meant that for the primary endpoint, the ESK-NS-56 + OAD arm could only be formally tested if the ESK-NS 84 + OAD arm reached statistical significance, and subsequently then the key secondary endpoints could only be tested if both primary endpoints were met. Accordingly, as the primary endpoint for the ESK-NS 84 + OAD arm did not reach statistical significance, subsequent endpoints could not be formally tested. However, both the primary endpoint and key secondary endpoints all showed nominal significance for the lower dose ESK-NS 56 + OAD.

A 3-fold higher early withdrawal rate in the ESK-NS-84 + OAD arm (n=19; 16.4%) compared with the ESK-NS-56 + OAD (n=6; 5.1%) and OAD + PBO-NS (n=6; 5.3%) arms and subsequent loss of statistical power likely contributed to the failure to achieve a statistically significant difference between the ESK-NS-84 + OAD and OAD + PBO-NS arms. Note that withdrawals in the ESK-NS-84 + OAD arm were not due to any new or dose-related safety finding, and 11 of the 19 early withdrawal patients (58%) withdrew after their first ESK-NS dose which was 56 mg as stipulated by the fixed titration study design (see Appendix M).

For TRANSFORM-3, there was a tendency for clinicians, given the age of patients enrolled in TRANSFORM-3, to prescribe ESK-NS at the lowest permitted dose (28 mg) and to only increase it slowly (if at all) over the course of the 4-week induction phase (only 53% of patients received the 84 mg ESK-NS dose prior to the TRANSFORM-3 interim analysis). Note that the 28 mg dose is below the minimum effective dose (56 mg). The slow dose increase likely contributed to the failure of the trial to demonstrate a statistically significant difference between patients in the ESK-NS + OAD versus OAD + PBO-NS arms since these patients were effectively receiving a sub-therapeutic dose of ESK-NS. Furthermore, subgroup analysis of TRANSFORM-3 results by patient age group (65–74 years versus ≥75 years) suggested a lack of response to treatment among patients aged ≥75 years, at least during the 4-week induction period (although there were only 22 patients in this subgroup so the results should be interpreted with caution [see Section B.2.7.2]). The data from the subgroup analysis of 65–74 years showed a similar efficacy to that observed in TRANSFORM-2.

B.2.13.2.9 Evidence for comparator treatments is sparse and considerable trial heterogeneity hindered NMA

Different treatment classes (e.g., SSRIs, SNRIs, tricyclics) and modalities (i.e., augmentation with antipsychotics, augmentation with lithium, combinations of OADs), as well as individual drugs/drug combinations, were considered for indirect comparison. Only a limited number of studies to inform the evidence base for an NMA of TRD treatments were identified, however, and for some comparators, no data were available for patients with TRD. In the clinical trials identified in the TRD population, there was a high level of heterogeneity in terms of study design, definitions of outcomes, and patient populations. It was only through relaxing the criteria for inclusion in the NMA could limited acute treatment comparisons between ESK-NS and various comparators be made. Given the acute treatment comparisons that were feasible were not robust, they were only used to inform scenario analyses in the CEA, with the base case using an in-trial analysis of TRANSFORM-2.

B.2.13.3 End of life

Not applicable.

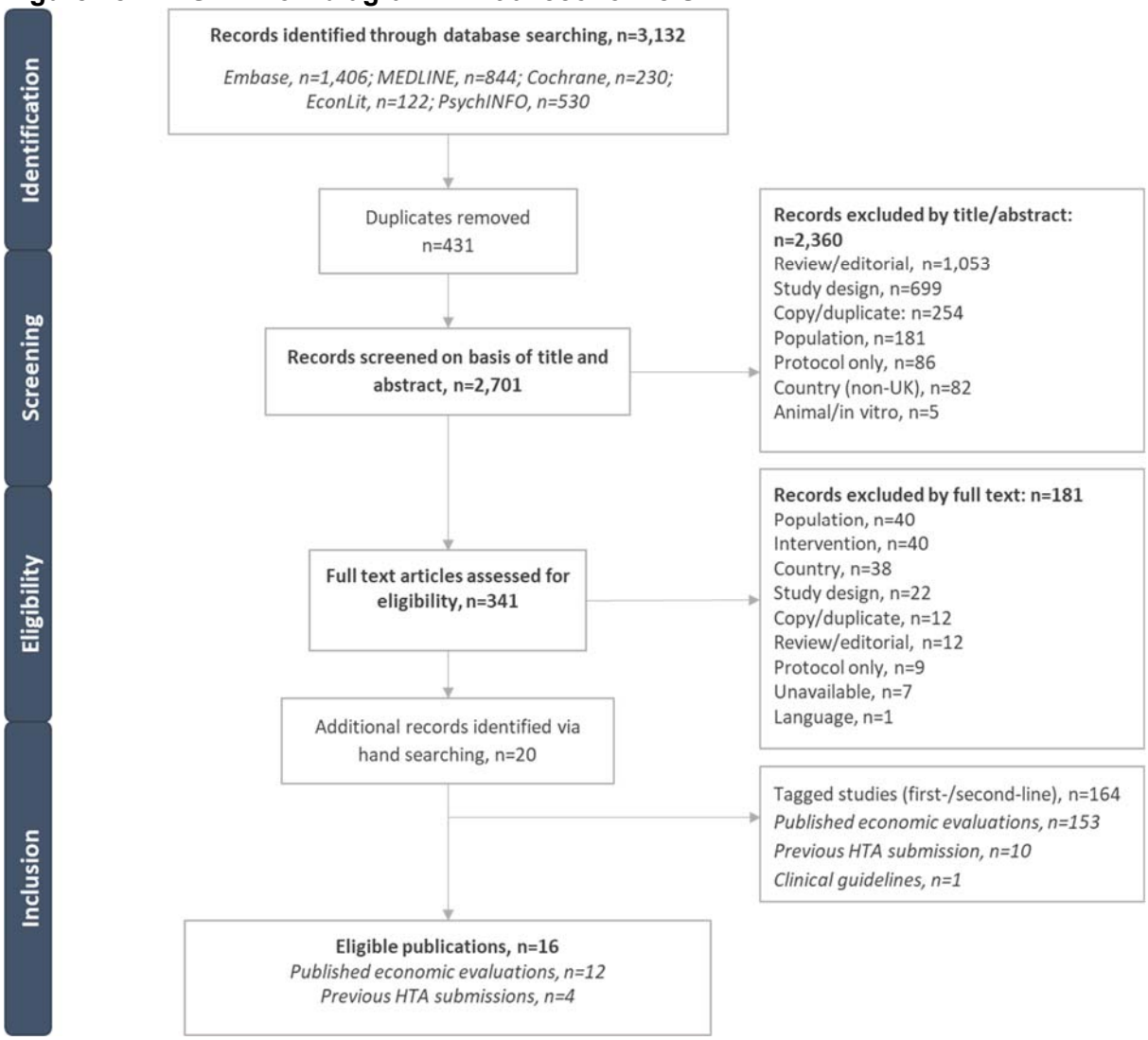
B.3 Cost-effectiveness

B.3.1 Published cost-effectiveness studies

An SLR was conducted to identify economic evaluations of relevant interventions in the management of TRD. Full details of the SLR methodology are presented in Appendix G. PRISMA flow diagrams detailing studies that were included and excluded at each stage of the initial SLR and April 2019 update are provided in Figure 18 and Figure 19, respectively.

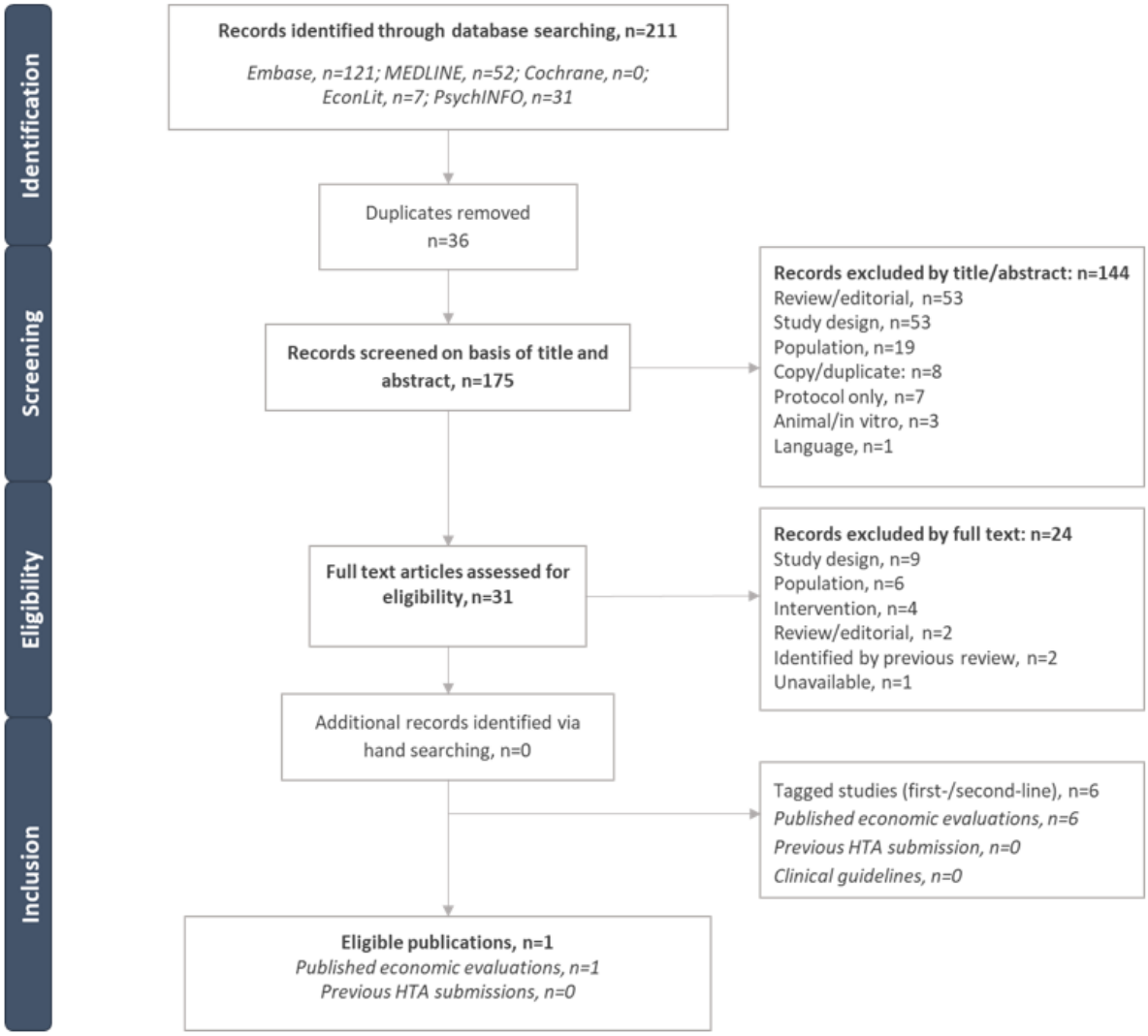
Overall, a total of 17 economic evaluations were identified for inclusion across the original review and the April 2019 update. Out of the 17 studies, five published economic studies and two HTA submissions were identified in a UK TRD population.

Figure 18. PRISMA flow diagram – initial economic SLR



Abbreviations: Abbreviations: HTA, health technology assessment; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

Figure 19. PRISMA flow diagram – economic SLR April 2019 update



Abbreviations: Abbreviations: HTA, health technology assessment; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

B.3.1.1 Summary of the cost effectiveness studies relevant to UK clinical practice

The majority of the included studies utilised a model to estimate the cost-effectiveness of treatments for MDD/TRD (n=11) (127-137). Modelling techniques utilised across the studies included: combined decision tree and Markov model (n=4) (128, 129, 132, 135), decision trees (n=2) (127, 130), deterministic state transition models (n=1) (137); and unspecified decision analytic models (n=1) (136).

Seven studies modelled the treatment of depression according to two phases: acute and maintenance (128-130, 132, 134-136). The duration of the acute phase ranged from 2 weeks (134) to 3 months (129, 135) and was most often modelled using the

decision tree component of the combined models. The duration of the maintenance phase ranged from 6 months (129, 130, 134-136) to 1 year (132) and was most commonly modelled using the Markov component of the combined models.

The time horizon ranged from 6 months (127) to 4 years (137). One of the 13 included published studies was a trial-based analysis conducted alongside a clinical trial and did not use a model to estimate costs and outcomes (138). Finally, one study did not report the approach to modelling (139).

The most relevant studies for the decision problem were UK TRD models. These included the HTA monograph on augmentation with lithium or an atypical antipsychotic (AAP) by Edwards et al. 2013 (128), the previous SMC submission (158/16) (140), and the previous NICE appraisal of vortioxetine for MDD (TA367) (46).

The submission to NICE (TA367) considered adult patients with moderate-to-severe MDD who had responded inadequately to initial antidepressant treatment; however, the model also considered a subsequent switch to third-line therapy (46). The model used in the submission to NICE was a decision tree model with a Markov component to model subsequent treatment switches to third and later lines. The decision tree included three phases: (i) an acute phase of treatment for eight weeks (months 0-2); (ii) a maintenance phase of six months (months 2-8); and (iii) a recovery phase (months 8–12). The amount of time patients spent in the decision tree was variable and depended upon whether treatment was successful in each phase. If treatment in all three phases was successful, with remission being achieved and sustained to recovery at the 12-month model horizon, the entire 12 months was spent in the tree. However, the model also included events in which treatment was not successful. These led to a further switch, i.e. to third-line treatment. During the acute phase, the modelled events leading to switch were withdrawal due to short-term side-effects and failure to achieve remission. Patients not completing the acute phase successfully left the decision tree and entered the Markov component of the model with a two-month cycle length. Similarly, the vortioxetine SMC submission also used the same model consisting of a decision tree with a Markov component to the model (140).

The NIHR monograph by Edwards et al. (128) considered patients with TRD who had failed to respond to two or more antidepressants in the current episode of depression. The modelling approach was a decision tree to model the acute phase (eight weeks) and Markov model to model the maintenance phase (10 months). The interventions considered were SSRI + lithium versus SSRI + AAP. The time horizon was one year.

None of the economic evaluations identified by the SLR evaluated the cost-effectiveness of ESK-NS + OAD and were therefore not directly generalisable to the NICE decision problem. The UK TRD economic studies identified above, however, were used to inform the structure and inputs used in the *de novo* model developed for ESK-NS + OAD.

B.3.2 Economic analysis

A *de novo* Markov cohort model was developed in Microsoft® Excel 2016 to model outcomes and costs experienced by a patient cohort over a 5-year time horizon. The model reported health outcomes including life-years, quality-adjusted life years (QALYs), and direct costs. The model perspective was the NHS and PSS in England. Indirect costs were explored in a sensitivity analysis.

The *de novo* model improves upon the approaches used in models found in the SLR and in TA367. The current model reflects the natural history and treatment phases of TRD in terms of the model structure, health states, sources of utility data, time horizon, and cost perspective.

The objective of the economic evaluation was to assess the cost-effectiveness of ESK-NS + OAD for the treatment of patients with TRD, versus all relevant comparators in the NICE scope. Potential comparators included in the scope were TCAs, MAOIs, vortioxetine, combination or augmentation treatments (with lithium or an antipsychotic), ECT, and best supportive care. As noted in Section B.2.9, clinical trial heterogeneity, in terms of overall study design, inclusion criteria, and patient population, meant that treatment comparisons were not deemed to be robust in either acute or maintenance treatment settings. The base case analysis therefore compares ESK-NS plus a newly initiated OAD versus a newly initiated OAD using

data from the TRANSFORM-2 and SUSTAIN-1 trials for clinical outcomes (see Section B.2.6).

B.3.2.1 Patient population

The economic evaluation included adults with TRD with a moderate to severe depressive episode. A moderate to severe episode of TRD was assumed to have minimum duration of two years. Treatment resistant MDD was defined as non-response to two or more OADs prescribed at an adequate dose and for an adequate duration in the current episode. This is consistent with the population detailed in the NICE scope, the population included in the TRANSFORM-2 and SUSTAIN-1 trials, and with the anticipated European Marketing Authorisation.

The majority (61.9%) of the model population was female with an average age of 45.7 years (SD: 11.89), as observed in TRANSFORM-2 and generalisable to the UK TRD population (2) (see Appendix P). The average MADRS total score at baseline was 37.1 (SD: 5.67) (Table 41).

Table 41. Patient population included in the economic model

Baseline characteristics	Value	Source
Age, mean years (SD)	45.7 (11.89)	TRANSFORM-2 (76, 77)
Female, %	61.9	
MADRS total score at baseline, mean (SD)	37.1 (5.67)	

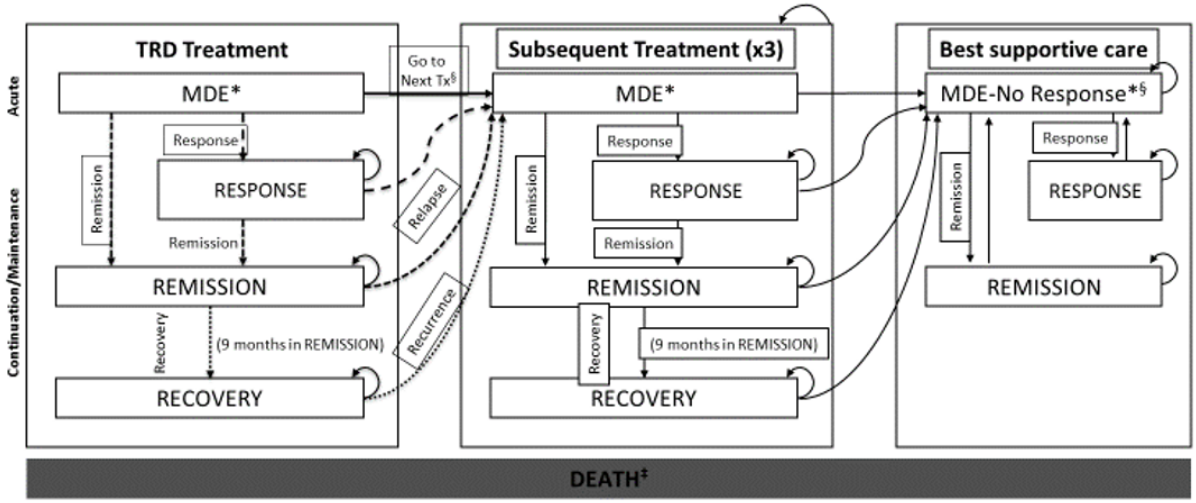
Abbreviations: MADRS, Montgomery-Asberg Depression Rating Scale; OAD, oral antidepressant; SD, standard deviation.

B.3.2.2 Model structure

As per Section B.3.1, Markov models are frequently used to model OAD therapies as they are able to maintain simplicity whilst adequately tracking disease progression and costs of patients with TRD (131, 133, 134). A Markov model is appropriate given the cyclical nature of remission and relapse often seen in patients with depression (141). [redacted]

A schematic of the model is presented in Figure 20.

Figure 20. Model schematic



Abbreviations: AE, adverse events; MDE, major depressive episode; TRD, treatment-resistant depression; Tx, treatment;
‡ Age- and sex-adjusted background mortality. Increased mortality was assigned to the MDE/response health state.
* Treatment-dependent AEs rates were assigned.
§ Included patients who had no response or stopped responding to the final treatment.

The model is consistent with the clinical pathway of care and natural history of the disease, as identified in Section B.1.3. A 5-year time horizon was used to fully capture consequences of a TRD episode due to the relative chronicity compared with MDD.

Patients enter the model in the MDE heath state, after having failed to achieve a clinically meaningful improvement after treatment with at least two OADs (prescribed in adequate dosages for adequate time). During each 4-weekly Markov cycle, patients can occupy MDE, response, remission, recovery or death health states. Patients can cycle through up to three subsequent treatments, switching to a new treatment following:

- a non-response to acute treatment (at 4 weeks),
- a loss of response or relapse from the response or remission health states respectively (5–40 weeks), or
- experience a recurrence of the MDE during the recovery health state (41 weeks+).

Definitions of the health states included in the model can be found below in Table 42. The relevance and definitions of the model health states were validated by clinical experts.

Table 42. Health state definitions

Health state	Health state definition
MDE	Patients experience moderate to severe symptoms of major depressive disorder with a MADRS ≥28 and failed to respond to at least two different OAD treatments of adequate dosage and duration.
Response	Patients experience a 50% or greater MDD symptom improvement from patient's baseline MADRS score but did not achieve the threshold for remission (MADRS ≤12).
Remission	Associated with a period during which the patient is either symptom-free or has only minimal symptoms. The threshold used in the model for achieving remission was MADRS ≤12.
Recovery	Represents an extended asymptomatic phase, achieved after a patient remains in relapse-free remission for 36 weeks in a row (or approximately nine months).

Abbreviations: MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; MDE, major depressive episode; OAD, oral antidepressant.

B.3.2.3 Treatment phases in the model

There are three discrete time intervals in the model: acute, continuation (or relapse prevention) and maintenance phase (or recurrence prevention). These time intervals align to the different treatment phases and treatment goals of TRD in clinical practice, as outlined in treatment guidelines (NICE CG90) (see Figure 3). This is also reflective of the main treatment phases seen in the clinical trials studied in a TRD population. The treatment phases and treatment objectives used in the model are presented in Table 43.

Table 43. TRD treatment phases in the model

Weeks	Treatment phase	TRD treatment objective
1–4	Acute	Remission of symptoms
5–8	Continuation (relapse prevention)	Loss of response and relapse prevention
9–40		
41+ (only for those patients in relapse-free remission after 36 weeks)	Maintenance (recurrence prevention)	Recurrence prevention

Abbreviations: TRD, treatment-resistant depression

Further explanation of the acute, continuation, and maintenance treatment phases are provided below.

B.3.2.3.1 Acute treatment phase

In TRD clinical practice, the acute treatment phase is 4–8 weeks with remission being the goal of this phase (see Figure 3). At the start of the model, all patients are in an MDE health state and by the end of the 4-week acute treatment period (i.e. at

the end of first cycle), patients' health states were evaluated in the model at which point they could:

- Respond to treatment and move into the response or remission health states (the specific transition depended on the level of response observed)
- Fail to respond to treatment, stay in the MDE health state, but move on to the next treatment in the sequence
- Discontinue treatment early (i.e. due to all-cause discontinuation risk) and stay in the MDE health state, or
- Die.

B.3.2.3.2 Continuation: relapse prevention

In treatment of TRD, after the patient reaches treatment success (remission) in the acute phase, the continuation phase focuses on relapse prevention and further stabilising remission. For patients that have had a response in the acute period the goal is to improve their depressive symptoms further and for them to achieve remission. The continuation phase can take up to nine months (42).

Within the model and according to the posology and method of administration in the expected EMA label, the continuation phase was stratified into Weeks 5–8 (weekly dosing per label) and Weeks 9–40 (every other week or weekly) for relapse prevention for remitters.

Upon entering the continuation phase, patients who responded to acute treatment, but did not achieve remission, could:

- Continue treatment and remain in the same health state,
- Improve their depressive symptoms further and transition into the remission health state,
- Lose treatment response, return to the MDE health state, and begin the next treatment in the sequence,
- Discontinue treatment and remain in the same health state, or
- Die.

Upon entering the continuation phase, patients who achieved remission during acute treatment could:

- Continue treatment and remain in the same health state,
- Enter the recovery health state after 36 weeks (approximately nine months) of relapse-free remission,
- Relapse (i.e. return to the MDE health state) and begin the next acute treatment in the sequence,
- Discontinue treatment and remain in the same health state, or
- Die.

Only patients who achieve nine months of continuous relapse-free remission can enter the maintenance phase. Responders after the acute treatment will need to achieve remission first and maintain that for nine months before being able to enter the maintenance phase.

B.3.2.3.3 Maintenance phase: recurrence prevention

Patients enter the maintenance phase and recovery health state after 36 weeks in continued relapse-free remission. See Section B.3.2.9.2.2 for further explanation of the definition of the recovery health state. Patients in the recovery health state could:

- Experience a recurrence event (i.e., return to the MDE health state) and move on to the next treatment in the sequence,
- Continue treatment and remain in the current recovery health state, or
- Die

For patients on ESK-NS + OAD in recovery, ESK-NS treatment was discontinued in the most stable patients who are in stable remission (35%) following 40 weeks treatment (4 weeks acute treatment + 36 weeks in remission). The remaining patients had a 25% monthly probability of discontinuation (see Section B.3.2.9.2.3 for further explanation). The patients who discontinued ESK-NS continued to receive OAD for recurrence prevention. OAD treatment was stopped upon experiencing recurrence or death.

B.3.2.3.4 Subsequent treatments

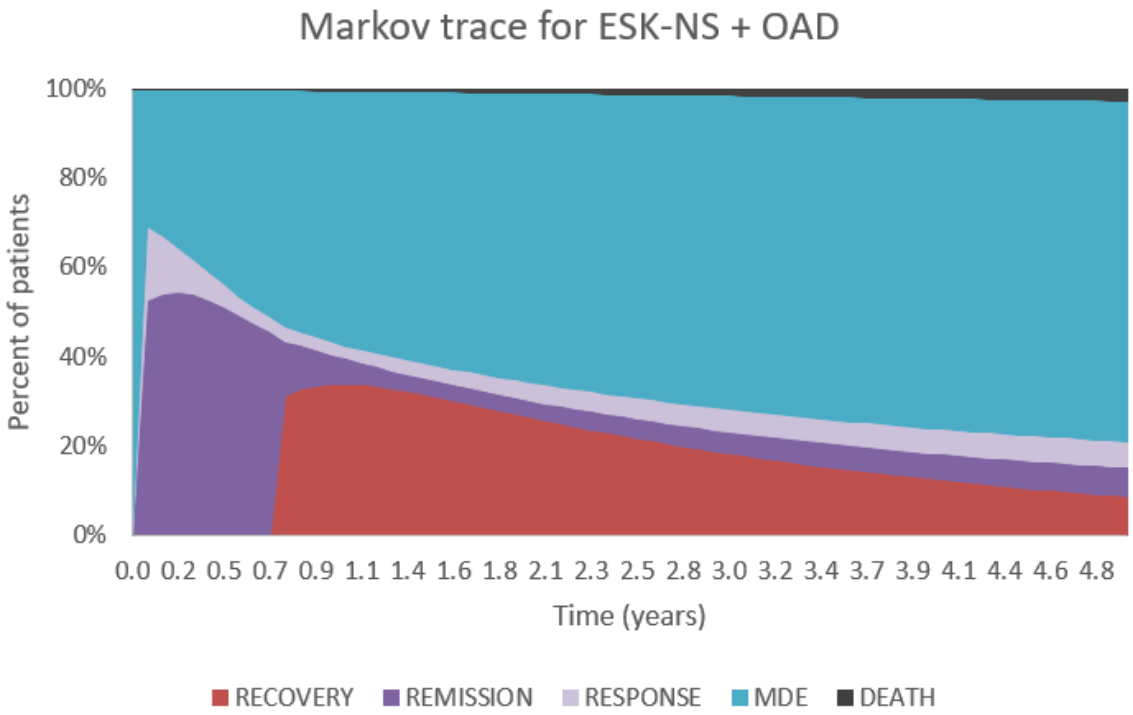
Following an inadequate response to treatment in the acute treatment phase, a relapse in the continuation phase or recurrence in the maintenance phase, patients can transition through up to three subsequent treatments. After exhausting three

subsequent treatments, patients are assumed to transition to a best supportive care (a non-specific treatment mix) phase, where they could still achieve response or remission. Edwards et al. (2013) (128) was used to inform these parameters, which used expert clinical opinion based on the available evidence. These parameters were further validated at an advisory board meeting in June 2019 (143). Those patients who achieved remission or response during the best supportive care phase could also experience relapse, in which case they transitioned back to the MDE no response health state, where they again had a chance to achieve remission or response. Patients were expected to cycle between these health states (MDE, response, and remission) during the best supportive care treatment phase.

B.3.2.4 Time horizon and cycle length

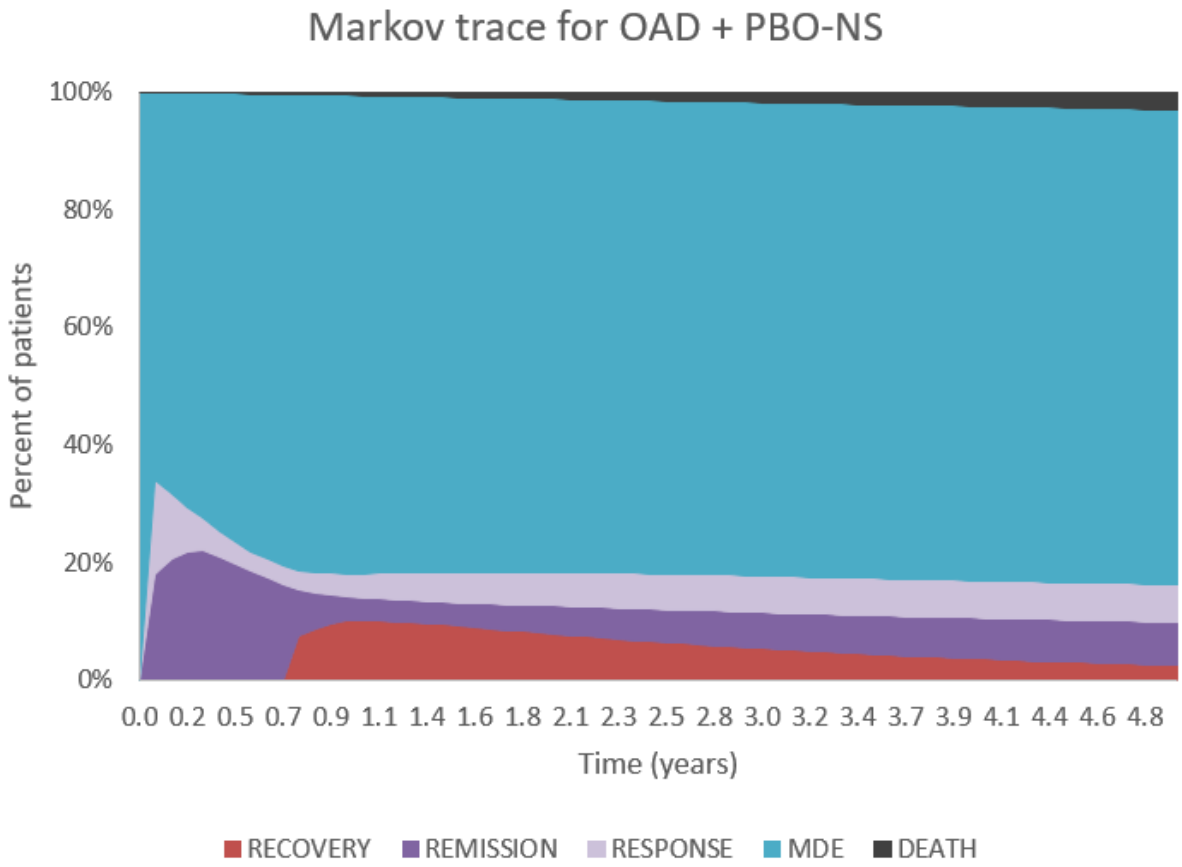
MDD is a disease that can in some patients last a lifetime and is recurring in nature. As described in Section B.1.3, TRD has more severe clinical manifestations than the broader non-TRD MDD, including worse prognosis, higher risk of suicidality, higher risk of relapse, and more and longer duration of depressive episodes (37, 38, 40, 41). The majority of MDD episodes last between 6–15 months (144) while episodes in patients with TRD are typically three times longer (37). The base case time horizon was 5 years. As per the model Markov trace in Figure 21 and Figure 22, a 5-year time horizon is justified to fully account for all relevant benefits and costs attributable to ESK-NS+ OAD. Accounting for all the treatment-related benefits and costs attributable to ESK-NS+ OAD is key to determine the appropriate time horizon, as advised by NICE Scientific Advice in April 2013 (7) [redacted]

Figure 21. Markov trace for ESK-NS + OAD



Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; MDE, major depressive episode.

Figure 22. Markov trace for OAD + PBO-NS



Abbreviations: MDE, major depressive episode; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray.

The model had a cycle length of 28 days, corresponding to the 4-week induction phase of TRANSFORM-2 and corresponding assessment of treatment response to ESK-NS. Furthermore, the cycle length corresponds to the average time to assess treatment continuation of OADs. The cycle length was sufficient to facilitate computational efficiency. A half-cycle correction was applied to ensure that outcomes were neither under- or over-estimated. This was done by averaging the number of patients in each health state at the beginning and the end of the cycle for each cycle (145, 146) The half-cycle-corrected patient counts were used to calculate life-years, costs, and QALYs.

B.3.2.5 Perspective and discounting

The base case analysis took the perspective of the NHS and PSS in England. Both costs and outcomes (LYs and QALYs) were discounted at 3.5%, in line with the

NICE Guide to the Methods of Technology Appraisal 2013 (147). The impact of discounting at 0% and 6% was assessed in sensitivity analyses.

B.3.2.6 Model outcomes

The results of the model were expressed in terms of incremental cost per life-year (LY) gained and incremental cost per QALY gained.

B.3.2.7 Intervention technology and comparators

The intervention in the analysis was ESK-NS co-administered with a newly initiated OAD (ESK-NS + OAD). The dosage used were those assessed in TRANSFORM-2 and SUSTAIN-1 and in line with the anticipated European Marketing Authorisation.

For the purposes of consistency with the clinical sections, the AC arm of TRANSFORM-2 has been defined as OAD + PBO-NS. The adjusted results (see Section B.2.3.7) from the OAD + PBO-NS arm are used in the base case and referred to as OAD hereafter.

B.3.2.8 Features of the economic analysis compared with previous appraisals

A summary of the main characteristics and assumptions used in the model in TA367 and the comparison with the current economic analysis is provided in Table 44. TA367 was previously conducted in an MDD population, which is a different population to the current decision problem. As such, differences to the approach in the previous economic analysis exist. These differences are justified below. Where deemed appropriate, data to inform model parameters was consistent with TA367.

Table 44. Features of the economic analysis

	Previous appraisals (MDD)	Current appraisal (TRD)	
Factor	**TA367**	**Chosen values**	**Justification**
Time horizon	2 years	5 years	5 years is necessary to capture the expected costs and benefits of ESK-NS. The majority of MDD episodes lasts between 6–15 months (144). Episodes of depression in patients with TRD are typically three times longer than in patients with non-treatment resistant MDD (37), with an

Factor	Previous appraisals (MDD)	Current appraisal (TRD)	
	TA367	Chosen values	Justification
			average duration of over 2.5 years (37, 40).
Treatment waning effect?	No	No	Consistent with previous appraisal
Source of utilities	REVIVE trial for all phases of the model	TRANSFORM-2	TRANSFORM-2 presents data directly relevant to the decision problem. Utility values are taken from the same source for consistency.
Source of costs/resource use	Unit Costs of Health and Social Care (2013) was applied to the below data sources: Acute phase: PERFORM study Maintenance phase: Byford et al, 2011 (148)	2016/2017 NHS reference costs, BNF, PSSRU 2017, literature were applied to resource use from a retrospective chart review of UK TRD patients	A review of previous NICE TAs and an SLR did not identify any relevant sources of costs and resource use in the literature. As such, a retrospective chart review (primary and secondary care) was commissioned by Janssen to inform HRU and costs per health state per month (see Appendix P).

Abbreviations: BNF, British National Formulary; HRU, healthcare resource use; MDD, major depressive disorder; NICE, National Institute for Health and Care Excellence; PSSRU, Personal Social Services Research Unit; SLR, systematic literature review; TA, technology appraisal; TRD, treatment-resistant depression;

B.3.2.9 Clinical parameters and variables

The sections below present the sources of data to inform the clinical data transition probabilities within the acute, continuation (relapse prevention) and maintenance (recurrence prevention) treatment phases.

B.3.2.9.1 Clinical data: Acute phase – treatment response and remission

Efficacy estimates (response and remission) for both ESK-NS + OAD and OAD + PBO-NS were taken from the TRANSFORM-2 trial. No significant differences in response and remission rates between the SSRI and SNRI OADs were observed in subgroup analyses of TRANSFORM-2 and are therefore referred to collectively as OADs in the model. The grouping of the SSRIs and SNRIs due to assumed similar efficacy is consistent with the conclusions of the NICE Depression Guideline Development Group (CG90) and NICE Appraisal Committee in TA367.

In TRANSFORM-2, response and remission rates in the base case were calculated using MMRM OC (see Section B.2.4.3) and are presented in Table 45. All remitters are also responders; to generate the proportion of responders (without remission) the remitters were subtracted from the total number of responders in TRANSFORM-

2. Within the model, response and remission rates for ESK-NS + OAD were taken directly from the trial without adjustment since it was assumed that administration, including the number of clinic visits and observation requirements, reflected how ESK-NS would be administered in NHS clinical practice when available. The remission and response rates of OAD + PBO-NS in TRANSFORM-2 were adjusted as the number of clinic visits and observation time are not representative of how newly initiated OADs are administered in NHS practice (see Table 6). Available evidence suggests it is appropriate to adjust the treatment effect to account for these differences (see Section B.2.3.7) and therefore the values of OAD + PBO-NS were adjusted *post hoc*. Scenario analyses considering the impact of the adjusted treatment effect are presented in Section B.3.4.4.1.

Table 45. Response and remission rates at the end of the acute treatment phase

Treatment	Remission, % (SE)[a]	Response (but not remission), % (SE)[b]	Response[c]
ESK-NS + OAD	52.48% (4.97)	16.83% (3.72)	69.31%
OAD + PBO-NS (unadjusted)	31.00% (4.26)	21.00% (4.07)	52.00%
OAD + PBO-NS (adjusted for six visits[d])	18.00% (3.84)	16.00% (3.67)	34.00%

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; MADRS, Montgomery-Asberg Depression Rating Scale; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; SE, standard error.
[a] MADRS ≤12.
[b] ≥50% reduction in MADRS from baseline but MADRS score >12.
[c] ≥50% reduction in MADRS from baseline.
[d] Base case.

B.3.2.9.2 Clinical data: Continuation phase and maintenance phase

B.3.2.9.2.1 Transition from response to remission in the continuation phase

Following the acute treatment phase, responders (those patients who have responded but not achieved remission [i.e., those with a 50% reduction in MADRS from baseline but a MADRS score >12]) could subsequently have a chance to move into the remission state.

Data from SUSTAIN-1 were used to inform the rate of transition from response to remission. Patients defined as “stable responders[5]” at the beginning of the

[5] In SUSTAIN-1, stable response was defined as a ≥50% reduction in the MADRS total score from baseline in each of the last two weeks of the optimisation phase without meeting the criteria for stable remission.

continuation (relapse prevention) phase in SUSTAIN-1 were followed over time to identify those who had a MADRS ≤12 for at least three of the last four weeks (three out of any four consecutive weeks during follow-up). Any patient who successfully achieved this threshold was assumed to have transitioned from response to remission. A Poisson regression analysis (see Appendix Q for further details) was used to estimate the transition probability (Table 46).

Table 46. 4-week transition of moving from response to remission (MADRS ≤12) state

Treatment	Response to remission (SE)
ESK-NS + OAD	19.93% (4.98)
OAD + PBO-NS	12.39% (3.10)

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; MADRS, Montgomery-Asberg Depression Rating Scale; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; SE, standard error.

B.3.2.9.2.2 Loss of response, relapse, and recurrence in the continuation and maintenance phase

For the ESK-NS + OAD patients in remission and response (without remission), data from SUSTAIN-1 were used to inform the relapse and loss of response risk (81, 82) during the continuation phase, Weeks 5–40 within the model. STAR*D was used to inform the relapse and loss of response risk for patients on OAD.

During the maintenance phase (for Weeks 41 and greater), the pooled relapse rates observed after Week 24 of maintenance in SUSTAIN-1 were used to estimate risk of recurrence for both ESK-NS + OAD and OAD.

The 4-week risk of relapse, loss of response and recurrence used in the model and taken from SUSTAIN-1 is presented in Table 47.

Table 47. 4-week risk of relapse, loss of response and recurrence

Treatment	Relapse (SE)	Loss of response (SE)	Recurrence (SE)
ESK-NS + OAD	5.57% (4.98)	4.19% (2.55)	2.88% (1.80)
OAD + PBO-NS	9.24% (3.10)	22.43% (5.43)	2.88% (1.80)

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; SE, standard error.

The sections below present the sources of data to inform the clinical data transition probabilities within the continuation (relapse prevention) and maintenance (recurrence prevention) treatment phases.

Loss of response in the continuation phase

Loss of response is the transition from the response health state back to an MDE health state. The loss of response transition for ESK-NS + OAD during the continuation phase of the model was based on data from SUSTAIN-1. Data were taken based on those patients who were 'stable responders[6]' at the end of the optimisation phase in SUSTAIN-1 (Week 16). All 'stable responders' who relapsed during the full follow-up of SUSTAIN-1 were counted in the loss of response rate calculation. The statistical analyses were based on the number of relapses from the start of follow-up of SUSTAIN-1 to a relapse event, or censoring. The 4-week loss of response for ESK-NS + OAD was 4.19%.

For the OAD loss of response transition, SUSTAIN-1 may not be the most appropriate data source. At the end of the optimisation phase of SUSTAIN-1, patients who were stable responders[6] or who were stable remitters[6] on ESK-NS + OAD were randomised 1:1 to either continue ESK-NS + OAD treatment or be switched to OAD + PBO-NS. Since those patients randomised to OAD + PBO-NS had received (and responded to) prior treatment with ESK-NS + OAD, it was unclear whether the withdrawal of ESK-NS might impact their loss of response or risk of relapse. To better reflect clinical practice, the model derived loss of response risk data for patients on OAD maintenance treatment from STAR*D (23). This is consistent with the approach taken in TA367 which used STAR*D for loss of response for OAD (46), in the absence of appropriate input data. The STAR*D trial is the largest study to examine the durability of OAD response in MDD and TRD and represents the best source for the loss of response on OAD in the model.

In STAR*D, patients were followed through up to four lines of OAD treatment for both MDD and TRD. Step 3 refers to patients who have had two OAD treatment failures, (corresponding to first-line TRD). Step 4 refers to patients who have had three treatment failures (second-line TRD). For the OAD loss of response transition, Kaplan-Meier plots for relapse during follow-up of patients who entered the follow-up

[6] In SUSTAIN-1, stable response was defined as a ≥50% reduction in the MADRS total score from baseline in each of the last two weeks of the optimisation phase without meeting the criteria for stable remission. Stable remission was defined as a MADRS total score of ≤12 for at least three of the last four weeks of the optimisation phase with one excursion of the MADRS total score >12 or one missing MADRS assessment permitted at Week 13 or 14 of the optimisation phase.

phase while not in remission after an average of 14 weeks (but had adequately benefited from acute treatment) were digitised. An exponential distribution was fitted to the data using published methodology (149). The mean of the fitted exponential distribution was used to inform the model. The 4-week loss of response risk for Step 3 (two treatment failures) was estimated as 22.2%, and 22.8% for Step 4 (three treatment failures).

A weighted average between Step 3 and 4 was used based on data from SUSTAIN-1. At baseline in SUSTAIN-1, 59% of patients had had two previous treatment failures (equivalent to Step 3), while 41% of patients had had three or more previous failures (equivalent to Step 4). This distribution of patients by previous treatment failures was combined with the relapse rates from STAR*D (Step 3 and Step 4) to calculate a weighted average 4-week loss of response rate of 22.4% for OADs which was deemed to be reflective of rates seen in clinical practice (143).

Risk of relapse in the continuation phase

Relapse is the transition from the remission health state to the MDE health state. The relapse rates for ESK-NS+OAD during the continuation phase of the model are derived from those patients who were 'stable remitters' at the beginning of the follow-up phase of SUSTAIN-1. In SUSTAIN-1, all 'stable remitters' who relapsed during the first 24 weeks of treatment were counted for the calculation of the relapse rates. The 24-week cut-off in SUSTAIN-1 corresponds to 36 weeks of treatment after the patient first reaches remission for ESK-NS+OAD post-acute treatment (12 weeks of optimisation + 24 weeks in SUSTAIN-1). The analysis counts the number of relapses over the total patient follow-up, from the start of maintenance to relapse or censoring over the first 24 weeks of maintenance. The corresponding 4-week relapse for ESK-NS + OAD was 5.57%.

For the OAD relapse transition, STAR*D was used. As noted above for the loss of response, SUSTAIN-1 had a re-randomised design, and as such, might be considered less suitable to inform the expected relapse rates for those patients receiving OADs. For relapse, the STAR*D Kaplan-Meier plot for risk of relapse during follow-up of patients who entered the follow-up phase while in remission after being on treatment for an average of 14 weeks was digitised. An exponential survival model was fitted to estimate the constant risk of relapse and loss of response.

Using this methodology, 4-week relapse risks for Step 3 and 4 were estimated to be 6.8% and 12.8%, respectively. Using the SUSTAIN-1 distributions of two (59%) and three or more (41%) failures, a weighted average relapse risk for OAD was estimated to be 9.2%.

Risk of recurrence in the maintenance phase

Recurrence is the transition from the recovery health state to the MDE health state. The pooled risk of relapse observed post-24 weeks of treatment in both study arms of the double-blind phase of the SUSTAIN-1 study were used to estimate the long-term risk of recurrence. It was conservatively assumed that there was no additional benefit for ESK-NS + OAD compared with OAD treatment in the maintenance phase of the model. This is conservative because a considerable proportion of patients continued ESK-NS + OAD treatment (see Figure 24). All stable remitters who relapsed after 24 weeks of maintenance treatment (equal to 36 weeks post-acute treatment) were counted for the calculation of the recurrence rates. The analysis counted the number of relapses over the total patient follow-up, from Week 25 to relapse or censoring. The 4-week recurrence rate for ESK-NS + OAD and for an OAD in the model was 2.88%.

B.3.2.9.2.3 Discontinuation for reasons other than relapse in the continuation and maintenance phase

As per SUSTAIN-1, patients discontinued treatment for reasons other than a lack of efficacy. SUSTAIN-1 provides data on all-cause discontinuation with relapse as a censoring event. Model discontinuation rates for any other reason (shown in Table 48) were comparator- and treatment phase-dependent and assumed to be independent of prior lines of treatment. Discontinuation for any other reason is presented in Table 48 for the acute, continuation, and maintenance phases.

No treatment discontinuation for other reasons was assumed in the acute treatment phase for ESK-NS + OAD or an OAD, as it was assumed that patients who do not respond or remit do not enter the continuation phase of treatment.

Discontinuation in continuation phase

For the continuation phase, a discontinuation risk for other reasons was derived from SUSTAIN-1 (81, 82, 150). An exponential distribution was fitted to the pooled data from the ESK-NS + OAD arm from stable responders and stable remitters to

estimate discontinuation for any reason. Relapse was counted as a censoring event. The estimated 4-week risk was 1.69% (20% annually) and is presented in Table 48. No treatment discontinuation for other reasons was assumed in the continuation phase for an OAD.

Table 48. Risk of discontinuation following initial treatment

Comparator	Acute		Maintenance Weeks 5–8		Maintenance in Response/Remission		Recovery	
	Risk	SE	Risk	SE	Risk	SE	Risk*	SE
ESK-NS + OAD	0.00%	0.00%	1.69%	0.42%	1.69%	0.42%	24.89%	6.22%

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; SE, standard error.
* Based on assumptions.

Discontinuation in maintenance phase

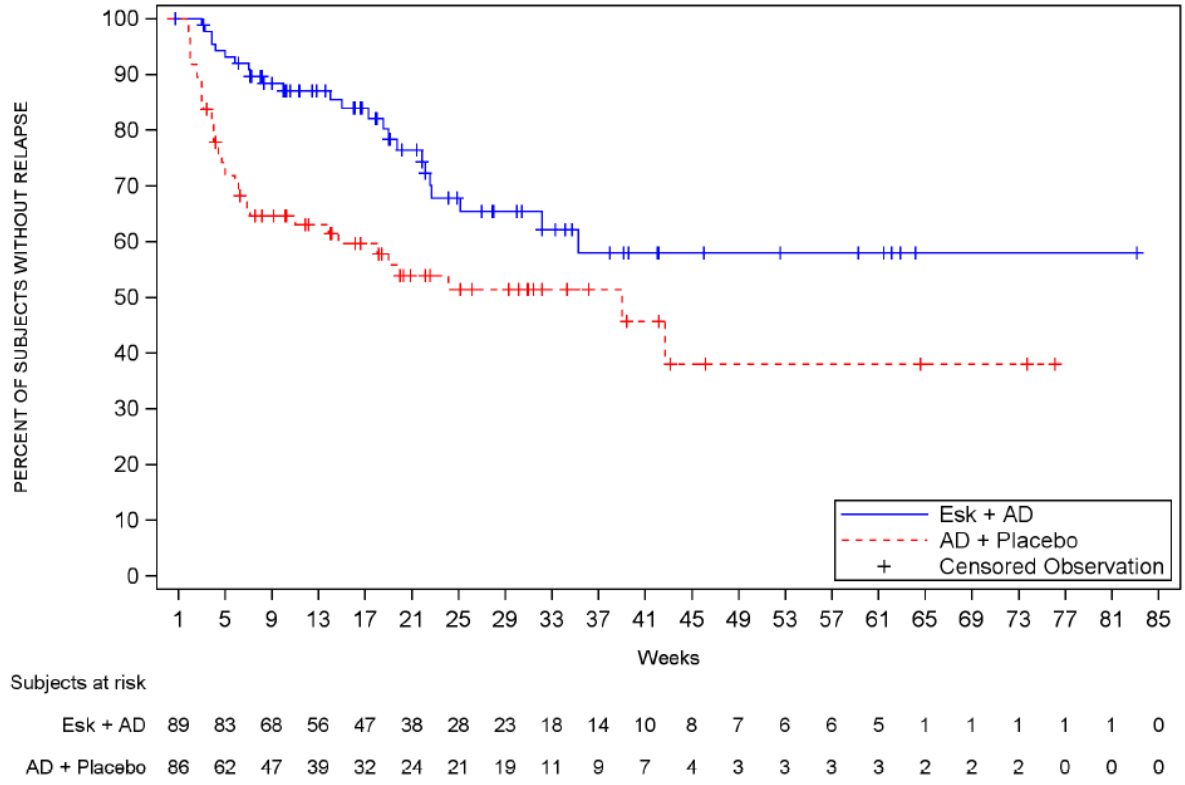
It is well established that when remission has been achieved and sustained for a sufficient period of time, the risk of relapse falls. In a clinical setting, a declaration of recovery raises the possibility that treatment can be discontinued or, if treatment is continued, the aim is prevention of a subsequent episode (151).

In the model, the definition of recovery was 36 weeks (approximately nine months) of relapse-free remission. This definition of recovery is supported by data on relapse among stable remitters from SUSTAIN-1 (81), which was discussed and validated by four UK clinicians in an advisory board held in June 2019 (143). In SUSTAIN-1, after 24 weeks of maintenance therapy (corresponding to 36 weeks after the acute treatment phase), patients from both treatment arms showed a considerable reduction in risk of relapse (Figure 23), indicating that patients have achieved stable remission of the disease.

In the model, therefore, from 36 weeks of relapse-free remission onwards, the subsequent emergence of depressive symptoms would be referred to as a recurrence.

For a proportion of remitters who are at high risk of relapse/recurrence, continued treatment for up to two years after achieving remission/recovery is recommended (5). OADs are used to prevent recurrence in the recurrence-prevention phase (5, 43), as per current clinical practice.

Figure 23. Relapse Kaplan-Meier curves – SUSTAIN-1 maintenance phase



Subjects at risk

Esk + AD	89	83	68	56	47	38	28	23	18	14	10	8	7	6	6	5	1	1	1	1	1	0
AD + Placebo	86	62	47	39	32	24	21	19	11	9	7	4	3	3	3	3	2	2	2	0	0	0

Abbreviations: AD, antidepressant; ESK + AD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant.

Once entering the maintenance phase, a benefit of ESK-NS is it can be discontinued while patients can still receive OAD for recurrence prevention. A total of 35.4% of patients were assumed to stop ESK-NS immediately upon achieving recovery. This percentage represents patients in SUSTAIN-1 who had ≤2 total number of MDD episodes, including the current episode (152). These patients were estimated to be at low risk of relapse based on available evidence (153-156) and could stop ESK-NS at recovery. UK clinical experts indicated this is aligned to the available evidence on risk of recurrence increasing after the first two depressive episodes (143). For the remainder of patients, treatment with ESK-NS +OAD was continued during the maintenance phase and discontinued over time. Based on UK expert opinion, a 4-week discontinuation risk of 25% for ESK-NS + OAD was used during recovery. This means that a proportion of patients continued therapy for up to 2 years in remission, depending on the level of risk of relapse/recurrence. This is aligned with NICE Clinical Guidelines. NICE CG90 recommends that treatment in patients at high risk of relapse is continued for two years, at which point a re-assessment should be performed to determine whether treatment continuation is required.

In the model, patients who achieved response (without remission) were assumed to continue ESK-NS + OAD in the maintenance (recurrence prevention) phase, as they are assumed to be at high risk of relapse. Evidence from the natural history of the disease shows that patients who have residual symptoms have a higher risk of relapse and recurrence compared with patients who are stable in remission (157). Patients in a response state have a higher level of symptoms than patients in remission.

Patients who stopped ESK-NS continued OAD for recurrence prevention, which is a conservative assumption as there are continued costs from the OAD.

Table 49. MDD episodes for patients in SUSTAIN-1

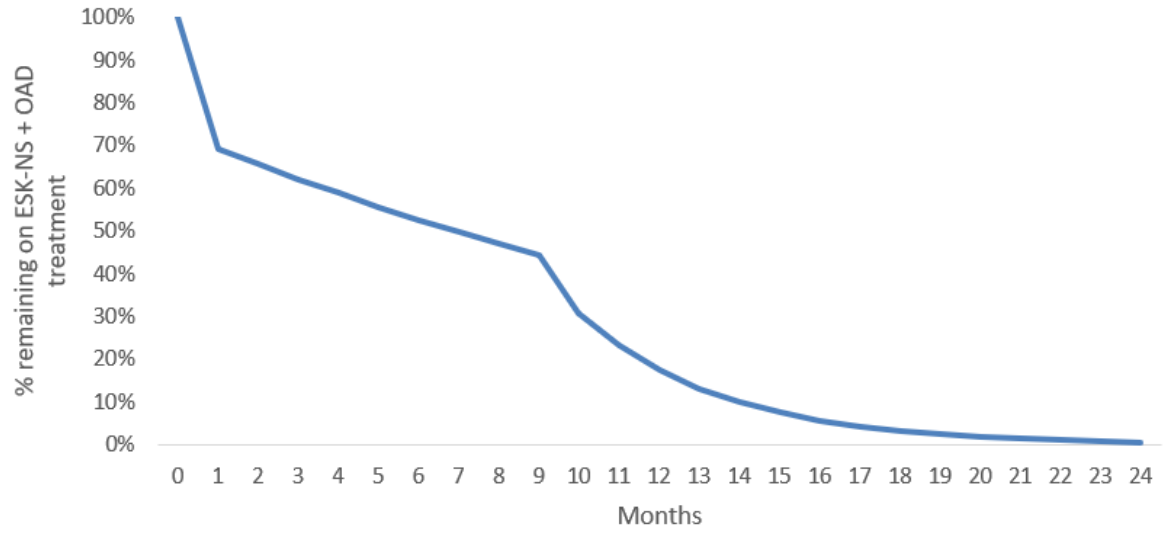
Number of MDD episodes	Frequency	Percent (%)	Cumulative frequency	Cumulative percent (%)
1	32	10.77	32	10.77
2	73	24.58	105	35.35
3	57	19.19	162	54.55
4	36	12.12	198	66.67
5	39	13.13	237	79.80
6	60	20.20	297	100.00

Abbreviations: MDD, major depressive disorder.
Source: Janssen data on file (152).

The above assumptions were discussed with UK clinical experts at an advisory board and based upon the available evidence it was concluded that these assumptions were valid.

The proportion of patients remaining on ESK-NS + OAD treatment using the discontinuation assumptions described above are shown in Figure 24.

Figure 24. Proportion of patients remaining on ESK-NS+ OAD until 24 months in the model



Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant

Note that the Phase 3 ESK-NS trials SUSTAIN-2 and SUSTAIN-3 (see Section B.2.2) were not appropriate for informing the duration of ESK-NS treatment in the model. In these trials, patients were encouraged to stay on treatment to fulfil the study protocol to assess long-term safety.

B.3.2.9.3 Clinical data: Subsequent treatments

As per the expected EMA licence wording, ESK-NS is indicated for adults with treatment-resistant major depressive disorder who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode. The clinical data to inform the economic model (TRANSFORM-2 and SUSTAIN-1) included patients who reflect the expected licence wording. As such, ESK-NS is positioned as first line TRD treatment.

As previously discussed (see Section B.1.3.7), the treatment paradigm for TRD is complex and no standard approach exists. In addition, there are no effectiveness data to consider for specific OADs or other treatment strategies explicitly as subsequent therapies in the model. As noted above in Section B.3.2.2, the model considers three further lines of subsequent treatment (2nd line, 3rd line and 4th line TRD). Clinical effectiveness transition probabilities for 2nd -4th line TRD were derived from STAR*D data (23), with data being converted to 4-week risks using standard

formulae (158). STAR*D included OAD and other augmentation strategies in 1st and 2nd line TRD.

Estimates of remission and response rates from STAR*D were used to derive an average reduction in effectiveness for 2nd line, 3rd line and 4th line TRD treatment. Using the SUSTAIN-1 distributions of two (59%) and three or more (41%) OAD failures, weighted averages were estimated for TRD lines two, three, and four. Although evidence suggests that risk of relapse increases with each subsequent failure (61), the loss of response and relapse for each subsequent line were conservatively assumed to be equal to that in STAR*D Step 4, in the absence of more appropriate data. Recurrence risk was assumed to be the same as the pooled estimate from SUSTAIN-1 used for the first line TRD treatment in the absence of more appropriate data (Section B.3.2.9.2.2). For sensitivity analysis, a confidence interval of ±10% of the mean was assumed for all probabilities shown in Table 50.

Note that the use of STAR*D data to inform the effectiveness of subsequent lines of treatment is consistent with TA367. In TA367, the ERG and clinical expert accepted that the absolute effectiveness of each OAD likely declines with each subsequent line of treatment. The NICE Appraisal Committee acknowledged that the chance of achieving remission likely decreased with each line of OAD treatment given. The Appraisal Committee accepted, with limitations, that the STAR*D trial provided the best data on the prognosis (including relapse rate) of patients requiring multiple lines of OAD treatment.

For the present cost-effectiveness analysis, the absolute treatment effect of OADs reduced with each subsequent line of treatment as presented in Table 50. This was validated in two separate advisory boards by a total of ten clinical experts in the UK based on available evidence (143).

Table 50. Health state transition probabilities – subsequent treatment

Treatment	MDE to Response*	MDE to Remission*	Response to Remission†	Loss of Response†	Relapse†	Recurrence†
TRD line 2	3.54%	0.86%	2.76%	12.79%	22.81%	2.88%
TRD line 3	2.75%	0.65%	2.76%	12.79%	22.81%	2.88%
TRD line 4	2.14%	0.49%	2.76%	12.79%	22.81%	2.88%

Abbreviations: MDE, major depressive episode; TRD, treatment-resistant depression.
* Evaluated at the end of the acute phase.
† Per 4-week cycle.

B.3.2.9.4 Clinical data: Best supportive care efficacy

The treatment paradigm for TRD is complex, particularly in later lines of treatment, and therefore one specific treatment strategy was not explicitly modelled. In the model, the best supportive care treatment phase is for patients whose disease has failed all previous treatments (5th line TRD and onwards). In this phase, patients could achieve response or remission at every cycle, and those who had achieved response or remission could experience loss of response or relapse at every cycle.

The efficacy estimates (response and remission) during the best supportive care treatment phase were based on the HTA monograph by Edwards et al. 2013 (128) which were estimated from expert UK clinical opinion based on available evidence. The authors from Edwards et al. were contacted to confirm how clinical opinion was derived and they confirmed that the results of the STAR*D trial formed part of the available evidence considered by the clinical experts informing the Edwards et al 2013 publication. The efficacy estimates from the study was further validated by clinical experts in June 2019 (143).

Standard calculations were used to convert the reported 2-month probabilities to 4-week probabilities. To avoid double counting, the transition probability for remission was subtracted from the probability for response to derive the transition probability for MDE to response (excluding remission) that was used in the current model.

For sensitivity analysis, a confidence interval of ±10% of the mean was assumed for all probabilities shown in Table 51.

Table 51. Health state transition probabilities – best supportive care treatment mix

Treatment	Response†*	Remission†	Loss of Response†	Relapse†
Best supportive care treatment mix	0.83%	0.41%	10.38%	4.20%

† Per four-week cycle.
* Response minus remission.

B.3.2.9.5 Adverse events

In TRANSFORM-2, AEs, defined as those first reported or worsening in severity after initiating study treatment, were of mild to moderate severity. There were 14 most commonly reported AEs, with incidence ≥5% and occurring more frequently in the ESK-NS + OAD over the OAD + PBO-NS arm. These include nausea/vomiting, dissociation, dizziness, headache, vertigo, dysgeusia (distortion of sense of taste),

somnolence, sedation, insomnia, blurry vision, increased blood pressure, paraesthesia, hypoesthesia (reduced sense of touch or sensation), and fatigue (see Section B.2.10.1.1). Over 90% of TEAEs resolved on the same day of nasal spray self-administration (159). Patients receiving ESK-NS + OAD were monitored during self-administration and post-administration for one hour on average. It was therefore assumed that, in the base case, there would be no cost or negative impact on quality of life associated with AEs.

For completeness, a scenario analysis including AEs was conducted based on the rates of AEs seen in TRANSFORM-2 (see Table 37 and Table 38 in Section B.2.10.1.1) and their associated disutility.

B.3.2.9.6 Mortality

Mortality was accounted for using two different sources for risk of death, which were applied concurrently: all-cause mortality risk, specific to age and sex, and an excess annual mortality for TRD, associated with suicide, of 0.47% (13) linked to the MDE health state. It was assumed that half the excess mortality risk associated with suicide would still be present in the response state.

Sex and age-specific all-cause mortality were sourced from the Office of National Statistics life tables (160). The model firstly derived a weighted mortality risk for each age. This was weighted according to the proportion of males and females in the cohort and the baseline age. The risk was applied to the number of patients alive at the beginning of the cycle in each health state:

$$n_{death\ all-cause\ cycle\ i} = n_{alive\ cycle\ i} \times p_{age},$$

where:

- i is the cycle under consideration,
- $n_{death\ all-cause\ cycle\ i}$ is the number of patients that die during cycle i, due to all-cause mortality,
- $n_{alive\ cycle\ i}$ is the number of patients alive at the beginning of cycle i, and
- p_{age} is the mortality risk (i.e., probability) at a specific age.

Additional mortality from suicide attempts was also explicitly modelled, which was performed in two steps. First, for patients in each health state, the number of suicide attempts was calculated, and second, a proportion of these suicide attempts were considered fatal, giving the total of patients who died from suicide. The calculation was as follows: risk was applied to the number of patients alive at the beginning of the cycle in each health state:

$$n_{death\ suicide\ cycle\ i} = n_{alive\ cycle\ i} \times SA_{hs} \times p_{fatal},$$

where:

- i is the cycle under consideration,
- $n_{death\ suicide\ cycle\ i}$ is the number of patients that die during cycle i due to suicide,
- $n_{alive\ cycle\ i}$ is the number of patients alive at the beginning of cycle i,
- SA_{hs} is the risk of suicide attempt (i.e., probability) at the current health state, and
- p_{fatal} is the risk of a suicide attempt being fatal.

B.3.2.10 Measurement and valuation of health effects

B.3.2.10.1 Health-related quality-of-life data from clinical trials

EQ-5D-5L was used to measure the quality of life of patients in the TRANSFORM-2 trial from which utility values could be derived:

- Data were retrospectively mapped to EQ-5D-3L based on the UK valuation set (161), as described in Section B.3.2.10.2.
- This represents NICE's preference as per the NICE reference case.
- Further details of the methodology used to derive the utilities are presented in Section B.3.2.10.2.

B.3.2.10.2 Mapping

Individual scores from the five dimensions were used to obtain a weighted health status index using the method from van Hout and colleagues (2012) (161), described below:

- Scores from each dimension were combined to obtain a 5L profile score or health state: e.g. a score of 1 for each dimension gives a 5L profile score of 11111. Dimension scores were combined in the following order: Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression.
- Utilities for each possible profile on the EQ-5D-3L were computed using the Dolan (1997) algorithm, which is specific to the UK (162).
- Patients were assigned probabilities for each possible profile on the EQ-5D-3L based on their profile on the EQ-5D-5L.
- The utility score on the EQ-5D-5L for each patient was computed as a weighted average of the utilities, where weights were the above-mentioned probabilities.

In the model, the utilities are stratified by health state. The health state QALYs at each cycle are calculated by multiplying the user-specified utility by the duration of the Markov cycle (28 days) expressed in years.

As noted above, disutility due to AEs was included as a scenario. For each AE included in the model, treatment-dependent inputs are used to calculate the associated utility decrement by treatment: the incidence for each AE by treatment, the duration of each event, and the utility decrement of each event. The per-cycle utility decrement is calculated for all AEs and then summed to give a per-cycle AE-associated utility decrement for each treatment. This decrement is added to the utility only for patients on treatment during the acute phase; it is assumed that patients who are not on treatment do not experience any AEs. AEs associated with treatment are assessed only in the acute treatment phase and not in the maintenance phase, as it is assumed that patients are likely to have adapted well to the treatment by this time. The inclusion of AE-associated utility decrement is likely a conservative assumption, as the impact of AE on quality of life may already be captured in the utility analysis for the health states. Thus, the inclusion of AE-associated utility decrements may be double counting the impact of AEs on quality of life.

After the patient utilities (and disutilities in the scenario) were calculated, the values were aggregated across the health states for each cycle to obtain QALYs over time.

Utility scores were estimated for all the following health states in the Markov model using data from the TRANSFORM-2 study:

- Baseline/Major Depressive Episode (MDE)
- Response at 4 weeks/each cycle
- Remission at 4 weeks/each cycle
- Recovery after 36 weeks in remission

The baseline utility data were used to inform the utility score for patients in MDE.

Remission was defined as having a total MADRS score of 12 or less at week 4 (Day 28).

Response was defined as an improvement of 50% or more in total MADRS score at week 4 (day 28) compared with baseline. In the economic model the health states “remission” and “response” are mutually exclusive, meaning that patients in the health state “response” are patients who showed response, but did not reach remission.

The utility score for patients achieving recovery was assumed to be the same as the utility score for patients achieving remission at 4 weeks.

A set of descriptive summaries, i.e. mean, standard deviation [SD], standard error [SE], minimum, lower quartile [Q1], median, upper quartile [Q3], and maximum was computed for all the corresponding utility scores.

Utility scores were assumed to depend only on the health state of the patient, and not to be treatment specific. Data from both treatment arms in the TRANSFORM-2 study were pooled to increase the robustness and precision of estimates.

Analyses were based on observed data only and no imputation for missing data was performed.

Table 52 provides a description of the utility score at baseline in TRANSFORM-2 study, which was used in the model to populate the utility for patients in the MDE health state.

Table 52. TRANSFORM-2 baseline utility score

Analysis visit	N	Mean	SD	SE	Minimum	Q1	Median	Q3	Maximum
Baseline	223	0.417	0.233	0.016	–0.183	0.259	0.414	0.599	0.906

Abbreviations: SD, standard deviation; SE, standard error.
Q1 = lower quartile ; Q3 = upper quartile.

Table 53 provides a description of the utility score at Week 4 (day 28) in the TRANSFORM-2 study by health state, which was used in the model to populate the utility for patients in the response and remission health states.

Table 53. TRANSFORM-2 Day 28 utility score (by health state)

Analysis Visit	Response	Remission	N	Mean	SD	SE	Minimum	Q1	Median	Q3	Maximum
Day 28	Yes	No	38	0.764	0.123	0.020	0.420	0.706	0.795	0.837	1.000
		Yes	87	0.866	0.122	0.013	0.209	0.806	0.879	1.000	1.000

Abbreviations: SD, standard deviation; SE, standard error.
Q1 = lower quartile; Q3 = upper quartile.

Aggregating results from the two tables above, the estimates used to populate the utilities per health state in the economic model are summarised in Table 54.

Table 54. Summary of utilities used in the model (by health state)

Health State	Utility	Standard deviation	SE	Source
MDE	0.417	0.233	0.016	TRANSFORM-2
Response	0.764	0.123	0.020	TRANSFORM-2
Remission	0.866	0.122	0.013	TRANSFORM-2
Recovery	0.866	0.122	0.013	Assumption*

Abbreviations: MDE, major depressive episode; SE, standard error
*Assumed to be the same as remission

B.3.2.10.3 Health-related quality-of-life studies

A SLR (initial search in July 2018 and updated in April 2019) was conducted to identify studies reporting on preference-based health state utility values (HSUVs) associated with MDD and TRD. Full details of the methodology and results of included studies are presented in Appendix H.

Only one study identified utilities for a TRD population but was not directly applicable to the NICE decision problem, since data were not reported per health state. The included study was not used in the economic model as EQ-5D data were directly available from TRANSFORM-2, which provides utility data directly relevant to the decision problem and the population of interest.

B.3.2.10.4 Health-related quality-of-life data used in the cost-effectiveness analysis

The HRQoL of the cohort over the time horizon of the model was considered by assigning a utility value to each health state.

As above, the health state utilities used in the analysis were derived from the EQ-5D-5L TRANSFORM-2 patient-level data pooled across both the ESK-NS + OAD and OAD arms, using the UK value set (161), and are presented in Table 54. Note that the utility for the recovery state was conservatively assumed to be equal to the remission health state, which was used by the NICE Appraisal Committee in TA367. Since the recovery state related to patients who had spent an extended period in the remission state, it could be hypothesised that these patients experienced an increase in utility. If this was the case, the current assumption could be conservative since ESK-NS + OAD has higher efficacy than OAD + PBO-NS and therefore more patients would be in the recovery state.

B.3.2.10.5 AE disutilities

Disutility due to dry mouth was obtained from Revicki. et al 1998 (163). The study reported utilities for patients in North America with MDD who had completed at least eight weeks of treatment. The disutility due to vision blurred was derived from Sullivan et al. 2006 (164) which reported EQ-5D index scores for chronic conditions in the US, estimated from the nationally representative Medical Expenditure Panel Survey pooled from 2000–2002 with 38,678 adults (164). Other disutilities listed in Table 55 were from the study by Sullivan et al 2004 (165), a cost-effectiveness study of eight OADs used as initial treatment for depression in the US.

Since the AEs related to ESK-NS observed in the ESK-NS + OAD arm of TRANSFORM-2 were transient and resolved within hours, the scenario analysis conservatively assumed a duration of one day for all AEs.

Table 55. AE disutilities for scenario analysis

AE	Disutility (SE)
Anxiety	–0.129 (0.032)
Blood pressure increased	0.000 (0.000)
Delusional perception	0.000 (0.000)
Derealisation	0.000 (0.000)
Diarrhoea	–0.044 (0.011)
Dissociation	0.000 (0.000)
Dizziness	–0.085 (0.021)
Dizziness postural	0.000 (0.000)
Dry mouth	–0.010 (0.003)
Dysgeusia	0.000 (0.000)
Fatigue	–0.085 (0.021)

AE	Disutility (SE)
Feeling abnormal	–0.085 (0.021)
Feeling drunk	–0.085 (0.021)
Headache	–0.115 (0.029)
Hypoaesthesia	0.000 (0.000)
Hypoaesthesia oral	0.000 (0.000)
Illusion	–0.085 (0.021)
Insomnia	–0.129 (0.032)
Nasal discomfort	0.000 (0.000)
Nausea	–0.065 (0.016)
Paraesthesia	0.000 (0.000)
Paraesthesia oral	0.000 (0.000)
Somnolence	–0.085 (0.021)
Throat irritation	–0.010 (0.003)
Vertigo	–0.085 (0.021)
Vision blurred	–0.050 (0.012)
Vomiting	–0.065 (0.016)

Abbreviations: AE, adverse event; SE, standard error.

B.3.2.10.6 Family and caregiver spill-over

The detrimental impact of MDD and particularly TRD on patient HRQoL is clear from the utility data (Section B.2.6.1.5.2) and from Section B.3.2.11.5. As described in NICE CG90 there are additional significant impacts on the carers of people with depression, “marital and family relationships are frequently negatively affected, and parental depression may lead to neglect of children and significant disturbances in children” (5). NICE CG90 recognises that the experience of depression can affect the whole family and often the community; however, measuring the associated impact is challenging and complex. A recent systematic review (166) investigated the spill-over effect of a spectrum of diseases and conditions. The review identified two studies that considered depression and mental illness. Additionally, in market research conducted by Janssen in the UK, 95% (n=90) of carers reported that looking after someone with TRD had an impact on their own quality of life, and 51% of carers reported that looking after someone with TRD impacts on their own relationships and mental health (167). The NICE reference case states that the perspective on outcomes should be all direct health effects, whether for patients or other people. As such, a scenario analysis was conducted where the impact on family and/or carers was considered, using assumptions.

This analysis assumed that there would be a negative impact on quality of life to family and/or caregivers while the patient was in and remains in the MDE health state. It is acknowledged that depression can often be associated with loneliness and in such instances the impact on society would be minimal. More often than not, multiple people will be affected (parents, partners, children, and friends) and as such it is appropriate to demonstrate the potential impact (including societal) this may have. According to the Office for National Statistics (ONS), the average household size is 2.4 and as such the utility decrements presented above could be spread across 1.4 additional household members or potentially increased by a factor of 40%. This would limit the impact to those living with a patient while the true impact may be much broader.

B.3.2.11 Cost and healthcare resource use identification, measurement, and valuation

A SLR (initial search in July 2018 and updated in April 2019) was conducted to identify studies reporting on UK-based costs and healthcare resource use associated with MDD and TRD. Details of the SLR of studies reporting cost and resource use data are presented in Appendix I.

In total,19 studies were identified that considered MDD, but only two specifically considered patients with TRD (4, 168). One study was a UK-based budget impact analysis presented as a conference abstract and which assessed the budget impact of Vagus Nerve Stimulation (VNS) for TRD in England (168). Although patients were referred to as treatment resistant, no formal definition of resistance was provided. The study was therefore not deemed appropriate for the model. The second study was a retrospective UK-based cost analysis which assessed the costs associated with a group of patients manifesting a severe form of TRD in the 12 months prior to participation in a major RCT (4). In this analysis, treatment resistance was defined as at least two failed prior treatment attempts, one of which must have included an OAD. The study highlighted the high costs associated with severe forms of TRD with an estimated total annual cost of £22,124 (SD £23,466) reported. A significant proportion of costs were attributed to social care (26%) and employment-related (54%) categories. Although reflective of the target population of this analysis, the

study did not contain the data granularity required to inform the analysis, as the study did not report data per health state.

Cost and resource use data were identified via a retrospective chart review conducted specifically for this submission (see Appendix P), as noted in Section B.3.2.11.5. In addition to health state costs, the model considered the costs of AEs associated with primary treatments, although these were not included in the base case.

Parameters used in the economic evaluation are presented in Table 60.

B.3.2.11.1 Intervention, resource, and comparator costs

ESK-NS comes as a single-use device that delivers a total of 28 mg of esketamine in two sprays (one spray per nostril). One device (for a 28 mg dose), two devices (for a 56 mg dose), or three devices (for an 84 mg dose) are to be used, with a five-minute interval between each device. The cost per device is £163, equating to a cost of £326 per 56 mg dose and £489 per 84 mg dose.

The average number of sessions per week and devices per session in the acute phase were derived from TRANSFORM-2, while for subsequent time-points they were derived from SUSTAIN-1. For sensitivity analysis, a confidence interval of ±10% of the mean of the number of sessions per week as well as number of devices per session was assumed for all probabilities shown in Table 57. In addition, as per the wording in the SmPC (see Appendix C), a plausibility limit was applied to prevent the number of ESK-NS devices being less than two (56 mg) or greater than three (84 mg). Similarly, the number of sessions was not allowed to drop below 0.5, equivalent to administration every other week, or go above two in the acute phase (equivalent to administration twice a week) or above one in the maintenance phase (equivalent to administration once a week).

B.3.2.11.2 Cost of supervision of self-administration and post-administration monitoring

ESK-NS is self-administered but this needs to be performed under the supervision of a healthcare professional. During and after ESK-NS administration, patients are monitored for sedation and dissociation until the patient is stable based on clinical

judgement. Patients will typically need to wait 5 minutes between self-administering each device, and so the typical administration time will be between 5–10 minutes for 56 mg (two devices) and 84 mg (three devices), respectively. The current draft SmPC states, “after dosing with Spravato®, reassess blood pressure at approximately 40 minutes and subsequently as clinically warranted. If blood pressure is decreasing, or no increase was observed, and the patient appears clinically stable, the patient may leave at the end of the post-dose monitoring period; if not continue to monitor.” Following the administration, therefore, patients will need to be observed for a minimum of 40 minutes. In the model, however, it was conservatively assumed that patients would be observed for 60 minutes on average. As per Table 38, 9.57% of patients experienced a blood pressure increase (169).

Following discussions with HCPs, it was assumed that the self-administration of ESK-NS would be managed in a clinic environment. Based on trial investigators’ experience, the supervision of self-administration of a group of six patients in a clinic could be managed by one or two nurses. It was conservatively assumed that two nurses were needed for the supervision of the self-administration of ESK-NS. One band 5 hospital nurse, with a rate of £90 per hour of patient contact and £37 per hour of non-patient contact, would be assisted by a band 4 hospital nurse with an hourly rate of £28. It was assumed that 0.25 hours (15 minutes) with the band 4 and 5 nurse would be required to prepare the medicine and complete associated paperwork. One hour would be required to supervise the six patients concurrently during the self-administration. Finally, 1.25 hours (1 hour and 15 minutes) of a band 5 nurse, would be sufficient to observe the six patients during the post-administration phase. This final step is for observation only and clinical experience from ESK-NS trialists indicate that the monitoring is minimal. It is therefore expected that the Band 5 nurse would be able to undertake other activities during the post self-administration monitoring phase and so the non-patient contact cost was used.

These assumptions resulted in an average cost per patient, per administration of £30.08. Table 56 provides a summary of the required resources and associated costs for the supervision of self-administering ESK-NS and the post-administration monitoring.

Table 56. Administration and observation resource use and costs

	Resource use	Cost per hour	Total duration HCP is required (hours)	Number of patients in cohort	Average cost per session per patient
Administration/ preparation	1x band 4 nurse	£28	0.25	6	£30.08
	1x band 5 nurse	£37	0.25		
Supervision of self-administration	1x band 4 nurse	£28	1		
	1x band 5 nurse	£90*	1		
Monitoring post self-administration	1x band 5 nurse	£37	1.25		

Abbreviations: HCP, healthcare professional.

The HCPs interviewed indicated that this time would likely reduce as clinics became more accustomed to the treatment and the associated observation required. In sensitivity analysis, a low value of £9.43 per administration was used, assuming one band 4 hospital nurse for 1.25 hours total per patient for the entire self-administration and subsequent observation period and high value of £120 per administration assuming the same time period with a band 5 hospital nurse.

B.3.2.11.3 Acquisition and resource costs

A summary of drug acquisition and resource costs through all treatment phases in the model is presented in Table 57.

Table 57. Acquisition and resource costs associated with ESK-NS administration

Items	Acute Weeks 1–4	Continuation (relapse prevention) Weeks 5–8	Continuation (relapse prevention) Weeks 9–40	Maintenance (recurrence prevention) Week 41 onwards
Average number of sessions per week	1.850	0.992	0.711	0.675
Average number of devices per session	2.530	2.605	2.605	2.571
Drug acquisition cost per 4-week cycle	£3,051.61	£1,684.73	£1,208.42	£1,131.00
Administration and observation costs	£222.60	£119.33	£85.60	£81.17
Total cost per 4-week cycle	£3,274.21	£1,804.06	£1,294.02	£1,212.17

Abbreviations: ESK-NS, esketamine nasal spray.

ESK-NS is initiated with a new OAD. The model assumed that the newly initiated OAD would be the same as that prescribed if ESK-NS was not available. The weekly/4-weekly cost of the OAD was therefore assumed to be equal for ESK-NS + OAD and OAD + PBO-NS.

B.3.2.11.4 Comparator costs

Prescription cost analysis (PCA) (170) was used to identify the average cost per mg of OADs and market share data was estimated from IQVIA data (2). The analysis considered the costs of all OADs with a market share greater than 3% of all treatments (note the data shown was reweighted to account for the omitted products). Although many OADs have multiple indications, the majority are low cost and as such the split was assumed to have minimal impact. Within the analysis, because ESK-NS was incremental to OADs, the associated cost was equal on both sides. As such, PCA offered a reflective price of the OADs considered for this analysis. The daily doses for duloxetine, escitalopram, sertraline, and venlafaxine were derived from the final doses of the OADs in TRANSFORM-2. For the other OADs a mid-point of the plausible dose ranges was chosen. For the purposes of sensitivity analysis, only the weighted average 4-week cost of the OADs was varied using the lowest (£0.66 for a 50 mg daily dose of sertraline) and highest (£18.05 for a 375 mg daily dose of venlafaxine) plausible costs estimates as the range.

Table 58. Weighted average OAD cost

OAD	Market share (%)	Daily dose (mg)	Average cost per mg	Average cost per 4-weeks
Amitriptyline	13.78	100.00 mg	£0.0029	£8.00
Citalopram	17.89	30.00 mg	£0.0031	£2.57
Duloxetine	5.40	59.00 mg	£0.0052	£8.54
Escitalopram	2.42	18.15 mg	£0.0050	£2.56
Fluoxetine	13.38	40.00 mg	£0.0026	£2.93
Mirtazapine	19.66	30.00 mg	£0.0027	£2.28
Sertraline	18.53	129.70 mg	£0.0005	£1.71
Venlafaxine	8.94	210.17 mg	£0.0017	£10.12
Weighted average cost per 4 weeks				£4.15

Abbreviations: OAD, oral antidepressant.

B.3.2.11.5 Health-state unit costs and resource use

In the absence of evidence from TRANSFORM-2, SUSTAIN-1 or the published literature, estimates of resource use in the MDE, relapse, recurrence, and recovery

states were based on a retrospective chart review of medical records of patients with TRD (see Appendix P).

Data from 295 patients with TRD in the UK were collected from both primary and secondary care in the UK from nine GPs and 30 psychiatrists, respectively. Each physician provided data on up to 10 patients, abstracting data from patient medical records into an electronic case report form (eCRF). Data captured included numbers of GP visits, psychiatrist visits, psychotherapies, psychiatric hospitalisations (general ward/psychiatric hospital), A&E visits, length of stay when hospitalised, antidepressant treatment history (including dosing, duration, line of therapy, adherence), other psychiatric medications prescribed (anxiolytics, hypnotics, and antipsychotics), ECT, medical devices, AEs, management of AEs, and suicides. Further details regarding the methodology and results of the chart review can be found in Appendix P.

This study is directly relevant to the decision problem as direct medical costs are collected from UK patients with TRD according to their health state. Furthermore, clinical experts participating in an advisory board in June 2019 suggested these costs are aligned, or perhaps even lower, than other analyses of the costs of symptomatic patients with TRD.

The 4-week (28-day) resource use cost per health state is shown in Table 59. Costs used are all monthly healthcare resource use (HCRU) costs, excluding drug treatment costs. The costs of response were conservatively considered to be equivalent to the costs of remission. This is a conservative assumption biased against ESK-NS, as patients in the OAD arm spend greater time in the response state, and it might be expected that patients in response have greater HCRU costs compared with patients in remission. For the cost of the MDE health state, the costs of the initial MDE health state was pooled with relapse health state costs, as this is aligned to the MDE health state as used in the model.

Table 59. List of health states and associated costs in the economic model

Health states	Value (95% CI)
MDE	£980.08 (761.48, 1,198.67)
Response	£164.46 (102.81, 226.11)
Remission	£164.46 (102.81, 226.11)
Recovery	£83.75 (47.97, 119.53)

Abbreviations: CI, confidence interval; MDE, major depressive episode.

Although the model considered the clinical impact associated with subsequent lines of therapy, we have conservatively excluded the costs from this analysis. The treatment paradigm for TRD is complex and could range from switching to another OAD, augmenting the current therapy, or initiating ECT, and this varies from patient to patient. Due to the significant variation, and for simplicity within the model, the analysis excluded the costs of augmentation and combination therapies. Other treatments, such as CBT or ECT, are captured within the health state costs.

It could be hypothesised that as patients with TRD progressed through further lines of treatment they become costlier to treat as the number of remaining available treatment options decreases. Omitting these costs is therefore conservative, especially for ESK-NS, given the high efficacy rates observed in clinical trials that would delay switching to subsequent treatments.

B.3.2.11.6 AE unit costs and resource use

As previously noted, in the base case analysis, AEs were not considered. However, for completeness, a scenario analysis including a GP contact (at £37 per contact) for all ESK-NS-associated AEs was considered. This is a conservative scenario as most AEs in TRANSFORM-2 were transient and resolved during the post-administration observation phase.

B.3.2.11.7 Miscellaneous unit costs and resource use

NICE CG90 states that “depression incurs significant non-healthcare costs such as social service costs, direct costs to patients and their families, and lost productivity costs due to morbidity or premature mortality” (5). McCrone et al. (2018) (4) showed that 80% of the total UK societal burden of TRD was due to lost productivity and carer burden. As this analysis was conducted from the health service perspective (as per NICE guidance), such non-healthcare costs were not considered in the base

case. Analyses have shown that including such costs would have further increased the probability of ESK-NS + OAD being cost-effective versus OAD alone (see Section B.3.4.4.7) .

B.3.2.12 Summary of base case analysis inputs and assumptions

B.3.2.12.1 Summary of base case analysis inputs

A table of variables and inputs used in the base case analysis is provided in Table 60.

Table 60. Parameters used in the economic model

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Section/table
All treatment phases			
Time horizon	5	1 to 5 (Not varied in PSA)	B.3.2.4
Discount rate: Costs	3.50%	0.00% to 6.00% (Not varied in PSA)	B.3.2.5
Discount rate: Outcomes	3.50%	0.00% to 6.00% (Not varied in PSA)	
Age at model entry	45.70	22.40 to 69.00 (Not varied in PSA)	B.3.2.1
Proportion of patients that are female	61.90%	61.30% to 68.35% (Not varied in PSA)	
Utility: MDE	0.42	0.39 to 0.45 (Gamma)	B.3.2.10.4
Utility: Response	0.76	0.72 to 0.80 (Gamma)	
Utility: Remission	0.87	0.84 to 0.89 (Gamma)	
Utility: Recovery	0.87	0.84 to 0.89 (Gamma)	
Admin and monitoring cost for ESK-NS + OAD	£30.08	£7.09 to £120.00 (Gamma)	B.3.2.11.2
Cost of OAD	£4.15	£0.66 to £18.05 (Gamma)	B.3.2.11.4
Mortality excess associated with MDE	0.47%	0.42% to 0.52% (Beta)	B.3.2.9.6
Mortality excess associated with response	0.24%	0.21% to 0.26% (Beta)	
Health state cost: MDE	£980	£761 to £1,199 (Gamma)	B.3.2.11.5
Health state cost: Response	£164	£103 to £226 (Gamma)	
Health state cost: Remission	£164	£103 to £226 (Gamma)	
Health state cost: Recovery	£84	£48 to £120 (Gamma)	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Section/table
ESK-NS treatment parameters			
ESK-NS + OAD administrations/week - Week 1-4	1.85	1.67 to 2.00 (Gamma)	B.3.2.11.3
ESK-NS + OAD administrations/week - Week 5-8	0.99	0.89 to 1.00 (Gamma)	
ESK-NS + OAD administrations/week - Remission	0.71	0.64 to 0.78 (Gamma)	
ESK-NS + OAD administrations/week - Recovery	0.67	0.61 to 0.74 (Gamma)	
ESK-NS + OAD devices/administration - Week 1-4	2.53	2.28 to 2.78 (Gamma)	
ESK-NS + OAD devices/administration - Week 5-8	2.61	2.34 to 2.87 (Gamma)	
ESK-NS + OAD devices/administration - Remission	2.61	2.34 to 2.87 (Gamma)	
ESK-NS + OAD devices/administration - Recovery	2.57	2.31 to 2.83 (Gamma)	
Acute treatment phase			
Remission during acute phase - ESK-NS + PBO	52.48%	42.74% to 62.21% (Beta)	B.3.2.9.1
Response during acute phase - ESK-NS + PBO	69.31%	60.31% to 78.30% (Beta)	
Remission during acute phase - OAD + PBO-NS	31.00%	21.94% to 40.06% (Beta)	B.3.2.9.1
Remission during acute phase - OAD + PBO-NS (Adjusted for 6 visits)	18.00%	16.20% to 19.80% (Not varied in PSA)	
Response during acute phase - OAD + PBO-NS	52.00%	42.21% to 61.79% (Beta)	
Response during acute phase - OAD + PBO-NS (Adjusted for 6 visits)	34.00%	30.60% to 37.40% (Beta)	
Discontinuation during induction: ESK-NS + OAD	0.00%	0.00% to 0.00% (Beta)	Table 48
Discontinuation during induction: OAD + PBO-NS	0.00%	0.00% to 0.00% (Beta)	
Continuation (relapse prevention) treatment phase			
Transition from response to remission (per 4-week cycle) - ESK-NS + OAD	19.93%	17.93% to 21.92% (Beta)	B.3.2.9.2.1
Transition from response to remission (per 4-week cycle) - OAD + PBO-NS	12.39%	11.15% to 13.63% (Beta)	
Loss of response (per 4-week cycle) - ESK-NS + OAD	4.19%	3.77% to 4.61% (Beta)	B.3.2.9.2.2
Relapse (per 4-week cycle) - EKS-NS + OAD	5.57%	5.01% to 6.12% (Beta)	B.3.2.9.2.2
Relapse rate from SUSTAIN-1 - OAD + PBO-NS	12.31%	11.08% to 13.54% (Beta)	B.3.2.9.2.2
Loss of response from SUSTAIN-1 - OAD + PBO-NS	14.86%	13.37% to 16.34% (Beta)	B.3.2.9.2.2
STAR*D - Relapse rate: step 3	6.77%	6.09% to 7.45% (Beta)	B.3.2.9.3

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Section/table
STAR*D - Relapse rate: step 4	12.79%	11.51% to 14.07% (Beta)	
STAR*D - Loss of response: step 3	22.16%	19.94% to 24.37% (Beta)	
STAR*D - Loss of response: step 4	22.81%	20.53% to 25.09% (Beta)	
Proportion of patients at treatment step 4 in SUSTAIN-1	41.00%	37.51% to 44.48% (Beta)	
Discontinuation during continuation (week 5-8) - ESK-NS + OAD	1.69%	1.52% to 1.86% (Beta)	B.3.2.9.2.2
Discontinuation during continuation (week 5-8) - OAD + PBO-NS	0.00%	0.00% to 0.00% (Beta)	
Discontinuation during continuation (week 9-40) - ESK-NS + OAD	1.70%	1.53% to 1.87% (Beta)	
Discontinuation during continuation (week 9-40) - OAD + PBO-NS	0.00%	0.00% to 0.00% (Beta)	
Maintenance (recurrence prevention) treatment phase			
Recurrence (per 4-week cycle) - ESK-NS + OAD	2.88%	2.59% to 3.17% (Beta)	B.3.2.9.2.2
Recurrence (per 4-week cycle) - OAD + PBO-NS	2.88%	2.59% to 3.17% (Beta)	
Discontinuation during maintenance recovery - OAD + PBO-NS	0.00%	0.00% to 0.00% (Beta)	B.3.2.9.2.2
Patients who discontinue after recovery - ESK-NS + OAD	35.40%	31.86% to 38.94% (Beta)	
Patients who discontinue after recovery - OAD + PBO-NS	0.00%	0.00% to 0.00% (Beta)	
Patients who discontinue in recovery - ESK-NS + OAD	99.00%	89.10% to 99.90% (Beta)	
Patients who discontinue in recovery - OAD + PBO-NS	0.00%	0.00% to 0.00% (Beta)	
Subsequent treatment phase			
Remission - TRD line 2	3.54%	3.19% to 3.89% (Beta)	B.3.2.9.3
Remission - TRD line 3	2.75%	2.47% to 3.02% (Beta)	
Remission - TRD line 4	2.14%	1.93% to 2.35% (Beta)	
Response - TRD line 2	0.86%	0.77% to 0.94% (Beta)	
Response - TRD line 3	0.65%	0.58% to 0.71% (Beta)	
Response - TRD line 4	0.49%	0.44% to 0.53% (Beta)	
Transition from response to remission (per 4-week cycle) - TRD line 2	2.76%	2.49% to 3.04% (Beta)	
Transition from response to remission (per 4-week cycle) - TRD line 3	2.76%	2.49% to 3.04% (Beta)	
Transition from response to remission (per 4-week cycle) - TRD line 4	2.76%	2.49% to 3.04% (Beta)	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Section/table
Relapse (per 4-week cycle) - TRD line 2	12.79%	11.51% to 14.07% (Beta)	
Relapse (per 4-week cycle) - TRD line 3	12.79%	11.51% to 14.07% (Beta)	
Relapse (per 4-week cycle) - TRD line 4	12.79%	11.51% to 14.07% (Beta)	
Recurrence (per 4-week cycle) - TRD line 2	2.88%	2.59% to 3.17% (Beta)	
Recurrence (per 4-week cycle) - TRD line 3	2.88%	2.59% to 3.17% (Beta)	
Recurrence (per 4-week cycle) - TRD line 4	2.88%	2.59% to 3.17% (Beta)	
Loss of response (per 4-week cycle) - TRD line 2	22.81%	20.53% to 25.09% (Beta)	
Loss of response (per 4-week cycle) - TRD line 3	22.81%	20.53% to 25.09% (Beta)	
Loss of response (per 4-week cycle) - TRD line 4	22.81%	20.53% to 25.09% (Beta)	
Best supportive care treatment phase			
Remission - BSC	0.41%	0.37% to 0.46% (Beta)	B.3.2.9.4
Response - BSC	0.83%	0.75% to 0.92% (Beta)	
Relapse - BSC	4.20%	3.78% to 4.62% (Beta)	
Loss of response (per 4-week cycle) - BSC	10.38%	9.34% to 11.42% (Beta)	

Abbreviations: BSC, best supportive care; CI, confidence interval; ESK-NS (+ OAD), Esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; MDE, major depressive episode; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; PSA, probabilistic sensitivity analysis; TRD, treatment-resistant depression.

B.3.2.12.2 Summary of assumptions

Table 61 provides an outline of the main assumptions of the economic model.

Table 61. Assumptions and justifications used in the economic model

Assumption	Brief justification	Reference to section in submission
Model structure		
Response and remission are evaluated at the end of the specified acute treatment period and so no benefit is generated before 4 weeks in the model for either treatment	Simplifying conservative assumption; this is expected to bias against ESK-NS given the fast-acting nature of response with ESK-NS.	B.3.2.3.1
After the acute phase (4 weeks), non-responders remain in the MDE health state and move to the next treatment in the sequence	Aligned to licence wording and also aligned to guideline recommendations (5, 45).	B.3.2.3.1
After 36 weeks of continuous remission, patients transition to the recovery health state	Based on SUSTAIN-1 which demonstrated that patients who had been on treatment after 36 weeks (12 weeks optimisation and 24 weeks in SUSTAIN-1) had a low risk of relapse.	B.3.2.3.2
Clinical inputs		
OAD + PBO-NS TRANSFORM-2 data were adjusted to reflect expected clinical effectiveness of OAD in real life clinical practice	The applied methodology adjusts the clinical efficacy for high HCP interaction seen in TRANSFORM-2 (a known treatment modifier in depression) to better reflect the effectiveness seen in clinical practice.	B.3.2.9.1 and B.3.4.4.1
OADs (including vortioxetine) are all of equivalent effectiveness in the TRD population	In TA367, the NICE Appraisal Committee concluded equal efficacy should be considered for the purposes of assessing the cost effectiveness of vortioxetine compared with other third-line antidepressants. This was also concluded by the Guideline Development Group in NICE CG90.	B.3.2.9.1
SUSTAIN-1 data is used for ESK-NS + OAD continuation (relapse prevention) phase efficacy. STAR*D steps 3 and 4 informed risk of relapse after the acute phase for the OAD.	SUSTAIN-1 is appropriate to inform the ESK-NS + OAD group of the model SUSTAIN-1 is less appropriate to inform expected relapse risk for OADs due to the study design. STAR*D provides a more appropriate source.	B.3.2.9.2.2
It is assumed that ~35% of patients discontinue ESK-NS treatment upon entering the recovery state, and subsequently, patients discontinue ESK-NS at a monthly probability of 25%.	Data from SUSTAIN-1, depression guidelines and clinical expert opinion are used to inform treatment duration and treatment discontinuation parameters.	B.3.2.3.3
The average reduction in effectiveness per treatment line from STAR*D (23) was extrapolated to subsequent lines of treatment.	This assumption reflects the decreasing efficacy with each subsequent line of treatment, as validated in NICE TA367 and by clinical experts at an advisory board (143).	B.3.2.9.3

Assumption	Brief justification	Reference to section in submission
Edwards et al, 2013 was used to estimate the efficacy of best supportive care	Expert clinical opinion in Edwards et al provided estimates on the annual probability of remission or response.	B.3.2.9.4
Utility inputs		
TRANSFORM-2 data are used to inform the utility data per health state	TRANSFORM-2 provides the most relevant utility data for the decision problem	B.3.2.10.4
MRU and cost inputs		
Administration and monitoring of ESK-NS is associated with additional administration costs	Administration and monitoring cost input assumptions have been derived and validated by clinical experts with experience of the administration of treatment	B.3.2.11.2
Costs of AEs are not included in the base case analysis	Due to the transient nature of AEs and mandatory monitoring period after administration of ESK-NS, no additional resource use is required due to AEs	B.3.2.9.5
Costs of health states derived from UK TRD cost study	A medical chart review of UK patients with TRD provides evidence which is directly relevant to the decision problem	B.3.2.11.5 and Appendix P
Inputs for dosing are derived from the Phase 3 trials: • For first 4 weeks: TRANSFORM-2 • Week 5–12: Optimisation phase (SUSTAIN-1) • Week 9 onwards: SUSTAIN-1	Dosing in trials reflect label recommendations and are based on clinical judgment considering efficacy and safety during the clinical trials, which will reflect future clinical practice.	B.3.2.11.1

Abbreviations: AE, adverse event; BAP, British Association of Psychopharmacology; ESK-NS, esketamine nasal spray; HCP, healthcare practitioner; HCRU, healthcare resource use; MDD, major depressive disorder; MDE, major depressive episode; MRU, medical resource use; NICE, The National Institute for Health and Care Excellence; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TA, technology appraisal; TRD, treatment-resistant depression.

B.3.3 Base case results

B.3.3.1 Base case incremental cost-effectiveness analysis results

The base case clinical and economic outcomes are presented in Table 62. Over a five-year time horizon, ESK-NS + OAD was associated with an additional 0.336 QALYs compared with OAD. The incremental drug cost for ESK-NS + OAD was £10,456; ESK-NS + OAD was estimated to have lower disease management costs, saving £8,243 compared with OAD. This is predominantly driven by the significant proportion of patients entering and remaining in remission with ESK-NS + OAD and thus the avoiding MDE-related health state costs. This results in an incremental cost difference of £2,213 and therefore a base case incremental cost-effectiveness ratio (ICER) of £6,582 per QALY.

Table 62. Base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
OAD	£48,478	4.508	2.239				
ESK-NS + OAD	£50,691	4.519	2.575	£2,213	0.011	0.336	£6,582

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant ICER, incremental cost-effectiveness ratio; LYG, life years gained; OAD oral antidepressant; QALYs, quality-adjusted life years.

Clinical outcomes from the model are provided in Appendix J. Disaggregated results of the base case cost-effectiveness analysis are provided in Appendix J.

B.3.4 Sensitivity analyses

B.3.4.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) tests the impact of second order uncertainty by random, simultaneous variation of the input parameters on the model. Second order uncertainty does not include cohort characteristics, which are part of first order uncertainty. Therefore, patient age, proportion of patients that were female, and baseline MADRS were not included in the PSA.

PSA analysis was performed by assigning probability distributions to certain variables in the model and repeatedly sampling values from these distributions to estimate the cost-effectiveness ratios. A Beta distribution was assigned to

probabilities, proportions, and utility and disutility data which take values between 0 and 1. A Gamma distribution was assigned to costs, doses, and resource use, which take positive values and are likely to be positively skewed. The Alpha and Beta values of the distribution were estimated based on the mean and standard deviation associated with each parameter.

If the standard deviation was not available from the reporting study, then it was calculated based on the following assumption:

= (Upper range – lower range)/(2*NORMSINV(0.975))

The upper and lower ranges were based on CIs where reported and if not, were based on a variation of +/- 10%.

A total of 10,000 Monte Carlo simulations were recorded. Results were plotted on the cost-effectiveness plane (CEP) and a cost-effectiveness acceptability curve (CEAC) was generated. The former showed the distribution of incremental cost and benefits under uncertainty and the latter the likelihood of being cost-effective at given acceptability thresholds.

Variables, estimates of uncertainty, and distributional assumptions used in PSA are presented in Table 60.

Figure 25 and Figure 26 present the CEP and CEAC, respectively. The probability that ESK-NS + OAD was cost-effective at a threshold of £20,000 per QALY was 99.7%. This increases to 100% at a threshold of £30,000 per QALY. Across 10,000 PSA simulations, ESK-NS + OAD was associated with a mean incremental cost of £1,987 (95% CI: –£840, £4,822) and a mean incremental QALY of 0.34 (95% CI: 0.27, 0.40) giving a probabilistic ICER of £5,903 per QALY (Table 63). These results are congruent with the deterministic incremental cost of £2,213 and the deterministic increase in QALYs of 0.34.

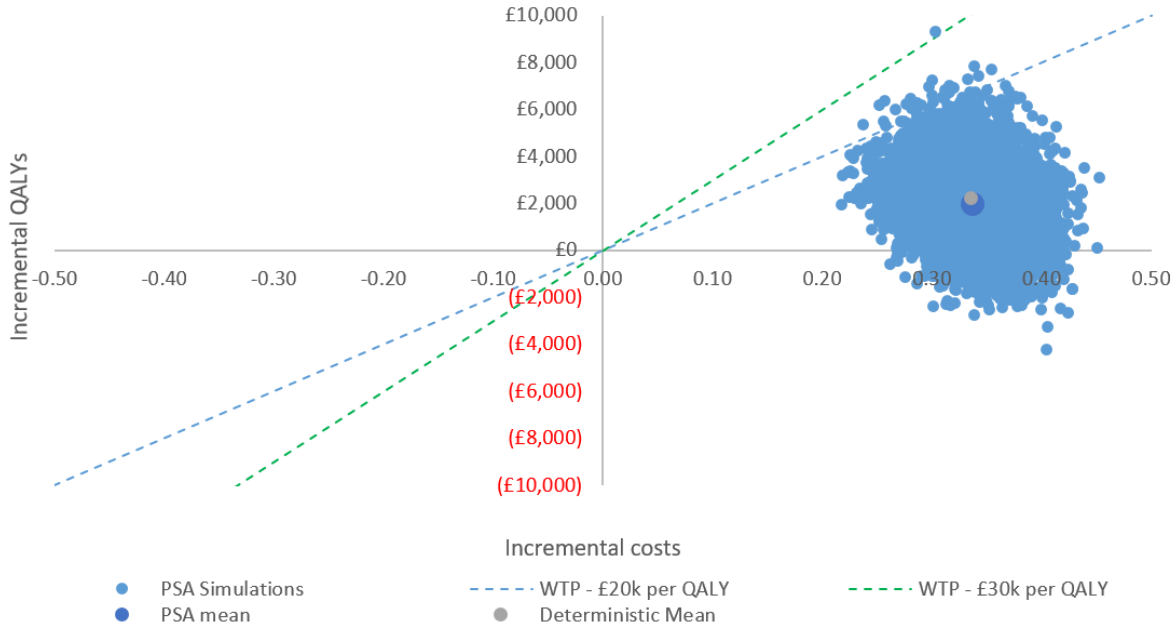
Table 63. Probabilistic sensitivity analysis results

Technologies	Total costs (95% CI)	Total QALYs (95% CI)	Incremental costs	Incremental LYG (95% CI)	ICER incremental (£/QALY))
OAD	£48,493 (£38,548, £59,404)	2.24 (2.10 to 2.38)			

Technologies	Total costs (95% CI)	Total QALYs (95% CI)	Incremental costs	Incremental LYG (95% CI)	ICER incremental (£/QALY))
ESK-NS + OAD	£50,479 (£42,209, £59,389)	2.58 (2.43 to 2.72)	£1,987 (–£840, £4,822)	0.34 (0.27 to 0.40)	£5,903

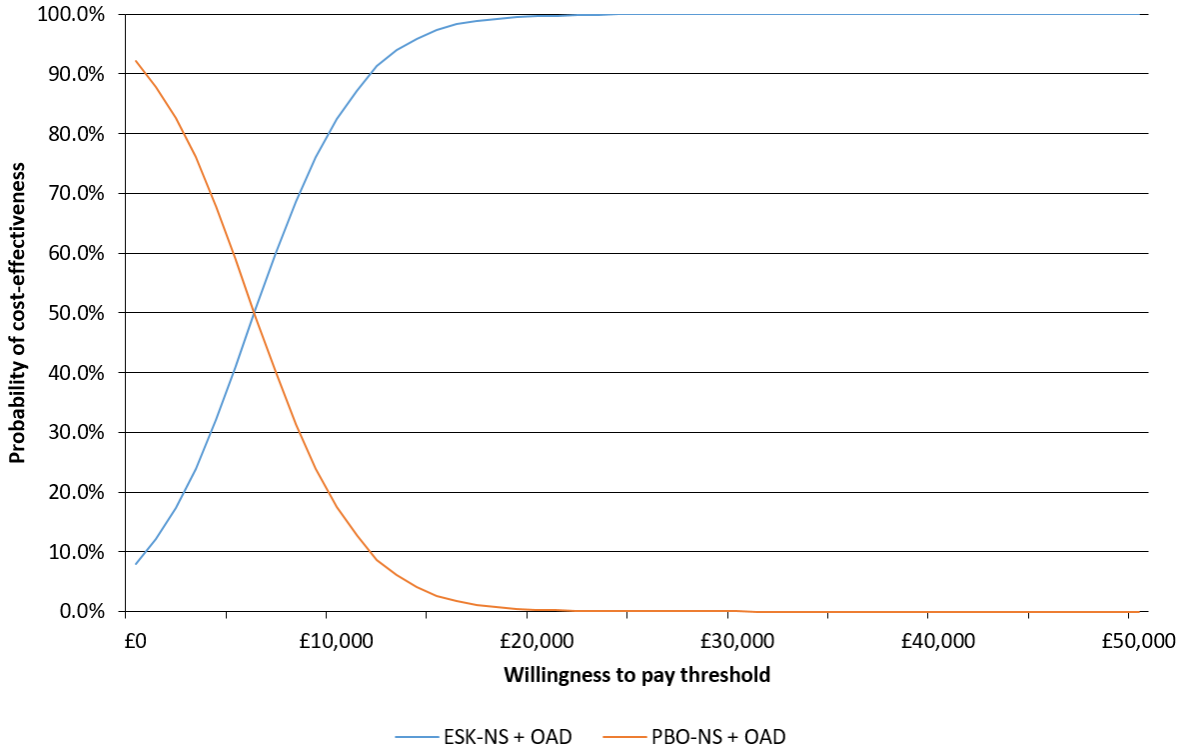
Abbreviations: CI, confidence interval; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant ICER, incremental cost-effectiveness ratio; LYG, life years gained; OAD, oral antidepressant; QALYs, quality-adjusted life years.

Figure 25. Cost-effectiveness plane



Abbreviations: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 26. Cost-effectiveness acceptability curve



Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray.

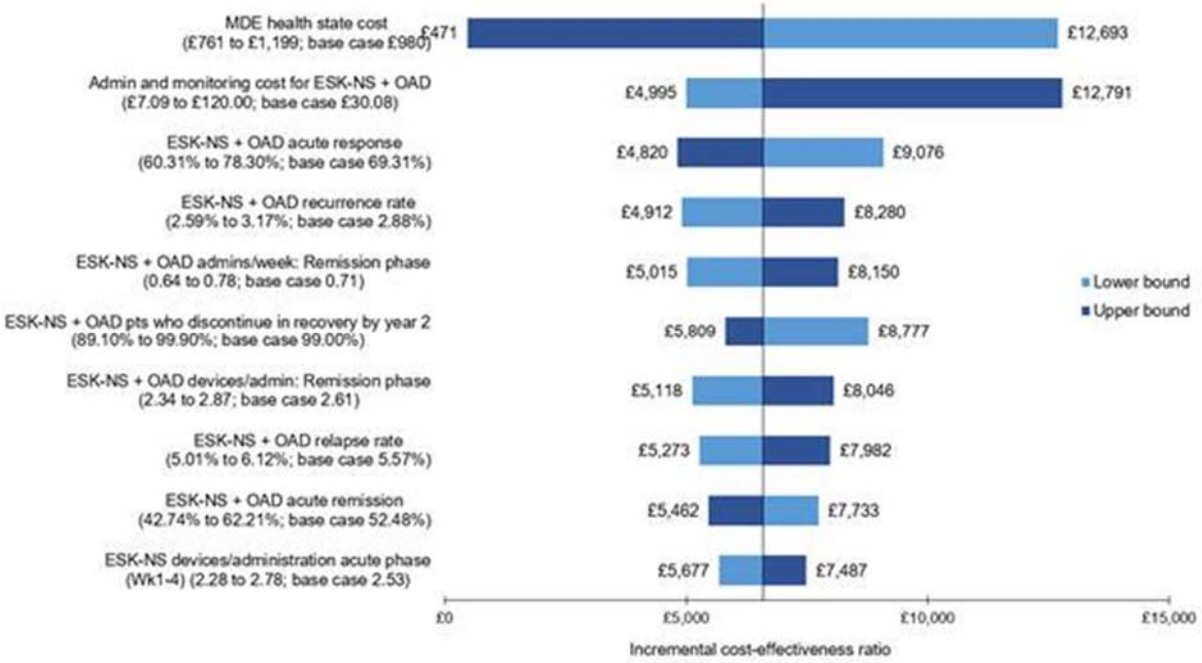
B.3.4.2 Deterministic sensitivity analysis

Parameter uncertainty was tested using univariate sensitivity analysis in which all model variables were systematically and independently varied over a plausible range determined by either the 95% CI, or +/- 10% where no estimates of precision were available. The ICER was recorded at the upper and lower values to produce a tornado diagram.

Figure 27 presents the results of the univariate sensitivity analysis in the form of a tornado diagram. Note that all parameters were varied but the figure shows the 10 parameters with the greatest impact. These results are also presented in Table 64. The most influential parameters included the medical cost of the MDE state, the administration/observation cost associated with ESK-NS + OAD, the frequency of administrative sessions during the remission phase, and the relapse and recurrence rates with ESK-NS + OAD. Importantly, no parameter tested in univariate sensitivity resulted in an ICER above £20,000 per QALY, further demonstrating the robustness of the base case result.

Upper and lower ranges of included parameters are presented in Table 60.

Figure 27. Results of univariate sensitivity analysis (tornado diagram)



Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; MDE, major depressive disorder.

Table 64. Results of univariate analysis

Variable (lower bound to upper bound; base case value)	ICER with lower bound	ICER with upper bound
MDE health state cost (£761 to £1,199; base case £980)	£12,693	£471
Admin and monitoring cost for ESK-NS + OAD (£7.09 to £120.00; base case £30.08)	£4,995	£12,791
ESK-NS + OAD acute response (60.31% to 78.30%; base case 69.31%)	£9,076	£4,820
ESK-NS + OAD recurrence rate (2.59% to 3.17%; base case 2.88%)	£4,912	£8,280
ESK-NS + OAD administrations/week continuation phase (0.64 to 0.78; base case 0.71)	£5,015	£8,150
ESK-NS + OAD pts who discontinue in recovery by Year 2 (89.10% to 99.90%; base case 99.00%)	£8,777	£5,809
ESK-NS + OAD devices/administration during continuation phase (2.34 to 2.87; base case 2.61)	£5,118	£8,046
ESK-NS + OAD relapse rate (5.01% to 6.12%; base case 5.57%)	£5,273	£7,982
ESK-NS + OAD acute remission (42.74% to 62.21%; base case 52.48%)	£7,733	£5,462
ESK-NS devices/administration acute phase (Wk1-4) (2.28 to 2.78; base case 2.53)	£5,677	£7,487

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; ICER, incremental cost-effectiveness ratio; MDE, major depressive disorder.

B.3.4.3 Threshold analysis

Threshold analysis was performed on the top 10 model parameters (as identified in the univariate sensitivity analysis above) to determine at which values ESK-NS + OAD would be cost-effective at a willingness to pay (WTP) threshold of £20,000 per QALY. In this analysis, all other parameters were kept at their original value. Results of the threshold analysis are presented in Table 65.

Table 65. Results of threshold analysis

Variable	Base case (Lower bound – Upper bound)	Value to achieve ICER of £20,000 per QALY
MDE health state cost	£980 (£761 to £1,199)	£500.09
Admin and monitoring cost for ESK-NS + OAD	£30.08 (£7.09 to £120.00)	£224.41
ESK-NS + OAD acute response	69.31% (60.31% to 78.30%)	41.67%
ESK-NS + OAD recurrence rate	2.88% (2.59% to 3.17%)	5.07%
ESK-NS + OAD administrations/week continuation phase	0.71 (0.64 to 0.78)	1.32
ESK-NS + OAD pts who discontinue in recovery by Year 2	99.00% (89.10% to 99.90%)	20.63%
ESK-NS + OAD devices/administration during continuation phase	2.61 (2.34 to 2.87)	4.99*
ESK-NS + OAD relapse rate	5.57% (5.01% to 6.12%)	9.74%
ESK-NS + OAD acute remission	52.48% (42.74% to 62.21%)	-46.8%*
ESK-NS devices/administration acute phase (Week 1-4)	2.53 (2.28 to 2.78)	6.28*

Abbreviations: ESK-NS (+ OAD), esketamine nasal spray (flexibly-dosed) (plus a newly initiated oral antidepressant); ICER, incremental cost-effectiveness ratio; MDE, major depressive disorder; QALY, quality-adjusted life year.
* Results not within plausible/credible ranges.

In this analysis when parameters were considered individually, and all other parameters remained unchanged, for the ICER for ESK-NS + OAD versus OAD to increase to £20,000 per QALY:

- The cost of the MDE health state would need to drop to £500.09 per month.
- The cost associated with the monitoring during and post ESK-NS administration would need to be above £224.41 per administration.
- The response rate for ESK-NS + OAD during the acute phase would need to drop to 41.67% below the unadjusted rate for OAD + PBO-NS.

- The recurrence rate for ESK-NS + OAD would need to nearly double to 5.07%.
- The number of ESK-NS + OAD administrations per week during the continuation phase would need to nearly double to 1.32.
- The number of ESK-NS devices per administration during the continuation phase would need to be 4.99 and during the acute phase (Weeks 1–4) would need to be 6.28, both of which are above the maximum dose limit of three per administration.

This analysis clearly demonstrates the robustness of the cost-effectiveness of ESK-NS + OAD, given the implausibility of these scenarios.

B.3.4.4 Scenario analyses

B.3.4.4.1 Treatment effect adjustment

As discussed in B.2.3.7, the base case efficacy estimates (response and remission) for the OAD + PBO-NS arm of the TRANSFORM-2 trial were high compared with other studies in TRD and significantly overestimate the benefits of the OADs in normal NHS practice. A set of scenarios are presented where the rate of relapse and/or remission for the OAD + PBO-NS arm was varied.

Table 66 and Figure 28 consider a scenario where the remission rate for OAD was varied from the unadjusted value of 31% in 10% decrements down to 10% of the original value. The base case analysis included an adjustment for the OAD remission rate, using the Posternak method assuming six additional physician visits. This resulted in a value of remission rate for OAD of 18%, equal to a 42% reduction. As noted, this is still higher than has been reported in many studies, including STAR*D where the remission rate has been reported as low as 15% (23). At this level, the ICER for ESK-NS + OAD would drop to £5,884, assuming all other parameters remain unadjusted.

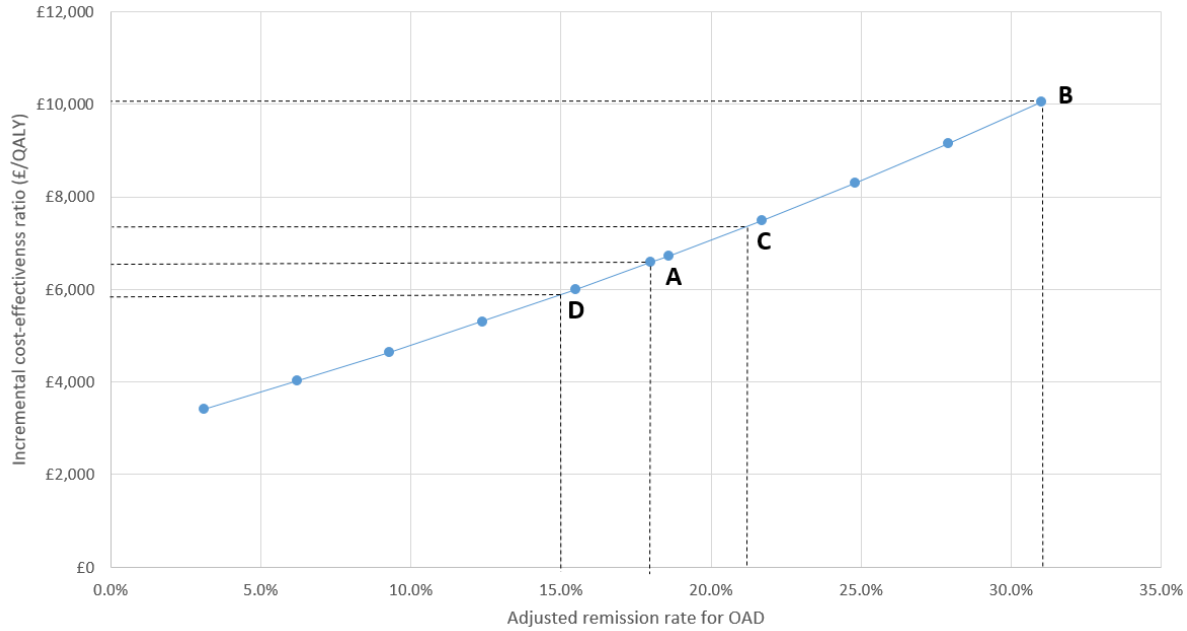
Table 66. Adjusting the remission rate for OAD

% change	Adjusted remission rate for OAD	ICER
Unadjusted	31.0%	£10,049
-10%	27.9%	£9,150
-20%	24.8%	£8,299
-30%	21.7%	£7,492

% change	Adjusted remission rate for OAD	ICER
-40%	18.6%	£6,726
Current base case value (adjusted for six visits)	**18.0%**	**£6,582**
-50%	15.5%	£5,998
-60%	12.4%	£5,305
-70%	9.3%	£4,645
-80%	6.2%	£4,015
-90%	3.1%	£3,414

Abbreviations: ICER, incremental cost-effectiveness ratio; OAD, oral antidepressant.

Figure 28. Adjusting the remission rate for OAD



Abbreviations: OAD, oral antidepressant; QALY, quality-adjusted life year.
Each point represents a ±10% change in the remission rate for OAD. The dashed line represents the following scenarios: A: base case (6-visit adjustment). B: unadjusted. C: 3-visit adjustment. D: Approximate remission rate from STAR*D (23).

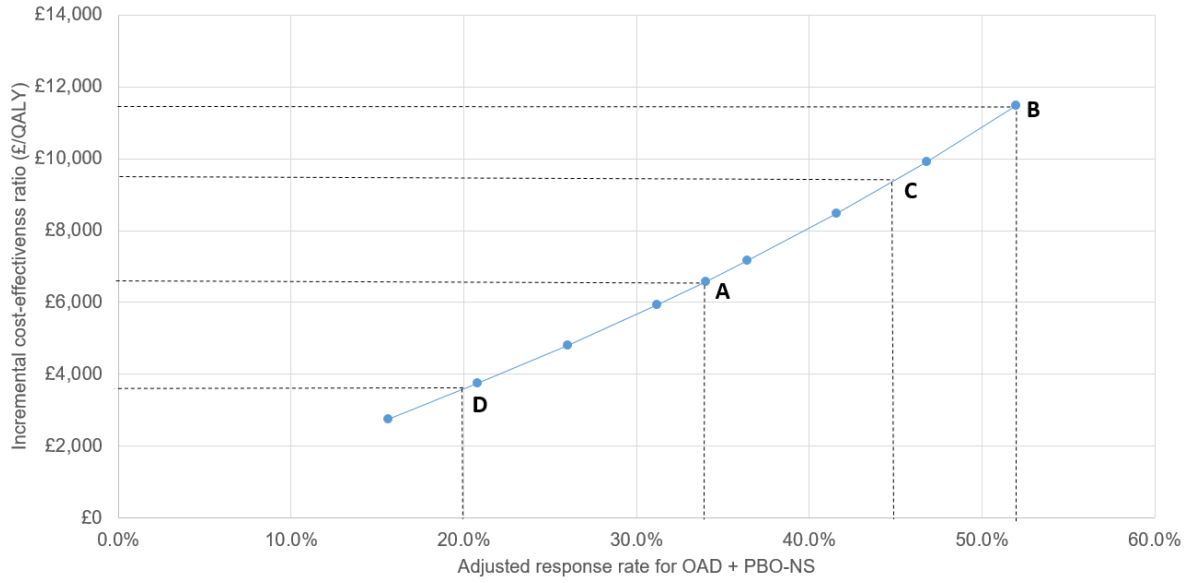
In a similar analysis to the above, Table 67 (and Figure 29) demonstrates the impact of varying the response rate for OAD from the unadjusted value of 52% in 10% decrements down to 10% of the original value. As noted previously, the base case analysis included an adjustment to the OAD response rate, using the Posternak method assuming six additional physician visits. This resulted in a value of remission rate for OAD of 34%, equal to a 35% reduction. As noted, this is still higher than has been reported in many studies, including STAR*D where the response rate has been reported at around 20% (23). At this level, the ICER for ESK-NS + OAD would drop to £3,582, when all other parameters remained unadjusted.

Table 67. Adjusting the response rate for OAD

Percent change	Adjusted response rate for OAD	ICER
Unadjusted	52.0%	£11,470
-10%	46.8%	£9,913
-20%	41.6%	£8,481
-30%	36.4%	£7,159
Current base case value (adjusted for six visits)	**34.0%**	**£6,582**
-40%	31.2%	£5,934
-50%	26.0%	£4,797
-60%	20.8%	£3,739
-70%	15.6%	£2,751
-80%	10.4%	£1,826
-90%	5.2%	£959

Abbreviations: ICER, incremental cost-effectiveness ratio; OAD, oral antidepressant.

Figure 29. Adjusting the response rate for OAD



Abbreviations: ICER, incremental cost-effectiveness ratio; OAD, oral antidepressant; QALY, quality-adjusted life year.
Each point represents a ±10% change in the response rate for OAD. The dashed line represents the following scenarios: A: base case (6-visit adjustment). B: unadjusted. C: 3-visit adjustment. D: Approximate remission rate from STAR*D (23).

Finally, Table 68 presents an analysis where both the remission and response rate for OAD were varied together. As before, this analysis demonstrated that even if the impact of the treatment effect adjustment was less than the current assumption in the base case, ESK-NS + OAD remained cost-effective versus OAD and in extreme scenarios, ESK-NS + OAD dominated OAD.

Table 68. Adjusting the remission and response rate for OAD

			Response rate for OAD										
	% change		Unadjusted	–10%	–20%	–30%	Base case	–40%	–50%	–60%	–70%	–80%	–90%
Remission rate for OAD	**% change**	**Adjusted rate**	52.0%	46.8%	41.6%	36.4%	34.0%	31.2%	26.0%	20.8%	15.6%	10.4%	5.2%
	Unadjusted	31.0%	£16,209	£14,223	£12,416	£10,765	£10,049	£9,249	NA	NA	NA	NA	NA
	-10%	27.9%	£14,963	£13,095	£11,390	£9,828	£9,150	£8,391	NA	NA	NA	NA	NA
	-20%	24.8%	£13,795	£12,034	£10,422	£8,942	£8,299	£7,577	£6,316	NA	NA	NA	NA
	-30%	21.7%	£12,697	£11,034	£9,508	£8,103	£7,492	£6,806	£5,603	NA	NA	NA	NA
	-40%	18.6%	£11,663	£10,090	£8,643	£7,308	£6,726	£6,072	£4,925	£3,857	NA	NA	NA
	Base case	**18.0%**	£11,470	£9,913	£8,481	£7,159	**£6,582**	£5,934	£4,797	£3,739	NA	NA	NA
	-50%	15.5%	£10,688	£9,197	£7,823	£6,553	£5,998	£5,374	£4,278	£3,257	£2,302	NA	NA
	-60%	12.4%	£9,766	£8,352	£7,045	£5,834	£5,305	£4,709	£3,661	£2,683	£1,767	NA	NA
	-70%	9.3%	£8,895	£7,550	£6,306	£5,151	£4,645	£4,075	£3,072	£2,134	£1,254	£428	NA
	-80%	6.2%	£8,069	£6,789	£5,603	£4,499	£4,015	£3,470	£2,509	£1,608	£762	ESK-NS dominates	NA
	-90%	3.1%	£7,285	£6,065	£4,933	£3,877	£3,414	£2,892	£1,969	£1,104	£291	ESK-NS dominates	ESK-NS dominates

Abbreviations: ESK-NS, esketamine nasal spray plus a newly initiated OAD; NA, not applicable; OAD, oral antidepressant.
Remission is a subset of response and could therefore not be greater than the response rate (indicated by NA in these scenarios).

Specifically adjusting the OAD efficacy data using the methods detailed in B.2.3.7 allowed consideration of the impact of clinic visits. Table 69 presents the analysis where the number of visits in the OAD arm was increased or decreased.

Table 69. Adjusting for the number of clinic visits in the OAD arm

Number of visits excluded	Adjusted remission rate	Adjusted total response rate	ICER
Unadjusted	31.00%	21.0%	£16,209
3 visits	21.00%	45.0%	£10,280
4 visits	19.00%	41.0%	£8,591
5 visits	18.00%	36.0%	£7,061
6 visits (base case)	**18.00%**	**34.0%**	**£6,582**
7 visits	18.00%	31.0%	£5,889
8 visits	16.00%	30.0%	£5,223

Abbreviations: ICER, incremental cost-effectiveness ratio; OAD, oral antidepressant.

B.3.4.4.2 Alternative efficacy estimates

The base case used observed cases clinical data for response and remission rates. Table 70 shows response and remission rates based on LOCF.

Table 70. LOCF response and remission rates at the end of the acute treatment phase

Treatment	Remission rate[a]	Response (but not remission) rate[b]	Response rate[c]
ESK-NS + OAD	48.2%	15.2%	63.4%
OAD (unadjusted)	30.3%	19.3%	49.5%
OAD (adjusted for six visits[d])	17.4%	15.6%	33.0%

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; LOCF, last observation carried forward; MADRS, Montgomery-Asberg Depression Rating Scale; OAD, Oral antidepressant; SE, standard error.
[a] MADRS ≤12.
[b] ≥50% reduction in MADRS from baseline but MADRS score >12.
[c] ≥50% reduction in MADRS from baseline.
[d] Base case

In a scenario analysis using LOCF response and remission rates, the ICER for ESK-NS + OAD increased to £8,253 per QALY compared with OAD (Table 71).

Table 71. Results using LOCF remission and response rates

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
OAD	£48,574	4.508	2.235				
ESK-NS + OAD	£51,052	4.517	2.535	£2,478	0.010	0.300	£8,253

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant ICER, incremental cost-effectiveness ratio; LOCF, last observation carried forward; LYG, life years gained; OAD oral antidepressant; QALYs, quality-adjusted life years.

B.3.4.4.3 Time horizon

In the base case analysis, the time horizon was set to 5 years which is of sufficient duration to represent the length of one TRD MDE and account for all the treatment-related costs and effects attributable to ESK-NS + OAD.

A simple one-way analysis is presented in Table 72 which demonstrates the impact on the ICER of varying the model time horizon.

Table 72. Time horizon sensitivity analysis

Time horizon (years)	ICER
2	£22,881
3	£13,265
5 (Base case)	**£6,582**
7	£4,496

Abbreviations: ICER, incremental cost-effectiveness ratio.

A threshold analysis identified that ESK-NS + OAD would be cost-effective at a WTP threshold of £20,000 per QALY after approximately 2.25 years.

B.3.4.4.4 Inclusion of AEs

Although the majority of AEs were mild and transient (and resolved during the post-administration observation period so are already accounted for in the model), a scenario analysis including the disutilities and an assumed GP contact cost of £37 (171) per event was included for completeness.

The inclusion of AEs in the acute phase had a minimal effect on outcomes. With the assumed GP contact, the associated cost with ESK-NS + OAD was £55.84 compared with £18.28 for OAD, an incremental cost of £38. Since the majority of AEs were assumed to be transient and last less than a day, the impact on utility was negligible. The ICER, including AEs, was £6,696 per QALY.

B.3.4.4.5 Exclusion of subsequent treatments

The base case analysis assumed that patients who did not respond or relapse would cycle through subsequent lines of treatments before receiving best supportive care. A number of assumptions were made to facilitate this analysis and thus a scenario analysis excluding subsequent lines of treatment was performed. In this scenario (Table 73), all patients progressed straight to best supportive care.

Table 73. Exclusion of subsequent lines of treatment

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY))
OAD + PBO-NS	£48,977	4.507	2.218				
ESK-NS + OAD	£51,114	4.518	2.557	£2,137	0.011	0.339	£6,295

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

In this scenario the total costs of each arm increased as more patients remained in the MDE state. Similarly, the QALYs of each arm decreased. This appeared to be consistent in both treatment arms and thus the overall ICER remained relatively unchanged at £6,295 per QALY.

B.3.4.4.6 Family and caregiver quality of life impact

As noted in Section B.3.2.10.6, TRD can affect not just the patient but also the whole family, and often the community. While the true impact is difficult to robustly assess, a simple scenario analysis was presented to demonstrate the potential implications. Table 74 presents an analysis in which the MDE health state utility was reduced by the proposed disutility amount.

Table 74. Family and caregiver utility spill-over

Proposed disutility	ICER
0.000	£6,582
0.050	£5,945
0.075	£5,671
0.100	£5,420
0.125	£5,191
0.150	£4,981
0.175	£4,787
0.200	£4,607

Abbreviations: ICER, incremental cost-effectiveness ratio.

To put this analysis into some context, it has been reported that the MCID for the EQ-5D scale, NICEs preferred measure, is 0.0795 (172, 173). At this level, assuming only one individual beyond the patient is impacted, the ICER would drop to approximately £5,624 per QALY.

B.3.4.4.7 Societal impact on costs

As noted in Section B.1.3.1, McCrone et al. 2018 (4) reported that there is a significant societal burden associated with TRD due to lost productivity and carer burden. In the analysis, the direct medical costs only accounted for 20% of the overall cost. We therefore conducted a simple scenario analysis in which the cost of the MDE health state was increased in increments of 10% up to 80% (Table 75).

Table 75. Societal cost analysis

Increase to MDE cost	Adjusted ICER
Base case (£980)	£6,582
+10% (£1,078)	£3,842
+20% (£1,176)	£1,102
+30% (£1,274)	ESK-NS + OAD dominates OAD
+40% (£1,372)	ESK-NS + OAD dominates OAD
+50% (£1,470)	ESK-NS + OAD dominates OAD
+60% (£1,568)	ESK-NS + OAD dominates OAD
+70% (£1,666)	ESK-NS + OAD dominates OAD
+80% (£1,764)	ESK-NS + OAD dominates OAD

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; ICER, incremental cost-effectiveness ratio; MDE, major depressive episode; OAD, oral antidepressant.

The analysis shows the significant impact that including the societal impact on costs could have on the analysis. A threshold analysis was conducted and an increase in the current base case MDE cost of 24% (equivalent to £1,216) would be required for ESK-NS + OAD to be considered dominant (i.e. cost-saving to the NHS and society and clinically superior). Any increase above 24% resulted in ESK-NS + OAD being a dominant treatment strategy. This simple analysis only considers the impact of increasing the costs in the MDE state; it could be hypothesised that there is a similar spill over into the response state as well.

A combined analysis considering the impact on societal costs from above and an incremental disutility of the MDE state associated with family and caregiver spill-over was also conducted, presented in Table 76.

Table 76. Combined societal cost and family/caregiver utility quality of life impact on ICERs

		Family/caregiver utility decrement							
		0.00	**0.05**	**0.08**	**0.10**	**0.13**	**0.15**	**0.18**	**0.20**
Increase to MDE cost	**Base case (£980)**	£6,582	£5,945	£5,671	£5,420	£5,191	£4,981	£4,787	£4,607
	+ 10% (£1,078)	£3,842	£3,470	£3,310	£3,164	£3,030	£2,908	£2,794	£2,690
	+ 20% (£1,176)	£1,102	£996	£950	£908	£870	£834	£802	£772
	+ 30% (£1,274)	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant
	+ 40% (£1,372)	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant

Abbreviations: MDE, major depressive episode.

B.3.4.4.8 Alternative OAD efficacy data in the maintenance phase

Data from SUSTAIN-1 were used to estimate the relapse and loss of response risk for patients on ESK-NS + OAD but it was not deemed appropriate to use the OAD + PBO-NS arm data to estimate the same parameter values for OAD. Instead these parameters were estimated using data from STAR*D (see Section B.3.2.9.2.2). As an alternative scenario, data from SUSTAIN-1 has been used to provide alternative estimates or relapse and loss of response for OAD (see Table 77).

Table 77: Alternative 4-week risk of relapse, loss of response and recurrence for OAD

Treatment	Relapse	Loss of response	Recurrence
ESK-NS + OAD	5.57%	4.19%	2.88%
OAD	12.31%	14.86%	2.88%

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; SE, standard error.

Both the risk of relapse and loss of response for OAD were higher than that estimated using the STAR*D. As a consequence, the ICER of ESK-NS + OAD decreased to £5,166 per QALY (Table 78) and as such the base case assumption is likely to be conservative.

Table 78: Results for alternative OAD efficacy scenario

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
OAD	£48,869	4.508	2.223				
ESK-NS + OAD	£50,691	4.519	2.575	£1,821	0.011	0.353	£5,166

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant ICER, incremental cost-effectiveness ratio; LYG, life years gained; OAD oral antidepressant; QALYs, quality-adjusted life years.

B.3.4.4.9 Other comparators

As previously discussed, systematic differences in study design, heterogeneity between patient populations, and inconsistency in the outcomes assessed by clinical trials evaluating these therapies precluded the inclusion of these comparators in a robust NMA, and as such, in the base case analysis, these treatments have not been considered. Despite these limitations, an NMA was attempted (as detailed in Appendix D) the outputs of which were used in the following analysis.

For the outputs of the NMA to be used in the model, the ORs outputs of the NMA were converted into RRs using the following formula:

$$RR = \frac{OR}{(1 - r_b) + (r_b \times OR)}$$

Where r_b = baseline risk of relapse or remission for OAD + PBO-NS.

The analysis applied these RR to the ESK-NS + OAD response and remission rates using the OR from the NMA which included the treatment adjustment (Table 35 and Table 36, respectively). Table 79 presents the estimated response and remission rates for each of the comparator treatments. The OAD data was reflective of STAR*D and would have included the alternative comparators considered in this analysis. Therefore, for all other parameters, the analysis assumed equivalence to OAD.

Table 79. Response and remission rates at the end of the acute treatment phase

Treatment	Remission, %[a]	Response (but not remission), %[b]
ESK-NS + OAD	52.48%	16.83%
OAD	17.71%	4.36%
Aug tricyclic (nortrip) ± PBO	22.70%	4.71%
Aug SSRI/SNRI + AAP	27.65%	4.04%
Aug SSRI/SNRI + lithium	21.98%	2.57%
Aug SSRI/SNRI ± PBO	16.25%	2.05%
Switch tetracyclic (mirtazapine)	13.28%	3.26%
Switch SSRI + AAP	22.38%	4.04%

Abbreviations: AAP, atypical antipsychotic; Aug, augmentation; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; MADRS, Montgomery-Asberg Depression Rating Scale; nortrip, nortriptyline; OAD, oral antidepressant; PBO, placebo; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
[a] MADRS ≤12.
[b] ≥50% reduction in MADRS from baseline but MADRS score >12.

This analysis uses market share data of augmentation treatments received in a cohort of UK patients with TRD (n=295) from a retrospective chart review (see Section B.3.2.11.5 and Appendix P).

The augmentation with AAP and augmentation with lithium market shares from the analysis were combined with drug costs from the BNF to estimate the average weekly cost of augmentation with AAP. Only therapies with a market share above 1% were considered. It was assumed that all AAP agents were prescribed in augmentation therapy. The dose was assumed to be the usual maintenance dose reported in the BNF. The market share and weighted drug costs used in the model are summarised in Table 80. For augmentation with a tricyclic, a 50 mg per day dose of nortriptyline was assumed and for the switch to a tetracyclic, a 30 mg per day dose of mirtazapine was assumed. It could be argued that the maximum licensed dose of each OAD should be used in the cost calculations, assuming patients eligible for augmentation will receive the maximum dose of their current OAD therapy. For simplicity, and as a conservative assumption, the same OAD costs reported previously were assumed for those patients receiving SSRI/SNRI augmentation therapy.

Table 80: Cost of other comparators

Drug	Dose	No. in pack	Cost/pack (£)	Cost/day (£)	Average 4-weekly cost (£)	Drug use
AAPs						
Quetiapine	300 mg	60	£3.31	£0.06	£1.54	33%
Aripiprazole	10 mg	28	£1.35	£0.05	£1.35	21%
Olanzapine	5 mg	28	£8.58	£0.31	£8.58	13%
Abilify	10 mg	28	£1.35	£0.05	£1.35	9%
Biquelle XL	300 mg	60	£3.31	£0.06	£1.54	7%
Risperidone	3 mg	60	£1.47	£0.02	£0.69	6%
Atrolak XL	300 mg	60	£169.99	£2.83	£79.33	4%
Seroquel	300 mg	60	£3.31	£0.06	£1.54	2%
Risperdal	3 mg	60	£1.47	£0.02	£0.69	2%
Psyquet XL	300 mg	60	£70.02	£1.17	£32.68	2%
Average 4-weekly cost of AAP						**£5.81**
Lithium						
Lithium carbonate	400 mg	100	£4.02	£0.04	£0.28	43%
Depakote	250 mg	90	£17.08	£0.19	£1.33	15%
Carbamazepine	400 mg	56	£5.02	£0.09	£0.63	11%
Lamictal	100 mg	56	£1.49	£0.03	£0.19	10%
Lamotrigine	100 mg	56	£1.49	£0.03	£0.19	10%
Priadel	400 mg	100	£4.02	£0.04	£0.28	7%
Carbagen	200 mg	84	£3.83	£0.05	£0.32	3%
Camcolit	400 mg	100	£4.02	£0.04	£0.28	2%
Average 4-weekly cost of lithium						**£1.83**

Abbreviations: AAP, atypical antipsychotic.

The results in Table 81 demonstrate that ESK-NS + OAD would remain a cost-effective treatment option versus all other treatments considered.

Table 81: Scenario analysis considering all comparators

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline* (£/QALY)	ICER incremental (£/QALY)	ICER versus ESK-NS + OAD (£/QALY)
Aug SSRI/SNRI + AAP	£48,059	4.5089	2.2597						£8,344
Aug tricyclic (nortrip) ± PBO	£48,634	4.5081	2.2358	£576	-0.0008	-0.0240	Dominated	Dominated	£6,058
Aug SSRI/SNRI + lithium	£48,837	4.5078	2.2268	£203	-0.0003	-0.0090	Dominated	Dominated	£5,320
OAD+PBO	£49,250	4.5072	2.2090	£413	-0.0006	-0.0177	Dominated	Dominated	£3,934
Aug SSRI/SNRI ± PBO	£49,580	4.5067	2.1958	£329	-0.0004	-0.0132	Dominated	Dominated	£2,929
Switch tetracyclic (mirtazapine)	£49,865	4.5063	2.1834	£285	-0.0004	-0.0124	Dominated	Dominated	£2,108
ESK+AD	£50,691	4.5188	2.5751	£826	0.0125	0.3917	£8,344	£2,108	

Abbreviations: AAP, atypical antipsychotic; Aug, augmentation; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; ICER, incremental cost-effectiveness ratio; LYG, life years gained; nortrip, nortriptyline; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; PBO, placebo; QALYs, quality-adjusted life years; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
* Baseline in this analysis is Aug SSRI/SNRI + AAP.

ESK-NS + OAD is cost-effective versus Aug SSRI/SNRI + AAP with an ICER of £8,344. Aug SSRI/SNRI + AAP and ESK-NS + OAD showed extended dominance over all other treatments. When comparing ESK-NS + OAD with all other comparators, the ICER ranged from £2,108 to £8,344.

The NMA did not allow for estimations of remission for ECT and so it was excluded from this analysis. However, the OR associated with achieving response was much lower than that for ESK-NS + OAD and the cost of ECT is significantly higher than the cost estimates of OAD. In NICE technology appraisal TA59 (46) Guidance on the use of electroconvulsive therapy, six treatment sessions of ECT were estimated to cost of £2,475 (excluding any inpatient stay). Uplifting to 2018 costs, using the Hospital and Community Health Services inflation index reported in the Unit costs of health and social care (171), the cost per session of ECT is estimated at £541.18. The ECT Accreditation Service reported that on average there are 10 treatments per course and so the total cost would be approximately £5,412. It is therefore assumed that ESK-NS + OAD would be cost effective, given the high cost compared with OAD and lower relative treatment efficacy compared with ESK-NS+OAD.

B.3.4.5 Summary of sensitivity analyses results

The results of PSA were found to be highly congruent with the deterministic base case results and showed ESK-NS + OAD to be cost-effective versus OAD in 99.7% of simulations, assuming a cost-effectiveness threshold of £20,000 per QALY increasing to 100% at a threshold of £30,000 per QALY.

The most influential parameters in deterministic sensitivity analysis were the MDE health state cost and the cost associated with the observation during self- and post-administration associated with ESK-NS + OAD. The effects of other model parameters on the base case ICER were found to be modest and the extensive scenario analyses demonstrated the robustness of the base case ICER.

The inclusion of family and caregiver spill-over on quality of life also demonstrated the conservative base case position for a disease area with significant societal impact.

B.3.5 Subgroup analyses

TRANSFORM-3 was a 4-week, randomised, double-blind, active-controlled, multicentre, Phase 3 trial that compared flexibly-dosed ESK-NS (28 mg, 56 mg, or 84 mg) plus a newly initiated OAD with a newly initiated OAD plus PBO-NS in adult patients aged ≥65 years (78, 79). TRANSFORM-3 was broadly similar in design to TRANSFORM-2 with the exception that patients were initiated with 28 mg dose of ESK-NS and then titrated up as required. This subgroup analysis considered a cohort of adults aged ≥65 years using the data from TRANSFORM-3 to populate the acute treatment phase (Weeks 1–4) of the model and then used the same assumptions as those described previously.

The majority (62.0%) of the model population was female with an average age of 70.0 years as observed in TRANSFORM-3. Efficacy estimates (response and remission) for ESK-NS + OAD were taken from TRANSFORM-3 patient-level data. As in the base case, the values of OAD + PBO-NS were adjusted *post hoc* using the Posternak adjustment detailed in B.2.3.7. Table 82 shows the response and remission rates used in this subgroup analysis.

Table 82. Response and remission rates at the end of the acute treatment phase for the TRANSFORM-3 subgroup analysis

Treatment	Remission, %[a]	Response (but not remission), %[b]	Response[c]
ESK-NS + OAD	17.46%	26.98%	44.44%
OAD (unadjusted)	6.67%	13.33%	20.00%
OAD (adjusted for six visits[d])	6.67%[e]	8.33%	15.00%

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; MADRS, Montgomery-Asberg Depression Rating Scale; OAD, oral antidepressant.
[a] MADRS ≤12.
[b] ≥50% reduction in MADRS from baseline but MADRS score >12.
[c] ≥50% reduction in MADRS from baseline.
[d] Base case.
[e] Remission was less sensitive to Posternak adjustment than response hence the lack of any difference between the adjusted and unadjusted remission rates.

Patients in TRANSFORM-3 initiated ESK-NS at the 28 mg dose. Accordingly, the average number of devices per session was lower than that seen in TRANSFORM-2. Table 83 presents the number of sessions per week and devices per session in the acute phase (Weeks 1–4) of the TRANSFORM-3 subgroup analysis. The base case assumptions were also applied for the other time periods.

Table 83. Acquisition and resource costs associated with ESK-NS administration in the TRANSFORM-3 subgroup analysis

Items	Weeks 1–4	Weeks 5–8	Maintenance Weeks 9–40	Maintenance in Recovery
Average number of sessions per week	1.844	0.992	0.711	0.675
Average number of devices per session	2.136	2.605	2.605	2.571
Drug acquisition cost per 4-week cycle	£2,567	£1,685	£1,208	£1,131
Administration and observation costs	£222	£119	£86	£81
Total cost per 4-week cycle	£2,789	£1,804	£1,294	£1,212

Abbreviations: ESK-NS, esketamine nasal spray.

The health state utilities used in the analysis were derived from the EQ-5D-5L TRANSFORM-3 patient level data, by converting to EQ-5D-3L and using the UK value set (161), and are presented in Table 84.

Table 84. Health state utility values used in the TRANSFORM-3 subgroup analysis

Health state	Utility
MDE	0.508
Response	0.779
Remission	0.843
Recovery	0.843

Abbreviations: MDE; major depressive episode; SE, standard error.

The base case clinical and economic outcomes are presented in Table 85. Over a five-year time horizon, ESK-NS + OAD was associated with an additional 0.175 QALYs compared with OAD. The incremental drug cost for ESK-NS + OAD was £7,302; however, over a five-year time horizon, ESK-NS + OAD was estimated to have lower disease management costs, saving £5,792 compared with OAD. This resulted in an incremental cost difference of £2,067 and an associated ICER of £11,809 per QALY, demonstrating that ESK-NS + OAD is also cost-effective in this patient subgroup.

Table 85. Subgroup analysis results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
OAD	£48,514	4.340	2.411				
ESK-NS + OAD	£50,581	4.347	2.586	£2,067	0.007	0.175	£11,809

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; ICER, incremental cost-effectiveness ratio; LYG, life years gained; OAD, oral antidepressant; QALY, quality-adjusted life years.

B.3.5.1 Rationale for not pooling TRANSFORM-2 and TRANSFORM-3 data in the model

In the completed TRD programme, a data pooling approach was conducted only for selected safety variables to provide additional precision in characterisation of the safety profile in similar subgroups of the studied TRD population.

Data for demographics, disposition, exposure, concomitant medications, AEs, clinical laboratory, vital signs, electrocardiogram (ECGs), and Columbia – Suicide Severity Rating Scale (C-SSRS) were pooled for the Phase 3 short-term studies in adults aged 18-64 years, TRANSFORM-1 and TRANSFORM-2. Due to differences in the study design (double-blind versus open-label), dose regimen, treatment duration, and/or population (adult versus elderly patients) among the Phase 3 studies in TRD, no other pooling of safety or efficacy data was done for these studies.

Key reasons for not pooling the adult and elderly patients in the evaluation of efficacy and safety in the completed TRD programme include:

- TRD in older adults is more heterogenous (174, 175), is characterised by diverse potential pathophysiological underpinnings (especially in those elderly patients with late-onset depression), and a higher degree of treatment resistance (176). In TRANSFORM-3, elderly patients with late-onset depression showed lower efficacy than those with early-onset depression. A *post hoc* analysis using age of onset as a continuous variable found a consistently greater difference between treatment groups with younger age of onset of depression (94).
- Dosing in TRANSFORM-3 included a lower starting dose (28 mg) than that in TRANSFORM-2 (56 mg). The 28 mg dose is likely a subtherapeutic dose for most patients (115). Since this dose was required as a first dose for all elderly

patients and was available throughout the study, lower dosing may have contributed to the reduced efficacy in the 3005 study.

- Elderly patients typically take longer to respond to antidepressants, so the time frame of 4 weeks offered in the TRANSFORM-3 study may have been too short to demonstrate optimal effect in elderly patients. Of note, elderly patients from TRANSFORM-3 who entered into the long-term open-label follow-up study SUSTAIN-1 showed continued improvement in the depressive symptoms with progression of the treatment suggesting that longer duration of treatment may be needed in elderly patients for inducing an optimal effect. The response and remission rates at 8 weeks (between the initial baseline of the randomised PBO-controlled study to Day 28 of SUSTAIN-2) were similar to those seen in younger adults following a 4-week treatment period. The need for a longer treatment period in older patients is supported by recent published studies in elderly patients showing that a longer duration of treatment is required to show significant differences from placebo as compared with younger patients (177, 178). In summary, an 8-week treatment period may have shown better improvement in the ESK-NS treatment group in elderly patients.

B.3.6 Validation

Quality assurance: Two independent senior health economic modellers, external to the model process, performed quality assurance, which entailed:

- Review of modelling structural assumption and techniques chosen.
- Review of technical deployment (formulas, functionality).
- Review of data inputs and sources.
- Conducting extreme scenario analyses and validation of results.

The first review was conducted in 2018 and the second in 2019.

[redacted]

Validation of model structure, assumptions and inputs: The final model structure, key assumptions and inputs were validated by both a clinical expert (with

experience in the treatment of TRD) and a health economic modelling expert. Both experts were provided with information on the model concept and proposed inputs and extrapolations.

- Further input from the clinical expert was sought via a face-to-face meeting, with the main objective being to ensure the clinical plausibility of the model structure and assumptions. Specific assumptions were checked as necessary with follow-up emails and phone calls.
- Input from the health economic modelling expert was sought, with the main objective being to ensure that the selected modelling approaches were methodologically sound and met the requirements of HTA bodies.

The clinical expert participated in one further advisory board to support the collation of inputs. No further direct financial or non-financial conflicts are applicable.

Two global advisory boards (in July 2017 and November 2018) and two UK HTA advisory boards (in October 2018 and June 2019) were also held to inform the development of the model.

B.3.7 Interpretation and conclusions of economic evidence

A systematic review of the economic literature did not identify any published economic evaluations for ESK-NS + OAD in adults with TRD that reflected the current decision problem (see Section B.3.6) therefore it was necessary to develop a *de novo* economic model. The model structure adopted is consistent with clinical practice.

The core assumptions of the economic evaluation were informed and validated by UK-based clinical experts (see Section B.3.6). These include the modelling of key outcomes of response with regards to the placebo effect and measurements of resource use and unit costs, which were taken from UK sources. The overall trial population of the pivotal TRANSFORM-2 and SUSTAIN-1 trials are reflective of the population in UK clinical practice with TRD (see Section B.2.13.2.3). The economic evaluation is therefore highly relevant to the population of patients with TRD in England and Wales.

The health economic analysis was driven predominantly by the primary treatment costs associated with ESK-NS itself. The current evidence from the clinical trials show that, over time, the maintenance doses reduce in frequency. The base case analysis included an adjustment for the treatment effect observed in the OAD + PBO-NS arm. Extensive sensitivity analysis demonstrated the robustness of the ICER associated with ESK-NS + OAD. Even in an extreme scenario excluding any treatment adjustment for OAD, the ICER for ESK-NS + OAD was £16,209 – still below the £20,000 per QALY threshold.

TRD has been shown to be associated with significant societal burden through lost productivity and carer burden. Incorporating this into the analysis improved the cost-effectiveness of ESK-NS, and in some scenarios resulted in ESK-NS dominating OAD (i.e. resulting in overall cost savings and improved clinical outcomes).

The base case analysis demonstrates that ESK-NS + OAD is highly cost-effective versus OAD, with a base case ICER of £6,582 per QALY. We believe this represents an underestimate of the true cost-effectiveness of esketamine, given the large wider societal burden associated with TRD.

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B.5 Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analyses

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Esketamine nasal spray dosing and administration chart

Appendix M: Additional methodology details for the pivotal and supporting studies

Appendix N: Additional results – all trials (pivotal and supporting)

Appendix O: MAIC report

Appendix P: Summary report: Quantifying Medical Care Costs of Treating Patients with Treatment Resistant Depression

Appendix Q: Poisson regression analysis to estimate response to remission transition probability

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Esketamine for treatment-resistant depression [ID1414]

Clarification questions

July 2019

File name	Version	Contains confidential information	Date
ID1414 esketamine clarification letter	Final	Yes - NICE PRIMA report (embedded pdf) and reference to NICE PRIMA report	13/08/2019

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Section A: Clarification on effectiveness data

Searching

A1. Neither the original or updated searches reported for Appendix D.1.1 (Acute management of patients) or 1.2 (Ongoing maintenance treatment of patients with TRD [treatment-resistant depression]) mention reference checking. Please clarify if reference checking was performed.

We confirm that reference checking was performed as part of both the original and updated searches reported in Appendix D.1.1 and D.1.2.

A2. Appendices D1.1 and 1.2 both report searches on ClinicalTrials.gov. Appendix D1.2 details a further search of the EU Clinical Trials registry. Please provide dates searched and full search strategies for all trials registry searches.

For the acute and maintenance treatment systematic literature review (SLR) updates, the International Clinical Trials Registry Platform (ICTRP) was searched, as outlined in Table 1.

Table 1. ICTRP search strategy

Trial platform	Methods of search
International Clinical Trials Registry Platform (ICTRP)	Key terms were searched through the search facility on the website (recruitment status: 'recruiting'): http://apps.who.int/trialsearch/ Terms included: • TRD • Resist AND depress • MDD • Major AND depress Date of updated search: 10th May 2019

Abbreviations: MDD, major depressive disorder; TRD, treatment-resistant depression.

A3. Please confirm whether searches reported in Appendices D 1.1 and 1.2 were intended to inform section B2.10 (Adverse events) of the company submission (CS).

Correct. The systematic literature reviews reported in Appendices D.1.1 and D.1.2 (acute and maintenance treatments, respectively) were conducted to identify studies reporting efficacy and safety data for treatment-resistant depression (TRD) treatments of interest.

A4. There appears to have been an error in line combinations in both the original and update search for Embase reported in Appendix D.1.1; lines #141-144 appear to be missing from the final combination in line #145.

a. **Please explain how this may have affected the recall of results.**
b. **Please update the searches, including screening for, and including of, potentially relevant references.**

The interventions that were missed in the Embase search were included in the search strategies for the Medline, PsychINFO, and EBM review. It is anticipated that the error identified will not have affected the recall of the results because any randomised-controlled trials (RCTs) for zotepine or electroconvulsive therapy (ECT) are unlikely to have only been in EMBASE. Further, the Embase search included the MeSH heading for zotepine.

However, we have updated the searches as requested and identified an additional 610 hits. These were screened for trials investigating zotepine or ECT and no further relevant trials were identified. The 610 additional studies were excluded on the grounds of study design (n=536), intervention (n=14), population (n=13), comparator not of interest/did not influence network (n=28), and duplicate (n=19).

A5. Please provide a rationale for the 1990 date limit applied to all searching/ screening in Appendix D1.1 (Acute management of patients with TRD).

The decision to include studies published from 1990 onward was based on internal clinical expert opinion that TRD-related publications started in the early 1990s. The

1990 date limit was therefore applied to ensure that the current standard of depression treatment was captured.

A6. The PRISMA flow chart "Clinical SLR update for acute treatment", reported as Figure 2 in section D.1.1.2, mentions additional records identified through searches of conference proceedings and HTA agencies. Please confirm if these were only searched for during the update. Please provide full details, including dates searched and full search strategies.

Hand searches of additional records were only performed as part of the update of the acute treatment SLR. Full details of the search strategy are provided in Appendix A.

A7. Whilst not mentioned in Appendix D, the description of searches for the maintenance treatment systematic literature review (SLR) in section B2.1.2 of the submission states that "Hand searches of conference proceedings for the previous two years were also performed".

a. **Please confirm if these are the same searches as described in question A6 or if these are separate searches.**

b. **Please provide full details including search date and any search strategies.**

Yes, these are the same searches as discussed in our response to Question A6. While independent SLRs for the acute and maintenance treatments were conducted, the hand searches were only performed for the SLR updates and took place only once, with identified studies being considered for inclusion in either the acute or maintenance treatment categories respectively.

Full details of the search strategy are provided in Appendix A.

A8. The strategies in Appendix D1.2 (Ongoing maintenance treatment of patients with TRD) appear to include fewer interventions than the strategies used in D1.1 for acute treatment, i.e. not all named drugs listed in Table 5 (Eligibility criteria) appear in the strategies. Whilst there are some

limited free text terms for the drug types of interest (see Embase strategy line #72), please explain the rationale behind this decision and what impact this may have had on the overall recall of results.

The same eligibility criteria for the interventions in both acute and maintenance treatment search strategy were implemented. We appreciate this clarification question, which helped us to identify a documentation error in Table 5 (Eligibility criteria for maintenance interventions on in Appendix D1.2). The class of tetracyclic antidepressants (TeCA), which included amoxapine, maprotiline, mianserin, mirtazapine, and setiptiline, were not listed in the table. However, all these interventions were included in the search strategy (see Embase strategy lines # 39-48). There should be no impact of this documentation error on the SLR results. Note that during screening for either the acute or maintenance treatment SLRs, any studies that were potentially relevant for inclusion in the other review were flagged and assessed for eligibility.

Methods of administration and dosage

A9. Priority question. According to Table 2 of the CS (Technology being appraised), "Dose adjustments should be made based on efficacy and tolerability".

Please list the criteria used to guide these dose adjustments, e.g. which thresholds were used.

- All esketamine nasal spray (ESK-NS) patients started with a lower initial dose of ESK-NS, i.e., 28 mg for adults ≥65 years in TRANSFORM-3 and 56 mg for adults <65 years in TRANSORM-1 and TRANSFORM-2.
- The patients in TRANSFORM-1 received the randomised dose 56 mg or 84 mg starting at the second dosing and remained on the assigned dose for the rest of the study period.
- Dose adjustments were allowed in TRANSFORM-2 up to Day 14 during the induction phase and were based on clinical judgment of the treating physicians based on efficacy and tolerability to the previous dose. The intention was to emulate real-world clinical practice, thus there was no prescriptive algorithm.

- The patients aged <65 years in SUSTAIN-1 were maintained on the same dose that they received at the end of the induction phase throughout the maintenance phase. During the maintenance phase, ESK-NS dosing was individualised to the lowest frequency to maintain remission/response.
- Dose adjustments for patients aged ≥65 years were made based on efficacy and tolerability to the previous dose during the induction phase in TRANSFORM-3 and maintenance phase in SUSTAIN-2 in 28 mg increments.

The dose recommendations for ESK-NS are shown in Table 2, as previously provided in the draft SmPC in Appendix C of the company submission.

Table 2. Recommended dosing for ESK-NS

Induction phase	Maintenance phase
Weeks 1–4: Starting Day 1 dose: • Patients aged <65 years: 56 mg • Patients aged ≥ 65 years: 28 mg Subsequent doses: • 56 mg or 84 mg twice weekly	**Weeks 5–8**: 56 mg or 84 mg once weekly **From Week 9**: 56 mg or 84 mg every 2 weeks or once weekly
Evidence of therapeutic benefit should be evaluated at the end of induction phase to determine need for continued treatment.	The need for continued treatment should be reexamined periodically.

Abbreviations: ESK-NS, esketamine nasal spray.
After depressive symptoms improve, treatment is recommended for at least 6 months.

A10. According to Table 6 of the CS (Current and future clinical treatment pathway for TRD), 'recurrence prevention' is given to prevent new episodes of major depressive disorder (MDD). Please provide further details, e.g. what proportion of patients will need relapse prevention and for how long.

All patients who continue treatment will require relapse prevention treatment after the acute treatment phase. Only patients who are still at risk of relapse after 4–9 months in stable remission will require treatment beyond the continuation phase for recurrence prevention. For further details on the proportion of patients at high risk of relapse and the continuation of treatment for recurrence prevention, please see Section B.3.2.9.2.2. and Section B.3.2.9.2.3 of the company submission. As described in Section B.1.3.6 of the submission, NICE CG90 recommends that for those patients at high risk of relapse, oral antidepressant (OAD) treatment should be

continued at the effective dose for at least 2 years, with a re-evaluation to assess if maintenance treatment needs to continue thereafter.

Decision problem

A11. Priority question. According to Table 1 (The decision problem), the intervention addressed in the CS was defined as "ESK-NS co-administered with a newly initiated oral antidepressant (OAD)".

a. **Please discuss the impact of differences of different types of OAD.**

b. **Please clarify if it is possible to administer ESK-NS with any OAD, or if there are any OADs that are contraindicated with ESK-NS. If so, why are these OADs contraindicated?**

c. **Please provide the frequency of each OAD used in each arm of the trials.**

d. **Please clarify how it was determined which OAD the patients received in combination with ESK-NS.**

e. **Please report subgroup analyses by named or type of new OAD.**

A11a. Evidence from the TRANSFORM-2 study shows that there is no difference in treatment effect between different types of OAD. TRANSFORM-2 study was not powered or stratified by OAD class (selective serotonin reuptake inhibitor [SSRI] / serotonin–norepinephrine reuptake inhibitor [SNRI]), but not by specific type of OAD. The subgroup analysis data by OAD class and type show that there is a consistent and similar benefit towards the esketamine nasal spray plus newly initiated oral antidepressant (ESK-NS + OAD) arm versus the newly initiated oral antidepressant plus placebo nasal spray (OAD + PBO-NS) arm. The overlap in confidence intervals between the subgroups by OAD class and type show that no conclusions can be drawn in terms of differences between subgroups. Odds ratios (ORs) for remission and response rates between both study arms by OAD class and type are presented in Table 3 below. For completeness, Montgomery-Asberg Depression Rating Scale (MADRS) change from baseline to Day 28 by OAD class and type is also presented below (Table 4 and Table 6).

Subgroup analysis per OAD class

The ORs for remission and response rates (Table 3) and change from baseline to Day 28 in MADRS (Table 4 and 5) show that the standard error (SE) for the two subgroups by OAD class is high. The subgroup analysis data by OAD class show that there is a consistent and similar benefit towards the ESK-NS + OAD arm versus the OAD + PBO-NS arm. The confidence intervals between ESK-NS + OAD arm and OAD + PBO-NS arms between the two subgroups also overlap meaning that no conclusions can be drawn regarding any differences per subgroup for OAD class.

Subgroup analysis per specific OAD

The ORs for remission and response rates between and MADRS change from baseline to Day 28 show that the SE for all four subgroups by type of OAD is high. The subgroup analysis data by OAD type show that there is a consistent and similar benefit towards the ESK-NS + OAD arm versus the OAD + PBO-NS arm. Again, there is an overlap in the confidence intervals between ESK-NS + OAD arm and OAD + PBO-NS arms for all subgroups (Table 7).

No conclusions can therefore be drawn on differences between subgroups from the subgroup-analysis by OAD class or type.

A11b. No OADs are contraindicated with ESK-NS. After receiving the Day 180 questions from the CHMP, it is expected that the label indication will change to: “SPRAVATO®, in combination with an SSRI or SNRI, is indicated for adults with treatment-resistant major depressive disorder, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode.”

The anticipated updated label indication makes clear that ESK-NS will need to be co-administered with an SSRI or SNRI, neither of which are contraindicated with ESK-NS.

There is a potential interaction of ESK-NS with monoamine oxidase inhibitors (MAOIs). The concomitant use of ESK-NS with MAOIs (e.g., tranylcypromine, selegiline, phenelzine) may increase blood pressure. Close monitoring of blood pressure with concomitant use of ESK-NS with MAOIs is therefore advised.

A11c. Frequencies of OAD use in each arm of the Phase 3 ESK-NS trials were presented in the company submission as follows:

- TRANSFORM-2: see Table 12 in the company submission.
- SUSTAIN-1 (OAD use by trial arm): see Table 13 in the company submission.
- TRANSFORM-1: see Table 77 in the company submission appendices.
- TRANSFORM-3: see Table 77 in the company submission appendices.
- SUSTAIN-2: see Table 78 in the company submission appendices.

A11d. OADs were assigned by the investigator based on review of the Massachusetts General Hospital Antidepressant Treatment History Questionnaire (MGH-ATRQ) – a validated scale used to retrospectively evaluate the adequacy of duration and dosage of OAD treatment, and to assess the degree of improvement on a scale from 0% (not improved at all) to 100% (completely improved). The MGH-ATRQ also takes into account:

- Whether the patient has a history of non-response to the OAD in question during the current depressive episode.
- Whether the patient has a history (lifetime) of intolerance to the OAD in question.
- Whether the OAD in question is available in the given country.

On day 1 of the induction phase of the ESK-NS trials, patients were initiated on a new OAD (open-label) which was continued for at least the duration of induction. The OAD could be one of four: duloxetine, escitalopram, sertraline, or venlafaxine XR.

After completion of the induction phase of TRANSFORM-1/2/3, and if eligible to transfer to one of the SUSTAIN-1/2/3 long-term trials, the same OAD as was initiated at the start of the respective TRANSFORM trial, was continued. (Patients who directly entered a SUSTAIN trial were initiated on a new OAD in the same manner as in the TRANSFORM trials).

A11e. Subgroup analyses for response/remission rates and for change from baseline in MADRS to Day 28 by type and class of OAD are presented in Table 3 and Table 4.

Table 3. TRANSFORM-2 unadjusted response and remission rates (Day 28) by OAD class and type (observed cases)

	ESK-NS + OAD N=114	OAD + PBO-NS N=109	OR between both arms (CI)
Day 28 Remission rates (%)			
SSRI	51.61 (n=36)	25.81 (n=34)	3.07 (1.05 – 8.93)
Sertraline	33.33 (n=15)	26.67 (n=16)	1.38 (0.26 – 7.22)
Escitalopram	63.16 (n=21)	26.67 (n=17)	4.71 (1.08 – 20.63)
SNRI	52.86 (n=76)	33.33 (n=75)	2.24 (1.13 – 4.45)
Duloxetine	50.00 (n=59)	32.73 (n=61)	2.06 (0.95 – 4.47)
Venlafaxine XR	62.50 (n=17)	33.33 (n=15)	3.33 (0.76 – 14.58)
Day 28 Response rates (%)			
SSRI	67.74 (n=36)	45.16 (n=34)	2.55 (0.91 – 7.17)
Sertraline	58.33 (n=15)	33.33 (n=16)	2.80 (0.58 – 13.48)
Escitalopram	73.68 (n=21)	53.33 (n=17)	2.45 (0.58 – 10.33)
SNRI	70.00 (n=76)	55.07 (n=75)	1.90 (0.95 – 3.82)
Duloxetine	70.37 (n=59)	60.00 (n=61)	1.58 (0.72 – 3.51)
Venlafaxine XR	68.75 (n=17)	40.00 (n=15)	3.30 (0.75 – 14.47)

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; XR, extended release.
Note that one patient was classified as having taken an SSRI (duloxetine) and is therefore not accounted for in the table.

Table 4. Change from baseline to Day 28 in MADRS by OAD class (observed cases)

OAD class	Treatment arm	N	Mean (SD) CFB	Minimum	Lower quartile	Median	Upper quartile	Maximum
SNRI	ESK-NS + OAD	70	–22.04 (11.99)	–44.00	–30.00	–24.50	–14.00	12.00
	OAD + PBO-NS	69	–18.07 (13.88)	–43.00	–28.00	–20.00	–6.00	8.00
SSRI	ESK-NS + OAD	31	–20.10 (13.13)	–42.00	–30.00	–23.00	–10.00	13.00
	OAD + PBO-NS	31	–14.61 (13.81)	–43.00	–25.00	–11.00	–3.00	6.00

Abbreviations: CFB, change from baseline; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; MADRS, Montgomery-Asberg Depression Rating Scale; SD, standard deviation; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Table 5. Change from baseline to Day 28 in MADRS by OAD class; difference between ESK-NS + OAD arm and OAD + PBO-NS arm (observed cases)

Timepoint	OAD class	Estimate	SE (95% CI)	Probt
Day 28	SNRI	–3.9947	2.0418 (–8.0195; 0.03012)	0.0517
Day 28	SSRI	–3.9130	3.0425 (–9.9105; 2.0845)	0.1998

Abbreviations: CI, confidence interval; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; MADRS, Montgomery-Asberg Depression Rating Scale; SE, standard error; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; XR, extended release.

Table 6. Change from baseline to Day 28 in MADRS by OAD type (observed cases)

OAD type	Treatment arm	N	Mean (SD) CFB	Minimum	Lower quartile	Median	Upper quartile	Maximum
Duloxetine	ESK-NS + OAD	54	–22.52 (11.82)	–44.00	–31.00	–25.00	–14.00	–1.00
	OAD + PBO-NS	55	–19.07 (12.97)	–43.00	–29.00	–21.00	–10.00	8.00
Escitalopram	ESK-NS + OAD	19	–21.47 (13.56)	–42.00	–31.00	–23.00	–11.00	13.00
	OAD + PBO-NS	15	–15.53 (13.98)	–43.00	–23.00	–17.00	–4.00	6.00
Sertraline	ESK-NS + OAD	12	–17.92 (12.68)	–37.00	–28.00	–21.00	–6.00	3.00

OAD type	Treatment arm	N	Mean (SD) CFB	Minimum	Lower quartile	Median	Upper quartile	Maximum
	OAD + PBO-NS	15	–12.93 (14.15)	–37.00	–25.00	–9.00	0.00	2.00
Venlafaxine XR	ESK-NS + OAD	16	–20.44 (12.83)	–41.00	–28.50	–24.00	–13.50	12.00
	OAD + PBO-NS	15	–14.93 (16.62)	–43.00	–28.00	–12.00	0.00	7.00

Abbreviations: CFB, change from baseline; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; MADRS, Montgomery-Asberg Depression Rating Scale; SD, standard deviation; XR, extended release.

Table 7. Change from baseline to Day 28 in MADRS by OAD type; difference between ESK-NS + OAD arm and OAD + PBO-NS arm (observed cases)

Timepoint	OAD type	Estimate	SE (95% CI)	Probt
Day 28	Duloxetine	–3.3478	2.3105 (–7.9029; 1.2072)	0.1489
Day 28	Escitalopram	–5.2546	4.1490 (–13.4341; 2.9250)	0.2068
Day 28	Sertraline	–2.1235	4.6946 (–11.3787; 7.1316)	0.6515
Day 28	Venlafaxine XR	–6.3471	4.4135 (–15.0481; 2.3539)	0.1519

Abbreviations: CI, confidence interval; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; MADRS, Montgomery-Asberg Depression Rating Scale; SE, standard error; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; XR, extended release.

A12. Priority question.

a. **For each trial, please provide the definition of "responder", "non-responder" and "remission", respectively.**

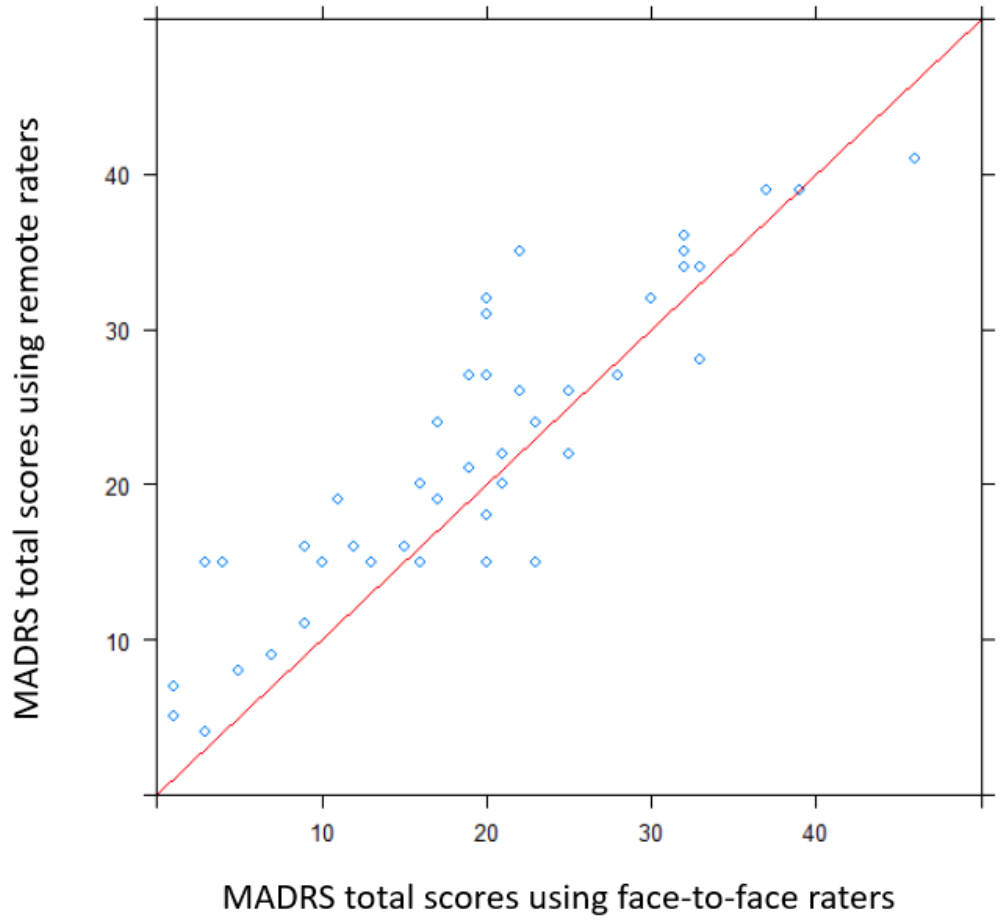
b. **In TA367 remission was defined as MADRS total score of 10 or less. Please justify the threshold of 12 in the CS.**

A12a. In each of the ESK-NS trials included in the company submission (TRANSFORM-1/2/3, SUSTAIN-1/2/3), the definitions of response, non-response, and remission were the same:

- **Responder:** A patient was defined as a responder at any given timepoint if the percent improvement (decrease) in MADRS total score from baseline was ≥50%.
- **Non-responder:** A patient was defined as a non-responder at any given timepoint if the percent improvement (decrease) in MADRS total score from baseline was <50%.
- **Remission:** A patient was defined as being in remission at any timepoint if their MADRS total score was ≤12.

A12b. A MADRS total score ≤12 was defined as the threshold for remission to account for the fact that remote (by phone) MADRS raters were used instead of face-to-face raters to assess treatment response. Dissociative effects of ESK-NS might have resulted in unblinding if face-to-face MADRS raters were used. Data from a Phase 0 study (1) suggested that remote MADRS raters scored slightly higher (by an average of 2 points) than face-to-face raters when patients demonstrated lower overall symptom severity (i.e., MADRS total score <15), as shown in Figure 1. A MADRS total score ≤12 was therefore used in the trials.

Figure 1. MADRS total scores based on remote versus face-to-face raters



Abbreviations: MADRS, Montgomery-Asberg Depression Rating Scale.
Based on 15 patients assessed at three visits by both a remote and face-to-face rater.

A13. Please provide the detailed results for the subgroup by severity of the condition in people with treatment-resistant depression.

As noted in the clarification TC with the ERG on 1st August 2019, it was clarified that the subgroup data of interest are the data relevant to the economic model (TRANSFORM-2). Response and remission rates – by subgroup of disease severity – at Day 28 of the induction phase of TRANSFORM-2, are presented in Table 8. Disease severity was assessed on the basis of MADRS, with a score of 18–34 indicating moderate depression, and a score of >34 indicating severe depression (2). See also the results for the change from baseline in MADRS by disease severity, presented in Table 9. The randomisation in the TRANSFORM-2 study was not powered or stratified by level of severity (moderate or severe). The subgroup analysis data by level of severity show that there is a consistent and similar benefit

towards the ESK-NS + OAD arm versus the OAD + PBO-NS arm. The overlap in confidence intervals of the ORs on the differences between ESK-NS + OAD arm and OAD + PBO-NS arm between the subgroups by OAD class and type show that no conclusions can be drawn in terms of differences between subgroups from the subgroup analysis data.

Table 8. TRANSFORM-2 Day 28 unadjusted response and remission rates by baseline disease severity (observed cases)

	ESK-NS + OAD (%)	OAD + PBO-NS (%)	OR between both arms (CI)
Remission			
Moderate[a] (n=65)	56.25	30.30	2.96 (1.07 – 8.20)
Severe[b] (n=136)	50.72	31.34	2.26 (1.12 – 4.54)
Response			
Moderate[a] (n=65)	59.38	36.36	2.56 (0.94 – 6.96)
Severe[b] (n=136)	73.91	59.70	1.91 (0.93 – 3.95)

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; MADRS, Montgomery-Asberg Depression Rating Scale; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray.
[a] MADRS total score at baseline: 18–34.
[b] MADRS total score at baseline: >34.

Table 9. TRANSFORM-2: Change from baseline to Day 28 in MADRS by baseline disease severity (observed cases)

Timepoint	Baseline severity	Treatment	N	Mean (SD)	Minimum	Lower quartile	Median	Upper quartile	Maximum
Day 28	Moderate	ESK-NS + OAD	32	–15.75 (10.52)	–29.00	–25.50	–18.50	–6.00	12.00
		OAD + PBO-NS	33	–10.00 (12.19)	–34.00	–19.00	–9.00	0.00	8.00
Day 28	Severe	ESK-NS + OAD	69	–24.09 (12.27)	–44.00	–32.00	–26.00	–19.00	13.0
		OAD + PBO-NS	67	–20.45 (13.43)	–43.00	–31.00	–23.00	–9.00	6.00

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; MADRS, Montgomery-Asberg Depression Rating Scale; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray.

Table 10. Change from baseline to Day 28 in MADRS by baseline disease severity; difference between ESK-NS + OAD arm and OAD + PBO-NS arm (observed cases)

Timepoint	Baseline severity	Estimate	SE (95% CI)	Probt
Day 28	Moderate	–5.7755	2.9394 (–11.5698; 0.01879)	0.0507
Day 28	Severe	–2.8573	2.0588 (–6.9158; 1.2011)	0.1666

Abbreviations: CI, confidence interval; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; MADRS, Montgomery-Asberg Depression Rating Scale; SE, standard error.

A14. Please comment on the impact on efficacy outcomes of using quantitative scales (MADRS, PHQ9) to determine depression severity compared to the qualitative (semi-structured interview) approaches used in NHS clinical practice.

Furthermore, please clarify which minimal clinically important difference was applied to the MADRS or PHQ-9 scales, respectively, and provide published evidence to support this threshold.

The MADRS is a quantitative scale that, in the ESK-NS Phase 3 trials, was conducted by a trained scale administrator using the structured interview guide for the MADRS (SIGMA). The minimal clinically important difference for MADRS was taken as 1.6–1.9 points, as reported by Duru 2008 (3).

The Patient Health Questionnaire – 9 questions (PHQ-9) is a patient-reported efficacy measure intended for completion without any assistance/interpretation by clinical staff or family members i.e., it is the patient's personal assessment of their depression severity. The PHQ-9 definition of response was defined as a ≥50% reduction from baseline in the PHQ-9 total score. A 50% reduction in score is a widely used metric for evaluation of response on a clinical outcome assessment where a minimum clinically meaningful change has not been defined. Using 50% reduction for the PHQ-9 was consistent with the similar criterion of 50% reduction used for the MADRS definition of response. There is precedent for this in clinical practice e.g. the National Quality Forum (https://www.qualityforum.org) which uses 50% reduction in the PHQ-9 as part of the endorsed measures 1885 – "Depression Response at Twelve Months- Progress Towards Remission" and 1884 – "Depression Response at Six Months- Progress Towards Remission". In addition, Vlasveld et al (4) used a 50% reduction in PHQ-9 in their work using the PHQ-9 in collaborative care of depressed patients.

Both the MADRS and PHQ-9 scales cover the key diagnostic criteria for major depressive disorder (MDD) according to DSM-IV criteria. The advantage of using these standardised formats in clinical trials is the reduced variability in the data by conducting assessments consistently, using the same assessment criteria over time. Test retest-reliability is acceptable for the PHQ-9 (5, 6) and inter- and intra-rater reliability also has been found acceptable for the MADRS, supporting that these scales are reproducible over time. Since the goal of using the MADRS and PHQ-9 in the clinical trials was to differentiate treatment effects between treatments, it was important to utilise these quantitative scales to enable detection of treatment effect.

In regular clinical practice, semi structured interview approaches are generally used since they provide the treating clinician the ability to be more flexible in the content of the interview and apply clinical judgement to decision making, which is vitally important to managing patients effectively in clinical practice. However, this non standardised method of assessing and treating patients is not suitable for clinical trials because standardised and generalisable assessments are required for efficacy and safety analyses. In the ideal situation, clinical practice might involve a semi structured interview to ensure appropriate evaluation of the patient used in conjunction with regular administration of quantitative scales such as the PHQ-9 to assess changes over time (see International Consortium for Health Outcomes Measurement [ICHOM] recommendations: https://www.ichom.org/portfolio/depression-anxiety/). This approach is used in some healthcare settings (particularly secondary mental health services) but this is often determined by clinician preference and is variable.

The NICE depression guidelines (CG90) state that “The score on a rating scale or questionnaire can contribute to the assessment of depression and rating scales are useful to monitor treatment progress.”

Systematic review

A15. Priority question.

a. **Please provide details on the quality assessment tool(s) used to assess the risk of bias of studies, i.e. provide reference and publication.**

b. **Please report the quality assessments of all trials included in the NMA.**

The risk of bias in studies included in the network meta-analysis (NMA) was assessed using the quality appraisal checklist detailed in Appendix F of the NICE "Methods for the development of NICE public health guidance."

The quality assessment of all trials included in the NMA (except for Luzny 2013 which was just an abstract) has been submitted separately alongside this response.

A16. Please explain the rationale behind conducting two separate SLRs, reported in Appendix D1 of the CS.

Two separate SLRs, one for the acute treatment phase and another one for the maintenance (relapse prevention and recurrence prevention) treatment phase, were conducted due to the difference in outcome measures between the acute (e.g., response and remission) and maintenance treatment phase (e.g., relapse). These outcomes are recognised to be relevant in clinical practice and are measured in the ESK-NS trials. Additionally, there were major differences in the ESK-NS induction and maintenance trial design including the patient inclusion criteria and study drug dosing as outlined in Table 11.

Table 11. ESK-NS major study design differences

Major study design differences	Induction trial (TRANSFORM-1/2/3)	Maintenance trial (SUSTAIN-1)
Patient population	Patients with TRD experiencing moderate to severe MDD symptoms	Stable responders or remitters to ESK-NS induction treatment
Randomisation	From a failed OAD treatment to ESK-NS + OAD or OAD + PBO-NS	Randomly withdraw ESK-NS and replace with PBO-NS while continuing OAD
Study treatment dose, dosing frequency, and duration	Induction dose twice a week for 4 weeks	Maintenance dose once weekly or bi-weekly with variable duration
Treatment outcomes	MADRS change from baseline, response, and remission	Relapse, time to relapse

Abbreviations: ESK-NS, esketamine nasal spray; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; OAD, oral antidepressant; PBO-NS, placebo nasal spray; TRD, treatment-resistant depression.

A17. Please clarify if any searches were conducted to identify non-randomised controlled trials (RCTs).

An SLR was conducted (December 2018) interrogating the same electronic databases as the clinical SLRs. A bespoke search strategy using a validated search filter to identify observational studies was employed. The patient population and interventions of interest were aligned with those employed for the acute clinical SLR. A single prospective, comparative observational study was identified that enrolled patients with TRD (Allen 2015 (7)). This study examined the change in serum brain-derived neurotrophic factor levels in patients with unipolar TRD treated with either ECT or ketamine infusion. No data relating to treatment outcomes of interest were reported in either arm of the trial (i.e. Hamilton Depression Rating Scale [HAM-D]/MADRS scores, or response/remission). Further, ECT was included as a comparator in the RCT base-case network and ketamine was not a comparator of interest; therefore, inclusion of the trial (if it had reported outcomes of interest at 4 weeks) would offer no additional comparative evidence for the comparators of interest.

Please see Appendix B for details of the search strategy.

A18. Table 1 of the appendices does not include buspirone hydrochloride, pregabalin, tryptophan or vilazodone. These are included in the British National Formulary (BNF) and Table 5 of the submission. Please clarify why these drugs were not included.

Of the treatments listed above, only vilazodone is mentioned in Table 5 of the company submission. These treatments were not included as comparators in the NICE scope, and real-world evidence confirm that these drugs are not relevant comparators for the decision problem since these are used only by a very limited number of patients with TRD. Furthermore:

- Buspirone hydrochloride is a serotonin receptor agonist indicated for anxiety only.
- Pregabalin is an anti-epileptic medication licenced for use in generalised anxiety disorder.
- Tryptophan is an essential amino acid; a dietary supplement that can be used for depression, anxiety and sleep problems, but is not included in the NICE guidelines for depression (CG90).
- Vilazodone is a selective serotonin reuptake inhibitor but is not listed in the BNF.

A19. The HTA agency publication which has been identified during the clinical SLR update for acute treatment (Figure 2 of the appendices) is not listed in Table 2 of the appendices (Included studies – original search and update). Please provide details of this HTA publication and send the PDF document.

The health technology assessment (HTA) publication referred to here is TA367. The PDF has been provided separately alongside this response.

Esketamine nasal spray trials

A20. Priority question. Please provide all relevant results for TRANSFORM-3 and SUSTAIN-2 in the same format as TRANSFORM-2.

Full results for TRANSFORM-3 and SUSTAIN-2 are provided in Appendix C.

A21. Priority question. The ERG noticed that population in TRANSFORM-2 and SUSTAIN-1 were aged 18 to 64 years.

a. **Please clarify whether the results of TRANSFORM-2 and SUSTAIN-1 are applicable to the age group ≥65 years.**

b. **Please confirm that the results of TRANSFORM-3 and SUSTAIN-2 are applicable to the age group ≥65 years.**

c. **Please also clarify what in clinical practice the dose of ESK-NS would be for those aged ≥65 years.**

d. **Is the dose of ESK-NS which participants of TRANSFORM-2, TRANSFORM-3, SUSTAIN-1 and SUSTAIN-2 received the same as would be expected in clinical practice and according to the expected license of ESK-NS?**

A21a. The results of TRANSFORM-2 and SUSTAIN-1 are applicable to the age group 18–64 years. Subgroup analysis of patients aged 65-74 in TRANSFORM-3 suggest that the efficacy results of TRANSFORM-2 are also generalisable to a population aged <75.

As stated in the NICE Checkpoint Meeting template, and Form B Sections B.1.4. and B.2.7.2, in a pre-specified analysis of TRANSFORM-3 patients aged 65–74 years (8), the treatment effect in patients that received ESK-NS + OAD was similar (or even greater considering the point estimate) to the treatment effect observed in TRANSFORM-2 patients who received ESK-NS + OAD. As shown in Table 12, the pre-specified analysis with patients aged 65–74 years showed a difference in least squares (LS) means (95% CI) of –4.9 (–8.96, –0.89) for the change from baseline in MADRS total score at Day 28 versus –0.4 (–10.38, 9.50) for patients aged ≥75 years. The results in the 65–74 year subgroup were similar in magnitude to those reported in the younger adult population included in TRANSFORM-2 (difference in LS means of –4.0 (SE: 1.69)). The small number of patients aged ≥75 years (n=22) means that the lack of efficacy in this older age group should be interpreted with caution.

Given the similar relative treatment effect between adults 18–64 years and adults aged 65–74 years, and the relatively small number (n=22) of patients enrolled that were aged ≥75 years, we consider the results from ≥65 years adult population to be consistent with the trials studied in a population of 18-65 year olds in TRANSFORM-2 and SUSTAIN-1.

Table 12. Change from baseline to Day 28 in MADRS by age group (observed cases)

Age group	Trial	Treatment	Diff in LS mean change versus OAD + PBO-NS
≤64 years	TRANSFORM-2	ESK-NS + OAD	–4.0
65–74 years	TRANSFORM-3	ESK-NS + OAD	–4.9
≥75 years	TRANSFORM-3	ESK-NS + OAD	–0.4

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; LS, least squares; MADRS, Montgomery-Asberg Depression Rating Scale; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray.

A21b. The results of TRANSFORM-3 and SUSTAIN-2 are applicable to the age group ≥65 years since TRANSFORM-3 exclusively enrolled patients aged ≥65 years and SUSTAIN-2 enrolled patients aged ≥18 years, of whom 22.2% were ≥65 years of age.

As noted in the response to questions A21a, the pre-specified analysis with patients aged 65–74 years showed a significant difference in change from baseline in MADRS total score at Day 28 versus patients aged ≥75 years. For SUSTAIN-2, the data are applicable to the age group ≥18, including ≥65 years. As described in the SUSTAIN-2 clinical study report (CSR) (page 64), patients aged ≥65 years made up 22.2% of patients enrolled and of these, there were 19 patients ≥75 years of age.

Patients with TRD aged ≥65 years have been studied separately (in TRANSFORM-3) from the younger adult population (18-64 years in TRANSFORM-2). The different dosing, comorbidities, number of previous failures, time until response and treatment received in clinical practice for this population were the reasons why a separate trial was conducted (Section B.1.4).

A21c. The recommended dose of ESK-NS in the expected label for patients with TRD aged ≥65 years will be:

- Starting (Day 1) dose: 28 mg

- Subsequent doses: 56 mg or 84 mg twice a week.

A21d. Yes, the dosing recommendations in the label are expected to reflect the different doses as recommended in the TRANSFORM-2, TRANSFORM-3, SUSTAIN-1, and SUSTAIN-2 trials. It is important to note the TRANSFORM-3 dosing does not fully reflect the expected use in clinical practice. As indicated in Form B section B.1.4., initially in the TRANSFORM-3 trial, investigators were cautious with the dose prescribed to older patients resulting in a substantial proportion of these patients receiving only 28 mg of ESK-NS. ESK-NS 56 mg is considered the lowest efficacious dose. In TRANSFORM-3, at Day 4, 29.6% of patients received 28mg, at Day 15, 12.3% of patients received 28mg and at Day 25, 9.7% of patients received the 28mg dose. As per Table 1 in the response to question A.9, subsequent doses for patients aged ≥65 years should be increased in increments of 28 mg up to 56 mg or 84 mg, based on efficacy and tolerability. This is more aligned to the dosing schedule in TRANSFORM-2. Results from the Phase 2 dose-response study SYNAPSE suggested that the 14 mg and 28 mg doses of ESK-NS had insufficient efficacy in young/mid-life adults. The 28 mg dose elicited the least improvement and appeared less able to sustain improvements versus the 56 mg and 84 mg doses. The ESK-NS 14 mg dose was not efficacious after one week of treatment and therefore was not considered further in the esketamine Phase 3 development program.

A medical education programme will need to be set up to educate clinicians on the dosing recommendations in the different age groups, and to minimise the underdosing of patients with TRD ≥65 years in clinical practice.

A22. Please provide any additional data pertaining to the development of addiction or addiction-related issues (e.g. withdrawal) during any of the identified studies. Please clarify if overdose and drug abuse outcomes were collected using an active or passive system.

Across all clinical studies, there were no cases of overdose or reports of drug abuse (9). Furthermore, there were no reports from the investigational sites of any patients engaging in drug-seeking behaviour or requesting an increase in the frequency of treatment sessions (as a potential early indicator of drug-seeking behaviour).

Approximately one-half of patients treated with ESK-NS in the Phase 2 and 3 studies reported at least one treatment-emergent adverse event (TEAE) suggestive of abuse potential after dosing; events of dizziness, somnolence, and dissociation were the most common. These symptoms are predominantly reported shortly after dosing on the day of ESK-NS administration, are transient and self-limiting, and mild or moderate in intensity. Dissociation, dizziness, sedation, euphoric mood, feeling abnormal, and feeling drunk are identified as adverse drug reactions for ESK-NS.

The Physicians Withdrawal Checklist - Standardised assessment of 20 symptoms (PWC-20) was developed as a reliable and sensitive instrument to assess benzodiazepine-like discontinuation symptoms (10). This scale includes some of the symptoms that have been reported with ketamine withdrawal by case reports. In the absence of a more specific scale, all Phase 3 studies included the PWC-20 to systematically assess the risk of dependence with short- and long-term use of esketamine nasal spray.

Across studies, the changes in withdrawal symptoms assessed by the PWC-20 after cessation of ESK-NS + OAD treatment were consistent with observed changes in symptoms of depression and anxiety. Reported symptoms were primarily mild to moderate in severity. New worsening of depressive symptoms was observed mostly in non-responders to ESK-NS who discontinued treatment due to lack of therapeutic response. Based on the PWC-20 results, there was no evidence suggestive of a distinct withdrawal syndrome in the longer-term studies, i.e., at 1 or 2 weeks after cessation of ESK-NS treatment in SUSTAIN-1 or at 1, 2, or 4 weeks after cessation of ESK-NS treatment in SUSTAIN-2.

Furthermore, stopping short-or long-term use of ESK-NS is shown highly unlikely to be associated with withdrawal syndrome as assessed by stability, frequency, onset, and severity of PWC-WS (Physicians Withdrawal Checklist- Withdrawal Symptoms-subscale), SAEs reported during follow-up phase, and low rate of positive urine drug screens and absence of drug-seeking behaviours. PWC-WS were higher in non-responders to ESK-NS; apart from discontinuation of ESK-NS, this may be related to other changes in therapy, i.e. discontinuation of current OAD and/or initiation of new antidepressant during follow up phase (11).

Levels of esketamine in the circulation do not accumulate with twice-weekly or lower dosing frequency. The steady state level for physical dependence is not achieved, therefore a drug withdrawal is not expected, as suggested by the PWC-20 results. Thus, if dosed as proposed in the EUPI posology, no clear withdrawal syndrome is expected after discontinuation of ESK-NS. The potential for abuse, diversion, and overdose of ESK-NS by the patient is minimised due to the product's design and the administration taking place under the supervision of a healthcare professional in the clinic. ESK-NS will be a prescription only medicine with Schedule 2 controlled drug status which will have to comply with the exisiting legal framework in the UK.

A23. Please justify the applicability of the TRANSFORM-2 population for the population in the decision problem i.e. patients with a major depressive episode (MDE) who have failed to achieve a clinically meaningful improvement after treatment with at least two OADs. In particular, please explain how those patients had been "…prescribed in adequate dosages for adequate time…", as described in Section B.3.2.2 (page 160).

The population included in TRANSFORM-2 is representative of the population specified in the decision problem, as this population had failed to achieve a clinically meaningful improvement after treatment with at least two OADs. In TRANSFORM-2, at the start of the screening/prospective observational phase, patients had documented non-response (≤25% improvement) to ≥1 but ≤5 OADs taken at adequate dosage (at least minimum therapeutic dose) and for adequate duration (defined as at least 6 weeks), as assessed using the MGH-ATRQ for the current episode of depression and confirmed by documented records. This is aligned to the NICE CG90 for the assessment of therapeutic response. If the current episode was >2 years, the upper limit (≤5 OADs) was applicable to only the last two years of OAD treatment.

In addition to the documented non-response to ≥1 but ≤5 OADs, the patient was taking a different OAD (on the MGH-ATRQ) for at least the previous two weeks at or above the minimum therapeutic dose. Patients who were non-responders to their current OAD from the screening/prospective observational phase may have been eligible for randomisation if all other entry criteria were met. Non-response at the end of the screening/prospective observational phase was defined as ≤25% improvement

in the MADRS total score from Week 1 to Week 4 and a MADRS total score of ≥28 on Week 2 and Week 4.

A24. Please provide a breakdown of how long people in clinical practice might be expected to take esketamine in an acute phase and in the maintenance phase. Kindly provide supporting evidence.

Discontinuation in acute phase

In the acute treatment phase, patients are expected to receive ESK-NS + OAD for 4 weeks, and patients who do not respond and/or reach remission at that timepoint, are expected to discontinue treatment. The final SmPC (see the draft SmPC in company submission Appendix C) will state the following: 'Evidence of therapeutic benefit should be evaluated at the end of induction phase to determine need for continued treatment.'

Discontinuation in maintenance phase

It is well established that when remission has been achieved and sustained for a sufficient period of time, the risk of relapse falls. In a clinical setting, a declaration of recovery raises the possibility that treatment can be discontinued or, if treatment is continued, the aim is prevention of a subsequent episode (12).

SUSTAIN-1 data on relapse among stable remitters indicated that a patient with TRD needed to be in relapse-free remission for 36 weeks (approximately nine months) to achieve recovery. At this timepoint, the SUSTAIN-1 data showed a considerable reduction in risk of relapse. The duration of 36 weeks to reach recovery was discussed and validated by four UK clinicians in an advisory board held in June 2019 (13).

For the proportion of remitters who are at high risk of relapse/recurrence, continued treatment for up to 2 years after achieving remission/recovery is recommended by NICE CG90 (14). OADs are used to prevent recurrence in the recurrence-prevention phase, as per current clinical practice. OADs will also be used to prevent recurrence in the recurrence-prevention phase for all patients initially treated with ESK-NS in the acute and continuation treatment phases.

Once entering the maintenance phase, a benefit of ESK-NS is that it can be discontinued while patients can still receive OAD for recurrence prevention. A total of 35.4% of patients were assumed to stop ESK-NS immediately upon achieving recovery. This percentage represents the number of patients in SUSTAIN-1 who had ≤2 total number of MDD episodes, including the current episode. These patients were estimated to be at low risk of relapse based on available evidence and could stop ESK-NS at recovery (15-18). UK clinical experts indicated this is aligned to the available evidence on risk of recurrence increasing after the first two depressive episodes (13).

For the remainder of patients, treatment with ESK-NS +OAD will be continued during the maintenance phase and discontinued over time. Based on UK expert opinion, a 4-week discontinuation risk of 25% for ESK-NS + OAD was used during recovery. This means that a proportion of patients continued therapy for ≥2 years in remission, depending on the level of risk of relapse/recurrence. This is aligned with NICE Clinical Guidelines. NICE CG90 recommends that treatment in patients at high risk of relapse is continued for two years, at which point a re-assessment should be performed to determine whether treatment continuation is required.

Patients who achieve response (without remission) are assumed to continue ESK-NS + OAD as long as they are in the response health state and have not reached remission, as they are assumed to be at high risk of relapse. Evidence from the natural history of the disease shows that patients who have residual symptoms have a higher risk of relapse and recurrence compared with patients who are stable in remission (19).

Patients who stop ESK-NS are expected to continue OAD for recurrence prevention (20, 21).

Supporting evidence

The above assumptions were discussed with UK clinical experts at an advisory board and based upon the available evidence it was concluded that these assumptions were representative of clinical practice (13).

For assumptions related to ongoing ESK-NS + OAD treatment during the continuation and maintenance phases of treatment, please also refer to Section B.4.3.9.2.3 of the company submission.

In SUSTAIN-1, patients discontinued treatment for reasons other than a lack of efficacy, which is expected to also be the case in clinical practice.

Network meta-analysis

A25. Please provide details of how many studies in the network meta-analysis (NMA) had HAM-D results converted to MADRS and provide further justification for the use of the formula used for conversion.

No trials in the NMA had HAM-D results converted to MADRS. While in the methods section of the NMA write-up (see Appendix D, Section D.1.3.1.1, “Outcomes of interest”) the method for converting HAM-D results to MADRS was presented, ultimately only trials that reported MADRS were included in the NMA. The method for converting HAM-D results to MADRS was used for the treatment adjustment method that is described in detail in Section B.2.3.7 of the company submission.

A26. Please provide the WinBUGs ODC file for each of the NMAs containing the relevant data used in the analysis in a suitable format for the ERG to recreate each set of results.

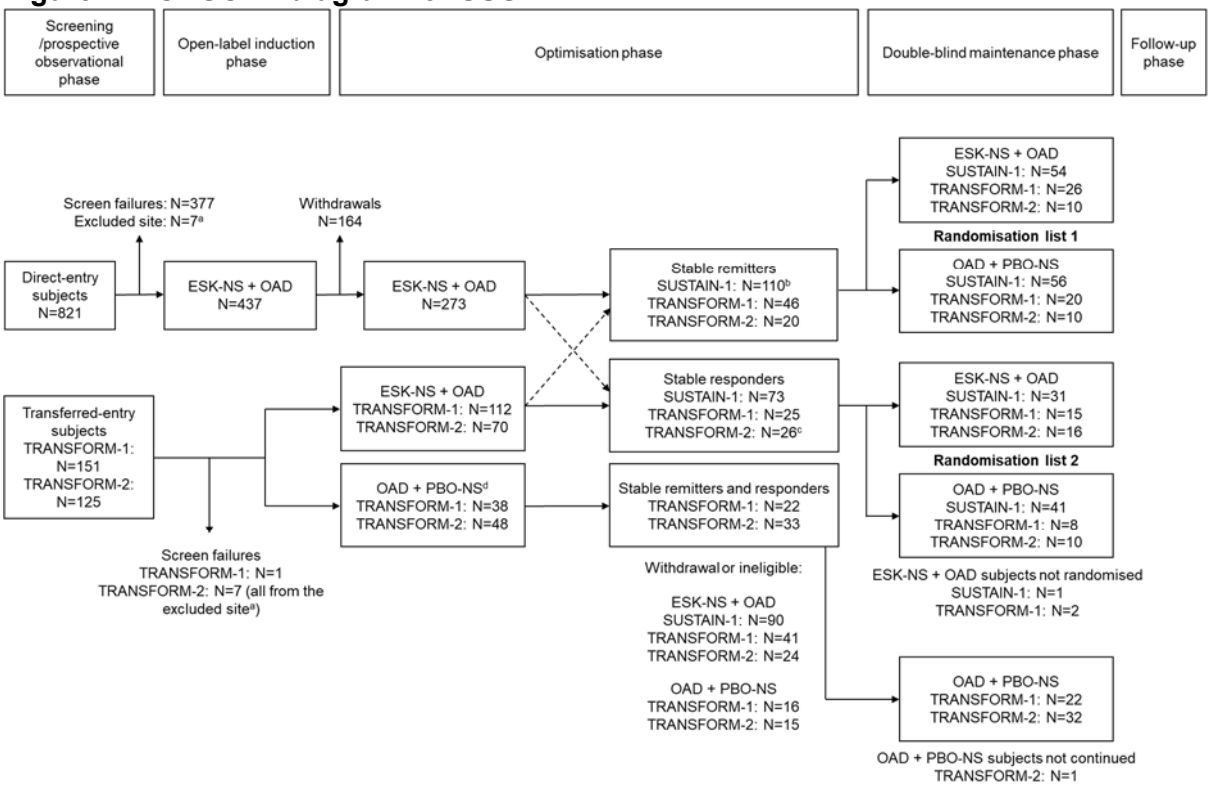
The WinBUGs ODC file has been submitted separately alongside this response.

A27. Please report how many patients in SUSTAIN-1 had transferred from each of TRANSFORM-1 and TRANSFORM-2.

As shown in Figure 2, SUSTAIN-1 enrolled a total of 705 patients, of whom:

- 437 (62.0%) were direct-entry,
- 150 (21.3%) were transferred-entry from TRANSFORM-1, and
- 118 (16.7%) were transferred-entry from TRANSFORM-2.

Figure 2. CONSORT diagram for SUSTAIN-1



Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; GCP, Good Clinical Practice, OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray.
[a] Patients from one site (n=14) were not included in any of the analyses due to GCP violations/noncompliance.
[b] One stable responder was incorrectly randomised as a stable remitter.
[c] One patient not meeting either stable remission or stable response criteria at the end of the optimisation phase was incorrectly randomised as a stable responder.
[d] Note that patients in this OAD + PBO-NS cohort are not appropriate for use to inform relapse rates on OAD + PBO-NS treatment. Rather, this cohort were kept to maintain the blinding of the acute treatment trials, TRANSFORM-1 and TRANSFORM-2.

Section B: Clarification on cost-effectiveness data

Searching

B1. Appendix G1.3.1.1, H1.3.1. and I1.3.1. report the hand searching of additional resources, including conference proceedings and HTA websites. Please provide details of the dates these resources were searched and details of any search terms used.

Conference proceedings, HTA agency websites, and numerous other resources were searched by hand using search terms including: major depressive disorder, MDD, treatment-resistant, and TRD. Full details of the search strategy are provided in Appendix D.

Cost effectiveness review

B2. Studies which appear to have been excluded at the final stages of the cost-effectiveness review in Figures 18 and 19 are described as "Tagged first-/second" but are not described in the narrative. Please explain how studies came to be excluded in the final "Inclusion" phases of the initial and follow up reviews of economic SLRs.

These studies were tagged on the basis they assessed the cost-effectiveness of MDD treatments in the first- or second-line setting, whereas the population of interest in the NICE scope was "adults with treatment-resistant depression" who have, by definition, failed to respond adequately to two prior OADs. Accordingly, the initial and updated cost-effectiveness SLRs focused on studies assessing the cost-effectiveness of treatments for MDD/TRD in the third-line setting and beyond. Those studies assessing first- or second-line treatments (n=164 in the initial search and n=6 in the updated search) were tagged but not included in the final included studies list.

Population

B3. Priority question. According to the CS, the trials TRANSFORM-3 and SUSTAIN-2 in the population aged 65 years and over are not comparable to the trials TRANSFORM-2 and SUSTAIN-1 in the population aged 18-64 years and used in the cost-effectiveness analysis. In that case, the results of the cost-effectiveness analysis cannot be applicable to patients aged 65 years and over.

a. **Please confirm that this is the case.**

b. **Given that the NICE scope has no upper age limit, the ERG requests that the company conduct a cost effectiveness analysis for the whole population by adding data specific for those aged 65 years over, including TRANSFORM-3 and SUSTAIN-2 to the existing data for those aged 18-64 years. This could be done by essentially combining two models, ideally by duplicating the Markov traces so that the results of deterministic sensitivity analyses and model checks could be observed**

instantaneously i.e. without recourse to a macro. Please ensure that all requested changes are incorporated as applicable within this analysis.

B3a. Given the similar relative treatment effect observed in adults 18–64 years and 65–74 years, we suggest considering the results of the cost-effectiveness analysis using TRANSFORM-2 and SUSTAIN-1 data to be applicable to those aged 18-74 years. Further clarification is provided in the paragraphs below.

The ages of the populations included in the ESK-NS Phase 3 clinical trials are summarised in Table 13.

Table 13. Patient age criteria for the ESK-NS Phase 3 trials

Study	Inclusion criteria (patient age)
TRANSFORM-1	18–64 years, inclusive.
TRANSFORM-2	18–64 years, inclusive.
TRANSFORM-3	Aged ≥65 years.
SUSTAIN-1	18–64 years, inclusive.
SUSTAIN-2	Aged ≥18 years.
SUSTAIN-3	Aged ≥18 years.

Abbreviations: ESK-NS, esketamine nasal spray.

Section B.3.4.1 of the company submission outlines the rationale for not pooling TRANSFORM-2 and TRANSFORM-3 data in the model.

As indicated in our response to question A.21 and as stated in the NICE Checkpoint Meeting template, Section B.1.4. and B.2.7.2 of the company submission, in a pre-specified analysis of TRANSFORM-3 patients aged 65–74 years, the treatment effect in patients that received ESK-NS + OAD was similar (or even greater considering the point estimate) to the treatment effect observed in TRANSFORM-2 patients who received ESK-NS + OAD. The pre-specified analysis with patients aged 65–74 years showed a difference in LS means (95% CI) of –4.9 (–8.96, –0.89) for the change from baseline in MADRS total score at Day 28 versus –0.4 (–10.38, 9.50) for patients aged ≥75 years. The results in the 65–74-year subgroup were similar to the magnitude of those reported in the younger adult population included in TRANSFORM-2 (difference in LS means of –4.0 (SE: 1.69)). The small sample size of patients aged ≥75 years (n=22) means that the lack of efficacy in this older age group should be interpreted with caution.

Given the similar relative treatment effect in adults 18–64 years and 65–74 years, and the relatively small number (n=22) of patients aged ≥75 years, it is appropriate to consider TRANSFORM-2 data for all adult patients.

B3b. Please see the submitted Markov model for the combined 18–64 years and ≥65 years populations. The model includes the derived weighted averages for clinical, utility, and cost inputs of the two populations.

The same model assumptions as previously submitted in the base case model are applied. Based on the 2011 Census of the Office of National Statistics, 20.8% of patients with TRD are ≥65 years. With this input, the incremental cost-effectiveness ratio (ICER) is £7,884 per quality-adjusted life year (QALY).

Comparators

B4. Priority question. Please conduct the analyses as described in section B.3.4.4.9 with odds ratios (ORs) from the NMA which exclude the treatment adjustment.

For the outputs of the NMA to be used in the model, the OR outputs of the NMA were converted into relative risks (RRs) using the following formula:

$$RR = \frac{OR}{(1 - r_b) + (r_b \times OR)}$$

Where r_b = baseline risk of relapse or remission for OAD + PBO-NS.

The analysis applied these RRs to the ESK-NS + OAD response and remission rates using the OR from the NMA which included the treatment adjustment (see Tables 35 and 36 in the company submission). Table 14 presents the estimated response and remission rates for each of the comparator treatments. The OAD data were reflective of STAR*D and would have included the alternative comparators considered in this analysis. Therefore, for all other parameters, the analysis assumed equivalence to OAD.

Table 14. Response and remission rates at the end of the acute treatment phase

Treatment	Remission, %[a]	Response (but not remission), %[b]
ESK-NS + OAD	52.48	16.83
OAD	30.81	8.79
Aug tricyclic (nortrip) ± PBO	37.78	9.49
Aug SSRI/SNRI + AAP	44.45	8.15
Aug SSRI/SNRI + lithium	36.88	5.24
Aug SSRI/SNRI ± PBO	28.80	4.19
Switch tetracyclic (mirtazapine)	24.09	6.67
Switch SSRI + AAP	37.51	8.15

Abbreviations: AAP, atypical antipsychotic; Aug, augmentation; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; MADRS, Montgomery-Asberg Depression Rating Scale; nortrip, nortriptyline; OAD, oral antidepressant; PBO, placebo; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
[a] MADRS ≤12.
[b] ≥50% reduction in MADRS from baseline but MADRS score >12.

The results in Table 15 demonstrate that ESK-NS + OAD would remain a cost-effective treatment option versus all other treatments considered. ESK-NS + OAD is cost-effective versus Aug SSRI/SNRI + AAP with an ICER of £22,823. Aug SSRI/SNRI + AAP and ESK-NS + OAD showed extended dominance over all other treatments. When comparing ESK-NS + OAD with all other comparators, the ICER ranged from £7,341 to £22,823.

Table 15: Scenario analysis considering all comparators

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline[a] (£/QALY)	ICER incremental (£/QALY)	ICER versus ESK-NS + OAD (£/QALY)
Aug SSRI/SNRI + AAP	£45,709	4.5121	2.3569						£22,823
Aug tricyclic (nortrip) ± PBO	£46,445	4.5111	2.3261	£737	-0.0010	-0.0307	Dominated	Dominated	£17,049
Aug SSRI/SNRI + lithium	£46,804	4.5106	2.3105	£359	-0.0005	-0.0156	Dominated	Dominated	£14,686
OAD+PBO	£47,327	4.5098	2.2877	£523	-0.0008	-0.0228	Dominated	Dominated	£11,701
Aug SSRI/SNRI ± PBO	£47,870	4.5091	2.2661	£543	-0.0007	-0.0216	Dominated	Dominated	£9,124
Switch tetracyclic (mirtazapine)	£48,287	4.5085	2.2477	£416	-0.0006	-0.0184	Dominated	Dominated	£7,341
ESK+AD	£50,691	4.5188	2.5751	£2,404	0.0103	0.3274	£22,823	£7,341	

Abbreviations: AAP, atypical antipsychotic; Aug, augmentation; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; ICER, incremental cost-effectiveness ratio; LYG, life years gained; nortrip, nortriptyline; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; PBO, placebo; QALYs, quality-adjusted life years; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a] Baseline in this analysis is Aug SSRI/SNRI + AAP.

B5. Priority question.

a. **Please justify why subgroup analyses by OAD was not conducted.**

b. **Please conduct these analyses and present the results.**

B5a. Subgroup analysis data for OAD class (SSRI or SNRI) has been described in Section B.2.6.1.6 and Appendix E of the company submission.

A subgroup analysis by OAD type was not conducted due to the following reasons:

- The study was not powered to draw conclusions from the subgroup analysis data.
- There is insufficient evidence to indicate a difference in efficacy (and tolerability) between individual OADs.

As described in Section B.1.3.6 of the company submission, based on an NMA conducted by Cipriani et al (22), the Guideline Development Group in NICE CG90 concluded that there was insufficient evidence to indicate a difference in efficacy and tolerability between individual OADs and therefore no specific OAD treatment recommendations were made. The same conclusion was reached in NICE TA367 (23). The meta-analysis has recently been updated with data from nine additional OADs, which again found few differences between antidepressants when all data were considered (24).

B5b. Please see response to question A11e.

B6. Priority question. The company submission state that "Efficacy estimates (response and remission) for the OAD + PBO-NS arm of the TRANSFORM-2 trial were high compared with other studies in TRD" and on this basis the response rate was adjusted down for OAD + PBS-NS. It also attributes this to the high number of clinic visits. However, any placebo effect (due to clinic visits or for any other reason) is likely to be present in both trial arms. Hence, only removing the placebo effect for OAD + PBO while not removing it for ESK would likely overestimate the ESK treatment benefit.

Please either use the unadjusted estimates of response for OAD + PBO-NS for the model base case or perform the same adjustment to ESK-NS + OAD.

The use of ESK-NS in real world clinical practice will require the same number of physician visits as observed in TRANSFORM-2, whereas the prescription of OADs in clinical practice do not. Therefore, adjustment for visit effect for the OAD + PBO-NS arm is appropriate, but adjustment of the ESK-NS + OAD arm is not.

Nevertheless, a scenario considering the unadjusted estimates of response for OAD + PBO-NS was conducted and presented in the company submission (see Section B.3.4.4.1). Specifically, Table 68 in the company submission shows that using the unadjusted response and remission rates for OAD would result in an ICER of £16,209 per QALY.

Please note that the unadjusted estimates of response and remission rates reported in TRANSFORM-2 are provided in Section B.2.6.1.3 of the company submission. Additionally, in Section B.3.4.4.1 of the submission, different levels of treatment adjustment (including no adjustment), are included as a scenario analysis of the cost effectiveness results.

As explained in Section B.2.1.4 of the company submission, we consider the clinical rationale supporting the adjustment of the treatment effect in the OAD + PBO-NS arm of TRANSFORM-2 trials to be strong, and validated by UK clinicians in two different advisory boards (13, 25). Not adjusting the treatment effect of the OAD + PBO-NS arm would result in an underestimation of the relative treatment effect of ESK-NS + OAD. It is important to note the difference in the design and

administration schedule of the OAD + PBO-NS arm in TRANSFORM-2 versus how OADs are prescribed and taken in UK clinical practice.

Reasons underlying the high treatment response observed in the OAD + PBO-NS arm of TRANSFORM-2

Possible reasons for the high treatment response observed in the OAD + PBO-NS arm of TRANSFORM-2 were discussed during an advisory board with seven UK clinical psychiatric experts, noted in the literature (26), and discussed by the FDA and EMA during their review of the ESK-NS regulatory dossier. Based on available evidence, it was concluded that the main reasons for the high TRANSFORM-2 treatment effect include:

1) Use of a nasal spray delivery system leading to patient expectation of 'something novel'.
2) High patient expectation of benefit due to the portrayal in the media of esketamine as a 'promising' new treatment option for depression.
3) Treatment effect of the newly initiated OAD, an active drug which is the first line standard of care for TRD.
4) High frequency and intensity of patient-health care professional interaction due to twice-weekly visits (of considerable length).

We accept that the first three of the potential placebo effects outlined above are likely to be applicable to both arms of the trials; however, the fourth effect, that is, the high frequency and intensity of health care professional interaction, will clearly differ between the two arms and therefore should be adjusted in the placebo arm of the trials.

High frequency and intensity of patient-health care professional interaction due to twice-weekly visits (of considerable length)

The use of ESK-NS in real world NHS clinical practice will require the same number of physician visits as occurred in TRANSFORM-2. Therefore, adjustment for the increased visit effect for the ESK-NS + OAD arm is not appropriate. Conversely, in real-life NHS clinical practice, patients with TRD on OADs do not receive the same intensive therapeutic contact as was the case in TRANSFORM-2, which amounted to eight clinic visits during the 4-week acute treatment period (see Table 16).

It is clear that the OAD + PBO-NS arm in the TRANSFORM-2 trial does not reflect the true treatment effect of a newly initiated OAD than is currently the case in NHS clinical practice. The OAD + PBO-NS arm of the TRANSFORM-2 trial consists of a newly initiated SSRI/SNRI, in addition to a PBO-NS and healthcare professional contact to supervise the self-administration of the placebo device. This was to ensure double-blinding of the randomised clinical trial; however, it clearly differs from current NHS clinical practice.

As shown in Table 16, current clinical practice when an OAD is prescribed is characterised by less frequent visits to healthcare professionals with shorter duration than future clinical practice after initiation of ESK-NS + OAD. Table 16 also shows the future practice of visits after initiation of ESK-NS treatment, which is aligned to the number of visits in TRANSFORM-2.

Table 16. Current and future clinical treatment pathway for TRD

Treatment phase	Existing NHS clinical practice when OAD is prescribed	Future clinical practice for ESK-NS + OAD
Acute treatment phase Aim: complete resolution of TRD symptoms	• Initiation of OAD • First visit on average 3–4 weeks after switching to a new OAD • On average, four visits in the first 3 months after switch to a new OAD • Visit of 20–30 minutes, usually with GP, to assess treatment effect, and consider continuation or change in treatment	• Initiation of ESK-NS + OAD • Eight visits in first 4 weeks • At visit eight (at 4 weeks), there will be time with a prescriber (psychiatrist) to assess treatment response, and consider continuation or change in treatment On average 1 hour and 10 minutes per visit: • 10 minutes self-administration (under supervision of nurse). Blood pressure will be measured before first self-administration • 1 hour observation (by healthcare assistant) where blood pressure is measured 1–3 times
Relapse prevention treatment phase Aim: preventing relapse of MDD episode	• One visit every 4–12 weeks • Visit of 10–30 minutes, usually with GP, to assess treatment effect, and consider continuation or change in treatment	Weeks 5–8: • Weekly visits Weeks 8 onwards: • Fortnightly or weekly visits On average 1 hour and 20 minutes per visit: • 10 minutes self-administration (under supervision of nurse). Blood pressure will be measured before first self-administration

Treatment phase	Existing NHS clinical practice when OAD is prescribed	Future clinical practice for ESK-NS + OAD
		• 1 hour observation (by healthcare assistant) where blood pressure is measured 1–3 times The need for continued treatment will be evaluated periodically
	After the depressive symptoms resolve, treatment for at least 6 months is recommended for consolidation of the anti-depressive response	After depressive symptoms improve, treatment is recommended for at least 6 months
Recurrence prevention Aim: prevent new episode of MDD	• Prevention of MDD recurrence is with an OAD following entry into a 'recovery' state	• Prevention of MDD recurrence is with an OAD following entry into a 'recovery' state • For patients at high risk of recurrence, ESK-NS treatment may be extended to up to 2 years based on clinical judgement

Abbreviations: GP, general practitioner; MDD, major depressive disorder; OAD, oral antidepressant; TRD, Treatment-resistant depression.
Sources: Janssen data on file (25, 27), Wiles 2018 (28).

Quantification of the impact of high frequency and intensity of patient-health care professional interaction on treatment effect

The literature indicates that increase in health care profession interaction has a positive impact on therapeutic treatment effect. Yesavage 2018 (29) showed the importance of close clinical surveillance, rigorous monitoring of concomitant medication, and regular interaction with clinic staff in bringing about significant improvement in a patient population with TRD. Quantification of the impact of additional visits in MDD trials has been undertaken by Posternak and Zimmerman (30). The study showed that follow-up visit assessments in OAD treatment trials translated into a significant therapeutic effect, representing about 40% of the response to placebo. NICE CG90 describes this study as "a systematic review that provides suggestive evidence that the chance of responding to treatment with placebo is higher if monitoring is carried out more frequently in the first few weeks of treatment." Dunlop 2012 (31) conducted a meta-analysis and found that the number of post-baseline visits was one of the significant positive predictors of clinical outcomes.

Full details regarding the adjustment methodology applied to the PBO-NS + OAD arm of TRANSFORM-2 are provided in Section B.2.3.7 of the company submission. It is important to highlight that the method applied only quantifies for one of the four reasons that are known to contribute to the treatment effect; the use of a nasal spray delivery system and patient's expectation of benefit of potentially receiving a 'promising' new treatment option have not been adjusted for. These two factors will not play a role when an OAD is prescribed to patients with TRD in clinical practice, but the impact on treatment effect currently cannot be quantified.

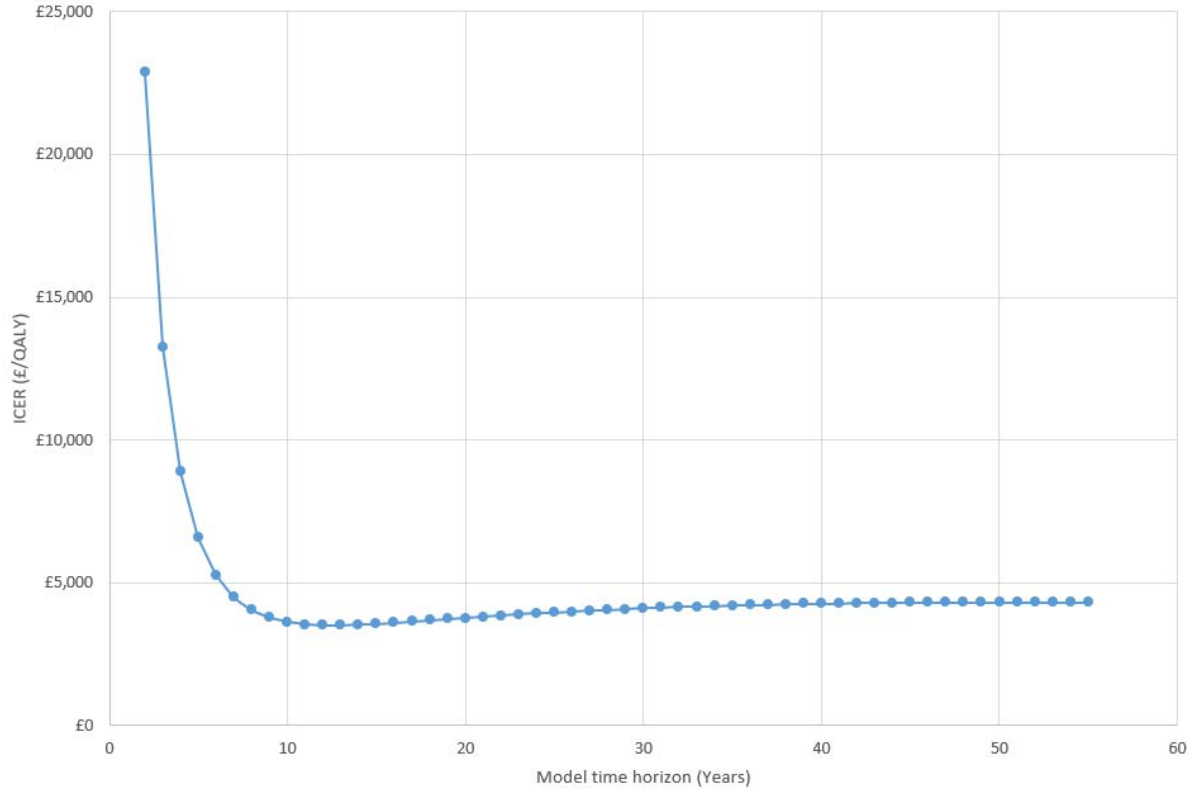
Model structure

B7. Priority question. Please justify the choice of 5 years as a time horizon, given that it is longer than the time horizon used in TA367 and Edwards et al. 2013, but shorter than a lifetime horizon. Please extend the time horizon to a lifetime given that this is according to the NICE reference case and to capture the chronic nature of the condition and to account for the effect on mortality associated with suicide.

In the base case analysis, the time horizon was set to 5 years which was deemed to be of sufficient duration to represent the length of one TRD major depressive episode (MDE) and account for all the treatment-related costs and effects attributable to ESK-NS + OAD.

A one-way analysis is presented in Figure 3 which demonstrates the impact on the ICER of varying the model time horizon (a selection of ICERs have also been presented in Table 17).

Figure 3: Incremental cost-effectiveness over time



Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 17. Time horizon sensitivity analysis

Time horizon (years)	ICER
2	£22,881
3	£13,265
5 (Base case)	**£6,582**
10	£3,619
20	£3,769
30	£4,102
40	£4,269
50	£4,314

Abbreviations: ICER, incremental cost-effectiveness ratio.

B8. Priority question. Section B.3.2.2 of the CS states that the relevance and definitions of the health states were validated by clinical experts.

a. **Please provide all of the evidence to support the definitions.**

b. **Please also provide justification for these health states based on current and/or expected UK clinical practice.**

B8a. The health state definitions included in the submitted cost effectiveness analysis (see Table 23) are aligned with the recognised natural history and management for MDD, including TRD (see also Section B.1.3.5.1 of the company submission) (32, 33).

UK clinicians attending the clinical advisory board or HTA advisory board supported the health states as defined in the ESK-NS cost effectiveness model.

The model health states are based on previous models in the field of MDD, including the model that was developed for the NICE appraisal of vortioxetine for MDD (TA367) and the NICE CG90 model, both of which were reflective of UK clinical practice. The specific health state definitions of MDE, response, and remission in the ESK-NS TRD model mirror the definitions as used in the ESK-NS TRD clinical trials.

The addition of the response health state was specifically welcomed by NICE during the NICE Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMA) model validation.

The specific timing of 36 weeks in the definition of recovery is based on analysis of SUSTAIN-1 data. (See response to question A24 and Section B.3.2.9.2.3 of the company submission).

B8b. [redacted]

[redacted]

TA367 criticisms were taken into account when developing the ESK-NS model. [redacted]

Patients in remission without a relapse for an uninterrupted period of time are considered in recovery (32). A key rationale for making a distinction between remission and recovery is to separate the expected higher risk of relapse in remission and lower risk of recurrence in recovery. While there is no consensus on how much time in remission constitutes recovery, 6 months is often mentioned in literature, or a range of 4–9 months. In the current model, a recovery definition of 9 months in remission was used, based on SUSTAIN-1 data (see response to question A24).

B9. Priority question. It is unclear which data from the SUSTAIN-1 study were used to inform some of the transition probabilities, given that patients appear to enter SUSTAIN-1 from various sources, including either of the TRANSFORM-1 or TRANSFORM-2 or by direct entry. Please confirm that the data sources for each of the transition probabilities appropriately reflect the starting health state, as defined by the MADRS, the treatment pathway and timing as set out below. If this is not the case then please re-estimate the transition probabilities using the correct data:

a. **Response to remission on ESK-NS+ OAD should be informed by data from patients who initially responded to ESK-NS + OAD after 4 weeks and then went into remission after 4 weeks (weeks 5-8) on ESK-NS+OAD**

b. **Response to remission on OAD + PBO-NS should be informed by data from patients who initially responded to OAD + PBO-NS. after 4 weeks**

and then went into remission after 4 weeks (weeks 5-8) on OAD + PBO-NS

c. **Relapse on ESK-NS + OAD should be informed by data from patients who initially:**

   1. **responded to ESK-NS + OAD after 4 weeks, then went into remission after 4 weeks (weeks 5-8) on ESK-NS+OAD and then relapsed at any time from week 9 onwards**

   2. **went into remission on ESK-NS + OAD after 4 weeks and then relapsed at any time from week 5 onwards**

d. **Loss of response on ESK-NS + OAD should be informed by data from patients who initially responded to ESK-NS + OAD after 4 weeks and then lost that response at any time from week 5 onwards**

During the open-label optimisation phase from Week 5–16 of SUSTAIN-1, no data were captured to inform the model. Eligible direct-entry subjects from the open-label induction phase and transferred-entry subjects from the two double-blind short-term studies TRANSFORM-1 and TRANSFORM-2 participated in this 12-week phase. The first 4–8 weeks were used to optimise the dosing. At the end of the optimisation phase, subjects in stable remission and those with stable response were eligible to continue into the randomised, double-blind phase of SUSTAIN-1. It was the data from this treatment phase of SUSTAIN-1 that were used to inform the transition probabilities from response to remission, risk of loss of response, and risk of relapse for ESK-NS + OAD. The STAR*D study data were used to inform these model inputs for the OAD arm (see response to question B10 for further detail).

Further details on the sources of the transition probabilities from response to remission, risk of loss of response, and risk of relapse are provided in Section B.3.2.9.2.1 and Section B.3.2.9.2.2 of the company submission.

B10. Priority question: Please explain why STAR*D was used as the source for transition probabilities for relapse and loss of response for patients on OAD + PBO-NS. If some patients who entered SUSTAIN-1 were originally randomised to OAD + PBO-NS in TRANSFORM-1 or TRANSFORM-2 then please re-estimate the transition probabilities using these data, in line with question B9, as set out below:

a. **Relapse on OAD + PBO-NS should be informed by data from patients who initially:**

    1. **responded to OAD + PBO-NS after 4 weeks, then went into remission during the next 4 weeks (weeks 5-8) on OAD + PBO-NS and then relapsed at any time from week 9 onwards**

    2. **went into remission on OAD + PBO-NS after 4 weeks and then relapsed at any time from week 5 onwards**

b. **Loss of response on OAD + PBO-NS should be informed by data from patients who initially responded to OAD + PBO-NS after 4 weeks and then lost that response at any time from week 5 onwards**

OAD+ PBO-NS was not included as a comparator in the economic model. As per the NICE scope and aligned to UK clinical practice, OAD + PBO-NS would not be given to patients with TRD in the UK NHS. The economic model includes OAD as the comparator instead of OAD + PBO-NS.

As noted in Section B.3.2.9 of the company submission, SUSTAIN-1 is not an appropriate data source to inform OAD relapse and loss of response transition probabilities. The transferred entry patients from TRANSFORM-1 and TRANSFORM-2 to SUSTAIN-1 who were on OAD + PBO-NS were not randomised in the maintenance phase. As noted in the footnote to Figure 11 in Appendix D.2.2, this group of patients within the SUSTAIN-1 trial is not informative on the transition probability of relapse and loss of response on OAD, as these patients were not included in the efficacy analyses. This cohort was kept to maintain the blinding of the acute treatment trials, and only considered in safety analyses.

As noted in Section B.3.2.9.2.2, SUSTAIN-1 may not be the most appropriate data source for the OAD loss of response transition. At the end of the optimisation phase of SUSTAIN-1, patients who were stable responders or who were stable remitters on ESK-NS + OAD were randomised 1:1 to either continue ESK-NS + OAD treatment or be switched to OAD + PBO-NS. Since those patients randomised to OAD + PBO-NS had received (and responded to) prior treatment with ESK-NS + OAD, it was unclear whether the withdrawal of ESK-NS might impact their loss of response or risk of relapse.

To better reflect clinical practice, the model derived loss of response risk data for patients on OAD maintenance treatment from STAR*D. The STAR*D trial is the largest study to examine the durability of OAD response in MDD and TRD and represents the best source to inform the loss of response probability on OAD treatment in the model. This is consistent with the approach taken and accepted by the NICE Committee in TA367 which also used STAR*D to inform loss of response for OAD, in the absence of appropriate input data.

B11. Involvement of clinical experts.

a. **Please provide all documentation related to the involvement of clinical experts, including the number and qualifications/status of the clinical expert, and the means of elicitation of opinion i.e. the questions asked and the answers provided.**

b. **Furthermore, please also provide the following references cited**

- **50. Janssen. Data on File. Esketamine_DoF_28May2019_HEMAR_TM_007**
- **142. Janssen. Esketamine_DoF_05Jul2019_HEMAR_TM_001**
- **143. Janssen. Data onFile.Esketamine_DoF_11June2019_HEMAR_TM_001**

For full reports relating to the advisory boards held on 18th October 2018 and 4th June 2019 respectively, please see Appendix E. 18th October 2018 advisory board notes

Summary

An advisory board was conducted to gain clinical opinion on the esketamine nasal spray clinical trial programme and how the drug would likely be used in clinical practice in patients with treatment resistant depression (TRD), including likely positioning and considering the observation requirements. The insights from the advisory board, together with responses from the pre-meeting questionnaire, have been used to guide the assumptions and approach considered in the NICE submission (with attendee permission). Attendees were asked if their input could be used anonymously to support the NICE submission. The respondents agreed that this would be acceptable.

Advisory board attendees:

Name
Psychiatrist
Professor in mental health and psychiatrist†
Professor in mental health and GP
Psychiatrist
Psychiatrist
Professor in Mental Health
Psychiatrist

†This clinician was unable to attend the advisory board but completed a separate questionnaire.

Meeting objectives and agenda

Objective: The objective of the advisory board was to validate the clinical assumptions for the UK Health Technology Appraisal submissions for esketamine nasal spray with regards to:

- Current and expected future treatment patterns for patients with TRD.
- The clinical value and interpretation of esketamine nasal spray phase 3 data.
- The expected duration of treatment with esketamine nasal spray in clinical practice.

Meeting agenda

09:30	Welcome and tea/coffee
09:45	Introductions and objectives
10:00	Presentation: Esketamine nasal spray phase 3 results and target profile summary overview
10:30	Q & A: What further information is required in relation to the clinical trials to aid participation in this advisory board?
11:00	Tea/coffee break
11:15	Q & A: How can the clinical trials be interpreted in relation to overall efficacy of esketamine nasal spray versus placebo nasal spray? (Part 1)
12:15	Lunch break
12:45	Q & A: How can the clinical trials be interpreted in relation to overall efficacy of esketamine nasal spray versus placebo nasal spray? (Part 2)
13:30	Q&A: What is the current and potential future treatment pathway for TRD and what are the relevant comparators for esketamine nasal spray?
14:30	Coffee/tea break
14:45	Q&A: What are the likely observation requirements for esketamine nasal spray in clinical practice and how can they be defined?
16:00	Summary of advisory board & close
16:30	Meeting ends

Summary

Key recommendation from the advisory board

- Further investigate the placebo effect by identifying other studies ideally in depression which have included a placebo arm with a novel mode of action. The aim of this would be to compare the size of the active comparator/placebo effect with other studies in mental health.

Efficacy of esketamine nasal spray

Key takeaway from discussions with advisers:

- The effect in the active comparator arm of the TRANSFORM-2 study is higher than the treatment effect of OADs shown in other clinical trials in the TRD population, and higher than in NHS clinical practice.
- Treatment adjustment of the TRANSFORM-2 active comparator arm is justified.

- Clinicians noted the pronounced treatment effect in the active comparator arm (newly initiated OAD plus placebo nasal spray) and highlighted that this would not usually be seen with an OAD, particularly so soon (Day 2) after treatment initiation (usually a treatment effect with OADs is not seen for at least 2 weeks).

- The attendees agreed that the treatment effect in the active comparator arm is not reflective of expected outcome of OADs in patients with TRD in clinical practice. The

clinicians agreed that the pronounced treatment effect in the active comparator arm is likely due to:

1. the novel treatment administration,
2. the anticipation of receiving esketamine nasal spray treatment, and
3. the intensive management approach (twice weekly 1-1 interaction with an HCP for >2 hours).

- Clinicians noted that similar effects have been seen in studies comparing ECT with sham ECT, and with TMS where patients have daily nurse interactions, showing that the amount of time spent in contact with HCPs can have a considerable impact on the treatment effect.

Treatment duration

Key takeaway from discussions with advisers:

- The largest proportion of patients with TRD (~80%) will discontinue esketamine nasal spray treatment if recovery is achieved.
- A small proportion of patients with TRD, the ones who are at high risk of relapse, will continue treatment with esketamine nasal spray for up to two years.
- Clinicians will motivate the most severe patients with TRD who failed all possible lines of AD treatment to continue treatment with esketamine nasal spray plus OAD if it is effective in these patients.

- The clinicians agreed that once a treatment is working in the TRD population, it is difficult to take patients off the treatment, because both physicians and patients will be reluctant to stop a treatment to which the patient is responding, at least in the short-term.
- Clinician consensus was that the most severe patients with TRD who failed all possible lines of AD treatment and who had achieved remission when using esketamine nasal spray + OAD should be motivated to continue esketamine nasal spray + OAD for an indefinite period.
- When clinicians were reminded of the logistics associated with esketamine nasal spray treatment (i.e. visits to the clinic for approx. 1 hour and 10 minutes every week or every other week) and it was explained that for HTA purposes it was necessary to get real-life estimates (instead of aspirational) and a timeframe for treatment, the clinicians agreed that:
    - The largest proportion of patients with TRD (~80%) will discontinue esketamine nasal spray treatment if recovery is achieved.
    - A small proportion of patients with TRD (~20%), the ones who are at high risk of relapse, will continue treatment with esketamine nasal spray for up to two years.

Subsequent treatments

- Potential treatments after esketamine nasal spray include augmentation therapy.
- One clinician indicated that ECT would be considered as a next step after esketamine nasal spray if the patient failed to respond or had a relapse.

Administration and observation costs

- Observation requirements did not seem to be a major concern for the clinicians.
- There was a high level of agreement with regard to the amount of time that administration (10 minutes) and monitoring (maximum 90 minutes) will take.
- Self- administration of esketamine nasal spray would need to be monitored by a qualified nurse.
- A physician would need to be accessible but not necessarily present, in case of an emergency.
- Due to the safety profile of esketamine nasal spray, the clinicians agreed that the ratio of healthcare professional (nurse) to patients could be increased in the maintenance phase from 1:8 to 1:20.

Current treatment pathway for TRD and relevant comparators for esketamine nasal spray

- Numerous treatment options were proposed for 1st, 2nd, and 3rd line TRD indicating the heterogeneity of the patient population. Treatment choice may be driven by presentation/symptoms.
- Clinicians may consider restarting the treatment algorithm if there is evidence that patients are non-compliant or not taking their medication correctly (applies to approximately 15% of patients).
- Treatment decisions are multifactorial in this patient group and will consider the treatments already given and the efficacy and side effect profile of subsequent treatments.
- The treatments agreed to be the most likely comparators to esketamine nasal spray (in order of ranking) were vortioxetine, augmentation therapy, serotonin, and noradrenaline re-uptake inhibitors (e.g. venlafaxine and duloxetine) and other ADs (e.g., agomelatine, mirtazapine, reboxetine, and non-reversible mono-amine oxidase inhibitors [such as phenelzine]).
- Several clinicians indicated that they would choose esketamine nasal spray before ECT.
- Psychological therapies (e.g. CBT) may also be provided to patients with TRD if they are responding to treatment.

Future esketamine nasal spray treatment dosing

- If there was a partial response to esketamine nasal spray, they would increase the dose to the maximum and increase to once weekly if not already done and potentially optimise the oral treatment.
- They noted that in a patient with severe depression even a 30% response is significant and will make a big difference to their quality of life.

Grouping of oral antidepressants

- Clinicians agreed that, based on available evidence, it is appropriate to consider the effectiveness of SSRI and SNRIs to be similar.
- One clinician indicated that it would be appropriate to conclude that all different oral antidepressant drug classes are of similar effectiveness.

MDD and TRD treatment response in patients ≥65 years

- The participants agreed that younger adults (aged 18–64 years) with TRD on average experience a greater magnitude of treatment response to OADs than older adults (aged ≥65 years) with TRD.
    - This may be due to duration of MDD, higher number of previous episodes and higher number of comorbidities.

Appendix F. 4th June 2019 advisory board notes

TREATMENT RESISTANT DEPRESSION HTA ADVISORY BOARD

Royal College of General Practitioners, London, 4th June 2019

SUMMARY REPORT

ATTENDEES

Panel
Health Economist
Professor of Psychiatry
Psychiatrist
Professor of Medical Statistics
Professor in Mental Health
Professor of Psychiatry

MEETING OBJECTIVES AND AGENDA

09:15	*Welcome and coffee/tea*
09:30	Introductions and objectives for the day
09:45	Presentation: Esketamine nasal spray phase 3 results and target profile summary overview
10:00	Q & A: What further information is required in relation to the clinical trials to aid participation in this advisory board?
10.15	Presentation: Esketamine nasal spray in TRD Cost Effectiveness model
10.30	Q & A: What are the optimal clinical inputs/assumptions in the cost effectiveness model (part 1)
11:00	*Coffee/tea break*
11:15	Q & A: What are the optimal clinical inputs/assumptions in the cost effectiveness model (part 2)
12:45	*Lunch break*
13.15	Presentation: The proposed indirect comparative approach for esketamine nasal spray for the acute and maintenance phase
13:30	Q & A: How will the indirect comparative approach for esketamine nasal spray for the acute phase be interpreted?
14:30	*Coffee/tea break*
14:45	Q & A: How will the indirect comparative approach for esketamine nasal spray for the maintenance phase be interpreted?
15:45	Wrap up and close

16:00	*Meeting ends*

This summary report captures the key points raised at Janssen's advisory board for esketamine nasal spray in TRD held on 4th June 2019. A brief summary of the conclusions from the discussion is provided for each discussion topic. Where similar points were raised in different sessions, there has been an attempt to collate them in the relevant section of the report for a more logical flow and to minimise repetition.

FULL NOTES

Janssen explained the proposed hypothesis for the mechanism of action (MoA) of esketamine nasal spray

- Feedback was to be less assertive on the hypothesis of MoA, and frame that this is still a hypothesis (one out of currently six hypothesises).
- It was fed back rather to show the difference in MoA compared to current therapies, using the objective empirical evidence as rationale (e.g. time scale of effect, pharmacology is very different).
- Ultimately, it was agreed that esketamine nasal spray (NS) is not directly working through monoaminergic mechanism, which existing therapies target.

Time to recovery: Janssen presented the concepts of remission and recovery, and specifically the reduced rate of recurrence when in the recovery state versus relapse in the remission state

- Clinicians explained the concepts of remission vs recovery are recognised in clinical practice and based on their understanding of the natural history of the disease.
- It was fed back that the Judd study 1998 (US) and Pakal study provided important information relating to the natural history of the disease.
- Judd et al 1998 data show that the presence of residual symptoms is important, even if in remission and recovery. Publication shows that difference in relapse rates between asymptomatic recovery and residual recovery. For people who have residual symptoms, median 68 weeks to relapse compared to 231 weeks for those without residual symptoms.

Assumptions regarding time to recovery in the economic model

- Advisors generally agreed with the proposed approach and all assumptions as presented during the meeting appeared to be reasonable to the extent of individual advisors' expert knowledge.
- Advisors agreed that the proposed approach to use the license wording (at least 6 months) as a priori data and use curves from the SUSTAIN-1 data to support the modelling assumptions appeared reasonable.

Treatment duration

- Clinical experts were not clear on the inclusion of the wording for recommendation of 6 months duration of treatment in the SmPC (which is included in other OAD treatment SmPCs, such as vortioxetine and paroxetine).
- Clinical consensus on the average duration of treatment to define recovery was not reached, (e.g. 6 months=recovery) due to inter patient variability.
- It was recommended to include scenarios with different treatment durations for esketamine nasal spray, and different stopping rules, and ensure alignment to expected clinical practice.
- It was advised that Janssen clearly communicate any rationale for not using the open label long term study to inform the treatment duration.

Assumptions regarding esketamine nasal spray treatment discontinuation

- All advisors generally agree with the assumptions for the base case regarding discontinuation of treatment and regarded them as reasonable assumptions.
- Discontinuation of treatment due to transitioning into a recovery health state is not assessed during the SUSTAIN-1 trial, as patients were continued on treatment until relapse.
- It was suggested that perhaps the biggest determinant for patient continuation or discontinuation beyond 9 months in remission is patient acceptability and budget pressures for the treatment administration.

Over 65 population (TRANSFORM-3)

- The health economist recommended against pooling TRANSFORM-2 (TF-2) and TRANSFORM-3 (TF-3) data due to fundamental differences in population (co-morbidities and age etc).
- It was suggested to reference to the average age of patients with TRD from real world data to reassure that TF-2 is the most relevant information for the decision problem.

Janssen explained the rationale for adjusting the short term clinical data (TRANSFORM-2)

- Advisors agreed with the proposed rationale for the approach and believe that there is a strong clinical rationale for the adjustment.
- It was explained the placebo effect is well recognised in depression.

Proposed methodology for adjustment in the active comparator arm

- Although the rationale for the adjustment in the active comparator arm is understood, there were concerns with the robustness of the methodology of the adjustment.

COST EFFECTIVENESS MODEL DISCUSSION POINTS

Definition of health states: (MDE, Response, Remission, Recovery)

- Advisors agreed with the health states included in the economic model.
- It was thought there would be a need to explain the mixture of absolute and relative definitions of health states to ensure they are mutually exclusive.

Model structure:

- It was suggested a clinical transition from the remission health state to the response health state would improve face validity of the model.
- Clinical advisors explained that in clinical practice when initiating esketamine nasal spray, for some patients who show a partial response to OAD, clinicians would consider keeping the same OAD and augment with esketamine NS rather than switching to a new OAD, as per the license.

Episodic vs lifetime approach

- All experts agreed that the episodic approach is the right approach for the model. The rationale is provided below:
    - TRD is defined on an episodic basis, defined on basis of resistance to acute treatment.
    - There are large data gaps for a lifetime model.
    - A lifetime model with many uncertainties would not be a useful model for decision making.

Data source to inform the maintenance efficacy of the OAD comparator

- Advisors were satisfied with the rationale for not using SUSTAIN-1 for OAD, due to the design of the trial. Advisors agreed with the rationale and approach for using STAR*D.
- Advisors observed that it would be a similar argument to adjusting for the short term active comparator arm, as the TRANSFORM-2 trial is not the best data source to model OAD efficacy.

Utility data

- The health economist agreed with using TRANSFORM-2 as the data source for utilities for the health states in the base case.

Time horizon

- Advisors agreed with the provided rationale for using the 5 year time horizon
- A 5 year time horizon is able to capture as much benefit of esketamine NS as possible, whilst avoiding modelling a future MDE episode.

Sources of data to inform the subsequent treatments in the model

- Overall, given the little data available, these sources were agreed to be appropriate.
- It was agreed that a basket of treatments makes sense for the downstream treatment.
- For the non-specific treatment phase, it was agreed that Edwards 2013 provides reasonable data, given that it represents 7th/ 8th/ 9th/10th line etc and not only 7th line.
- A further rationale proposed by advisors is that Edwards 2013 was published subsequent to STAR*D, therefore the clinical opinion uses the information from STAR*D into account when estimating efficacy .

Health state cost

- Janssen proposed to use the results of an unpublished UK cost study to inform the health state costs.
- It was advised to compare the UK TRD cost study results with the costs of TRD in the literature. (E.g. mean annual total service costs for patients with TRD were £4388 (McCrone, 2017), which covered all health states of patients (MDE, response, remission, relapse)). However, there is no other study that reports the data per health state.
- Advisors were aware that patients with TRD are very costly and estimated that the costs of the MDE state may be an underestimation of the true costs of TRD patients.

Administration assumptions

- Advisors suggested an alternative method of costing where the cost per session (6 people), is estimated based on the staff required for the supervision and monitoring.
- Advisors suggested a band 5 minimum nurse would be required to supervise the self-administration. Two nurses would be required to be present for release of a controlled drug (at least 1 qualified = band 5).
- Clinical advisors with experience of using esketamine nasal spray are planning on having a divider between patients allowing 6 patients to be monitored at any one time, and a doctor being present in the building for clinical support.
- Advisors suggested that monitoring of this kind happens already in group setting e.g. clozapine clinic.
- It was agreed that a doctor would be present initially after launch, and for modelling purposes, it was reasonable to exclude the need for a clinician being present, once confidence in the administration increased.
- It was advised that Band 5 nurses would be the most likely to supervise self-administration and band 4 to monitor patients. It is unlikely that Band 6 and above would be involved on a day to day basis (unless short staffed etc).

Administration logistics for esketamine nasal spray

- Clinical advisors suggested that community health teams and CRHT more credible than being administered in GP practices (after explaining that self-administration would not be cost-effective in a patient's home).
- Clinical advisors expect to only monitor blood pressure prior to self-administration, if there are symptoms present and at end of the monitoring period.

NMA approach

Advisors agreed with the proposed approach to undertake an NMA and present the results, although present it to be not robust for input into the cost effectiveness model.

In the absence of a feasible network including 2-6-week outcomes, the criteria were extended for 2-8-week outcomes.

and **Error! Reference source not found.**. These reports contain a summary of the discussions that took place and the conclusions reached.

During the 4th June 2019 advisory board, assumptions used in the base case submission were presented to the advisors. Advisors were asked if they agreed with the assumptions presented. The attendees at the advisory board held on 4th June 2019 consisted of a health economist, three psychiatrists, a chief pharmacist and a medical statistician. .

Table 18. 4th June 2019 advisory board attendees

Role
Health Economist
Professor in Psychiatry
Psychiatrist
Professor of Medical Statistics
Director or Pharmacy and Pathology
Professor in Psychiatry

An advisory board was conducted on 18th October 2018 to gain clinical opinion on the ESK-NS clinical trial programme and how the drug would likely be used in clinical practice in patients with TRD, including likely positioning and considering the observation requirements. The attendees at the advisory board held on 18th October 2018 are listed in Table 19.

Table 19. 18th October 2018 advisory board attendees

Role
Psychiatrist
Professor in mental health and psychiatrist
Professor in mental health and GP
Psychiatrist
Psychiatrist
Professor in Mental Health
Psychiatrist

B12. Section B.3.2.3 of the CS states that the time intervals for treatment phases align to those in clinical practice, citing NICE CG90. Figure 3 is referred to, but this figure was not taken from CG90. Also, the acute phase in Figure 3 is longer than in CG90 (6-12 weeks compared to 4 weeks) and the maintenance phase in Figure 3 starts later than in CG90 (12 months compared to 9 months). Please justify the choice of the treatment phases by reference to CG90 and/or the specific treatment phases shown in Figure 3.

Duration of acute treatment phase

The treatment phases as described in Figure 3 of Section B.1.3.5.1 of the company submission, and those recommended in NICE CG90 do align. Additionally, there is overlap in the durations of the treatment phases, some of which are still poorly defined in the literature. There is no clinical consensus on the exact duration of the acute treatment phase, however there is broad consensus that 4 weeks after initiation of treatment is the appropriate timing to assess whether to continue treatment or not. NICE CG90 recommends tolerability and response should be assessed after 4 weeks on a therapeutic dose of treatment. A switch to another OAD is recommended in the case of inadequate response or because of patient preference/tolerability. NICE CG90 also recommends conducting subsequent assessments every 2–4 weeks in the first 3 months to monitor treatment outcomes because of the slow onset of action of currently available OADs. The 3 months align with the 12 weeks described in Figure 3 as the maximum duration of the acute treatment phase.

Figure 3 is derived from Qaseem 2016 (32), which is a Clinical Practice Guideline from the American College of Physicians. We presented Figure 3 in order to demonstrate the different treatment phases (and their objectives) of treatment for MDD. As stated in Section B.1.3.5.1 of the submission, the acute treatment phase ranges from between 4–8 weeks and sometimes up to 12 weeks.

Figure 3 states a range of 6–12 weeks for the acute treatment duration since this is the time that many of the currently antidepressant therapies (pharmacological as well as non-pharmacological) require to exert their full therapeutic effect.

Duration of treatment continuation phase and starting point maintenance (recurrence prevention) phase

The timing of the start of the maintenance phase (of which the aim of treatment is recurrence prevention) is dependent on the time that patients are in stable remission, which can vary significantly in clinical practice. For the continuation phase (relapse prevention), NICE CG90 recommends patients who respond to treatment continue to take their OAD at the effective dose for at least 6 months after remission. At this point it is recommended to review if OAD treatment should continue based on relapse risk. This aligns with the treatment duration of 4–9 months for the continuation phase as described in Figure 3. The duration of the continuation phase could arguably be longer in patients with TRD (closer to 9–months) than in patients with MDD (closer to 4–months) since patients with TRD might need to remain in stable remission longer before the risk of relapse is deemed sufficiently reduced and OAD treatment may be discontinued.

Figure 3 and the NICE CG90 do not provide one exact starting point of the maintenance treatment phase; it would start after the treatment continuation phase, which is when patients are four to nine months in stable remission. NICE CG90 advises patients continue OADs for at least 2 years if they are at risk of relapse.

Mortality

B13. Priority question. Please provide justification for the method of estimating mortality associated with TRD. In particular, it appears that the mortality risk of 0.47% was applied only to each suicide attempt. However, this figure from Bergfeld 2018 appears to be the incidence in the TRD population, i.e. not conditional on making a suicide attempt. Please amend the model in order to apply the mortality risk to all patients with a MDE.

Bergfeld et al (2018) (34) show that the overall suicide risk is high in patients with TRD, irrespective of which treatment is initiated. Excess mortality risk was assumed for patients in the MDE and response states. From all health states, patients could die, based on general mortality. Bergfeld 2018 (34) estimated the annual incidence of death from suicide was 0.47% in patients with TRD. This additional risk was

assumed only for patients in the MDE state, additive to general mortality. For patients in the response state, half of the additional risk of death was assumed.

Adverse events

B14. Priority question. Table 55 in the CS lists adverse event (AE) disutilities for scenario analysis. The CS suggests that these have been modelled in scenario analysis yet there appears to be no facility for this in the current model. Please provide a facility in the models whereby costs and utilities of adverse events can be incorporated as a scenario or, alternatively, explain how this can be easily produced within the existing model.

Within the model on the **Utility Inputs** tab there are place holders for adverse event related disutilities (**Cells D17:G47**). In this section the user can define the disutility and duration of disutility. Adverse event management costs are defined on the Cost Inputs tab (**Cells D77:F108**) The associated adverse event rates are entered in the Clinical Inputs tab (**Cells D129:AH31**).

B15. Priority question. Please specify follow up periods for adverse events for all trials. Related to this, longer term ketamine use (as opposed to esketamine) has been associated with bladder and urinary pain with the potential need for surgical intervention. Please confirm that long term related adverse events were tested for and that no significant difference was found against placebo.

Post-treatment follow-up adverse event reporting occurred in the ESK-NS trials as follows:

- TRANSFORM-1: 24 weeks
- TRANSFORM-2: 24 weeks
- TRANSFORM-3: 2 weeks
- SUSTAIN-1: 2 weeks
- SUSTAIN-2: 4 weeks

No significant long-term differences were found in terms of bladder and urinary pain between patients in the ESK-NS + OAD versus the OAD + PBO-NS arms in any of the trials. Rates of renal and urinary disorder adverse events reported in the trial

arms of TRANSFORM-2 and SUSTAIN-1 are presented in Table 20 and Table 21, respectively.

Table 20. Renal and urinary disorders reported during TRANSFORM-2 (safety analysis set)

	ESK-NS + OAD N=115	OAD + PBO-NS N=109
Induction phase (4 weeks)		
Renal and urinary disorders	9 (7.8%)	1 (0.9%)
Dysuria	4 (3.5%)	0
Pollakiuria	3 (2.6%)	0
Bladder discomfort	2 (1.7%)	0
Bladder pain	1 (0.9%)	0
Nocturia	1 (0.9%)	0
Urine flow decreased	0	1 (0.9%)
Follow-up phase (24 weeks)		
Renal and urinary disorders	0	0
Dysuria	0	0
Pollakiuria	0	0
Bladder discomfort	0	0
Bladder pain	0	0
Nocturia	0	0
Urine flow decreased	0	0

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray.

Table 21. Renal and urinary disorders reported during SUSTAIN-2

	ESK-NS + OAD	OAD + PBO-NS
Induction phase (4 weeks) (Safety [IND] analysis set; N=437)		
Renal and urinary disorders	15 (3.4%)	NA
Pollakiuria	5 (1.1%)	NA
Dysuria	3 (0.7%)	NA
Micturition urgency	3 (0.7%)	NA
Bladder discomfort	1 (0.2%)	NA
Haematuria	1 (0.2%)	NA
Nephrolithiasis	1 (0.2%)	NA
Urinary hesitation	1 (0.2%)	NA
Urinary retention	1 (0.2%)	NA

	ESK-NS + OAD	OAD + PBO-NS
Optimisation phase (12 weeks) (Safety [OP] analysis set; N=455)		
Renal and urinary disorders	13 (2.9%)	NA
Dysuria	4 (0.9%)	NA
Pollakiuria	4 (0.9%)	NA
Polyuria	2 (0.4%)	NA
Urinary incontinence	2 (0.4%)	NA
Bladder irritation	1 (0.2%)	NA
Bladder pain	1 (0.2%)	NA
Haematuria	1 (0.2%)	NA
Lower urinary tract symptoms	1 (0.2%)	NA
Micturition urgency	1 (0.2%)	NA
Nephrolithiasis	1 (0.2%)	NA
Maintenance phase (variable duration) (Safety [MA] analysis set; N=297)		
	N=152	N=145
Renal and urinary disorders	2 (1.3%)	5 (3.4%)
Dysuria	1 (0.7%)	0
Pollakiuria	1 (0.7%)	1 (0.7%)
Bladder discomfort	0	1 (0.7%)
Lower urinary tract symptoms	0	2 (1.4%)
Renal colic	0	1 (0.7%)
Follow-up phase (2 weeks) (Follow-up analysis set; N=545)		
	N=481	N=64
Renal and urinary disorders	1 (0.2%)	1 (1.6%)
Lower urinary tract symptoms	1 (0.2%)	0
Dysuria	0	1 (1.6%)

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; IND, induction phase; MA, maintenance phase; NA, not applicable; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; OP, optimisation phase.

Utilities

B16. Priority question. Did you consider using the DSU EQG (EuroQoL) method when mapping utilities from EQ-5D-5L as recommended by the Decision Support Unit "Methods for Mapping Between the EQ-5D-5L and the 3L for technology appraisal"? Please explain your rationale for not using this. If appropriate, please provide analysis based on the recommended approach.

EuroQol-5 Dimension-5 Level (EQ-5D-5L) scores were mapped to EQ-5D-3L scores using the mapping function developed by Van Hout 2012 (35), which is recommended by NICE in their official position statement on this topic (https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l). The position statement states: "The mapping function developed by van Hout et al. (2012) should be used for reference-case analyses".

The DSU EQG (EuroQoL) method describes three methods, of which the 'Van Hout' method is one. Since the NICE position statement on this topic is clear, we do not think it is appropriate to use any other method than the already applied 'Van Hout' method.

B17. Priority question. Please provide a worked example of how utility data in the TRANSFORM-2 trial were assigned to the four health sates (MDE, response at 4 weeks, remission at 4 weeks, recovery after 36 weeks). EQ-5D-5L scores should be provided for each state. Separately, please provide a worked example of how these data were converted to EQ-5D-3L. Finally, the model states that utility values are based on a "UK value set". Please explain this and comment on whether data from the trial (multinational) has been adjusted in any way to reflect UK values.

The mapping process from the EQ-5D-5L to the EQ-5D-3L is fully described in the article by van Hout and colleagues (2012). When combined with the Dolan (1997) algorithm, which is specific to the UK, this allows deriving UK-specific utilities from the EQ-5D-5L data. This two-step process has been combined into a single

instrument, providing the utilities specific to the UK (as well as other countries), which is available on the following website:

https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator/

As an example, in the TRANSFORM-2 baseline data (which are used to estimate the utility for the MDE health state in the pharmaco-economic model), the most frequently reported EQ-5D-5L profiles (in 5 or more patients) were the following: 11213, 11313, 11314, 11324, 11424, 13414, 13424, 13434. Overall, these indicate:

- No problems on mobility
- No or moderate problems on self-care
- Slight to severe problems on usual activities
- No to moderate problems on pain/discomfort
- Moderate to severe problems on anxiety/depression

The last item (anxiety/depression) is of particular interest and shows the consistency between clinicians (who included patients with a moderate to severe MDE into the study) and patients (who filled the EQ-5D-5L questionnaire) perspectives.

When running these different profiles into the crosswalk index value calculator, the resulting utilities (using UK tariffs) are provided in Table 22.

Table 22. Utilities following crosswalk

5L profile	Utility
11213	0.819
11313	0.812
11314	0.599
11324	0.501
11424	0.437
13414	0.431
13424	0.333
13434	0.308

All patients were assigned a utility score at each visit corresponding to their profile on the EQ-5D-5L using the method described above. These data were used to estimate the utility for the different health states in the model, using the observed average utility score for the base case analysis, and combining it with the

corresponding standard deviation to estimate the relevant beta distribution parameters in the probabilistic analysis. The details of which analysis of the TRANSFORM-2 data was used to provide the estimate of which health state is provided in Table 23.

Table 23. Health state utilities derived from TRANSFORM-2

Health State	Estimate for base case analysis	Source	Timepoint	Population
MDE	0.417	TRANSFORM-2	Baseline	All patients (moderate to severe MDE)
Response	0.764	TRANSFORM-2	Day 28	Patients with ≥50% improvement on MADRS total score from baseline (responders) and MADRS >12 (non-remitters)
Remission	0.866	TRANSFORM-2	Day 28	Patients with MADRS ≤12 (remitters)
Recovery	0.866	Assumption*		

Abbreviations: MADRS, Montgomery-Asberg Depression Rating Scale; MDE, major depressive episode.
*Assumed to be the same as remission.

It should be noted that the UK-specific algorithm was used for all patients in the TRANSFORM-2 study, regardless of the actual country patients were living in. the study was conducted in the following countries: Czech Republic (58 patients), Germany (20), Poland (38), Spain (18) and the United States (89). In particular, the TRANSFORM-2 study did not include patients from the UK, so that it was not possible to assess if the response profiles of UK patients on the EQ-5D-5L would have been potentially different from the profiles of patients from other countries.

B18. Please explain why the number of participants reporting EQ-5D-5L in TRANSFORM-2 (reported in Table 97, Appendix N), fell disproportionately in the treatment arm (111 at baseline compared to 104 at follow-up) compared to the comparator arm (104 compared to 100). Please provide a sensitivity analysis to explore the possible impact of missing values.

The main reason for the difference in dropout rates between the ESK-NS + OAD and OAD + PBO arms in TRANSFORM-2 was withdrawal due to adverse events.

Overall dropouts from Day 15 to Day 28:

- In the ESK-NS + OAD arm:
  - Seven patients had a Day 15 evaluation but no Day 28 evaluation:
    - ◊ "Adverse event" for six patients
    - ◊ "Withdrawal by subject/other" for one patient
- In the OAD + PBO-NS arm:
  - Five patients had a Day 15 evaluation but no Day 28 evaluation
  - One patient had a Day 28 evaluation but no Day 15 evaluation
    - ◊ "Withdrawal by subject/other" for four patients
    - ◊ One patient was a completer but did not complete the EQ-5D assessment at Day 28.

Missing EQ-5D data was only descriptive and was not imputed. Given the time constraints and other priority questions, no sensitivity analysis has been conducted.

Costs

B19. The summary of acquisition and resource costs (see Table 57 of the CS), states that 0.675 sessions per week will be provided for ESK-NS administration for week 41 onwards. Please indicate whether you expect this level to be maintained for the rest of the patient's life or whether you anticipate an upper limit. If you anticipate an upper limit, please outline what this is.

Please refer to the response provided to question A.24.

As per the anticipated SmPC wording (see Appendix C of the company submission), the recommended dosing schedule will be once weekly or once every two weeks from Week 9. The SmPC will also state that dose adjustments should be made based on efficacy and tolerability to the previous dose. During the maintenance phase, dosing should be individualised to the lowest frequency to maintain remission/response. According to the licence wording, therefore, the maximum upper limit is once per week, although this is not considered clinically plausible for all patients in the cohort.

In the absence of alternative data, it is assumed in the base case that 0.675 sessions of ESK-NS per week is maintained for week 41 onwards whilst remaining

on ESK-NS treatment. This can be considered a conservative assumption given the trend toward less frequent administrations per week as observed in the clinical trial programme (see Table 57, Section B.3.2.11.3).

B20. Section B.3.2.11.2 of the CS sets out the cost of supervision of self-administration and post-administration monitoring. It states that 9.57% of patients experienced a blood pressure increase. Please provide information as to whether increased blood pressure prolongs or intensifies the monitoring of a patient. Is any medication required to control blood pressure (and over what period)? Please add any such costs to the model.

In general, blood pressure elevation had resolution within 90 minutes post dose and it does not prolong the monitoring period, so no costs were added to the model specific to antihypertensive medication. Approximately 90% of visits with a <10 mmHg blood pressure increase were resolved by 90 minutes post dose.

At least 90% of the reported TEAEs of increased blood pressure occurred on the day of dosing in the Phase 3 studies/study phases and of these, >93% resolved spontaneously the same day. There were 20 ESK-NS-treated patients who experienced TEAEs of increased blood pressure on the day of dosing that were not reported as resolved on the same day. Further clinical review indicated that for 19 patients, objective blood pressure measurements were at or near pre-dose levels by 1.5 hours after dose administration or the patient was considered clinically stable and discharged on the same day with no additional measures (including blood pressure monitoring) required.

Unless clinically indicated, it is recommended that transient increases in blood pressure not be treated, as the blood pressure typically returns to pre-dose level within two hours. The effect of any treatment may result in hypotension.

In the Phase 3 studies, dosing with ESK-NS was deferred in patients having a supine systolic/diastolic blood pressure of >140/90 mm Hg (>150/90 mm Hg for patients ≥65 years) until blood pressure values normalised.

Blood pressure should be monitored after dose administration. Blood pressure should be measured around 40 minutes post-dose and subsequently as clinically warranted until values decline. If blood pressure remains elevated for a prolonged

period of time post administration i.e. a sustained increase which does not resolve by 90 minutes to 2 hours and remains elevated thereafter, assistance should promptly be sought from practitioners experienced in blood pressure management. Patients who experience symptoms of a hypertensive crisis should be referred immediately for emergency care.

A post hoc analysis (36) of the Phase 2 and Phase 3 trials showed that one patient out of 1708 ESK-NS + OAD had a hypertensive crisis, a clinical state which would require the patient to undergo further assessment, treatment and monitoring. Among the patients without a history of hypertension who participated in the double-blind short-term studies, new antihypertensive medication was initiated by 6/280 (2.1%) patients in the ESK-NS + OAD group vs. 2/171 (1.2%) patients in the OAD + PBO-NS group.

B21. In section B.3.2.11.2 of the CS, the average cost per session per patient is based on a clinic size of 6 patients.

a. **Please provide evidence that this is an appropriate workload for one band 4 nurse and one band 5 nurse.**
b. **Please conduct an additional sensitivity analysis for average cost per session where the number of patients in a clinic varies between plausible levels (evidenced from clinical experience).**

B21a. ESK-NS is self-administered but this needs to be performed under the supervision of a healthcare professional. During and after ESK-NS administration, patients are monitored for sedation, dissociation and raised blood pressure until the patient is stable based on clinical judgement.

Two nurses would be required to be present for release of a controlled drug (at least 1 qualified = Band 5). Both nurses are not necessarily needed to supervise the self-administration of ESK-NS.

The feedback of clinicians attending the clinical advisory board or HTA advisory board was that clinical advisors with experience of using ESK-NS are planning on having a divider between patients allowing six patients to be monitored at any one time by one nurse Band 4 or Band 5, and a doctor being present in the building for

emergency clinical support. Due to the safety profile of ESK-NS, the clinicians agreed that the ratio of healthcare professional (nurse) to patients could be increased in the maintenance phase from 1:8 to 1:20. Clinical advisors suggested that monitoring of this kind (e.g. clozapine) happens already in a group setting for other drugs for which monitoring is required.

B21b. The model base case assumed six patients attending the clinic at a time with an average cost per patient per administration of £30.08, generating an ICER of £6,582.

A sensitivity analysis was run to assess the impact on the average administration cost per session per patient of varying the number of patients seen in a clinic at any one time. In the event that patients would be monitored by nurses on a one-to-one basis, then assuming 15 minutes of Band 5 nursing time at £37/hour for pre-administration preparation, 15 minutes at £90/hour for supervision of self-administration, and 1 hour at £37/hour for post self-administration monitoring, the estimated cost per patient per administration is £68.75, giving an ICER of £9,252. If, on the other hand, as described above 20 patients were to attend a clinic, monitored by two nurses: one band 5 and one band 4, assuming: 15 minutes preparation time with both nurses (band 5 at £37/hour), 4 hours and 15 minutes with both nurses for supervising self-administration (band 5 at £90/hour), and 1 hour for post self-administration monitoring (band 5 at £37/hour), the estimated cost per patient per administration reduces to £27.74, giving an ICER of £6,420 (Table 24).

Table 24. Sensitivity analysis: 1:1 versus 20:1 patient monitoring

Patient to nurse ratio	Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
1:1	OAD	£48,478	4.508	2.239				
	ESK-NS + OAD	£51,588	4.519	2.575	£3,111	0.011	0.336	£9,252
20:1	OAD	£48,478	4.508	2.239				
	ESK-NS + OAD	£50,636	4.519	2.575	£2,159	0.011	0.336	£6,420

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant ICER, incremental cost-effectiveness ratio; LYG, life years gained; OAD oral antidepressant; QALYs, quality-adjusted life years.

B22. At visit 8 (4 weeks) a psychiatrist is required to assess response according to the pathway given. Please add the costs of this in the model (or explain where these costs feature in the model).

This cost was omitted from the analysis; however, its inclusion is expected to have a minimal impact. Since all patients, irrespective of their initial treatment, would be assessed at Week 4, this consultation cost would cancel out in each treatment arm and therefore not impact the base case ICER. Since ESK-NS has a higher efficacy rate and patients are therefore less likely to require a treatment switch, exclusion of this psychiatrist contact following an initiation of a subsequent therapy can be considered a conservative assumption.

B23. Please explain how the average cost per person of £10,554.25 was derived in Table 2 of Document B in the submission.

To estimate the average treatment duration of ESK-NS, the number of sessions was estimated using the economic model in the company submission. The number of sessions in the acute phase was summed with the expected number of treatment sessions in the continuation (relapse prevention) and maintenance (recurrence prevention) phase, accounting for variation in treatment frequency and expected discontinuation of treatment due to relapse. Using these assumptions, the average total number of treatment sessions per patient initiated on ESK-NS treatment is estimated to be 25.

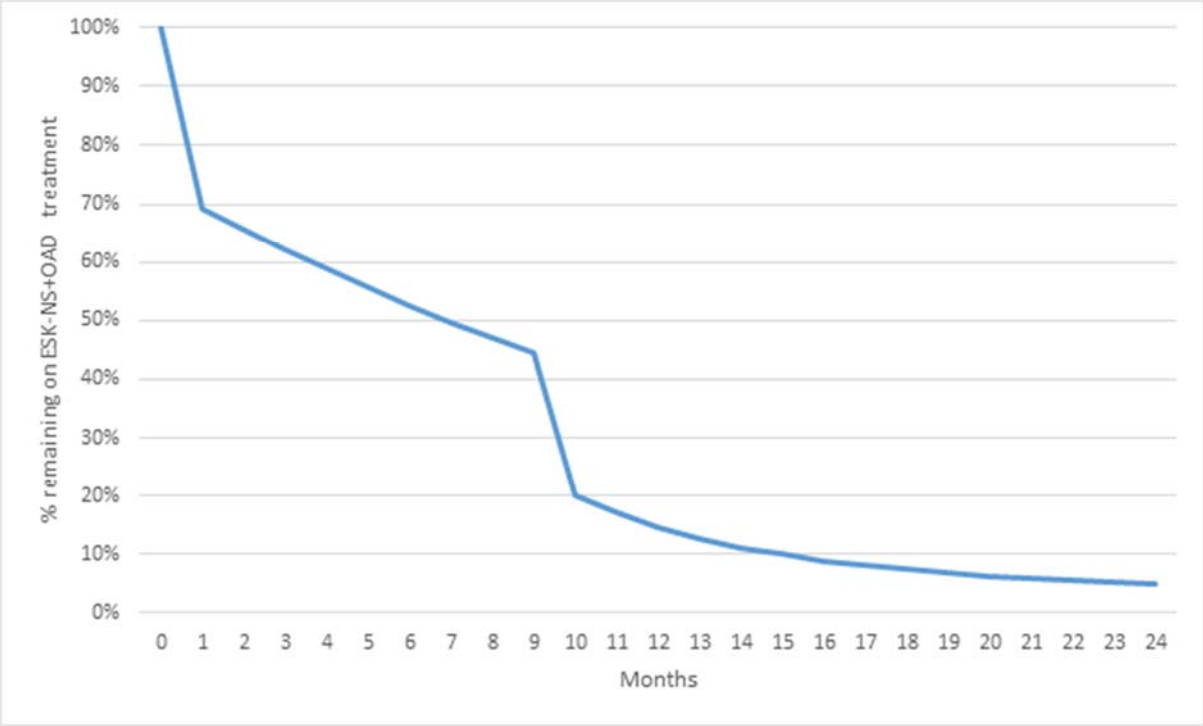
The average number of ESK-NS devices per session was based on TRANSFORM-2 and SUSTAIN-1 (Table 25). Based on the average number of devices in TRANSFORM-2 and SUSTAIN-1, the average number of devices per session through all the treatment phases was estimated at 2.59 (Table 25).

Table 25: Average number of devices per session per treatment phase

	Acute Weeks 1–4	Continuation (relapse prevention) Weeks 5–8	Continuation (relapse prevention) Weeks 9–40	Maintenance (recurrence prevention) Week 41 onwards	Average through all treatment phases
Average number of devices per session	2.53	2.61		2.57	2.59

Figure 4 shows the estimated proportion of patients on treatment from initiation through to year 2. For further explanation regarding the inputs and assumptions for the estimated treatment duration, please see Form B Section B.3.2.12.

Figure 4: Estimated proportion of patients on treatment from initiation until year 2



Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant.

The average cost per person treated for TRD with ESK-NS over the average course of therapy is estimated to be around £10,554.25. This is informed from the Markov trace from the base case economic model over a 5-year time horizon. The Markov trace is able to estimate the proportion of patients remaining on treatment, using the base case treatment discontinuation assumptions (as detailed in Section B.3.2.9.2.3

of the company submission). Note that to accurately estimate the average number of ESK-NS sessions using the Markov model, the 'Subsequent treatments' and 'Non-specific treatment' inputs were disabled, as these inputs affect the proportion in each health state at each cycle.

To calculate the average cost per patient, the unit cost per device (£163 per 28-mg device) was multiplied with the average number of devices and average frequency per week (as detailed in Table 57 of Section B.3.2.11.3 of the company submission) per treatment phase to estimate the average cost per person initiated with ESK-NS + OAD. The Markov trace background data and calculations to inform the average number of sessions from the base case model are presented in Appendix G.

Model validation

B24. The CS states that TA367 was conducted in a different population to the current decision problem. However, the population for which vortioxetine was recommended was adults with major depressive episodes "…whose condition has responded inadequately to 2 antidepressants within the current episode." (p.4, Technology appraisal guidance) and the population in the current decision problem is also adults who have not responded to at least 2 treatments in the current episode (see Table 1 of the CS). It also uses the term TRD, but according to the CS, the failure of 2 treatments is the definition of TRD. Please explain the difference between the population in TA367 and the current decision problem.

While in TA367 vortioxetine was recommended as a third line treatment for adults with MDD whose condition has responded inadequately to two antidepressants within the current episode, the clinical evidence for the vortioxetine submission was based on patients "with moderate-to-severe MDD who are experiencing an MDE who have responded inadequately in terms of efficacy or tolerability to initial antidepressant treatment, and who require and want to switch to an alternative antidepressant." There was no evidence in a TRD population for vortoxetine. The patient population in the ESK-NS clinical trial programme, on the other hand, had all responded inadequately to two or more OADs.

As noted in Section B.1.3.5, the difference in population between MDD and TRD is well characterised. Episodes of depression in patients with TRD are typically three times longer than in patients with non-treatment resistant MDD (37) and are associated with increased all-cause mortality (38), mainly due to a seven times increased risk of suicide relative to non-treatment resistant MDD (39). The impact of TRD on patient health-related quality of life (HRQoL) is profound; patients with TRD have around 35% greater reductions in HRQoL compared with non-treatment resistant MDD, and report impairment in HRQoL in the range of metastatic cancer or acquired blindness (40). Compared to patients with non-treatment resistant MDD, patients with TRD utilise more medical resources, have 50% lower labour force participation and a 20% increase in work activity impairment (40-42).

Effectiveness

B25. Priority question.

a. **Please give further details on the rationale for not including TRANSFORM-1 data in the economic model.**

b. **Please provide further details about the difference between the fixed dosing used in TRANSFORM-1 and the flexible dosing used in TRANSFORM-2.**

c. **Please provide a sensitivity analysis where the TRANSFORM-1 data are included together with the existing TRANSFORM-2 and SUSTAIN-1 data in the economic model.**

We recommend the ERG only consider the clinical evidence that is aligned with the anticipated SmPC to evaluate the clinical and cost-effectiveness of ESK-NS (see Appendix C in the company submission). The fixed dosing schedule of TRANSFORM-1 is not consistent with the dosing recommendations in the expected SmPC for ESK-NS. The flexibly-dosed TRANSFORM-2 trial was the short-term trial that forms the basis of ESK-NS regulatory approval. Based on this, the expected SmPC for ESK-NS recommends flexible dosing which is consistent with how ESK-

NS will be used in clinical practice. We therefore do not consider it appropriate to pool the data from TRANSFORM-1 (fixed doses; 84 mg and 56 mg) and TRANSFORM-2 (flexibly dosed; 56–84 mg per session). Historically, flexibly-dosed OAD trials are more likely to be successful (in terms of demonstrating a statistically significant difference) compared with fixed-dose OAD trials (59.6% successful versus 31.4%) (43) which underscores the value in allowing clinicians to adjust and individualise treatment doses. Pooling the remission and response rates TRANSFORM-1 and TRANSFORM-2 would likely reduce or mask the significant benefit associated with flexible dosing permitted in TRANSFORM- 2 and diminishes the real-world applicability of the cost effectiveness analysis.

Section C: Textual clarification and additional points

C1. Please provide the reference associated with "[redacted]".

[redacted]The submitted model approach considered [redacted] clinical and health economic expert opinion, evidence from the literature, and additional studies conducted to support the submission.

Model errors

C2. Priority question. There appears to be an error in the PSA of the latest version of the model: ID1414_ESKNS_NICE_CEM_AllComparators_190715 [noACIC]. When restricting the analysis to the base case comparison to OAD + PBO-NS, the ICER is very different to that in that produced in the other model: ID1414_ESK-NS_NICE_CEM_190715 [noACIC] or in the CS, i.e. £ 30,798.13 instead of £5,903 (Table 63 of the CS). Please fix this problem so that the PSA can produce reliable results for both the base case analysis and the scenario presented in section B.3.4.4.9.

As previously noted, the model submitted to allow for the analysis of all comparators (ID1414_ESKNS_NICE_CEM_AllComparators_190715) was for a scenario only as

the NMA did not provide credible and robust ORs for such a comparative analysis. We feel strongly that, due to the limitations previously highlighted with the NMA, this scenario should be considered illustrative and was only included for completeness. As a consequence, for a single scenario analysis it was not deemed appropriate for the inclusion of enhanced functionality such as probabilistic sensitivity analysis (PSA).

Notwithstanding, a version of the model allowing for consideration of the other comparators has been produced with PSA. Please note that due to the use of a single engine, generation of simulations is significantly slowed compared with the base case model.

A total of 5,000 Monte Carlo simulations were recorded. Results were plotted on the cost-effectiveness plane (CEP) and a cost-effectiveness acceptability curve (CEAC) was generated. The former showed the distribution of incremental cost and benefits under uncertainty and the latter the likelihood of being cost-effective at given acceptability thresholds.

Variables, estimates of uncertainty, and distributional assumptions used in PSA were previously presented in Table 60 of the company submission. The costs of the additional comparators were varied by ±10% of the figures previously reported (Table 80 of the submission) and varied with a Beta distribution. The only other additional parameters included to allow for consideration of the other comparators, were the odds ratios for achieving remission (Table 26) and the odds ratio for achieving response (Table 27) and these were varied with a lognormal distribution.

Table 26. NMA results – OR (95% CrI) for achieving remission

ESK-NS + OAD versus:	OR (95% CrI)	
	Unadjusted TRANSFORM-2 OAD + PBO-NS data	Adjusted TRANSFORM-2 OAD data
Newly initiated OAD	0.40 (0.23, 0.72)	0.19 (0.10, 0.37)
Switch tetracyclic (mirtazapine)	0.29 (0.12, 0.71)	0.14 (0.05, 0.36)
Aug tricyclic (nortrip) ± PBO	0.55 (0.2, 1.47)	0.27 (0.09, 0.74)
Aug SSRI/SNRI + lithium	0.53 (0.2, 1.41)	0.26 (0.09, 0.70)
Aug SSRI/SNRI + AAP	0.72 (0.27, 1.85)	0.35 (0.13, 0.93)
Switch SSRI + AAP	0.54 (0.23, 1.30)	0.26 (0.10, 0.65)
Aug SSRI/SNRI ± PBO	0.37 (0.14, 0.95)	0.18 (0.06, 0.48)

Abbreviations: AAP, atypical antipsychotic; Aug, augmentation; CrI, credible interval; ESK-NS, esketamine nasal spray; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; NMA, network meta-analysis; nortrip, nortriptyline; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; OR, odds ratio; PBO, placebo; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Table 27. NMA results – OR (95% CrI) for achieving response

ESK-NS + OAD versus:	OR (95% CrI)	
	Unadjusted TRANSFORM-2 OAD+PBO-NS data	Adjusted TRANSFORM-2 OAD data
Newly initiated OAD	0.48 (0.27, 0.84)	0.23 (0.12, 0.40)
Switch tetracyclic (mirtazapine)	0.35 (0.14, 0.87)	0.17 (0.07, 0.41)
Aug tricyclic (nortrip) ± PBO	0.52 (0.22, 1.20)	0.24 (0.10, 0.57)
Aug SSRI/SNRI + lithium	0.27 (0.11, 0.65)	0.13 (0.05, 0.31)
Aug SSRI/SNRI + AAP	0.44 (0.17, 0.96)	0.21 (0.08, 0.46)
Switch SSRI + AAP	0.44 (0.20, 0.93)	0.21 (0.09, 0.45)
Aug SSRI/SNRI ± PBO	0.22 (0.09, 0.51)	0.10 (0.04, 0.24)

Abbreviations: AAP, atypical antipsychotic; Aug, augmentation; CrI, credible interval; ESK-NS, esketamine nasal spray; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; NMA, network meta-analysis; nortrip, nortriptyline; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; OR, odds ratio; PBO, placebo; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Figure 5 and Figure 6 present the CEP and CEAC, respectively. The probability that ESK-NS + OAD was cost-effective at a threshold of £20,000 per QALY was 79.9%. This increases to 94.2% at a threshold of £30,000 per QALY. The cost-effectiveness frontier consists of augmented SSRI/SNRI plus an AAP up to a willingness to pay threshold of £8,000 per QALY after which point ESK-NS + OAD becomes the most cost-effective treatment. As per the deterministic analysis, Aug SSRI/SNRI + AAP

and ESK-NS + OAD showed extended dominance over all other treatments. When comparing ESK-NS + OAD with all other comparators, the ICER ranged from £2,103 to £8,505 (See Table 28).

Figure 5: Cost-effectiveness plane

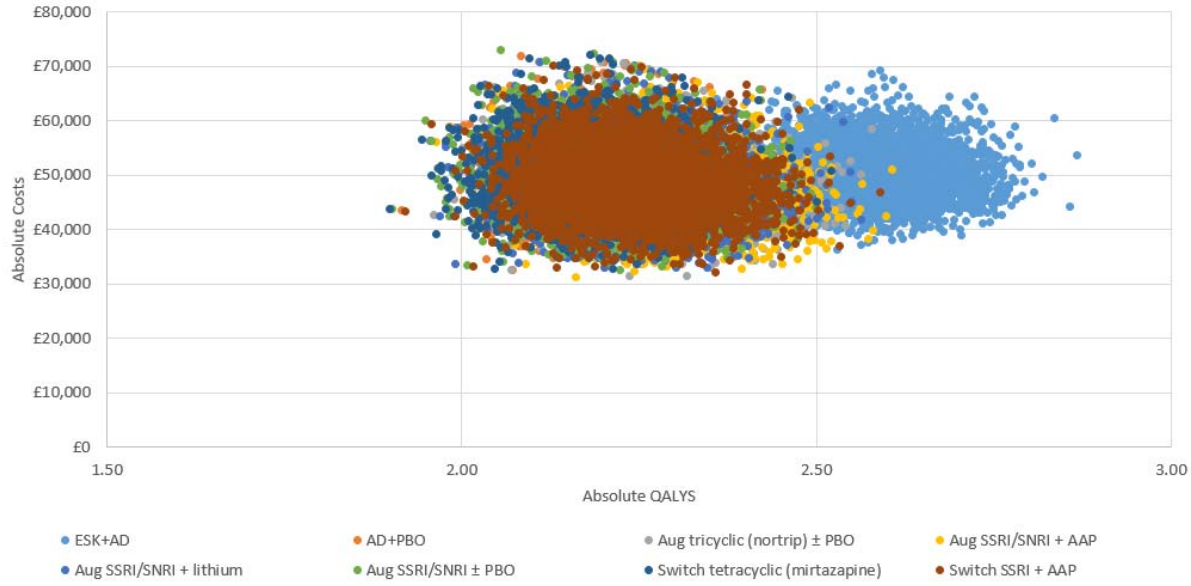


Figure 6: Multiple Cost-effectiveness acceptability curve (CEAC)

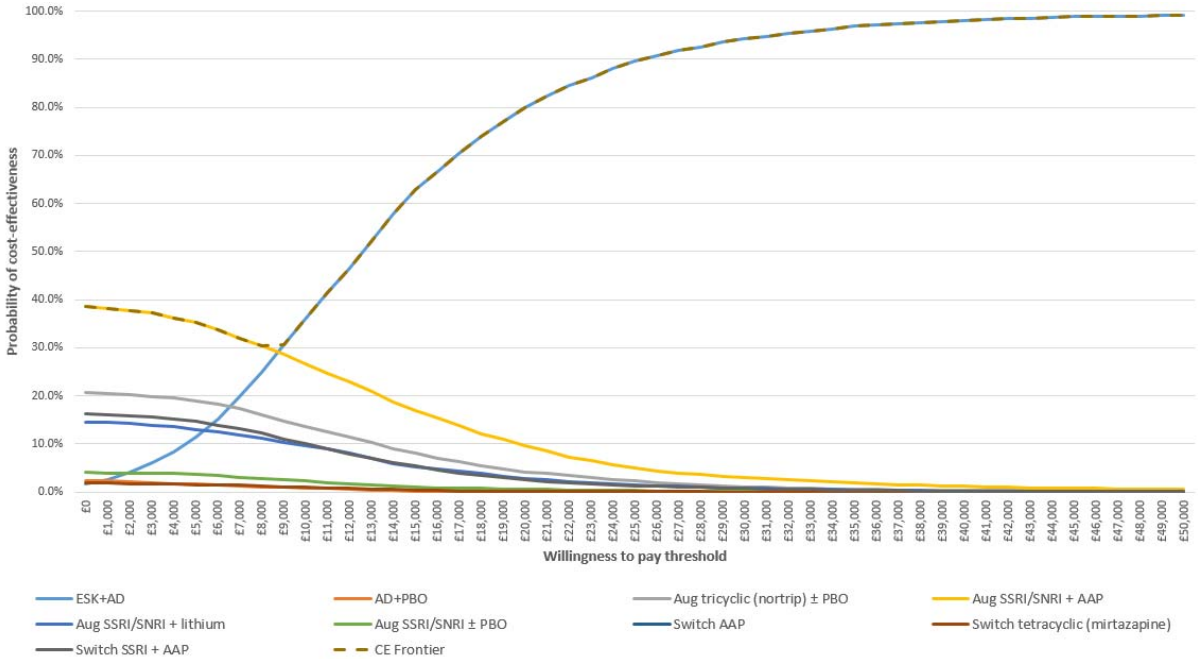


Table 28: Probabilistic incremental analysis

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	ICER versus ESK-NS + OAD
Aug SSRI/SNRI + AAP	£47,816 (£37,999, £59,383)	2.27 (2.11, 2.45)					£8,505
Aug tricyclic (nortrip) ± PBO	£48,338 (£38,518, £59,992)	2.25 (2.09, 2.42)	£522	-0.0219	Dominated	Dominated	£6,358
Aug SSRI/SNRI + lithium	£48,615 (£38,643, £60,302)	2.24 (2.08, 2.41)	£277	-0.0118	Dominated	Dominated	£5,326
OAD + PBO-NS	£49,109 (£39,235, £60,812)	2.21 (2.07, 2.37)	£495	-0.0212	Dominated	Dominated	£3,650
Aug SSRI/SNRI ± PBO	£49,347 (£39,377, £61,219)	2.20 (2.06, 2.37)	£238	-0.0094	Dominated	Dominated	£2,919
Switch tetracyclic (mirtazapine)	£49,625 (£39,538, £61,640)	2.19 (2.05, 2.35)	£278	-0.0122	Dominated	Dominated	£2,103
ESK-NS + OAD	£50,433 (£42,370, £59,936)	2.58 (2.43, 2.73)	£808	0.3843	£8,505	£2,103	

Abbreviations: AAP, atypical antipsychotic; Aug, augmentation; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; ICER, incremental cost-effectiveness ratio; nortrip, nortriptyline; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; QALY, quality-adjusted life year; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

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Appendices

Appendix A. Hand searching details for acute treatment SLR update

Table 29. Hand searching details for acute treatment SLR update

Source	Date searched	Search details	Additional info	Search terms	No. hits	No. downloaded	Comments
Conference proceedings							
Anxiety and Depression Association of America Conference 2019	24/05/2019			MDD			Unable to find abstract handbook for this society: • For 2019, 2018, 2017 or 2016 • via the society website • via the associated Depression and Anxiety journal. • via google search engine Email to information@adaa.org sent (31/10/2018 and 24/05/2019) with no reply.
				Major depressive disorder			
				TRD			
				Treatment-resistant			
Anxiety and Depression Association of America Conference 2018	31/10/18			MDD			
				Major depressive disorder			
				TRD			
				Treatment-resistant			
Anxiety and Depression Association of America Conference 2017	31/10/18			MDD			
				Major depressive disorder			
				TRD			
				Treatment-resistant			
Anxiety and Depression Association	31/10/18			MDD			
				Major depressive disorder			

Source	Date searched	Search details	Additional info	Search terms	No. hits	No. downloaded	Comments
of America Conference 2016				TRD			
				Treatment-resistant			
International Conference on Management of Depression 2019	24/05/2019			MDD			Unable to find abstract handbook for this society: • For 2019, 2018, 2017, 2016 • via the society website • via the associated journal. • via google search engine No contact found for society; no email has been sent to enquire.
				Major depressive disorder			
				TRD			
				Treatment-resistant			
International Conference on Management of Depression 2018	31/10/18			MDD			
				Major depressive disorder			
				TRD			
				Treatment-resistant			
International Conference on Management of Depression 2017	31/10/18			MDD			
				Major depressive disorder			
				TRD			
				Treatment-resistant			
International Conference on Management of	31/10/18			MDD			
				Major depressive disorder			
				TRD			

Source	Date searched	Search details	Additional info	Search terms	No. hits	No. downloaded	Comments
Depression 2016				Treatment-resistant			
American Psychiatry Association Annual Meeting 2019	23/05/2019	Searched annual poster proceedings via: https://www.psychiatry.org/psychiatrists/search-directories-databases/library-and-archive		MDD			Annual meeting was conducted recently on 18-22nd May 2019. Posters and new research abstracts for 2019 are not available yet.
				Major depressive disorder			
				TRD			
				Treatment-resistant			
American Psychiatry Association Annual Meeting 2018	1/10/18	Searched annual poster proceedings via: https://www.psychiatry.org/psychiatrists/search-directories-databases/library-and-archive Link to 2018 poster proceedings: file:///C:/Users/CharlotteFleming/Downloads/Poster-Proceedings%20(1).pdf	Ctrl + F search term within the poster proceedings document.	Major depressive disorder	211	14	Names of (potential) downloaded abstracts: • no 176 Eunsaem, L; no 104 Romero- Guillena, S.L; no 64 Sheehan, J; no 110 Greden, J; no 167 Baker, R; no 210 He, H; no 69 Hefting, N; no 171 Watnick, J; no 46 Stahl, S; no 140 Park, S; no Thase, M; no 49 Shawi, M; no 51 Alphs, L; no54 Popova, V; n0 186 Xiao, L • • no 209 Snyder, D; no 65 Ochs-Ross, R; no 52 alphs, L;
				MDD	412	0	
				Treatment-resistant	54	2	
				TRD	71	0	
American Psychiatry Association	1/10/18	Searched annual poster proceedings via: https://www.psychiatry.	Ctrl + F search term within the poster proceedings document.	Major depressive disorder	103	9	Names of (potential) downloaded abstracts:

Source	Date searched	Search details	Additional info	Search terms	No. hits	No. downloaded	Comments
Annual Meeting 2017		org/psychiatrists/search-directories-databases/library-and-archive Link to 2017 poster proceedings: file:///C:/Users/CharlotteFleming/Downloads/Poster-Proceedings.pdf		MDD	149	1	• no 95 P, Ittasakul; no 78 Chin-Lun Hung, G; no 16 Vieta, E; no 19 Kramer, K; no 22 Hobart, M; no 23 Durgam, S; no 27 Lepola, U; no 63 Diberardo, A; no 81 Lee, GH; • no 58 Tendler, A • no 6 Hsu, J; no 79 Haque, Z; no 27 Nunez, N; • no 42 Delmonte, D;
				Treatment-resistant	62	3	
				TRD	58	1	
American Psychiatry Association Annual Meeting 2016	5/10/18	Searched annual poster proceedings via: https://www.psychiatry.org/psychiatrists/search-directories-databases/library-and-archive Link to annual new research posters: file:///C:/Users/CharlotteFleming/Downloads/am_newresearch_2016%20(1).pdf	Ctrl + F search term within the poster proceedings document.	Major depressive disorder	95	6	Names of (potential) downloaded abstracts: • No 27 Cress, K; saragoussi; no 8 Baker, R; no 11 Brock, D; no 36 Ghabrash, M; no 137 Weiller, E • • no 99 Nielsen, R; • • no 67 Sharon, H; •
				MDD	245	1	
				Treatment-resistant	40	1	
				TRD	14	0	
European Congress of	23/05/2019	Searched: https://www.europsy.n		Major depressive disorder			Annual meeting was conducted recently on 6-9th April 2019. Posters

Source	Date searched	Search details	Additional info	Search terms	No. hits	No. downloaded	Comments
Psychiatry 2019		et/ecp-congress-programmes/		MDD			and new research abstracts for 2019 are not available yet and are 'upcoming'.
				Treatment-resistant			
				TRD			
European Congress of Psychiatry 2018	05/11/2018	Previous congresses: https://epa-congress.org/2018/useful-links/previous-congresses#.W-Bhi5P7SUk Online abstract book from Journal of European Psychiatric Association 2018: https://epa-congress.org/2018/programme-submission/abstract-book-2018#.W-BiS5P5CUk	Ctrl + F search term within the poster proceedings document.	Major depressive disorder	81	9	Names of (potential) downloaded abstracts: • OR0063 Carvalho, S; OR0087 Wagner, PW0276 Batail, J; PW0280 Jamilian, H; PW0286 Romero Guillena, S; PW0592 Santamaria, O; PW0597 Wagner, S; EV0258 Homorogan, C; EV0281 Serra, G; • PW0583 Khaustova, O;
				MDD	164	1	
				Treatment-resistant	29	0	
				TRD	21	0	
European Congress of Psychiatry-Italy 2017	06/11/2018	Online abstract book for 2017: https://epa-congress.org/2017/2017-abstract-book-(2)/2017-abstract-book#.W-FcLJP5CUl	Ctrl + F search term within the poster proceedings document.	Major depressive disorder	89	3	Names of (potential) downloaded abstracts: • EW0105 Soussia, R; EW0107 Verhoeven, J; EV0375 Ellouze, F • EW0351 Hou, Z; •
				MDD	240	1	
				Treatment-resistant	27	1	
				TRD	12	0	

Source	Date searched	Search details	Additional info	Search terms	No. hits	No. downloaded	Comments
							• EW0116 Vasiliu, O;
European Congress of Psychiatry-Spain 2016	06/11/2018	Online abstract book for 2016: https://epa-abstracts-2016.elsevierdigitaledition.com/index.html	Ctrl + F search term within the poster proceedings document.	Major depressive disorder	60	3	Names of (potential) downloaded studies: • EW442 Jeong, J; EV540 Neirenberg, A; EV885 Prisco, V;
				MDD	182	0	
				Treatment-resistant	30	0	
				TRD	8	0	
The Royal College of Psychiatrists International Congress 2019	24/05/2019			Major depressive disorder			Annual meeting is not until 1st-4th July 2019.
				MDD			
				Treatment-resistant			
				TRD			
The Royal College of Psychiatrists International Congress 2018	06/11/2018			Major depressive disorder			Unable to find abstract handbook for this society: • For the last 3 years • via the society website • via the associated journal. • via google search engine Email to congress@rcpsych.ac.uk sent (06/11/2018) with no reply.
				MDD			
				Treatment-resistant			
				TRD			
The Royal College of Psychiatrists International Congress 2017	06/11/2018			Major depressive disorder			
				MDD			
				Treatment-resistant			
				TRD			
The Royal College of	06/11/2018			Major depressive disorder			

Source	Date searched	Search details	Additional info	Search terms	No. hits	No. downloaded	Comments
Psychiatrists International Congress 2016				MDD			
				Treatment-resistant			
				TRD			
WPA World Congress of Psychiatry 2019	23/05/2019			Major depressive disorder			Annual meeting is not until 21-24th August 2019.
				MDD			
				Treatment-resistant			
				TRD			
WPA World Congress of Psychiatry 2018	06/11/2018			Major depressive disorder			Unable to find abstract handbook for this society: • Follow up email received from WPA 2018 (15/11/2018) reported that this congress did not produce an abstract book.
				MDD			
				Treatment-resistant			
				TRD			
WPA World Congress of Psychiatry 2017	06/11/2018			Major depressive disorder			Unable to find abstract handbook for this society: • Follow up email received 14/11/2018 reported that an abstract handbook of the WAP 2017 is not available.
				MDD			
				Treatment-resistant			
				TRD			
WPA World Congress of	06/11/2018	Link to download page for all abstracts from		Major depressive disorder	5	0	

Source	Date searched	Search details	Additional info	Search terms	No. hits	No. downloaded	Comments
Psychiatry – South Africa 2016		2016, segregated by 5 topics: https://www.wpacapetown2016.org.za/index.php/sessions-abstracts/download-abstracts Link to 'cultural, religious care' abstracts: https://www.wpacapetown2016.org.za/images/Pdf/WPA-2016-Abstracts-PSY_TH.pdf	Ctrl + F search term within the poster proceedings document.	MDD	16	0	
				Treatment-resistant	0	0	
				TRD	0	0	
		Link to 'integrated care' abstracts: https://www.wpacapetown2016.org.za/images/Pdf/WPA-2016-Abstracts-_INT.pdf	Ctrl + F search term within the poster proceedings document.	Major depressive disorder	7	0	
				MDD	5	0	
				Treatment-resistant	0	0	
				TRD	0	0	
		Link to 'neuroscience' abstracts: https://www.wpacapetown2016.org.za/images/abstracts/WPA-2016-Abstracts-NS.pdf	Ctrl + F search term within the poster proceedings document.	Major depressive disorder	23	0	
				MDD	52	0	
				Treatment-resistant	6	0	
				TRD	1	0	
		Link to 'psychotherapy' abstracts: https://www.wpacapetown2016.org.za/images	Ctrl + F search term within the poster proceedings document.	Major depressive disorder	3	0	
				MDD	0	0	
				Treatment-resistant	0	0	

Source	Date searched	Search details	Additional info	Search terms	No. hits	No. downloaded	Comments
		/Pdf/WPA-2016-Abstracts-PSY_TH.pdf		TRD	0	0	
		Link to 'social involvement' abstracts: https://www.wpacapetown2016.org.za/images/Pdf/WPA-2016-Abstracts_SOC.pdf	Ctrl + F search term within the poster proceedings document.	Major depressive disorder	3	0	
				MDD	5	0	
				Treatment-resistant	0	0	
				TRD	0	0	
ISPOR Europe 2019 Denmark	23/05/2019			Major depressive disorder			Annual meeting is not until 2nd-6th Nov 2019.
				MDD			
				Treatment-resistant			
				TRD			
ISPOR US 2019 New Orleans	23/05/2019			Major depressive disorder			Annual meeting on 18-22 May 2019. Posters and new research abstracts for 2019 are not available yet.
				MDD			
				Treatment-resistant			
				TRD			
ISPOR Europe 2018-Barcelona, Spain -2018	23/05/2019	https://tools.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp	Search feature using 'abstract' setting.	Major depressive disorder	9	5	Names of (potential) downloaded studies: • Suthoff; Lachaine; Clay; Jaffe; Jaffe (b). • Diamantopoulos
				MDD	7	0	
				Treatment-resistant	3	1	
				TRD	3	0	
ISPOR 2018-Baltimore, MD, USA-2018	23/05/2019	https://tools.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp	Search feature using 'abstract' setting.	Major depressive disorder	11	1	Names of (potential) downloaded studies: • Chow
				MDD	7	0	
				Treatment-resistant	2	0	
				TRD	4	0	

Source	Date searched	Search details	Additional info	Search terms	No. hits	No. downloaded	Comments
ISPOR 20th Annual European Congress- Glasgow, Scotland- 2017	23/05/2019	https://tools.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp	Search feature using 'keyword' and 'abstracts' setting.	Major depressive disorder	4	3	Names of (potential) downloaded studies: • O'Connel, M; Ereshefsky,L; Zhang, L; Francois;
				MDD	4	0	
				Treatment-resistant	1	0	
				TRD	0	0	
ISPOR 22nd Annual International Meeting – Boston, MA, USA- 2017	23/05/2019	https://tools.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp	Search feature using 'keyword' and 'abstracts' setting.	Major depressive disorder	10	3	Names of (potential) downloaded studies: • Zhang; Francois; Adilgozhina • Olfson
				MDD	11	0	
				Treatment-resistant	1	1	
				TRD	2	0	
ISPOR 19th Annual European Congress – Vienna, Austria- 2016	23/05/2019	https://tools.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp	Search feature using 'keyword' and 'abstracts' setting.	Major depressive disorder	5	0	
				MDD	4	0	
				Treatment-resistant	0	0	
				TRD	1	0	
ISPOR 21st Annual International Meeting – Washington, USA – 2016	23/05/2019	https://tools.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp	Search feature using 'keyword' and 'abstracts' setting.	Major depressive disorder	5	1	Names of (potential) downloaded studies: • Tamayo; • Bashyral
				MDD	6	1	
				Treatment-resistant	1	0	
				TRD	0	0	
ISPOR 18th Annual European	23/05/2019	https://tools.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp	Search feature using 'keyword' and 'abstracts' setting.	Major depressive disorder	6	1	Names of (potential) downloaded studies:
				MDD	5	0	

Source	Date searched	Search details	Additional info	Search terms	No. hits	No. downloaded	Comments
Congress-Milan, Italy – 2015				Treatment-resistant	1	0	• Ignatyeva; Papadimitropoulou
				TRD	2	1	
ISPOR 20TH Annual International Meeting – Philadelphia, PA, USA - 2015	23/05/2019	https://tools.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp	Search feature using 'keyword' and 'abstracts' setting.	Major depressive disorder	13	4	Names of (potential) downloaded abstracts: • Gordon; Jung; Zhou; Diamand; Pere • Hagiwara, M; Diamand, F;
				MDD	13	2	
				Treatment-resistant	2	0	
				TRD	0	0	
HTA agencies- hand searching for clinical studies							
NICE	30/05/2019	https://www.nice.org.uk/guidance/published?type=ta&title=major%20dep Also searched: https://www.nice.org.uk/guidance/published?type=ta&title=major%20dep	Search bar, filtered for technology appraisal guidance. Evidence was reviewed for each 'hit'.	Major depressive disorder			Reasons why hits not downloaded: • Evidence was either reviewed by NICE pre-2016 • Intervention not relevant • No link to report which included list of relevant RCTs for this purpose • Link to vortioxetine submission for MDD indication: https://www.nice.org.uk/guidance/ta367
				MDD			
				Treatment-resistant depression	16	0	
				TRD			
SMC	30/05/2019	https://www.scottishmedicines.org.uk/	Search bar	Major depressive disorder			
				MDD			
				Treatment-resistant	50	0	
				TRD			

Source	Date searched	Search details	Additional info	Search terms	No. hits	No. downloaded	Comments
PBAC	30/05/2019	Public Summary Documents by product: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/public-summary-documents-by-product	NA	NA	NA	NA	The PBS website lists hundreds of drug interventions in alphabetical order- there is no way of filtering on our preferred search terms. Unsure how to proceed without looking through each MDD intervention.
CADTH	30/05/2019	https://cadth.ca/	Search bar, filtered for reports and HTA.	Major depressive disorder			No other reports with relevant lists of RCTs are on CADTH.
				MDD			
				Treatment-resistant	435		
				TRD			
NCPE	30/05/2019	http://www.ncpe.ie/	Search bar	Major depressive disorder			
				MDD			
				Treatment-resistant	0	0	
				TRD			
HTA agencies- hand searching for relevant economic reviews/ cost report/ HSUV + QoL reports							
NICE	23/05/2019	https://www.nice.org.uk/	Search bar, filtered for technology appraisal guidance.	Major depressive disorder	4	0	No new regulatory submissions have been added since last hand search on 30/08/2018.
NICE	30/08/2018	https://www.nice.org.uk/	Search bar, filtered for technology appraisal guidance.	Major depressive disorder	4	0	
SMC	23/05/2019	https://www.scottishmedicines.org.uk/	Search bar	major depressive disorder	4	0	No new regulatory submissions have been added since last hand search on 30/08/2018.
SMC	30/08/2018	https://www.scottishmedicines.org.uk/	Search bar	major depressive disorder	4	1	

Source	Date searched	Search details	Additional info	Search terms	No. hits	No. downloaded	Comments
PBAC	23/05/2019	Public Summary Documents by product: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/public-summary-documents-by-product	NA	NA	NA	NA	The PBS website lists hundreds of drug interventions in alphabetical order- unable to filter on our preferred search terms. Unsure how to proceed without looking through each MDD intervention.
PBAC	30/08/2018	Public Summary Documents by product: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/public-summary-documents-by-product	Searched by product	NA	NA	9	
CADTH	23/05/2019	https://cadth.ca/	Search bar, filtered for reports and HTA	major depressive disorder	9	0	No new regulatory submissions have been added since last hand search on 30/08/2018.
CADTH	30/08/2018	https://cadth.ca/	Search bar, filtered for reports and HTA	major depressive disorder	9	0	
NCPE	23/05/2019	http://www.ncpe.ie/	Search bar	major depressive disorder	1	0	No new regulatory submissions have been added since search on 31/08/2019.
NCPE	30/08/2018	http://www.ncpe.ie/	Search bar	major depressive disorder	1	1	
Additional sources- hand searching for relevant economic reviews/ cost report/ HSUV + QoL reports							
CEA registry	24/05/2019	http://healtheconomics.tuftsmedicalcenter.org/	Search bar, filtered for 'methods'	major depressive disorder	20	0	No relevant 2018 or 2019 studies have been added to the registry since search on 31/08/2019.

Source	Date searched	Search details	Additional info	Search terms	No. hits	No. downloaded	Comments
		cear2n/search/search.aspx					
CEA registry	24/05/2019	http://healtheconomics.tuftsmedicalcenter.org/cear2n/search/search.aspx	Search bar, filtered for 'ratios'	major depressive disorder	100	0	No relevant 2018 or 2019 studies have been added to the registry since search on 31/08/2019.
CEA registry	24/05/2019	http://healtheconomics.tuftsmedicalcenter.org/cear2n/search/search.aspx	Search bar, filtered for 'utility weights'	major depressive disorder	100	0	No relevant 2018 or 2019 studies have been added to the registry since search on 31/08/2019.
CEA registry	31/08/2018	http://healtheconomics.tuftsmedicalcenter.org/cear4/home.aspx	Search bar	major depressive disorder	34	0	
EconPapers within RePEC	24/05/2019	https://econpapers.repec.org/scripts/search.pf	Advanced search feature, title and keyword search	"major depressive disorder"	18	0	No relevant 2018 or 2019 studies have been added to the registry since search on 31/08/2019.
EconPapers within RePEC	31/08/2018	https://econpapers.repec.org/scripts/search.pf	Advanced search feature, title and keyword search	"major depressive disorder"	79	0	
INAHTA	24/05/2019	http://www.inahta.org/	Search bar	major depressive disorder	0	0	
INAHTA	31/08/2018	http://www.inahta.org/	Search bar	major depressive disorder	0	0	
NIHR HTA	24/05/2019	https://www.crd.york.ac.uk/CRDWeb/	Search facility using MeSH search option. Tick boxes 'DARE' 'NHD EED' HTA'.	"major depressive disorder"	350	0	No relevant 2018 or 2019 studies have been added to the registry since search on 31/08/2019.
NIHR HTA	31/08/2018	https://www.crd.york.ac.uk/CRDWeb/	Search facility	"major depressive disorder"	597	6	

Source	Date searched	Search details	Additional info	Search terms	No. hits	No. downloaded	Comments
ICER	24/05/2019	https://icer-review.org/	Search bar	major depressive disorder	0	0	
ICER	31/08/2018	https://icer-review.org/	Search bar	major depressive disorder	4	1	
Ad hoc	Multiple	Reference lists, google scholar	NA	NA	NA	2	
EuroQoL website	24/05/2019	Search for EQ-5D publications: https://euroqol.org/search-for-eq-5d-publications/	Advanced search using 'abstract' and 'title' filter; sort by date.	major depressive disorder	10	4	10 of 77 hits were published between 2016-2019. Names of downloaded studies: • Minsu; Min; Molina; Hiranyatheb
ScHARRHUD	24/05/2019	https://www.scharrhud.org/index.php?recordsN1&m=search	Search feature	major depressive disorder OR MDD in abstract.	0	0	7 hits in total, 0 of which were published between 2016-2019.

Appendix B. Observational studies SLR search strategy

Embase 1974 to 2018 December 17, ran 18 December 2018

#	Searches	Results
1	exp major depression/	56520
2	exp treatment resistant depression/	2287
3	((chronic or resistan* or untreatable or unrespon* or non-respon* or nonrespon* or major) adj3 depressi*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	86997
4	(MDD* or MDE* or TRD*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	22784
5	1 or 2 or 3 or 4	92722
6	clinical study/	151395
7	exp case control study/	152275
8	family study/	25051
9	longitudinal study/	119809
10	retrospective study/	720340
11	prospective study/	490971
12	cross-sectional study/	280009
13	cohort analysis/	427204
14	follow up/	1343761
15	cohort*.ti,ab.	819407
16	14 and 15	181400
17	case control.ti,ab.	144554
18	(cohort adj (study or studies or analys*)).ti,ab.	249704
19	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.	299426
20	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.	1835784
21	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 16 or 17 or 18 or 19 or 20	3053685
22	esketamine/	337
23	esketamine.ti,ab.	79
24	ketamine/	34841
25	(ketamine or CI-581 or CI 581 or CI581 or Ketalar or Ketaset or Ketanest or Calipsol or Kalipsol or Calypsol or Ketamine or Hydrochloride).ti,ab.	79401
26	sertraline/	24378

27	(sertraline or Zoloft or Altruline or Lustral or Apo Sertraline or Aremis or Sealdin or Gladem or Novo-Sertraline or Novo Sertraline or ratio-Sertraline or ratio Sertraline or Rhoxal-sertraline or Rhoxal sertraline or Gen-Sertraline or Gen Sertraline).ti,ab.	6161
28	fluoxetine/	44152
29	(fluoxetin* or "N Methyl gamma (4(trifluoromethyl)phenoxy)benzenepropanamine" or Lilly-110140 or Lilly 110140 or Lilly110140 or Sarafem or Fluoxetine Hydrochloride or Prozac).ti,ab.	15402
30	citalopram/	21462
31	(citalopram or cytalopram or Lu-10-171 or Lu10171 or Escitalopram or Lexapro).ti,ab.	9674
32	paroxetine/	26552
33	(paroxetine or BRL29060 or FG7051 or Paroxetine Acetate or Hydrochloride, Paroxetine or Hemihydrate or Hemihydrate Paroxetine Hydrochloride, Hemihydrate Paroxetine or Paroxetine Hydrochloride Hemihydrate or Hemihydrate, Paroxetine Hydrochloride or hydrochloride Hemihydrate, Paroxetine or Seroxat or Paroxetine Maleate or Maleate, Paroxetine or Paroxetine, cis Isomer or Paroxetine, cis Isomer or Paroxetine, trans Isomer or Paxil or Aropax or Paroxetine Hydrochloride Anhydrous or Anhydrous, Paroxetine Hydrochloride or Hydrochloride Anhydrous, Paroxetine).ti,ab.	8104
34	fluvoxamine/	12605
35	(fluvoxamine or fluvoxadura or Fluvoxamin AL or Fluvoxamin beta or Fluvoxamin Stada or Fluvoxamin-neuraxpharm or Fluvoxamin neuraxpharm or Fluvoxamin-ratiopharm or Fluvoxamin ratiopharm or ratio-Fluvoxamine or ratio Fluvoxamine or Fluvoxamina Geminis or Geminis, Fluvoxamina or Fluvoxamine Maleate or Fluvoxamine Maleate, E Isomer or Fluvoxamine, Z Isomer or Luvox or Fevarin or Floxyfral or Dumirox or Faverin or Novo-Fluvoxamine or Novo Fluvoxamine or Nu-Fluvoxamine or Nu Fluvoxamine or PMS-Fluvoxamine or PMS Fluvoxamine or Desiflu or DU-23000 or DU 23000 or DU23000).ti,ab.	3318
36	trazodone/	11508
37	(trazodone or AF1161 or Deprax or Trazodone Hydrochloride or Desyrel or Gen-Trazodone or Gen Trazodone or Molipaxin or Novo Trazodone or Trittico or PMS Trazodone or ratio Trazodone or Thombran or Trazodon-neuraxpharm or Trazodon neuraxpharm or Trazodone Hydrochloride or Trazon or Apo-Trazodone or Apo Trazodone or Nu-Trazodone or Nu Trazodone).ti,ab.	2511
38	Vortioxetine/	812
39	(vortioxetine or brintellix or 1,2,2,4-dimethylphenylsulfanyl phenyl piperazine or vortioxetine hydrobromide or Lu AA21004 or LuAA21004 or Lu-AA21004).ti,ab.	609
40	desvenlafaxine/	1462
41	(Succinate , Desvenlafaxine or O-desmethylvenlafaxine Succinate Monohydrate or Monohydrate, O desmethylvenlafaxine Succinate or O desmethylvenlafaxine Succinate	707

	Monohydrate or Succinate Monohydrate, O desmethylvenlafaxine or hydroxycyclohexyl 4 hydroxyphenyl ethyl dimethylammonium 3 carboxypropanoate monohydrate or O-desmethylvenlafaxine Succinate or O desmethylvenlafaxine Succinate or Succinate, O desmethylvenlafaxine or WY 45,233 or 45,233, WY or WY-45,233 or WY45,233 or WY-45233 or WY45233 or WY 45233 or 45233, WY or Pristiq or Desvenlafaxine or O-desmethylvenlafaxine or O desmethylvenlafaxine or 4 2 dimethylamino 1 1 hydroxycyclohexyl ethyl phenol).ti,ab.	
42	duloxetine/	9936
43	(duloxetine or Hydrochloride, Duloxetine or Duloxetine HCl or HCl, Duloxetine or LY 248686 or LY-248686 or LY248686 or Duloxetine Ethanedioate, isomer T353987 or LY 227942 or LY227942 or LY227942 or Duloxetine or N methyl 3 1 naphthalenyloxy 3 2 thiophene propanamide or N-methyl 3 1 naphthalenyloxy 2 thiophenepropanamine or Duloxetine, isomer or Cymbalta).ti,ab.	3843
44	Levomilnacipran/	2057
45	(levomilnacipran or midalcipran or levomilnacipran or milnacipran hydrochloride or 1-phenyl-1-diethylaminocarbonyl-2-aminomethylcyclopropane HCl or Savella or F 2207 or F-2207 or Ixel).ti,ab.	193
46	venlafaxine/	20055
47	(venlafaxine or Hydrochloride, Venlafaxine or Cyclohexanol, 1 2 dimethylamino 2 4methoxyphenyl ethyl , hydrochloride or 1 2 dimethylamino 1 4 methoxyphenyl ethyl cyclohexanol HCl or Wy 45030 or Wy-45030 or Wy45030 or Wy-45,030 or Wy 45,030 or Wy45,030 or Sila-Venlafaxine or Sila Venlafaxine or Effexor or Trevilor or Vandral or Efexor or Venlafaxine or Dobupal).ti,ab.	5834
48	milnacipran/	2480
49	(milnacipran or levomilnacipran or Savella or F 2207 or Ixel).ti,ab.	1092
50	bupropion/	16591
51	(bupropion or Amfebutamone or 1 3 Chlorophenyl 2 1, dimethylethyl amino propanone or Bupropion Hydrochloride, Isomer or Zyntabac or Quomen or Wellbutrin or Zyban or Bupropion Hydrochloride).ti,ab.	5738
52	isocarboxazid/	1226
53	isocarboxazid.ti,ab.	136
54	phenelzine/	5207
55	(phenelzine or beta Phenylethylhydrazine or 2 Phenethylhydrazine or Fenelzin or Phenethylhydrazine or Phenelzine Sulfate or Sulfate, Phenelzine or Nardelzine).ti,ab.	1065
56	selegiline/	9472
57	(Selegiline or Selegyline or L-Deprenyl or E-250 or Eldepryl or Emsam or Zelapar or Selegiline Hydrochloride or Deprenil or Deprenalin or Yumex or Jumex or Humex or Deprenyl).ti,ab.	3752

58	Tranylcypromine/	5421
59	(tranylcypromine or trans 2 Phenylcyclopropylamine or Tranylcypromine Sulfate or Sulfate, Tranylcypromine or Jatrosom or Transamine or Parnate).ti,ab.	1517
60	amoxapine/	2301
61	(Desmethylloxapine or CL67772 or Demolox or amoxapine or Asendin or Defanyl or Asendise).ti,ab.	487
62	maprotiline/	6073
63	(Dibencycladine or maprotilin* or Psymion or Ludiomil or Maprolu or Mesylate or Maprotilin Holsten or maprotilin von ct or Maprotilin neuraxpharm or Maprotilin ratiopharm or Maprotilin TEVA or Maprotiline Hydrochloride or Maprotiline Mesylate or Mirpan or Novo Maprotiline or Ba34276 or Deprilept).ti,ab.	10257
64	mianserin/	7633
65	(mianserin or mianserin Hydrochloride or Mianserin Monohydrochloride or Tolvon Lerivon or Org GB 94).ti,ab.	2308
66	mirtazapine/	11693
67	(mirtazapine or 6 azamianserin or esmirtazapine or Remeron or Remergil or Zispin or Norset or Rexer or Org 50081 or ORG 3770 or ORG-3770).ti,ab.	3038
68	Setiptiline/	101
69	(setiptiline or ORG 8282 or MO 8282).ti,ab.	28
70	amitriptyline/	36821
71	(Amitriptyline or Amineurin or Amitrip or Amitriptylin beta or Amitriptylin Desitin or Amitriptylin RPh or Amitriptylin-neuraxpharm or Amitriptyline Hydrochloride or Amitrol or Tryptine or Apo Amitriptyline or Damilen or Domical or Laroxyl or Endep or Lentizol or Novoprotect or Saroten or Sarotex or Syneudon or Triptafen or Tryptizol or Tryptanol or Elavil or Anapsique).ti,ab.	8323
72	doxepin/	9086
73	(doxepin or deptran or Desidox or Doneurin or Doxepia or Doxepin beta or Doxepin Hydrochloride or Doxepin RPh or Espadox or Mareen or Novo-Doxepin or Prudoxin or Quitaxon or Sinequan or Sinquan or Zonalon or Xepin or Aponal or Apo-Doxepin).ti,ab.	1441
74	imipramine/	32263
75	(imipramine or Imizin or Norchlorimipramine or Imidobenzyle or Tofranil or Melipramine or Pryleugan Imipramine Hydrochloride or Imipramine Monohydrochloride or Janimine).ti,ab.	10354
76	desipramine/	20626
77	(Desipramine or Desmethylimipramine or Demethylimipramine or Desipramine Hydrochloride or Norpramin or ratio-Desipramine or Nu-Desipramine or Pertofrane or Pertrofran or Pertofran or Petylyl or PMS-Desipramine or Apo-Desipramine or Novo-Desipramine).ti,ab.	6918

78	lithium/	47303
79	lithium.ti,ab.	43463
80	Risperidone/	34707
81	(Risperidone or Risperdal Consta or Risperidal or R 64766 or R64766).ti,ab.	13160
82	Olanzapine/	32036
83	(Olanzapine or Zolafren or Zyprexa or LY 170053 or olanzapine pamoate).ti,ab.	12183
84	Quetiapine/	22016
85	(Fumarate, Quetiapine or ICI204636 or 204636, ICI or Seroquel or Quetiapine).ti,ab.	7637
86	brexpiprazole/	322
87	brexpiprazole.ti,ab.	234
88	aripiprazole/	13982
89	(aripiprazole or aripiprazole or OPC 14597 or 14597, OPC or abilify).ti,ab.	6019
90	Lamotrigine/	23234
91	(lamotrigine or Crisomet or Lamictal or Lamiktal or BW-430C or Labileno).ti,ab.	7882
92	Agomelatine/	2046
93	(thymanax or valdoxan or agomelatine or S20098 or AGO 178).ti,ab.	1290
94	Amisulpride/	5301
95	(Barnetil or DAN 2163 or Solian or sultopride or hydrochloride amisulpride or LIN 1418).ti,ab.	238
96	Amineptine/	958
97	(amineptine or Survector or S 1694 or amineptin hydrochloride or amineptin sodium salt).ti,ab.	359
98	Amitriptylinoxide/	225
99	(amitriptylinoxide or Amioxid-neuraxpharm or Equilibrin).ti,ab.	38
100	Asenapine/	1307
101	(saphris or ORG 5222or asenapine maleate).ti,ab.	20
102	Bicifadine/	43
103	bicifadine hydrochloride.ti,ab.	2
104	Butriptyline/	205
105	(butriptylene or AY 62014 or Evadyne or AY 2014 or butriptyline hydrochloride).ti,ab.	20
106	exp Clomipramine/	17080
107	(Clomipramine or Chlorimipramine or Hydiphen or Anafranil or Clomipramine Hydrochloride).ti,ab.	4345
108	exp Clozapine/	31139
109	(Clozaril or Leponex).ti,ab.	238
110	Demexiptiline/	38
111	demexiptiline hydrochloride.ti,ab.	2

112	Dibenzepin/	693
113	(Noveril or dibenzepin hydrochloride).ti,ab.	39
114	Dimetacrine/	101
115	(dimetacrine or isotonil or SD 709 or dimethacrine tartrate or miroistonil).ti,ab.	57
116	exp Dothiepin/	2363
117	(Dosulepin or Prothiaden or Dothiepin Hydrochloride).ti,ab.	172
118	Escitalopram/	10652
119	Iloperidone/	737
120	(Zomaril or Fanapt or HP 873).ti,ab.	18
121	Imipraminoxide.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	97
122	exp Iprindole/	773
123	exp Lofepramine/	1074
124	(Lopramine or Gamanil or Deftan or Gamonil or Lomont or Feprapax or Leo 640).ti,ab.	11
125	Lurasidone/	1356
126	(SM 13496 or Lurasidone or Latuda).ti,ab.	870
127	exp Mazindol/	1815
128	(Mazindol* or Diestet or Mazanor or Solucaps or Teronac or Teronak or Sanorex or Sanjorex).ti,ab.	901
129	Melitracen/	371
130	(flupentixol - melitracen or Deanxit).ti,ab.	76
131	Metapramine/	124
132	19560 RP.ti,ab.	8
133	exp Moclobemide/	4412
134	Nitroxazepine/	42
135	(nitroxazepine or 233 Go).ti,ab.	14
136	exp Nortriptyline/	14136
137	(Desitriptyline or Desmethylamitriptylin or Aventyl or Allegron or Paxtibi or Norfenazin or Nortriptyline Hydrochloride or Pamelor or Nortrilen).ti,ab.	80
138	Noxiptiline/	190
139	exp Opipramol/	810
140	(Insidon or Opipramol Hydrochloride).ti,ab.	14
141	Paliperidone/	4019
142	(Paliperidone or Invega or Invega Sustenna or R 76477).ti,ab.	2059
143	Pipfezine.mp.	0
144	Pirlindole/	258

145	(pyrlindole or pirlindol or pirlindole hydrochloride or pyrazidol).ti,ab.	74
146	(propizepin or pyridobenzodiazepine or UP 106 or Vagran 50 or propizepine hydrochloride).ti,ab.	156
147	exp Protriptyline/	2476
148	(Vivactil or Protriptyline Hydrochloride).ti,ab.	9
149	Quinupramine/	111
150	quinupramine monohydrochloride.ti,ab.	0
151	Reboxetine/	3257
152	(Vestra or reboxetine mesylate).ti,ab.	4
153	exp Triiodothyronine/	34751
154	(T3 Thyroid Hormone or Liothyronine or Cytomel).ti,ab.	345
155	Sibutramine/	4405
156	Symbyax/	339
157	Symbyax.ti,ab.	12
158	Tianeptine/	1521
159	(coaxil or Stablon).ti,ab.	56
160	exp Trimipramine/	3552
161	(Trimepramine or Herphonal or Trimineurin or Novo Tripramine or Nu Trimipramine or Rhotrimine or Stangyl or Surmontil or Surmontil Maleate or Trimidura or Trimineurin Maleate or Apo Trimip or Eldoral).ti,ab.	47
162	Ziprasidone/	8604
163	(ziprazidone or Geodon or CP 88059 or ziprasidone hydrochloride).ti,ab.	107
164	Zotepine/	1409
165	(Zoleptil or Nipolept).ti,ab.	2
166	electroconvulsive therapy/	17293
167	Transcranial Magnetic Stimulation/	19986
168	(Electroconvulsive therapy or Repetitive transcranial magnetic stimulation or transcranial direct current stimulation).ti,ab.	18017
169	cognitive behavioral therapy/	7019
170	Repetitive transcranial magnetic stimulation/	1687
171	psychotherapy/	81589
172	Vagus nerve stimulation/	9396
173	Magnetic seizure therapy/	109
174	Deep brain stimulation/	35096
175	Transcranial direct current stimulation/	5270
176	Behavioral activation/	81
177	Interpersonal psychotherapy/	215

178	(Electroconvulsive therapy or Repetitive transcranial magnetic stimulation or cognitive behavioral therapy or Psychotherapy or vagus nerve stimulation or Magnetic seizure therapy or deep brain stimulation or transcranial direct current stimulation or behavioral activation or Interpersonal psychotherapy).ti,ab.	86642
179	(imipramine or Imiprex or Elepsin).ti,ab.	10300
180	Pipofezine.ti,ab.	4
181	(adaptol or dixeran or melixeran or thymeol or trausabun).ti,ab.	50
182	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181	613801
183	5 and 21 and 182	4103
184	**limit 183 to yr="1990 -Current"**	**4030**

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to December 17, 2018, ran 18 December 2018

#	Searches	Results
1	exp Depressive Disorder, Major/	26802
2	exp Depressive Disorder, Treatment-Resistant/	905
3	((chronic or resistan* or untreatable or unrespon* or non-respon* or nonrespon* or major) adj depressi*).mp.	45521
4	(MDD* or MDE* or TRD*).mp.	15557
5	1 or 2 or 3 or 4	58010
6	clinical study/	3048
7	exp Case-Control Studies/	959511
8	family study.mp.	4199
9	Longitudinal Studies/	119378
10	Retrospective Studies/	721842
11	Prospective Studies/	489124
12	Cross-Sectional Studies/	281083
13	Cohort Studies/	231776
14	Follow up Studies/	603928
15	cohort*.ti,ab.	489528
16	14 and 15	52405
17	case control.ti,ab.	112099
18	(cohort adj (study or studies or analys*)).ti,ab.	172320
19	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.	216324
20	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.	1236912
21	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 16 or 17 or 18 or 19 or 20	2457004
22	esketamine.ti,ab.	47
23	ketamine/	11375
24	(ketamine or CI-581 or CI 581 or CI581 or Ketalar or Ketaset or Ketanest or Calipsol or Kalipsol or Calypsol or Ketamine or Hydrochloride).ti,ab.	62335
25	SERTRALINE/	2845
26	(sertraline or Zoloft or Altruline or Lustral or Apo Sertraline or Aremis or Sealdin or Gladem or Novo-Sertraline or Novo Sertraline or ratio-Sertraline or ratio Sertraline or Rhoxal-sertraline or Rhoxal sertraline or Gen-Sertraline or Gen Sertraline).ti,ab.	4179
27	FLUOXETINE/	8686

28	(fluoxetin* or "N Methyl gamma (4(trifluoromethyl)phenoxy)benzenepropanamine" or Lilly-110140 or Lilly 110140 or Lilly110140 or Sarafem or Fluoxetine Hydrochloride or Prozac).ti,ab.	11625
29	CITALOPRAM/	4528
30	(citalopram or cytalopram or Lu-- or Lu or Escitalopram or Lexapro).ti,ab.	12373
31	PAROXETINE/	3856
32	(paroxetine or BRL29060 or FG7051 or Paroxetine Acetate or Hydrochloride, Paroxetine or Hemihydrate or Hemihydrate Paroxetine Hydrochloride, Hemihydrate Paroxetine or Paroxetine Hydrochloride Hemihydrate or Hemihydrate, Paroxetine Hydrochloride or hydrochloride Hemihydrate, Paroxetine or Seroxat or Paroxetine Maleate or Maleate, Paroxetine or Paroxetine, cis Isomer or Paroxetine, cis Isomer or Paroxetine, trans Isomer or Paxil or Aropax or Paroxetine Hydrochloride Anhydrous or Anhydrous, Paroxetine Hydrochloride or Hydrochloride Anhydrous, Paroxetine).ti,ab.	6071
33	FLUVOXAMINE/	1811
34	(fluvoxamine or fluvoxadura or Fluvoxamin AL or Fluvoxamin beta or Fluvoxamin Stada or Fluvoxamin-neuraxpharm or Fluvoxamin neuraxpharm or Fluvoxamin-ratiopharm or Fluvoxamin ratiopharm or ratio-Fluvoxamine or ratio Fluvoxamine or Fluvoxamina Geminis or Geminis, Fluvoxamina or Fluvoxamine Maleate or Fluvoxamine Maleate, E Isomer or Fluvoxamine, Z Isomer or Luvox or Fevarin or Floxyfral or Dumirox or Faverin or Novo-Fluvoxamine or Novo Fluvoxamine or Nu-Fluvoxamine or Nu Fluvoxamine or PMS-Fluvoxamine or PMS Fluvoxamine or Desiflu or DU-23000 or DU 23000 or DU23000).ti,ab.	2543
35	TRAZODONE/	1249
36	(trazodone or AF1161 or Deprax or Trazodone Hydrochloride or Desyrel or Gen-Trazodone or Gen Trazodone or Molipaxin or Novo Trazodone or Trittico or PMS Trazodone or ratio Trazodone or Thombran or Trazodon-neuraxpharm or Trazodon neuraxpharm or Trazodone Hydrochloride or Trazon or Apo-Trazodone or Apo Trazodone or Nu-Trazodone or Nu Trazodone).ti,ab.	1691
37	(vortioxetine or brintellix or 1,2,2,4-dimethylphenylsulfanyl phenyl piperazine or vortioxetine hydrobromide or Lu AA21004 or LuAA21004 or Lu-AA21004).ti,ab.	310
38	Desvenlafaxine Succinate/	270
39	(Succinate , Desvenlafaxine or O-desmethylvenlafaxine Succinate Monohydrate or Monohydrate, O desmethylvenlafaxine Succinate or O desmethylvenlafaxine Succinate Monohydrate or Succinate Monohydrate, O desmethylvenlafaxine or hydroxycyclohexyl 4 hydroxyphenyl ethyl dimethylammonium 3 carboxypropanoate monohydrate or O-desmethylvenlafaxine Succinate or O desmethylvenlafaxine Succinate or Succinate, O desmethylvenlafaxine or WY 45,233 or 45,233, WY or WY-45,233 or WY45,233 or WY-45233 or WY45233 or WY 45233 or 45233, WY or Pristiq or Desvenlafaxine or O-	453

	desmethylvenlafaxine or O desmethylvenlafaxine or 4 2 dimethylamino 1 1 hydroxycyclohexyl ethyl phenol).ti,ab.	
40	Duloxetine Hydrochloride/	1434
41	(duloxetine or Hydrochloride, Duloxetine or Duloxetine HCl or HCl, Duloxetine or LY 248686 or LY-248686 or LY248686 or Duloxetine Ethanedioate, isomer T353987 or LY 227942 or LY227942 or LY227942 or Duloxetine or N methyl 3 1 naphthalenyloxy 3 2 thiophene propanamide or N-methyl 3 1 naphthalenyloxy 2 thiophenepropanamine or Duloxetine, isomer or Cymbalta).ti,ab.	2227
42	(levomilnacipran or midalcipran or levomilnacipran or milnacipran hydrochloride or 1-phenyl-1-diethylaminocarbonyl-2-aminomethylcyclopropane HCl or Savella or F 2207 or F-2207 or Ixel).ti,ab.	101
43	Venlafaxine Hydrochloride/	2414
44	(venlafaxine or Hydrochloride, Venlafaxine or Cyclohexanol, 1 2 dimethylamino 2 4methoxyphenyl ethyl , hydrochloride or 1 2 dimethylamino 1 4 methoxyphenyl ethyl cyclohexanol HCl or Wy 45030 or Wy-45030 or Wy45030 or Wy-45,030 or Wy 45,030 or Wy45,030 or Sila-Venlafaxine or Sila Venlafaxine or Effexor or Trevilor or Vandral or Efexor or Venlafaxine or Dobupal).ti,ab.	3722
45	(milnacipran or levomilnacipran or Savella or F 2207 or Ixel).ti,ab.	679
46	BUPROPION/	2871
47	(bupropion or Amfebutamone or 1 3 Chlorophenyl 2 1, dimethylethyl amino propanone or Bupropion Hydrochloride, Isomer or Zyntabac or Quomen or Wellbutrin or Zyban or Bupropion Hydrochloride).ti,ab.	4028
48	ISOCARBOXAZID/	358
49	isocarboxazid.ti,ab.	164
50	PHENELZINE/	1343
51	(phenelzine or beta Phenylethylhydrazine or 2 Phenethylhydrazine or Fenelzin or Phenethylhydrazine or Phenelzine Sulfate or Sulfate, Phenelzine or Nardelzine).ti,ab.	1009
52	SELEGILINE/	2311
53	(Selegiline or Selegyline or L-Deprenyl or E-250 or Eldepryl or Emsam or Zelapar or Selegiline Hydrochloride or Deprenil or Deprenalin or Yumex or Jumex or Humex or Deprenyl).ti,ab.	2991
54	TRANYLCYPROMINE/	1743
55	(tranylcypromine or trans 2 Phenylcyclopropylamine or Tranylcypromine Sulfate or Sulfate, Tranylcypromine or Jatrosom or Transamine or Parnate).ti,ab.	1406
56	AMOXAPINE/	329
57	(Desmethylloxapine or CL67772 or Demolox or amoxapine or Asendin or Defanyl or Asendise).ti,ab.	399
58	MAPROTILINE/	866

59	(Dibencycladine or maprotilin* or Psymion or Ludiomil or Maprolu or Mesylate or Maprotilin Holsten or maprotilin von ct or Maprotilin neuraxpharm or Maprotilin ratiopharm or Maprotilin TEVA or Maprotiline Hydrochloride or Maprotiline Mesylate or Mirpan or Novo Maprotiline or Ba34276 or Deprilept).ti,ab.	7456
60	MIANSERIN/	2499
61	(mianserin or mianserin Hydrochloride or Mianserin Monohydrochloride or Tolvon Lerivon or Org GB 94).ti,ab.	1981
62	(mirtazapine or 6 azamianserin or esmirtazapine or Remeron or Remergil or Zispin or Norset or Rexer or Org 50081 or ORG 3770 or ORG-3770).ti,ab.	1926
63	(setiptiline or ORG 8282 or MO 8282).ti,ab.	13
64	AMITRIPTYLINE/	6443
65	(Amitriptyline or Amineurin or Amitrip or Amitriptylin beta or Amitriptylin Desitin or Amitriptylin RPh or Amitriptylin-neuraxpharm or Amitriptyline Hydrochloride or Amitrol or Tryptine or Apo Amitriptyline or Damilen or Domical or Laroxyl or Endep or Lentizol or Novoprotect or Saroten or Sarotex or Syneudon or Triptafen or Tryptizol or Tryptanol or Elavil or Anapsique).ti,ab.	6539
66	DOXEPIN/	810
67	(doxepin or deptran or Desidox or Doneurin or Doxepia or Doxepin beta or Doxepin Hydrochloride or Doxepin RPh or Espadox or Mareen or Novo-Doxepin or Prudoxin or Quitaxon or Sinequan or Sinquan or Zonalon or Xepin or Aponal or Apo-Doxepin).ti,ab.	1157
68	IMIPRAMINE/	9834
69	(imipramine or Imizin or Norchlorimipramine or Imidobenzyle or Tofranil or Melipramine or Pryleugan Imipramine Hydrochloride or Imipramine Monohydrochloride or Janimine).ti,ab.	9586
70	DESIPRAMINE/	5521
71	(Desipramine or Desmethylimipramine or Demethylimipramine or Desipramine Hydrochloride or Norpramin or ratio-Desipramine or Nu-Desipramine or Pertofrane or Pertrofran or Pertofran or Petylyl or PMS-Desipramine or Apo-Desipramine or Novo-Desipramine).ti,ab.	6310
72	LITHIUM/	21466
73	lithium.ti,ab.	42578
74	RISPERIDONE/	5920
75	(Risperidone or Risperdal Consta or Risperidal or R 64766 or R64766).ti,ab.	8437
76	(Olanzapine or Zolafren or Zyprexa or LY 170053 or olanzapine pamoate).ti,ab.	7849
77	Quetiapine Fumarate/	2584
78	(Fumarate, Quetiapine or ICI204636 or 204636, ICI or Seroquel or Quetiapine).ti,ab.	4351
79	brexpiprazole.ti,ab.	118
80	ARIPIPRAZOLE/	2113

81	(aripiprazole or aripiprazole or OPC 14597 or 14597, OPC or abilify).ti,ab.	3558
82	(lamotrigine or Crisomet or Lamictal or Lamiktal or BW-430C or Labileno).ti,ab.	4898
83	(thymanax or valdoxan or agomelatine or S20098 or AGO 178).ti,ab.	685
84	(Barnetil or DAN 2163 or Solian or sultopride or hydrochloride amisulpride or LIN 1418).ti,ab.	140
85	(amineptine or Survector or S 1694 or amineptin hydrochloride or amineptin sodium salt).ti,ab.	241
86	(amitriptylinoxide or Amioxid-neuraxpharm or Equilibrin).ti,ab.	30
87	(saphris or ORG 5222or asenapine maleate).ti,ab.	16
88	bicifadine hydrochloride.ti,ab.	2
89	(butriptylene or AY 62014 or Evadyne or AY 2014 or butriptyline hydrochloride).ti,ab.	14
90	exp CLOMIPRAMINE/	2766
91	(Clomipramine or Chlorimipramine or Hydiphen or Anafranil or Clomipramine Hydrochloride).ti,ab.	3407
92	exp CLOZAPINE/	7775
93	(Clozaril or Leponex).ti,ab.	164
94	demexiptiline hydrochloride.ti,ab.	0
95	(Noveril or dibenzepin hydrochloride).ti,ab.	53
96	(dimetacrine or isotonil or SD 709 or dimethacrine tartrate or miroistonil).ti,ab.	38
97	exp DOTHIEPIN/	275
98	(Dosulepin or Prothiaden or Dothiepin Hydrochloride).ti,ab.	114
99	Escitalopram.ti,ab.	2204
100	Iloperidone.ti,ab.	190
101	(Zomaril or Fanapt or HP 873).ti,ab.	14
102	Imipraminoxide.mp.	0
103	exp IPRINDOLE/	180
104	exp LOFEPRAMINE/	102
105	(Lopramine or Gamanil or Deftan or Gamonil or Lomont or Feprapax or Leo 640).ti,ab.	12
106	Lurasidone Hydrochloride/	189
107	(SM 13496 or Lurasidone or Latuda).ti,ab.	364
108	exp MAZINDOL/	603
109	(Mazindol* or Diestet or Mazanor or Solucaps or Teronac or Teronak or Sanorex or Sanjorex).ti,ab.	781
110	Melitracen.ti,ab.	53
111	(flupentixol - melitracen or Deanxit).ti,ab.	33
112	Metapramine.ti,ab.	39
113	19560 RP.ti,ab.	5

114	exp MOCLOBEMIDE/	671
115	(nitroxazepine or 233 Go).ti,ab.	9
116	exp NORTRIPTYLINE/	2112
117	(Desitriptyline or Desmethylamitriptylin or Aventyl or Allegron or Paxtibi or Norfenazin or Nortriptyline Hydrochloride or Pamelor or Nortrilen).ti,ab.	79
118	Noxiptiline.ti,ab.	8
119	exp OPIPRAMOL/	240
120	(Insidon or Opipramol Hydrochloride).ti,ab.	78
121	Paliperidone Palmitate/	731
122	(Paliperidone or Invega or Invega Sustenna or R 76477).ti,ab.	995
123	Pipofezine.mp.	2
124	(pyrlindole or pirlindol or pirlindole hydrochloride or pyrazidol).ti,ab.	82
125	(propizepine or pyridobenzodiazepine or UP 106 or Vagran 50 or propizepine hydrochloride).ti,ab.	90
126	exp PROTRIPTYLINE/	188
127	(Vivactil or Protriptyline Hydrochloride).ti,ab.	11
128	quinupramine.ti,ab.	19
129	Reboxetine.ti,ab.	816
130	(Vestra or reboxetine mesylate).ti,ab.	3
131	exp TRIIODOTHYRONINE/	24964
132	(T3 Thyroid Hormone or Liothyronine or Cytomel).ti,ab.	274
133	Sibutramine.ti,ab.	1141
134	Symbyax.ti,ab.	11
135	Tianeptine.ti,ab.	522
136	(coaxil or Stablon).ti,ab.	42
137	exp TRIMIPRAMINE/	330
138	(Trimepramine or Herphonal or Trimineurin or Novo Tripramine or Nu Trimipramine or Rhotrimine or Stangyl or Surmontil or Surmontil Maleate or Trimidura or Trimineurin Maleate or Apo Trimip or Eldoral).ti,ab.	45
139	(ziprazidone or Geodon or CP 88059 or ziprasidone).ti,ab.	1771
140	Zotepine.ti,ab.	265
141	(Zoleptil or Nipolept).ti,ab.	2
142	Electroconvulsive Therapy/	12593
143	Transcranial Magnetic Stimulation/	9949
144	(Electroconvulsive therapy or Repetitive transcranial magnetic stimulation or transcranial direct current stimulation).ti,ab.	13555
145	Cognitive Therapy/	22511

146	Repetitive transcranial magnetic stimulation.ti,ab.	3755
147	PSYCHOTHERAPY/	52039
148	Vagus Nerve Stimulation/	1231
149	Magnetic seizure therapy.ti,ab.	113
150	Deep Brain Stimulation/	7329
151	Transcranial Direct Current Stimulation/	1670
152	Behavioral activation.ti,ab.	1243
153	Interpersonal psychotherapy.ti,ab.	806
154	(Electroconvulsive therapy or Repetitive transcranial magnetic stimulation or cognitive behavioral therapy or Psychotherapy or vagus nerve stimulation or Magnetic seizure therapy or deep brain stimulation or transcranial direct current stimulation or behavioral activation or Interpersonal psychotherapy).ti,ab.	62560
155	(imipramine or Imiprex or Elepsin).ti,ab.	9296
156	Pipofezine.ti,ab.	2
157	(adaptol or dixeran or melixeran or thymeol or trausabun).ti,ab.	45
158	or/22-157	375385
159	5 and 21 and 158	2370
160	**limit 159 to yr="1990 -Current"**	**2323**

Cochrane library (All EBM Reviews - Cochrane DSR, ACP Journal Club, DARE, CCA, CCTR, CMR, HTA, and NHSEED), ran 18 December 2018

#	Searches	Results
1	exp Depressive Disorder, Major/	4149
2	exp Depressive Disorder, Treatment-Resistant/	279
3	((chronic or resistan* or untreatable or unrespon* or non-respon* or nonrespon* or major) adj depressi*).mp.	11541
4	(MDD* or MDE* or TRD*).mp.	3174
5	1 or 2 or 3 or 4	12723
6	clinical study/	1
7	exp Case-Control Studies/	14602
8	family study.mp.	1442
9	Longitudinal Studies/	5968
10	Retrospective Studies/	9763
11	Prospective Studies/	87136
12	Cross-Sectional Studies/	4635
13	Cohort Studies/	8041

14	Follow up Studies/	56892
15	cohort*.ti,ab.	44363
16	14 and 15	2810
17	case control.ti,ab.	5453
18	(cohort adj (study or studies or analys*)).ti,ab.	11103
19	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.	18751
20	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.	158804
21	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 16 or 17 or 18 or 19 or 20	234773
22	esketamine.ti,ab.	59
23	ketamine/	1772
24	(ketamine or CI-581 or CI 581 or CI581 or Ketalar or Ketaset or Ketanest or Calipsol or Kalipsol or Calypsol or Ketamine or Hydrochloride).ti,ab.	11044
25	SERTRALINE/	900
26	(sertraline or Zoloft or Altruline or Lustral or Apo Sertraline or Aremis or Sealdin or Gladem or Novo-Sertraline or Novo Sertraline or ratio-Sertraline or ratio Sertraline or Rhoxal-sertraline or Rhoxal sertraline or Gen-Sertraline or Gen Sertraline).ti,ab.	1800
27	FLUOXETINE/	1365
28	(fluoxetin* or "N Methyl gamma (4(trifluoromethyl)phenoxy)benzenepropanamine" or Lilly-110140 or Lilly 110140 or Lilly110140 or Sarafem or Fluoxetine Hydrochloride or Prozac).ti,ab.	2726
29	CITALOPRAM/	1270
30	(citalopram or cytalopram or Lu-- or Lu or Escitalopram or Lexapro).ti,ab.	2676
31	PAROXETINE/	946
32	(paroxetine or BRL29060 or FG7051 or Paroxetine Acetate or Hydrochloride, Paroxetine or Hemihydrate or Hemihydrate Paroxetine Hydrochloride, Hemihydrate Paroxetine or Paroxetine Hydrochloride Hemihydrate or Hemihydrate, Paroxetine Hydrochloride or hydrochloride Hemihydrate, Paroxetine or Seroxat or Paroxetine Maleate or Maleate, Paroxetine or Paroxetine, cis Isomer or Paroxetine, cis Isomer or Paroxetine, trans Isomer or Paxil or Aropax or Paroxetine Hydrochloride Anhydrous or Anhydrous, Paroxetine Hydrochloride or Hydrochloride Anhydrous, Paroxetine).ti,ab.	2125
33	FLUVOXAMINE/	378
34	(fluvoxamine or fluvoxadura or Fluvoxamin AL or Fluvoxamin beta or Fluvoxamin Stada or Fluvoxamin-neuraxpharm or Fluvoxamin neuraxpharm or Fluvoxamin-ratiopharm or Fluvoxamin ratiopharm or ratio-Fluvoxamine or ratio Fluvoxamine or Fluvoxamina Geminis or Geminis, Fluvoxamina or Fluvoxamine Maleate or Fluvoxamine Maleate, E Isomer or Fluvoxamine, Z Isomer or Luvox or Fevarin or	733

	Floxyfral or Dumirox or Faverin or Novo-Fluvoxamine or Novo Fluvoxamine or Nu-Fluvoxamine or Nu Fluvoxamine or PMS-Fluvoxamine or PMS Fluvoxamine or Desiflu or DU-23000 or DU 23000 or DU23000).ti,ab.	
35	TRAZODONE/	200
36	(trazodone or AF1161 or Deprax or Trazodone Hydrochloride or Desyrel or Gen-Trazodone or Gen Trazodone or Molipaxin or Novo Trazodone or Trittico or PMS Trazodone or ratio Trazodone or Thombran or Trazodon-neuraxpharm or Trazodon neuraxpharm or Trazodone Hydrochloride or Trazon or Apo-Trazodone or Apo Trazodone or Nu-Trazodone or Nu Trazodone).ti,ab.	407
37	(vortioxetine or brintellix or 1,2,2,4-dimethylphenylsulfanyl phenyl piperazine or vortioxetine hydrobromide or Lu AA21004 or LuAA21004 or Lu-AA21004).ti,ab.	168
38	Desvenlafaxine Succinate/	84
39	(Succinate , Desvenlafaxine or O-desmethylvenlafaxine Succinate Monohydrate or Monohydrate, O desmethylvenlafaxine Succinate or O desmethylvenlafaxine Succinate Monohydrate or Succinate Monohydrate, O desmethylvenlafaxine or hydroxycyclohexyl 4 hydroxyphenyl ethyl dimethylammonium 3 carboxypropanoate monohydrate or O-desmethylvenlafaxine Succinate or O desmethylvenlafaxine Succinate or Succinate, O desmethylvenlafaxine or WY 45,233 or 45,233, WY or WY-45,233 or WY45,233 or WY-45233 or WY45233 or WY 45233 or 45233, WY or Pristiq or Desvenlafaxine or O-desmethylvenlafaxine or O desmethylvenlafaxine or 4 2 dimethylamino 1 1 hydroxycyclohexyl ethyl phenol).ti,ab.	181
40	Duloxetine Hydrochloride/	404
41	(duloxetine or Hydrochloride, Duloxetine or Duloxetine HCl or HCl, Duloxetine or LY 248686 or LY-248686 or LY248686 or Duloxetine Ethanedioate, isomer T353987 or LY 227942 or LY227942 or LY227942 or Duloxetine or N methyl 3 1 naphthalenyloxy 3 2 thiophene propanamide or N-methyl 3 1 naphthalenyloxy 2 thiophenepropanamine or Duloxetine, isomer or Cymbalta).ti,ab.	920
42	(levomilnacipran or midalcipran or levomilnacipran or milnacipran hydrochloride or 1-phenyl-1-diethylaminocarbonyl-2-aminomethylcyclopropane HCl or Savella or F 2207 or F-2207 or Ixel).ti,ab.	68
43	Venlafaxine Hydrochloride/	593
44	(venlafaxine or Hydrochloride, Venlafaxine or Cyclohexanol, 1 2 dimethylamino 2 4methoxyphenyl ethyl , hydrochloride or 1 2 dimethylamino 1 4 methoxyphenyl ethyl cyclohexanol HCl or Wy 45030 or Wy-45030 or Wy45030 or Wy-45,030 or Wy 45,030 or Wy45,030 or Sila-Venlafaxine or Sila Venlafaxine or Effexor or Trevilor or Vandral or Efexor or Venlafaxine or Dobupal).ti,ab.	1389
45	(milnacipran or levomilnacipran or Savella or F 2207 or Ixel).ti,ab.	274
46	BUPROPION/	757

47	(bupropion or Amfebutamone or 1 3 Chlorophenyl 2 1, dimethylethyl amino propanone or Bupropion Hydrochloride, Isomer or Zyntabac or Quomen or Wellbutrin or Zyban or Bupropion Hydrochloride).ti,ab.	1365
48	ISOCARBOXAZID/	22
49	isocarboxazid.ti,ab.	29
50	PHENELZINE/	144
51	(phenelzine or beta Phenylethylhydrazine or 2 Phenethylhydrazine or Fenelzin or Phenethylhydrazine or Phenelzine Sulfate or Sulfate, Phenelzine or Nardelzine).ti,ab.	186
52	SELEGILINE/	235
53	(Selegiline or Selegyline or L-Deprenyl or E-250 or Eldepryl or Emsam or Zelapar or Selegiline Hydrochloride or Deprenil or Deprenalin or Yumex or Jumex or Humex or Deprenyl).ti,ab.	455
54	TRANYLCYPROMINE/	69
55	(tranylcypromine or trans 2 Phenylcyclopropylamine or Tranylcypromine Sulfate or Sulfate, Tranylcypromine or Jatrosom or Transamine or Parnate).ti,ab.	89
56	AMOXAPINE/	28
57	(Desmethylloxapine or CL67772 or Demolox or amoxapine or Asendin or Defanyl or Asendise).ti,ab.	69
58	MAPROTILINE/	158
59	(Dibencycladine or maprotilin* or Psymion or Ludiomil or Maprolu or Mesylate or Maprotilin Holsten or maprotilin von ct or Maprotilin neuraxpharm or Maprotilin ratiopharm or Maprotilin TEVA or Maprotiline Hydrochloride or Maprotiline Mesylate or Mirpan or Novo Maprotiline or Ba34276 or Deprilept).ti,ab.	1165
60	MIANSERIN/	448
61	(mianserin or mianserin Hydrochloride or Mianserin Monohydrochloride or Tolvon Lerivon or Org GB 94).ti,ab.	359
62	(mirtazapine or 6 azamianserin or esmirtazapine or Remeron or Remergil or Zispin or Norset or Rexer or Org 50081 or ORG 3770 or ORG-3770).ti,ab.	628
63	(setiptiline or ORG 8282 or MO 8282).ti,ab.	1
64	AMITRIPTYLINE/	1137
65	(Amitriptyline or Amineurin or Amitrip or Amitriptylin beta or Amitriptylin Desitin or Amitriptylin RPh or Amitriptylin-neuraxpharm or Amitriptyline Hydrochloride or Amitrol or Tryptine or Apo Amitriptyline or Damilen or Domical or Laroxyl or Endep or Lentizol or Novoprotect or Saroten or Sarotex or Syneudon or Triptafen or Tryptizol or Tryptanol or Elavil or Anapsique).ti,ab.	1965
66	DOXEPIN/	162

67	(doxepin or deptran or Desidox or Doneurin or Doxepia or Doxepin beta or Doxepin Hydrochloride or Doxepin RPh or Espadox or Mareen or Novo-Doxepin or Prudoxin or Quitaxon or Sinequan or Sinquan or Zonalon or Xepin or Aponal or Apo-Doxepin).ti,ab.	391
68	IMIPRAMINE/	1050
69	(imipramine or Imizin or Norchlorimipramine or Imidobenzyle or Tofranil or Melipramine or Pryleugan Imipramine Hydrochloride or Imipramine Monohydrochloride or Janimine).ti,ab.	1744
70	DESIPRAMINE/	405
71	(Desipramine or Desmethylimipramine or Demethylimipramine or Desipramine Hydrochloride or Norpramin or ratio-Desipramine or Nu-Desipramine or Pertofrane or Pertrofran or Pertofran or Petylyl or PMS-Desipramine or Apo-Desipramine or Novo-Desipramine).ti,ab.	603
72	LITHIUM/	653
73	lithium.ti,ab.	2256
74	RISPERIDONE/	1291
75	(Risperidone or Risperdal Consta or Risperidal or R 64766 or R64766).ti,ab.	2676
76	(Olanzapine or Zolafren or Zyprexa or LY 170053 or olanzapine pamoate).ti,ab.	2673
77	Quetiapine Fumarate/	587
78	(Fumarate, Quetiapine or ICI204636 or 204636, ICI or Seroquel or Quetiapine).ti,ab.	1386
79	brexpiprazole.ti,ab.	104
80	ARIPIPRAZOLE/	463
81	(aripiprazole or aripiprazole or OPC 14597 or 14597, OPC or abilify).ti,ab.	1114
82	(lamotrigine or Crisomet or Lamictal or Lamiktal or BW-430C or Labileno).ti,ab.	962
83	(thymanax or valdoxan or agomelatine or S20098 or AGO 178).ti,ab.	228
84	(Barnetil or DAN 2163 or Solian or sultopride or hydrochloride amisulpride or LIN 1418).ti,ab.	23
85	(amineptine or Survector or S 1694 or amineptin hydrochloride or amineptin sodium salt).ti,ab.	61
86	(amitriptylinoxide or Amioxid-neuraxpharm or Equilibrin).ti,ab.	13
87	(saphris or ORG 5222or asenapine maleate).ti,ab.	6
88	bicifadine hydrochloride.ti,ab.	1
89	(butriptylene or AY 62014 or Evadyne or AY 2014 or butriptyline hydrochloride).ti,ab.	6
90	exp CLOMIPRAMINE/	402
91	(Clomipramine or Chlorimipramine or Hydiphen or Anafranil or Clomipramine Hydrochloride).ti,ab.	855
92	exp CLOZAPINE/	475
93	(Clozaril or Leponex).ti,ab.	24

94	demexiptiline hydrochloride.ti,ab.	0
95	(Noveril or dibenzepin hydrochloride).ti,ab.	13
96	(dimetacrine or isotonil or SD 709 or dimethacrine tartrate or miroistonil).ti,ab.	9
97	exp DOTHIEPIN/	61
98	(Dosulepin or Prothiaden or Dothiepin Hydrochloride).ti,ab.	33
99	Escitalopram.ti,ab.	1179
100	Iloperidone.ti,ab.	56
101	(Zomaril or Fanapt or HP 873).ti,ab.	2
102	Imipraminoxide.mp.	1
103	exp IPRINDOLE/	5
104	exp LOFEPRAMINE/	30
105	(Lopramine or Gamanil or Deftan or Gamonil or Lomont or Feprapax or Leo 640).ti,ab.	2
106	Lurasidone Hydrochloride/	79
107	(SM 13496 or Lurasidone or Latuda).ti,ab.	353
108	exp MAZINDOL/	50
109	(Mazindol* or Diestet or Mazanor or Solucaps or Teronac or Teronak or Sanorex or Sanjorex).ti,ab.	86
110	Melitracen.ti,ab.	45
111	(flupentixol - melitracen or Deanxit).ti,ab.	76
112	Metapramine.ti,ab.	9
113	19560 RP.ti,ab.	2
114	exp MOCLOBEMIDE/	189
115	(nitroxazepine or 233 Go).ti,ab.	2
116	exp NORTRIPTYLINE/	423
117	(Desitriptyline or Desmethylamitriptylin or Aventyl or Allegron or Paxtibi or Norfenazin or Nortriptyline Hydrochloride or Pamelor or Nortrilen).ti,ab.	26
118	Noxiptiline.ti,ab.	3
119	exp OPIPRAMOL/	26
120	(Insidon or Opipramol Hydrochloride).ti,ab.	11
121	Paliperidone Palmitate/	193
122	(Paliperidone or Invega or Invega Sustenna or R 76477).ti,ab.	429
123	Pipofezine.mp.	12
124	(pyrlindole or pirlindol or pirlindole hydrochloride or pyrazidol).ti,ab.	11
125	(propizepine or pyridobenzodiazepine or UP 106 or Vagran 50 or propizepine hydrochloride).ti,ab.	13850
126	exp PROTRIPTYLINE/	15
127	(Vivactil or Protriptyline Hydrochloride).ti,ab.	2

128	quinupramine.ti,ab.	6
129	Reboxetine.ti,ab.	278
130	(Vestra or reboxetine mesylate).ti,ab.	1
131	exp TRIIODOTHYRONINE/	541
132	(T3 Thyroid Hormone or Liothyronine or Cytomel).ti,ab.	58
133	Sibutramine.ti,ab.	319
134	Symbyax.ti,ab.	1
135	Tianeptine.ti,ab.	119
136	(coaxil or Stablon).ti,ab.	16
137	exp TRIMIPRAMINE/	64
138	(Trimepramine or Herphonal or Trimineurin or Novo Tripramine or Nu Trimipramine or Rhotrimine or Stangyl or Surmontil or Surmontil Maleate or Trimidura or Trimineurin Maleate or Apo Trimip or Eldoral).ti,ab.	21
139	(ziprazidone or Geodon or CP 88059 or ziprasidone).ti,ab.	601
140	Zotepine.ti,ab.	80
141	(Zoleptil or Nipolept).ti,ab.	1
142	Electroconvulsive Therapy/	550
143	Transcranial Magnetic Stimulation/	1237
144	(Electroconvulsive therapy or Repetitive transcranial magnetic stimulation or transcranial direct current stimulation).ti,ab.	4845
145	Cognitive Therapy/	7242
146	Repetitive transcranial magnetic stimulation.ti,ab.	1921
147	PSYCHOTHERAPY/	2269
148	Vagus Nerve Stimulation/	72
149	Magnetic seizure therapy.ti,ab.	32
150	Deep Brain Stimulation/	274
151	Transcranial Direct Current Stimulation/	398
152	Behavioral activation.ti,ab.	344
153	Interpersonal psychotherapy.ti,ab.	505
154	(Electroconvulsive therapy or Repetitive transcranial magnetic stimulation or cognitive behavioral therapy or Psychotherapy or vagus nerve stimulation or Magnetic seizure therapy or deep brain stimulation or transcranial direct current stimulation or behavioral activation or Interpersonal psychotherapy).ti,ab.	14891
155	(imipramine or Imiprex or Elepsin).ti,ab.	1727
156	Pipofezine.ti,ab.	1
157	(adaptol or dixeran or melixeran or thymeol or trausabun).ti,ab.	18
158	or/22-157	74817

159	5 and 21 and 158	936
160	**limit 159 to yr="1990 -Current" [Limit not valid in DARE; records were retained]**	**926**

PsycINFO <1806 to December Week 2 2018>, ran 19 December 2018

#	Searches	Results
1	Major Depressive Disorder.ti,ab.	17885
2	Treatment-Resistant Depressive Disorder.ti,ab.	8
3	((chronic or resistan* or untreatable or unrespon* or non-respon* or nonrespon* or major) adj depressi*).mp.	125726
4	(MDD* or MDE* or TRD*).mp.	10688
5	1 or 2 or 3 or 4	126191
6	clinical study.ti,ab.	2693
7	Case-Control Studies.ti,ab.	1117
8	family study.mp.	1455
9	Longitudinal Studies.ti,ab.	8801
10	Retrospective Studies.ti,ab.	622
11	Prospective Studies.ti,ab.	3632
12	Cross-Sectional Studies.ti,ab.	2282
13	Cohort Studies.ti,ab.	1953
14	Follow up Studies.ti,ab.	2429
15	cohort*.ti,ab.	68141
16	14 and 15	144
17	(cohort adj (study or studies or analys*)).ti,ab.	18769
18	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.	34280
19	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.	203907
20	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 16 or 17 or 18 or 19	239584
21	esketamine.ti,ab.	10
22	ketamine/	1748
23	(ketamine or CI-581 or CI 581 or CI581 or Ketalar or Ketaset or Ketanest or Calipsol or Kalipsol or Calypsol or Ketamine or Hydrochloride).ti,ab.	6178
24	SERTRALINE/	1224
25	(sertraline or Zoloft or Altruline or Lustral or Apo Sertraline or Aremis or Sealdin or Gladem or Novo-Sertraline or Novo Sertraline or ratio-Sertraline or ratio Sertraline or Rhoxal-sertraline or Rhoxal sertraline or Gen-Sertraline or Gen Sertraline).ti,ab.	2707

26	FLUOXETINE/	3667
27	(fluoxetin* or "N Methyl gamma (4(trifluoromethyl)phenoxy)benzenepropanamine" or Lilly-110140 or Lilly 110140 or Lilly110140 or Sarafem or Fluoxetine Hydrochloride or Prozac).ti,ab.	6558
28	CITALOPRAM/	1227
29	(citalopram or cytalopram or Lu-- or Lu or Escitalopram or Lexapro).ti,ab.	4200
30	PAROXETINE/	1653
31	(paroxetine or BRL29060 or FG7051 or Paroxetine Acetate or Hydrochloride, Paroxetine or Hemihydrate or Hemihydrate Paroxetine Hydrochloride, Hemihydrate Paroxetine or Paroxetine Hydrochloride Hemihydrate or Hemihydrate, Paroxetine Hydrochloride or hydrochloride Hemihydrate, Paroxetine or Seroxat or Paroxetine Maleate or Maleate, Paroxetine or Paroxetine, cis Isomer or Paroxetine, cis Isomer or Paroxetine, trans Isomer or Paxil or Aropax or Paroxetine Hydrochloride Anhydrous or Anhydrous, Paroxetine Hydrochloride or Hydrochloride Anhydrous, Paroxetine).ti,ab.	3195
32	FLUVOXAMINE/	798
33	(fluvoxamine or fluvoxadura or Fluvoxamin AL or Fluvoxamin beta or Fluvoxamin Stada or Fluvoxamin-neuraxpharm or Fluvoxamin neuraxpharm or Fluvoxamin-ratiopharm or Fluvoxamin ratiopharm or ratio-Fluvoxamine or ratio Fluvoxamine or Fluvoxamina Geminis or Geminis, Fluvoxamina or Fluvoxamine Maleate or Fluvoxamine Maleate, E Isomer or Fluvoxamine, Z Isomer or Luvox or Fevarin or Floxyfral or Dumirox or Faverin or Novo-Fluvoxamine or Novo Fluvoxamine or Nu-Fluvoxamine or Nu Fluvoxamine or PMS-Fluvoxamine or PMS Fluvoxamine or Desiflu or DU-23000 or DU 23000 or DU23000).ti,ab.	1541
34	TRAZODONE/	367
35	(trazodone or AF1161 or Deprax or Trazodone Hydrochloride or Desyrel or Gen-Trazodone or Gen Trazodone or Molipaxin or Novo Trazodone or Trittico or PMS Trazodone or ratio Trazodone or Thombran or Trazodon-neuraxpharm or Trazodon neuraxpharm or Trazodone Hydrochloride or Trazon or Apo-Trazodone or Apo Trazodone or Nu-Trazodone or Nu Trazodone).ti,ab.	868
36	(vortioxetine or brintellix or 1,2,2,4-dimethylphenylsulfanyl phenyl piperazine or vortioxetine hydrobromide or Lu AA21004 or LuAA21004 or Lu-AA21004).ti,ab.	164
37	Desvenlafaxine Succinate/	0
38	(Succinate , Desvenlafaxine or O-desmethylvenlafaxine Succinate Monohydrate or Monohydrate, O desmethylvenlafaxine Succinate or O desmethylvenlafaxine Succinate Monohydrate or Succinate Monohydrate, O desmethylvenlafaxine or hydroxycyclohexyl 4 hydroxyphenyl ethyl dimethylammonium 3 carboxypropanoate monohydrate or O-desmethylvenlafaxine Succinate or O desmethylvenlafaxine Succinate or Succinate, O desmethylvenlafaxine or WY 45,233 or 45,233, WY or WY-45,233 or WY45,233 or	164

	WY-45233 or WY45233 or WY 45233 or 45233, WY or Pristiq or Desvenlafaxine or O-desmethylvenlafaxine or O desmethylvenlafaxine or 4 2 dimethylamino 1 1 hydroxycyclohexyl ethyl phenol).ti,ab.	
39	Duloxetine Hydrochloride/	0
40	(duloxetine or Hydrochloride, Duloxetine or Duloxetine HCl or HCl, Duloxetine or LY 248686 or LY-248686 or LY248686 or Duloxetine Ethanedioate, isomer T353987 or LY 227942 or LY227942 or LY227942 or Duloxetine or N methyl 3 1 naphthalenyloxy 3 2 thiophene propanamide or N-methyl 3 1 naphthalenyloxy 2 thiophenepropanamine or Duloxetine, isomer or Cymbalta).ti,ab.	981
41	(levomilnacipran or midalcipran or levomilnacipran or milnacipran hydrochloride or 1-phenyl-1-diethylaminocarbonyl-2-aminomethylcyclopropane HCl or Savella or F 2207 or F-2207 or Ixel).ti,ab.	38
42	Venlafaxine Hydrochloride/	0
43	(venlafaxine or Hydrochloride, Venlafaxine or Cyclohexanol, 1 2 dimethylamino 2 4methoxyphenyl ethyl , hydrochloride or 1 2 dimethylamino 1 4 methoxyphenyl ethyl cyclohexanol HCl or Wy 45030 or Wy-45030 or Wy45030 or Wy-45,030 or Wy 45,030 or Wy45,030 or Sila-Venlafaxine or Sila Venlafaxine or Effexor or Trevilor or Vandral or Efexor or Venlafaxine or Dobupal).ti,ab.	2244
44	(milnacipran or levomilnacipran or Savella or F 2207 or Ixel).ti,ab.	365
45	BUPROPION/	920
46	(bupropion or Amfebutamone or 1 3 Chlorophenyl 2 1, dimethylethyl amino propanone or Bupropion Hydrochloride, Isomer or Zyntabac or Quomen or Wellbutrin or Zyban or Bupropion Hydrochloride).ti,ab.	2070
47	ISOCARBOXAZID/	33
48	isocarboxazid.ti,ab.	67
49	PHENELZINE/	341
50	(phenelzine or beta Phenylethylhydrazine or 2 Phenethylhydrazine or Fenelzin or Phenethylhydrazine or Phenelzine Sulfate or Sulfate, Phenelzine or Nardelzine).ti,ab.	573
51	SELEGILINE/	0
52	(Selegiline or Selegyline or L-Deprenyl or E-250 or Eldepryl or Emsam or Zelapar or Selegiline Hydrochloride or Deprenil or Deprenalin or Yumex or Jumex or Humex or Deprenyl).ti,ab.	595
53	TRANYLCYPROMINE/	237
54	(tranylcypromine or trans 2 Phenylcyclopropylamine or Tranylcypromine Sulfate or Sulfate, Tranylcypromine or Jatrosom or Transamine or Parnate).ti,ab.	470
55	AMOXAPINE/	0
56	(Desmethylloxapine or CL67772 or Demolox or amoxapine or Asendin or Defanyl or Asendise).ti,ab.	163

57	MAPROTILINE/	222
58	(Dibencycladine or maprotilin* or Psymion or Ludiomil or Maprolu or Mesylate or Maprotilin Holsten or maprotilin von ct or Maprotilin neuraxpharm or Maprotilin ratiopharm or Maprotilin TEVA or Maprotiline Hydrochloride or Maprotiline Mesylate or Mirpan or Novo Maprotiline or Ba34276 or Deprilept).ti,ab.	693
59	MIANSERIN/	349
60	(mianserin or mianserin Hydrochloride or Mianserin Monohydrochloride or Tolvon Lerivon or Org GB 94).ti,ab.	686
61	(mirtazapine or 6 azamianserin or esmirtazapine or Remeron or Remergil or Zispin or Norset or Rexer or Org 50081 or ORG 3770 or ORG-3770).ti,ab.	1204
62	(setiptiline or ORG 8282 or MO 8282).ti,ab.	4
63	AMITRIPTYLINE/	1306
64	(Amitriptyline or Amineurin or Amitrip or Amitriptylin beta or Amitriptylin Desitin or Amitriptylin RPh or Amitriptylin-neuraxpharm or Amitriptyline Hydrochloride or Amitrol or Tryptine or Apo Amitriptyline or Damilen or Domical or Laroxyl or Endep or Lentizol or Novoprotect or Saroten or Sarotex or Syneudon or Triptafen or Tryptizol or Tryptanol or Elavil or Anapsique).ti,ab.	2338
65	DOXEPIN/	57
66	(doxepin or deptran or Desidox or Doneurin or Doxepia or Doxepin beta or Doxepin Hydrochloride or Doxepin RPh or Espadox or Mareen or Novo-Doxepin or Prudoxin or Quitaxon or Sinequan or Sinquan or Zonalon or Xepin or Aponal or Apo-Doxepin).ti,ab.	377
67	IMIPRAMINE/	2292
68	(imipramine or Imizin or Norchlorimipramine or Imidobenzyle or Tofranil or Melipramine or Pryleugan Imipramine Hydrochloride or Imipramine Monohydrochloride or Janimine).ti,ab.	4096
69	DESIPRAMINE/	1140
70	(Desipramine or Desmethylimipramine or Demethylimipramine or Desipramine Hydrochloride or Norpramin or ratio-Desipramine or Nu-Desipramine or Pertofrane or Pertrofran or Pertofran or Petylyl or PMS-Desipramine or Apo-Desipramine or Novo-Desipramine).ti,ab.	2267
71	LITHIUM/	5452
72	lithium.ti,ab.	10185
73	RISPERIDONE/	3621
74	(Risperidone or Risperdal Consta or Risperidal or R 64766 or R64766).ti,ab.	6677
75	(Olanzapine or Zolafren or Zyprexa or LY 170053 or olanzapine pamoate).ti,ab.	5966
76	Quetiapine Fumarate/	0
77	(Fumarate, Quetiapine or ICI204636 or 204636, ICI or Seroquel or Quetiapine).ti,ab.	3387
78	brexpiprazole.ti,ab.	56

79	ARIPIPRAZOLE/	1506
80	(aripiprazole or aripiprazole or OPC 14597 or 14597, OPC or abilify).ti,ab.	2494
81	(lamotrigine or Crisomet or Lamictal or Lamiktal or BW-430C or Labileno).ti,ab.	1903
82	(thymanax or valdoxan or agomelatine or S20098 or AGO 178).ti,ab.	405
83	(Barnetil or DAN 2163 or Solian or sultopride or hydrochloride amisulpride or LIN 1418).ti,ab.	38
84	(amineptine or Survector or S 1694 or amineptin hydrochloride or amineptin sodium salt).ti,ab.	102
85	(amitriptylinoxide or Amioxid-neuraxpharm or Equilibrin).ti,ab.	8
86	(saphris or ORG 5222or asenapine maleate).ti,ab.	7
87	bicifadine hydrochloride.ti,ab.	0
88	(butriptylene or AY 62014 or Evadyne or AY 2014 or butriptyline hydrochloride).ti,ab.	4
89	exp CLOMIPRAMINE/	1132
90	(Clomipramine or Chlorimipramine or Hydiphen or Anafranil or Clomipramine Hydrochloride).ti,ab.	1992
91	exp CLOZAPINE/	4598
92	(Clozaril or Leponex).ti,ab.	76
93	demexiptiline hydrochloride.ti,ab.	0
94	(Noveril or dibenzepin hydrochloride).ti,ab.	18
95	(dimetacrine or isotonil or SD 709 or dimethacrine tartrate or miroistonil).ti,ab.	10
96	exp DOTHIEPIN/	0
97	(Dosulepin or Prothiaden or Dothiepin Hydrochloride).ti,ab.	40
98	Escitalopram.ti,ab.	1442
99	Iloperidone.ti,ab.	95
100	(Zomaril or Fanapt or HP 873).ti,ab.	6
101	Imipraminoxide.mp.	0
102	exp IPRINDOLE/	0
103	exp LOFEPRAMINE/	0
104	(Lopramine or Gamanil or Deftan or Gamonil or Lomont or Feprapax or Leo 640).ti,ab.	8
105	Lurasidone Hydrochloride/	0
106	(SM 13496 or Lurasidone or Latuda).ti,ab.	199
107	exp MAZINDOL/	0
108	(Mazindol* or Diestet or Mazanor or Solucaps or Teronac or Teronak or Sanorex or Sanjorex).ti,ab.	123
109	Melitracen.ti,ab.	5
110	(flupentixol - melitracen or Deanxit).ti,ab.	4
111	Metapramine.ti,ab.	13

112	19560 RP.ti,ab.	0
113	exp MOCLOBEMIDE/	157
114	(nitroxazepine or 233 Go).ti,ab.	0
115	exp NORTRIPTYLINE/	311
116	(Desitriptyline or Desmethylamitriptylin or Aventyl or Allegron or Paxtibi or Norfenazin or Nortriptyline Hydrochloride or Pamelor or Nortrilen).ti,ab.	25
117	Noxiptiline.ti,ab.	7
118	exp OPIPRAMOL/	0
119	(Insidon or Opipramol Hydrochloride).ti,ab.	5
120	Paliperidone Palmitate/	0
121	(Paliperidone or Invega or Invega Sustenna or R 76477).ti,ab.	584
122	Pipofezine.mp.	0
123	(pyrlindole or pirlindol or pirlindole hydrochloride or pyrazidol).ti,ab.	16
124	(propizepine or pyridobenzodiazepine or UP 106 or Vagran 50 or propizepine hydrochloride).ti,ab.	8
125	exp PROTRIPTYLINE/	0
126	(Vivactil or Protriptyline Hydrochloride).ti,ab.	6
127	quinupramine.ti,ab.	7
128	Reboxetine.ti,ab.	526
129	(Vestra or reboxetine mesylate).ti,ab.	2
130	exp TRIIODOTHYRONINE/	231
131	(T3 Thyroid Hormone or Liothyronine or Cytomel).ti,ab.	17
132	Sibutramine.ti,ab.	169
133	Symbyax.ti,ab.	9
134	Tianeptine.ti,ab.	258
135	(coaxil or Stablon).ti,ab.	9
136	exp TRIMIPRAMINE/	0
137	(Trimepramine or Herphonal or Trimineurin or Novo Tripramine or Nu Trimipramine or Rhotrimine or Stangyl or Surmontil or Surmontil Maleate or Trimidura or Trimineurin Maleate or Apo Trimip or Eldoral).ti,ab.	7
138	(ziprazidone or Geodon or CP 88059 or ziprasidone).ti,ab.	1271
139	Zotepine.ti,ab.	140
140	(Zoleptil or Nipolept).ti,ab.	1
141	Electroconvulsive Therapy/	0
142	Transcranial Magnetic Stimulation/	7544
143	(Electroconvulsive therapy or Repetitive transcranial magnetic stimulation or transcranial direct current stimulation).ti,ab.	9518

144	Cognitive Therapy/	13111
145	Repetitive transcranial magnetic stimulation.ti,ab.	2527
146	PSYCHOTHERAPY/	50655
147	Vagus Nerve Stimulation/	0
148	Magnetic seizure therapy.ti,ab.	105
149	Deep Brain Stimulation/	2726
150	Transcranial Direct Current Stimulation/	0
151	Behavioral activation.ti,ab.	1527
152	Interpersonal psychotherapy.ti,ab.	1249
153	(Electroconvulsive therapy or Repetitive transcranial magnetic stimulation or cognitive behavioral therapy or Psychotherapy or vagus nerve stimulation or Magnetic seizure therapy or deep brain stimulation or transcranial direct current stimulation or behavioral activation or Interpersonal psychotherapy).ti,ab.	107626
154	(imipramine or Imiprex or Elepsin).ti,ab.	4037
155	Pipofezine.ti,ab.	0
156	(adaptol or dixeran or melixeran or thymeol or trausabun).ti,ab.	6
157	or/21-156	196313
158	5 and 20 and 157	1808
159	**limit 158 to yr="1990 -Current"**	**1766**

Appendix C. TRANSFORM-3 and SUSTAIN-2 full results

TRANSFORM-3

Treatment exposure

Between Day 8 and Day 25 of the induction phase, on any given ESK-NS administration day, 9.7–13.6%, 12.3–50.0%, and 38.2–75.4% of patients were receiving ESK-NS doses of 28 mg, 56 mg, and 84 mg, respectively. (Beyond Day 15, no dose increases were permitted).

Primary efficacy outcome: Change in MADRS total score from baseline to the end of induction

Table 30. MADRS total score: Change from baseline to the end of induction (observed cases MMRM and LOCF ANCOVA; full analysis set)

	ESK-NS + OAD N=72	OAD + PBO-NS N=65
Baseline (observed cases)		
N	72	65
Mean (SD)	35.5 (5.91)	34.8 (6.44)
Day 28 (observed cases)		
N	63	60
Mean (SD)	25.4 (12.70)	28.7 (10.11)
Change from baseline to Day 28 (observed cases)		
N	63	60
Mean (SD)	–10.0 (12.74)	–6.3 (8.86)
MMRM (observed cases)[a]		
Difference in LS means (SE)	–3.6	-
95% CI	–7.20; –0.07	-
1-sided p-value	0.029	-
Baseline (LOCF)		
N	72	65
Mean (SD)	35.5 (5.91)	34.8 (6.44)
Endpoint of induction (LOCF)		
N	71	64
Mean (SD)	26.3 (12.29)	29.2 (10.06)
Change from baseline to endpoint of induction (LOCF)		

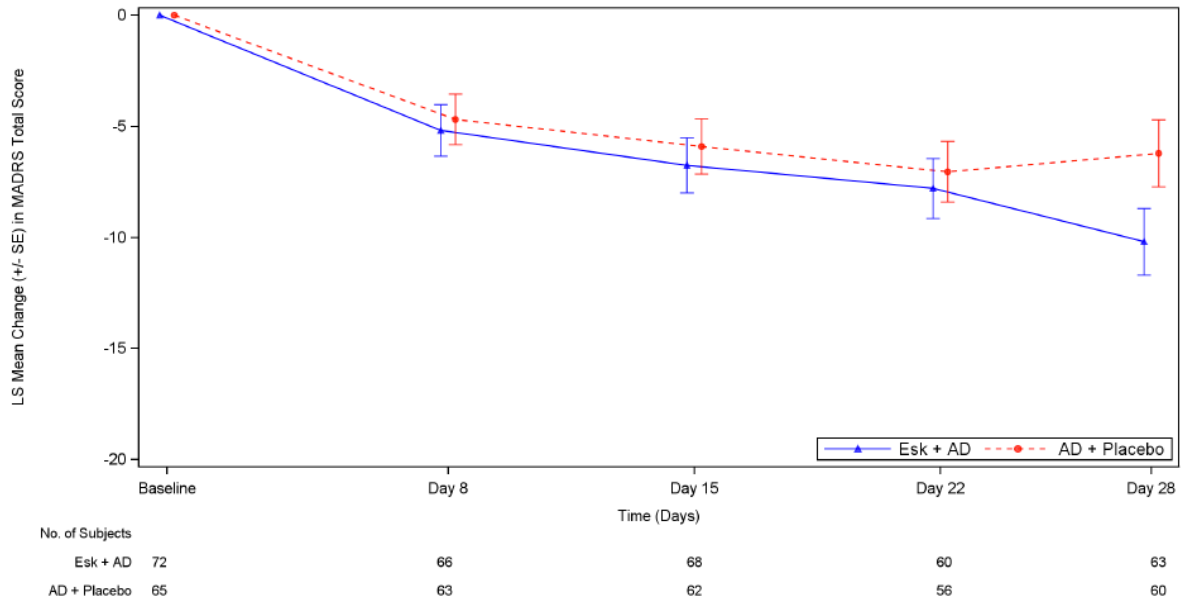
	ESK-NS + OAD N=72	OAD + PBO-NS N=65
N	71	64
Mean (SD)	–9.3 (12.28)	–5.6 (9.11)
ANCOVA (LOCF)[b]		
Difference in LS means	–3.6	-
95% CI	–7.16; –0.03	-
1-sided p-value	0.026	-

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; LOCF, last observation carried forward; LS, least squares; MADRS, Montgomery-Asberg Depression Rating Scale; MMRM, mixed-effects model using repeated measures; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; SD, standard deviation; SE, standard error; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
[a] Change from baseline was the response variable and fixed effect model terms for treatment, day, country, class of OAD (SNRI or SSRI), treatment-by-day, and baseline MADRS value were covariates.
[b] Change from baseline was the response variable and treatment, country, class of OAD (SNRI or SSRI), and baseline MADRS value were covariates.

Least squares mean change in MADRS total score over time

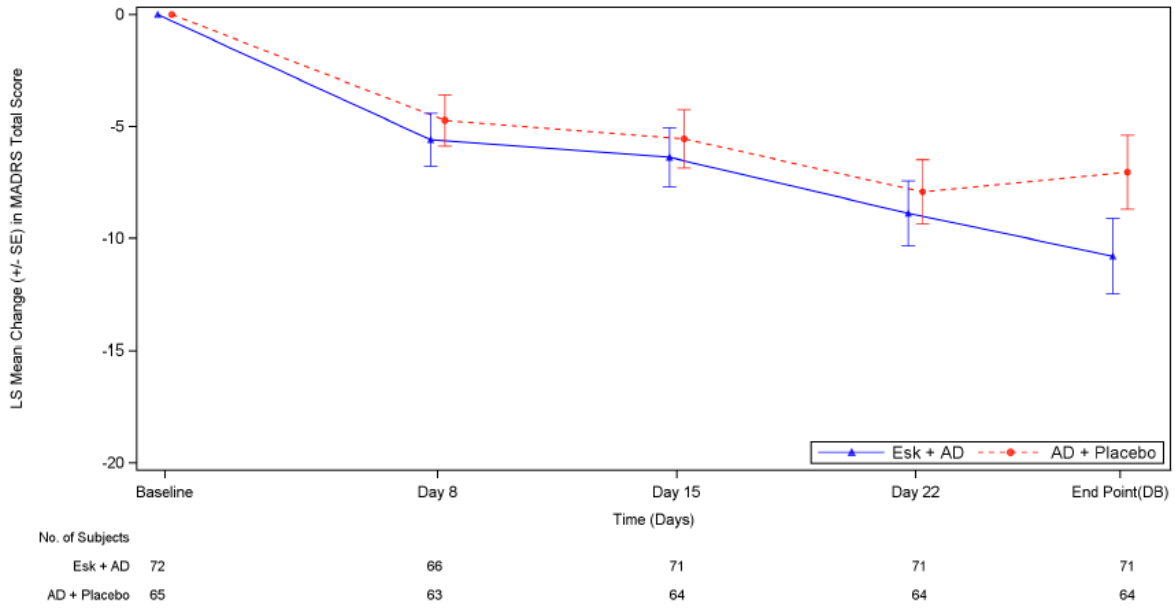
At Day 28/endpoint of induction, LS mean changes in MADRS total score favoured ESK-NS + OAD over OAD + PBO-NS based on observed cases (–4.0; MMRM; 1-sided p=0.018) and LOCF (–3.9; ANCOVA; 1-sided p=0.017).

Figure 7. LS mean (SE) changes in MADRS total score over time (observed cases MMRM; full analysis set)



Abbreviations: AD, antidepressant; ESK, esketamine nasal spray; LS, least squares; MADRS, Montgomery-Asberg Depression Rating Scale; MMRM, mixed-effects model using repeated measures; SE, standard error.
Note: Change from baseline was the response variable and fixed effect model terms for treatment, day, country, class of OAD (SNRI or SSRI), treatment-by-day, and baseline MADRS value were covariates.

Figure 8. LS mean (SE) changes in MADRS total score over time (LOCF ANCOVA; full analysis set)



Abbreviations: AD, antidepressant; ANCOVA, analysis of covariance; ESK, esketamine nasal spray; LOCF, last observation carried forward; LS, least squares; MADRS, Montgomery-Asberg Depression Rating Scale; OAD, oral antidepressant; SE, standard error; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
Note: Change from baseline was the response variable and treatment, country, class of OAD (SNRI or SSRI), and baseline MADRS value were covariates. Day 28 LOCF is the same as the end of induction.

Response and remission rates based on MADRS and SDS

Table 31. Response and remission rates over time based on MADRS and SDS

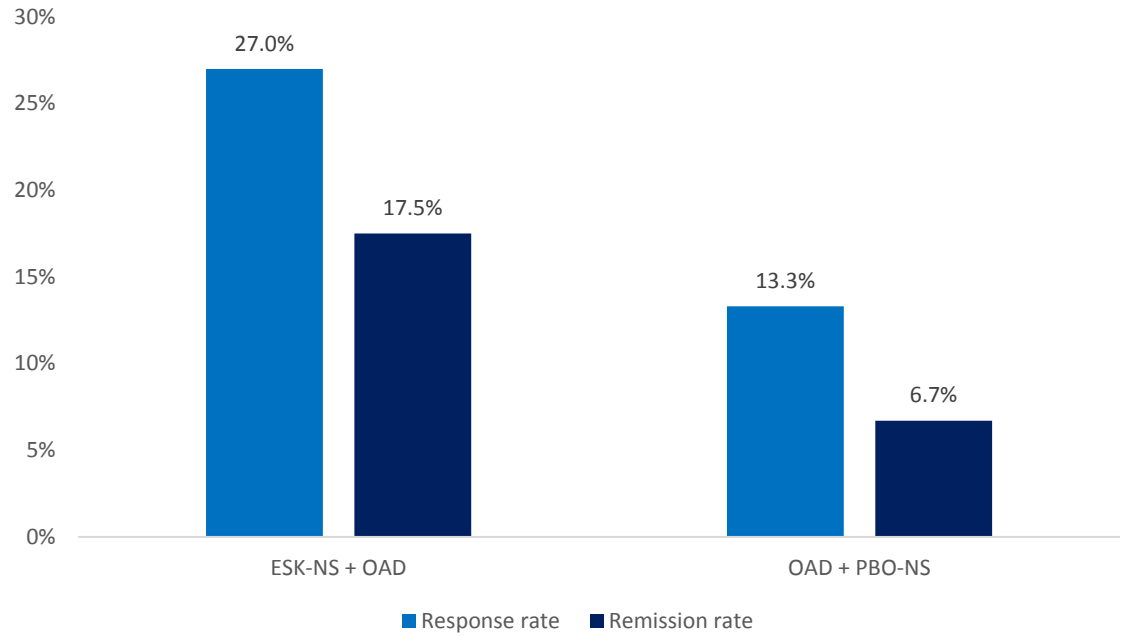
	ESK-NS + OAD N=72	OAD + PBO-NS N=65
Response rates over time based on MADRS		
Observed cases		
N	66	63
Responder at Day 8, n (%)	4 (6.1)	3 (4.8)
Observed cases		
N	68	62
Responder at Day 15, n (%)	4 (5.9)	8 (12.9)
Observed cases		
N	60	56
Responder at Day 22, n (%)	9 (15.0)	8 (14.3)
Observed cases		
N	63	60
Responder at Day 28, n (%)	17 (27.0)	8 (13.3)
LOCF		

	ESK-NS + OAD N=72	OAD + PBO-NS N=65
N	71	64
Responder at Day 15, n (%)	4 (5.6)	8 (12.5)
LOCF		
N	71	64
Responder at Day 22, n (%)	9 (12.7)	10 (15.6)
LOCF		
N	71	64
Responder at endpoint, n (%)	17 (23.9)	8 (12.5)
Remission rates over time based on MADRS		
Observed cases		
N	66	63
Remitter at Day 8, n (%)	4 (6.1)	1 (1.6)
Observed cases		
N	68	62
Remitter at Day 15, n (%)	2 (2.9)	5 (8.1)
Observed cases		
N	60	56
Remitter at Day 22, n (%)	4 (6.7)	4 (7.1)
Observed cases		
N	63	60
Remitter at Day 28, n (%)	11 (17.5)	4 (6.7)
LOCF		
N	71	64
Remitter at Day 15, n (%)	2 (2.8)	5 (7.8)
LOCF		
N	71	64
Remitter at Day 22, n (%)	4 (5.6)	5 (7.8)
LOCF		
N	71	64
Remitter at endpoint, n (%)	11 (15.5)	4 (6.3)
Response rates over time based on SDS		
N	28	30
Responder at Day 15, n (%)	6 (21.4)	9 (30.0)
N	44	44
Responder at Day 28, n (%)	15 (34.1)	10 (22.7)

	ESK-NS + OAD N=72	OAD + PBO-NS N=65
Remission rates over time based on SDS		
N	28	30
Remitter at Day 15, n (%)	3 (10.7)	2 (6.7)
N	44	44
Remitter at Day 28, n (%)	7 (15.9)	2 (4.5)

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; LOCF, last observation carried forward; MADRS, Montgomery-Asberg Depression Rating Scale; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; SDS, Sheehan Disability Scale.

Figure 9. Day 28 response and remission rates based on MADRS (observed cases)



Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; MADRS, Montgomery-Asberg Depression Rating Scale; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray.

Number needed to treat to achieve response and remission

The NNT (95% CI) to achieve response and remission, respectively, based on MADRS total score at Day 28 was 7.3 (–0.2; 14.8) and 9.3 (–0.4; 19)

Other secondary efficacy outcomes

Change in SDS total score from baseline to the end of induction

Table 32. SDS total score: Change from baseline to Day 28 (observed cases MMRM and LOCF ANCOVA; full analysis set)

	ESK-NS + OAD N=72	OAD + PBO-NS N=65
Baseline		
N	45	44
Mean (SD)	21.8 (5.90)	22.9 (4.74)
Day 28 (observed cases)		
N	36	37
Mean (SD)	14.3 (9.33)	19.2 (7.25)
Change from baseline to Day 28 (observed cases)		
N	29	85
Mean (SD)	–7.5 (8.24)	–3.8 (5.57)
MMRM (observed cases)[a]		
Difference in LS means (SE)	–4.6 (1.82)	-
95% CI	–8.21; –0.94)	-
1-sided p-value	0.007	-
Endpoint of induction (LOCF)		
N	44	44
Mean (SD)	15.5 (8.88)	18.2 (8.05)
Change from baseline to endpoint of induction (LOCF)		
N	35	36
Mean (SD)	–6.1 (8.35)	–3.8 (5.95)
ANCOVA (LOCF)[b]		
Difference in LS means (SE)	–2.8 (1.79)	-
95% CI	–6.39; 0.75	-
1-sided p-value	0.060	-

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; LOCF, last observation carried forward; LS, least squares; MMRM, mixed-effects model using repeated measures; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; SD, standard deviation; SDS, Sheehan Disability Scale; SE, standard error; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a] Change from baseline was the response variable and fixed effect model terms for treatment, day, country, class of OAD (SNRI or SSRI), treatment-by-day, and baseline SDS value were covariates.

[b] Change from baseline was the response variable and treatment, country, class of OAD (SNRI or SSRI), and baseline SDS value were covariates.

Change in PHQ-9 total score from baseline to the end of induction

Table 33. PHQ-9 total score: Change from baseline to Day 28 (observed cases MMRM and LOCF ANCOVA; full analysis set)

	ESK-NS + OAD N=72	OAD + PBO-NS N=65
Baseline		
N	72	65
Mean (SD)	17.6 (4.99)	17.4 (6.33)
Day 28 (observed cases)		
N	64	57
Mean (SD)	11.6 (7.04)	13.5 (6.81)
Change from baseline to Day 28 (observed cases)		
N	64	57
Mean (SD)	–6.4 (7.24)	–4.1 (6.36)
MMRM (observed cases)[a]		
Difference in LS means (SE)	–2.8 (1.16)	-
95% CI	–5.08; –0.48	-
1-sided p-value	0.009	-
End of induction (LOCF)		
N	69	61
Mean (SD)	11.9 (7.04)	14.2 (7.06)
Change from baseline to the end of induction (LOCF)		
N	69	61
Mean (SD)	–6.0 (7.17)	–3.3 (7.09)
ANCOVA (LOCF)[b]		
Difference in LS means (SE)	–2.7 (1.16)	-
95% CI	–5.02; –0.45	-
1-sided p-value	0.010	-

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; LOCF, last observation carried forward; LS, least squares; MMRM, mixed-effects model using repeated measures; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; SD, standard deviation; SE, standard error; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a] Change from baseline was the response variable and fixed effect model terms for treatment, day, country, class of OAD (SNRI or SSRI), treatment-by-day, and baseline PHQ-9 value were covariates.

[b] Change from baseline was the response variable and treatment, country, class of OAD (SNRI or SSRI), and baseline PHQ-9 value were covariates.

Change in CGI-S from baseline to the end of induction

Table 34. PHQ-9 total score: Change from baseline to Day 28 (observed cases MMRM and LOCF ANCOVA; full analysis set)

	ESK-NS + OAD N=72	OAD + PBO-NS N=65
Baseline		
N	72	65
Mean (SD)	5.1 (0.76)	4.8 (0.80)
Day 28 (observed cases)		
N	64	60
Mean (SD)	3.9 (1.33)	4.3 (1.20)
Change from baseline to Day 28 (observed cases)		
N	64	60
Mean (SD)	–1.2 (1.30)	–0.5 (1.03)
MMRM (observed cases)[a]		
Difference in LS means (SE)	–0.7 (0.21)	-
95% CI	–1.10; –0.27	-
1-sided p-value	<0.001	-
Baseline		
N	72	65
Median (range)	5.0 (3; 7)	5.0 (3; 6)
End of induction (LOCF)		
N	71	65
Median (range)	4.0 (1; 6)	5.0 (1; 7)
Change from baseline to the end of induction (LOCF; ANCOVA)		
N	71	65
Median (range)	–1.0 (–4; 1)	0.0 (–4; 3)
1-sided p-value[a,b]	<0.001	

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; LOCF, last observation carried forward; LS, least squares; MMRM, mixed-effects model using repeated measures; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; SD, standard deviation; SE, standard error; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a] Change from baseline was the response variable and fixed effect model terms for treatment, day, country, class of OAD (SNRI or SSRI), treatment-by-day, and baseline CGI-S value were covariates.

[b] p-value is descriptive and not inferential as there was no multiplicity adjustment to control type I error for this endpoint.

EQ-5D-5L

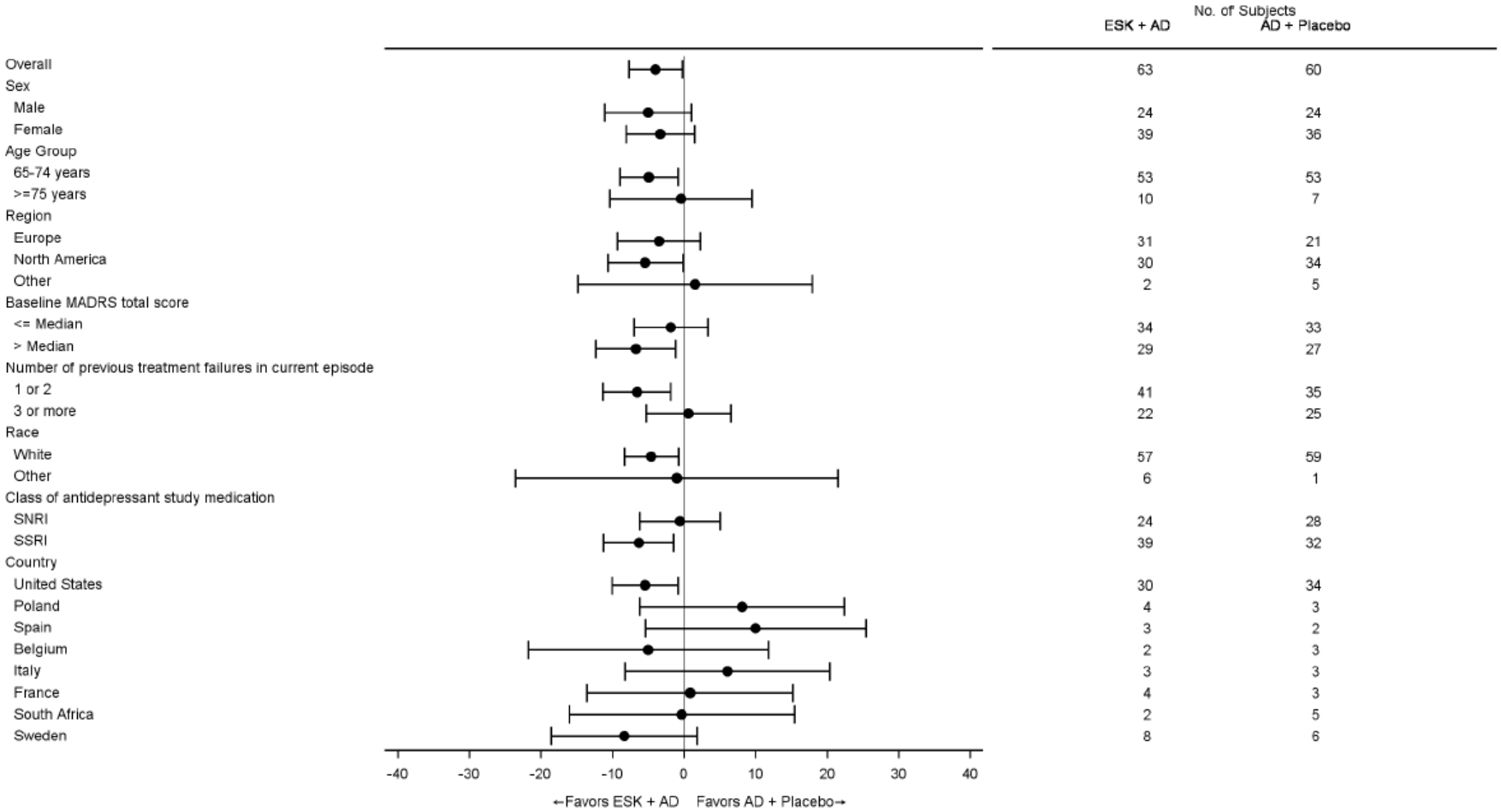
Table 35. EQ-5D-5L HSI score: Change from baseline to Day 28 (observed cases and LOCF, full analysis set)

	ESK-NS + OAD N=72	OAD + PBO-NS N=65
Baseline		
N	72	65
Mean (SD)	0.581 (0.2258)	0.635 (0.2276)
Day 28 (observed cases)		
N	65	59
Mean (SD)	0.658 (0.2608)	0.680 (0.1918)
Change from baseline to Day 28 (observed cases)		
N	65	59
Mean (SD) change	0.086 (0.2674)	0.041 (0.2074)
End of induction (LOCF)		
N	70	64
Mean (SD)	0.653 (0.2552)	0.657 (0.2113)
Change from baseline to end of induction (LOCF)		
N	70	105
Mean (SD) change	0.081 (0.2624)	0.026 (0.2235)

Abbreviations: EQ-5D-5L, EuroQol-5 Dimension-5 Level; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; HSI, health status index; LOCF, last observation carried forward; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; SD, standard deviation.

Subgroups

Figure 10. Forest plot of LS mean treatment difference (95% CI) in change in MADRS total score from baseline to Day 28 by subgroup (MMRM; full analysis set)



Abbreviations: AD, antidepressant; CI, confidence interval; ESK, esketamine; LS, least squares; MADRS, Montgomery-Asberg Depression Rating Scale; MMRM, mixed-effects model using repeated measures; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Table 36. MADRS total score: change from baseline to the end of induction by subgroup (observed cases MMRM and LOCF ANCOVA; full analysis set)

Subgroup	ESK-NS + OAD N=114	OAD + PBO-NS N=109
Gender		
Male		
Mean (SD) CFB to Day 28 (OC)	–10.3 (11.96) (n=24)	–5.5 (7.64) (n=24)
Diff in LS means (SE; 95% CI) (MMRM)[a]	–5.0 (3.05; –11.05, 1.03)	-
Mean (SD) CFB to endpoint (LOCF)	–9.3 (12.01) (n=26)	–4.5 (8.49) (n=25)
Diff in LS means (SE; 95% CI) (MMRM)[a]	–5.2 (2.98; –11.09, 0.69)	-
Female		
Mean (SD) CFB to Day 28 (OC)	–9.9 (13.34) (n=39)	–6.9 (9.65) (n=36)
Diff in LS means (SE; 95% CI) (MMRM)[a]	–3.4 (2.41; –8.14, 1.41)	-
Mean (SD) CFB to endpoint (LOCF)	–9.2 (12.57) (n=45)	–6.3 (9.54) (n=39)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	–3.1 (2.33; –7.75, 1.49)	-
Age group		
65–74 years		
Mean (SD) CFB to Day 28 (OC)	–10.9 (12.90) (n=53)	–6.2 (9.06) (n=53)
Diff in LS means (SE; 95% CI) (MMRM)[a]	–4.9 (2.04; –8.96, –0.89)	-
Mean (SD) CFB to endpoint (LOCF)	–10.2 (12.64) (n=58)	–5.6 (9.24) (n=56)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	–5.2 (1.99; –9.13, –1.26)	-
≥75 years		
Mean (SD) CFB to Day 28 (OC)	–5.1 (11.14) (n=10)	–7.0 (7.72) (n=7)
Diff in LS means (SE; 95% CI) (MMRM)[a]	–0.4 (5.02; –10.38, 9.50)	-
Mean (SD) CFB to endpoint (LOCF)	–5.1 (9.91) (n=13)	–5.3 (8.78) (n=8)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	1.3 (4.72; –8.05, 10.62)	-
Region		
Europe		
Mean (SD) CFB to Day 28 (OC)	–7.8 (12.94) (n=31)	–4.7 (7.75) (n=21)
Diff in LS means (SE; 95% CI) (MMRM)[a]	–3.5 (2.94; –9.30, 2.31)	-
Mean (SD) CFB to endpoint (LOCF)	–7.1 (12.44) (n=35)	–2.9 (8.48) (n=24)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	–3.5 (2.81; –9.04, 2.10)	-
North America		
Mean (SD) CFB to Day 28 (OC)	–12.2 (12.70) (n=30)	–6.6 (8.88) (n=34)
Diff in LS means (SE; 95% CI) (MMRM)[a]	–5.4 (2.64; –10.65, –0.19)	-

Subgroup	ESK-NS + OAD N=114	OAD + PBO-NS N=109
Mean (SD) CFB to endpoint (LOCF)	–11.5 (12.35) (n=33)	–6.6 (8.67) (n=35)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	–5.0 (2.57; –10.03, 0.13)	-
Other		
Mean (SD) CFB to Day 28 (OC)	–11.5 (7.78) (n=2)	–11.6 (12.56) (n=5)
Diff in LS means (SE; 95% CI) (MMRM)[a]	1.5 (8.26; –14.81, 17.89)	
Mean (SD) CFB to endpoint (LOCF)	–10.3 (5.86) (n=3)	–11.6 (12.56) (n=5)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	1.8 (7.73; –13.47, 17.12)	
Baseline MADRS total score		
≤36		
Mean (SD) CFB to Day 28 (OC)	–8.2 (10.04) (n=34)	–7.2 (9.95) (n=33)
Diff in LS means (SE; 95% CI) (MMRM)[a]	–1.9 (2.60; –6.99, 3.28)	-
Mean (SD) CFB to endpoint (LOCF)	–7.5 (10.03) (n=37)	–6.0 (10.29) (n=36)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	–2.1 (2.53; –7.16, 2.87)	-
>36		
Mean (SD) CFB to Day 28 (OC)	–12.1 (15.23) (n=29)	–5.3 (7.37) (n=27)
Diff in LS means (SE; 95% CI) (MMRM)[a]	–6.8 (2.83; –12.36, –1.16)	-
Mean (SD) CFB to endpoint (LOCF)	–11.3 (14.23) (n=34)	–5.0 (7.48) (n=28)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	–6.6 (2.75; –12.05, –1.16)	-
Number of previous treatment failures in the current episode of depression (induction phase)		
2		
Mean (SD) CFB to Day 28 (OC)	–12.3 (14.15) (n=41)	–6.1 (8.39) (n=35)
Diff in LS means (SE; 95% CI) (MMRM)[a]	–6.6 (2.38; –11.31, –1.87)	-
Mean (SD) CFB to Day 28 (LOCF)	–11.9 (13.52) (n=45)	–5.1 (8.92) (n=37)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	–6.2 (2.32; –10.74, –1.56)	-
≥3		
Mean (SD) CFB to Day 28 (OC)	–5.8 (8.32) (n=22)	–6.7 (9.65) (n=25)
Diff in LS means (SE; 95% CI) (MMRM)[a]	0.6 (3.00; –5.30, 6.57)	-
Mean (SD) CFB to Day 28 (LOCF)	–4.7 (8.18) (n=26)	–6.2 (9.50) (n=27)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	–0.0 (2.91; –5.78, 5.73)	-
Race		

Subgroup	ESK-NS + OAD N=114	OAD + PBO-NS N=109
White		
Mean (SD) CFB to Day 28 (OC)	–10.8 (12.92) (n=57)	–6.4 (8.92) (n=59)
Diff in LS means (SE; 95% CI) (MMRM)[a]	–4.6 (1.91; –8.35, –0.79)	-
Mean (SD) CFB to endpoint (LOCF)	–9.9 (12.45) (n=65)	–5.7 (9.18) (n=63)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	–4.5 (1.85; –8.15, –0.81)	-
Other		
Mean (SD) CFB to Day 28 (OC)	–2.2 (7.78) (n=6)	–2.0 (-) (n=1)
Diff in LS means (SE; 95% CI) (MMRM)[a]	–1.0 (11.37; –23.53, 21.48)	-
Mean (SD) CFB to endpoint (LOCF)	–2.2 (7.78) (n=6)	–2.0 (-) (n=1)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	–2.1 (11.29; –24.43, 20.25)	-
Class of OAD		
SNRI		
Mean (SD) CFB to Day 28 (OC)	–7.9 (11.79) (n=24)	–7.6 (8.79) (n=28)
Diff in LS means (SE; 95% CI) (MMRM)[a]	–0.6 (2.86; –6.27, 5.06)	-
Mean (SD) CFB to endpoint (LOCF)	–6.9 (10.95) (n=30)	–6.7 (9.65) (n=29)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	–0.8 (2.73; –6.22, 4.60)	-
SSRI		
Mean (SD) CFB to Day 28 (OC)	–11.3 (13.31) (n=39)	–5.2 (8.90) (n=32)
Diff in LS means (SE; 95% CI) (MMRM)[a]	–6.4 (2.50; –11.30, –1.41)	-
Mean (SD) CFB to endpoint (LOCF)	–11.0 (13.02) (n=41)	–4.7 (8.68) (n=35)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	–6.4 (2.44; –11.24, –1.59)	-
Country		
United States		
Mean (SD) CFB to Day 28 (OC)	–12.2 (12.70) (n=30)	–6.6 (8.88) (n=34)
Diff in LS means (SE; 95% CI) (MMRM)[a]	–5.4 (2.33; –10.07, –0.81)	-
Mean (SD) CFB to endpoint (LOCF)	–24.8 (13.25) (n=29)	–21.8 (15.34) (n=28)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	–3.7 (3.21; –10.00, 2.65)	-
South Africa		
Mean (SD) CFB to Day 28 (OC)	–11.5 (7.78) (n=2)	–11.6 (12.56) (n=5)
Diff in LS means (SE; 95% CI) (MMRM)[a]	–0.3 (7.93; –16.03, 15.42)	-
Mean (SD) CFB to endpoint (LOCF)	–11.5 (7.78) (n=2)	–11.6 (12.56) (n=5)

Subgroup	ESK-NS + OAD N=114	OAD + PBO-NS N=109
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	–0.4 (7.88; –16.03, 15.23)	-
Sweden		
Mean (SD) CFB to Day 28 (OC)	–9.3 (13.16) (n=8)	–0.2 (4.07) (n=6)
Diff in LS means (SE; 95% CI) (MMRM)[a]	–8.4 (5.13; –18.55, 1.77)	-
Mean (SD) CFB to endpoint (LOCF)	–9.3 (13.16) (n=8)	0.2 (3.66) (n=6)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	–7.8 (5.10; –17.96, 2.26)	-
United Kingdom		
Mean (SD) CFB to Day 28 (OC)	–11.0 (-) (n=1)	- (n=0)
Diff in LS means (SE; 95% CI) (MMRM)[a]	-	-
Mean (SD) CFB to endpoint (LOCF)	–11.0 (-) (n=1)	- (n=0)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	-	-
Finland		
Mean (SD) CFB to Day 28 (OC)	–22.0 (-) (n=1)	–22.0 (-) (n=1)
Diff in LS means (SE; 95% CI) (MMRM)[a]	0.3 (13.38; –26.25, 26.78)	-
Mean (SD) CFB to endpoint (LOCF)	–22.0 (-) (n=1)	–22.0 (-) (n=1)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	0.5 (13.27; –25.76, 26.85)	-
Brazil		
Mean (SD) CFB to Day 28 (OC)	- (n=0)	- (n=0)
Diff in LS means (SE; 95% CI) (MMRM)[a]	-	-
Mean (SD) CFB to endpoint (LOCF)	–8.0 (-) (n=1)	- (n=0)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	-	-
Poland		
Mean (SD) CFB to Day 28 (OC)	0.5 (2.08) (n=4)	–7.3 (3.21) (n=3)
Diff in LS means (SE; 95% CI) (MMRM)[a]	8.1 (7.23; –6.23, 22.43)	-
Mean (SD) CFB to endpoint (LOCF)	–18.7 (12.90) (n=44)	–13.5 (13.31) (n=44)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	–4.6 (2.58; –9.72, 0.46)	-
Spain		
Mean (SD) CFB to Day 28 (OC)	–1.0 (4.58) (n=3)	–14.5 (9.19) (n=2)
Diff in LS means (SE; 95% CI) (MMRM)[a]	10.0 (7.76; –5.40, 25.38)	-
Mean (SD) CFB to endpoint (LOCF)	–0.8 (3.77) (n=4)	–3.3 (14.13) (n=4)

Subgroup	ESK-NS + OAD N=114	OAD + PBO-NS N=109
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	6.2 (6.71; –7.11, 19.50)	-
Belgium		
Mean (SD) CFB to Day 28 (OC)	–5.5 (2.12) (n=2)	–1.3 (11.59) (n=3)
Diff in LS means (SE; 95% CI) (MMRM)[a]	–5.0 (8.46; –21.78, 11.76)	-
Mean (SD) CFB to endpoint (LOCF)	–5.5 (2.12) (n=2)	–0.5 (9.61) (n=4)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	–4.0 (8.18; –20.24, 12.18)	-
Italy		
Mean (SD) CFB to Day 28 (OC)	2.3 (2.31) (n=3)	–4.0 (4.36) (n=3)
Diff in LS means (SE; 95% CI) (MMRM)[a]	6.1 (7.22; –8.26, 20.38)	-
Mean (SD) CFB to endpoint (LOCF)	0.3 (4.97) (n=6)	–0.7 (8.50) (n=3)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	0.6 (6.67; –12.57, 13.85)	-
France		
Mean (SD) CFB to Day 28 (OC)	–0.8 (3.40) (n=4)	–3.0 (3.61) (n=3)
Diff in LS means (SE; 95% CI) (MMRM)[a]	0.8 (7.25; –13.53, 15.20)	-
Mean (SD) CFB to endpoint (LOCF)	–0.8 (3.40) (n=4)	–3.0 (3.61) (n=3)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	–0.7 (7.21; –14.96, 13.63)	-
Bulgaria		
Mean (SD) CFB to Day 28 (OC)	–35.3 (9.87) (n=3)	- (n=0)
Diff in LS means (SE; 95% CI) (MMRM)[a]	-	-
Mean (SD) CFB to endpoint (LOCF)	–35.3 (9.87) (n=3)	- (n=0)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	-	-
Lithuania		
Mean (SD) CFB to Day 28 (OC)	–10.5 (7.78) (n=2)	- (n=0)
Diff in LS means (SE; 95% CI) (MMRM)[a]	-	-
Mean (SD) CFB to endpoint (LOCF)	–10.5 (7.78) (n=2)	- (n=0)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	-	-

Abbreviations: ANCOVA; analysis of covariance; CFB, change from baseline; CI, confidence interval; Diff, difference; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; LS, least squares; MADRS, Montgomery-Asberg Depression Rating Scale; MMRM, mixed-effects model using repeated measures; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; OC, observed cases; SD, standard deviation; SDS, Sheehan Disability Scale; SE, standard error; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a] Change from baseline was the response variable and the fixed effect model terms for treatment, day, country, class of OAD (SNRI or SSRI), defined subgroup, treatment-by-day, treatment-by-sex, treatment-by-day-by-sex, and baseline value were covariates.

[b] Change from baseline was the response variable and treatment, country, class of OAD (SNRI or SSRI), treatment-by-defined subgroup, and baseline MADRS value were covariates.

Overall summary of AEs

Table 37. Overall summary of AEs reported during the induction (safety analysis set) and follow-up (follow-up analysis set) phases of TRANSFORM-3

	ESK-NS + OAD	OAD + PBO-NS
Induction phase, n (%)	**N=72**	**N=65**
AE	51 (70.8)	39 (60.0)
AE possibly related to nasal spray drug[a]	42 (58.3)	22 (33.8)
AE possibly related to OAD[a]	13 (18.1)	11 (16.9)
AE leading to death	0	0
≥1 serious AE	3 (4.2)	2 (3.1)
AE leading to nasal spray drug being withdrawn[b]	4 (5.6)	2 (3.1)
AE leading to OAD being withdrawn[b]	1 (1.4)	1 (1.5)
Follow-up phase, n (%)	**N=12**	**N=3**
AE	1 (8.3)	1 (33.3)
AE possibly related to nasal spray drug[a]	0	1 (33.3)
AE possibly related to OAD[a]	1 (8.3)	0
AE leading to death	0	0
≥1 serious AE	0	0
AE leading to OAD being withdrawn[b]	0	0

Abbreviations: AE, adverse event; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; MedDRA, Medical Dictionary for Regulatory Activities; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray.
[a] Study drug relationships of possible, probable, and very likely were included in this category.
[b] An AE that started in the double-blind induction phase and resulted in discontinuation in the follow-up phase was counted as treatment-emergent in the double-blind induction phase.
Note: Incidence was based on the number of patients experiencing ≥1 AE, not the number of events.
Note: AEs were coded using MedDRA version 20.0.

AEs reported in ≥5% of patients

Table 38. AEs reported in ≥5% of patients (safety analysis set) during the induction phase of TRANSFORM-3

	ESK-NS + OAD (N=72)	OAD + PBO-NS (N=65)
Total number of patients with an AE, n (%)	51 (70.8)	39 (60.0)
Psychiatric disorders, n (%)	26 (36.1)	11 (16.9)
Dissociation	9 (12.5)	1 (1.5)
Dysphoria	4 (5.6)	0

	ESK-NS + OAD (N=72)	OAD + PBO-NS (N=65)
Insomnia	4 (5.6)	3 (4.6)
Anxiety	2 (2.8)	5 (7.7)
Nervous system disorders, n (%)	24 (33.3)	16 (35.8)
Dizziness	15 (20.8)	5 (7.7)
Headache	9 (12.5)	2 (3.1)
Dysgeusia	4 (5.6)	3 (4.6)
Hypoaesthesia	4 (5.6)	1 (1.5)
Paraesthesia	4 (5.6)	2 (3.1)
Gastrointestinal disorders, n (%)	19 (26.4)	8 (12.3)
Nausea	13 (18.1)	3 (4.6)
Hypoaesthesia oral	4 (5.6)	0
Vomiting	4 (5.6)	1 (1.5)
General disorders and administration site conditions, n (%)	14 (19.4)	8 (12.3)
Fatigue	9 (12.5)	5 (7.7)
Investigations, n (%)	14 (19.4)	6 (9.2)
Blood pressure increased	9 (12.5)	3 (4.6)
Ear and labyrinth disorders, n (%)	10 (13.9)	4 (6.2)
Vertigo	8 (11.1)	2 (3.1)
Infections and infestations, n (%)	8 (11.1)	6 (9.2)
Urinary tract infections	6 (8.3)	1 (1.5)

Abbreviations: AE, adverse event; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; MedDRA, Medical Dictionary for Regulatory Activities; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray.
Note: Incidence was based on the number of patients experiencing ≥1 AE, not the number of events.
Note: AEs were coded using MedDRA version 20.0.

SUSTAIN-2

Treatment exposure

The final esketamine dose in the optimisation/maintenance phase was evenly distributed among the patients in the 56 mg and 84 mg dose groups (56 mg in 45.6% of patients [275] and 84 mg in 50.2% of patients [303]). In addition, 4.0% of patients received 28 mg.

Change in MADRS total score from baseline to the end of the induction and optimisation/maintenance phases

Table 39. MADRS total score: Change from baseline to the end of induction (LOCF; full [IND] analysis set) and optimisation/maintenance phases (LOCF; full [OP/MA] analysis set)

	ESK-NS + OAD N=779 in full (IND) analysis set N=603 in full (OP/MA) analysis set
Baseline (IND)	
N	779
Mean (SD)	31.2 (5.29)
Endpoint of induction	
N	756
Mean (SD)	14.8 (8.83)
Change from baseline to endpoint of induction	
N	756
Mean (SD)	–16.4 (8.76)
Baseline (OP/MA)	
N	603
Mean (SD)	11.0 (4.52)
Endpoint of OP/MA	
N	603
Mean (SD)	11.3 (7.87)
Change from baseline to endpoint of OP/MA	
N	603
Mean (SD)	0.3 (8.12)

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; IND, induction phase; LOCF, last observation carried forward; MA, maintenance phase; MADRS, Montgomery-Asberg Depression Rating Scale; OP, optimisation phase; SD, standard deviation.

Response and remission rates based on MADRS and SDS

Response and remission rates (based on MADRS and SDS) over the course of the induction phase of SUSTAIN-2 are presented in Table 40.

For response and remission rates over the course of the optimisation/maintenance phase of SUSTAIN-2, please see the following attachments in the CSR for TRANSFORM-3 (supplied in the company submission reference pack):

- Attachment TEFMADRP01B (response based on MADRS)

- Attachment TEFMADRM01B (remission based on MADRS)
- Attachment TEFSDSRP01B (response based on SDS)
- Attachment TEFSDSRM01B (remission based on SDS)

Briefly, at Week 1 and at the endpoint of the optimisation/maintenance phase:

- Based on MADRS:
  - 88.0% and 76.5% of patients, respectively, were in response (LOCF)
  - 55.7% and 58.2% of patients, respectively, were in remission (LOCF)
- Based on SDS:
  - 59.5% and 63.0% of patients, respectively, were in response (LOCF)
  - 25.2% and 39.5% of patients, respectively, were in remission (LOCF)

Table 40. Response and remission rates over time (induction phase) based on MADRS and SDS (full [IND] analysis set)

	ESK-NS + OAD N=779
Response rates over time based on MADRS	
Observed cases N Responder at Day 8, n (%)	 739 86 (11.6)
Observed cases N Responder at Day 15, n (%)	 702 185 (26.4)
Observed cases N Responder at Day 22, n (%)	 683 312 (45.7)
Observed cases N Responder at Day 28, n (%)	 688 581 (84.4)
LOCF N Responder at Day 8, n (%)	 739 86 (11.6)
LOCF N Responder at Day 15, n (%)	 751 188 (25.0)
LOCF N	 753

	ESK-NS + OAD N=779
Responder at Day 22, n (%)	322 (42.8)
LOCF	
N	756
Responder at endpoint, n (%)	593 (78.4)
Remission rates over time based on MADRS	
Observed cases	
N	739
Remitter at Day 8, n (%)	54 (7.3)
Observed cases	
N	702
Remitter at Day 15, n (%)	115 (16.4)
Observed cases	
N	683
Remitter at Day 22, n (%)	199 (29.1)
Observed cases	
N	688
Remitter at Day 28, n (%)	349 (50.7)
LOCF	
N	739
Remitter at Day 8, n (%)	54 (7.3)
LOCF	
N	751
Remitter at Day 15, n (%)	117 (15.6)
LOCF	
N	753
Remitter at Day 22, n (%)	205 (27.2)
LOCF	
N	756
Remitter at endpoint, n (%)	357 (47.2)
Response rates over time based on SDS	
Observed cases	
N	570
Responder at Day 15, n (%)	141 (24.7)
Observed cases	
N	571

	ESK-NS + OAD N=779
Responder at Day 28, n (%)	295 (51.7)
LOCF N Responder at Day 15, n (%)	 570 141 (24.7)
LOCF N Responder at endpoint, n (%)	 648 310 (47.8)
Remission rates over time based on SDS	
Observed cases N Remission at Day 15, n (%)	 570 52 (9.1)
Observed cases N Remission at Day 28, n (%)	 571 132 (23.1)
LOCF N Remission at Day 15, n (%)	 570 52 (9.1)
LOCF N Remission at endpoint, n (%)	 648 137 (21.1)

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; IND, induction phase; LOCF, last observation carried forward; MADRS, Montgomery-Asberg Depression Rating Scale; SDS, Sheehan Disability Scale.

Change in SDS total score from baseline to the end of the induction and optimisation/maintenance phases

Table 41. SDS total score: Change from baseline to the end of induction (LOCF; full [IND] analysis set) and optimisation/maintenance phases (LOCF; full [OP/MA] analysis set)

	ESK-NS + OAD N=779 in full (IND) analysis set N=603 in full (OP/MA) analysis set
Baseline (IND) N Mean (SD)	 709 22.2 (5.45)
Endpoint of induction	

	ESK-NS + OAD N=779 in full (IND) analysis set N=603 in full (OP/MA) analysis set
N	648
Mean (SD)	12.8 (7.89)
Change from baseline to endpoint of induction	
N	626
Mean (SD)	–9.3 (7.86)
Baseline (OP/MA)	
N	564
Mean (SD)	11.3 (7.27)
Endpoint of OP/MA	
N	557
Mean (SD)	9.5 (7.89)
Change from baseline to endpoint of OP/MA	
N	541
Mean (SD)	–1.6 (8.25)

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; IND, induction phase; LOCF, last observation carried forward; MA, maintenance phase; OP, optimisation phase; SD, standard deviation; SDS, Sheehan Disability Scale.

Change in PHQ-9 total score from baseline to the end of the induction and optimisation/maintenance phases

Table 42. PHQ-9 total score: Change from baseline to the end of induction (LOCF; full [IND] analysis set) and optimisation/maintenance phases (LOCF; full [OP/MA] analysis set)

	ESK-NS + OAD N=779 in full (IND) analysis set N=603 in full (OP/MA) analysis set
Baseline (IND)	
N	779
Mean (SD)	17.3 (5.00)
Endpoint of induction	
N	746
Mean (SD)	8.4 (5.80)
Change from baseline to endpoint of induction	
N	746
Mean (SD)	–8.9 (6.67)
Baseline (OP/MA)	

	ESK-NS + OAD N=779 in full (IND) analysis set N=603 in full (OP/MA) analysis set
N	603
Mean (SD)	6.5 (4.23)
Endpoint of OP/MA	
N	603
Mean (SD)	6.3 (5.33)
Change from baseline to endpoint of OP/MA	
N	603
Mean (SD)	–0.2 (5.65)

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; IND, induction phase; LOCF, last observation carried forward; MA, maintenance phase; OP, optimisation phase; PHQ-9, Patient Health Questionnaire – 9 questions; SD, standard deviation.

Change in CGI-S total score from baseline to the end of the induction and optimisation/maintenance phases

Table 43. CGI-S total score: Change from baseline to the end of induction (LOCF; full [IND] analysis set) and optimisation/maintenance phases (LOCF; full [OP/MA] analysis set)

	ESK-NS + OAD N=779 in full (IND) analysis set N=603 in full (OP/MA) analysis set
Baseline (IND)	
N	779
Median (range)	5.0 (1; 7)
Endpoint of induction	
N	763
Median (range)	3.0 (1; 7)
Change from baseline to endpoint of induction	
N	763
Median (range)	–2.0 (–6; 2)
Baseline (OP/MA)	
N	603
Median (range)	3.0 (1; 6)
Endpoint of OP/MA	
N	603
Median (range)	3.0 (1; 6)
Change from baseline to endpoint of OP/MA	

	ESK-NS + OAD N=779 in full (IND) analysis set N=603 in full (OP/MA) analysis set
N	603
Median (range)	0.0 (–3; 4)

Abbreviations: CGI-S, Clinical Global Impression – Severity; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; IND, induction phase; LOCF, last observation carried forward; MA, maintenance phase; OP, optimisation phase.

Change in GAD-7 total score from baseline to the end of the induction and optimisation/maintenance phases

Table 44. GAD-7 total score: Change from baseline to the end of induction (LOCF; full [IND] analysis set) and optimisation/maintenance phases (LOCF; full [OP/MA] analysis set)

	ESK-NS + OAD N=779 in full (IND) analysis set N=603 in full (OP/MA) analysis set
Baseline (IND)	
N	771
Mean (SD)	11.3 (5.45)
Endpoint of induction	
N	732
Mean (SD)	5.3 (1; 7)
Change from baseline to endpoint of induction	
N	724
Mean (SD)	–5.9 (5.85)
Baseline (OP/MA)	
N	580
Mean (SD)	4.2 (3.69)
Endpoint of OP/MA	
N	597
Mean (SD)	4.4 (4.39)
Change from baseline to endpoint of OP/MA	
N	574
Mean (SD)	0.2 (4.23)

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; GAD-7, Generalised Anxiety Disorder – 7-item scale; IND, induction phase; LOCF, last observation carried forward; MA, maintenance phase; OP, optimisation phase; SD, standard deviation.

EQ-5D-5L

Table 45. EQ-5D-5L HSI score: Change from baseline to the end of induction (LOCF; full [IND] analysis set) and optimisation/maintenance phases (LOCF; full [OP/MA] analysis set)

	ESK-NS + OAD N=779 in full (IND) analysis set N=603 in full (OP/MA) analysis set
Baseline (IND)	
N	779
Mean (SD)	0.601 (0.2056)
Endpoint of induction	
N	745
Mean (SD)	0.792 (0.1725)
Change from baseline to endpoint of induction	
N	745
Mean (SD)	0.190 (0.2138)
Baseline (OP/MA)	
N	603
Mean (SD)	0.838 (0.1185)
Endpoint of OP/MA	
N	603
Mean (SD)	0.829 (0.1517)
Change from baseline to endpoint of OP/MA	
N	603
Mean (SD)	–0.009 (0.1411)

Abbreviations: EQ-5D-5L, EuroQol-5 Dimension-5 Level; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; IND, induction phase; LOCF, last observation carried forward; MA, maintenance phase; OP, optimisation phase; SD, standard deviation.

Subgroups

Table 46. MADRS total score: change from baseline to the end of induction (LOCF; full [IND] analysis set) and optimisation/maintenance phases (LOCF; full [OP/MA] analysis set)

Subgroup	**ESK-NS + OAD N=779 in full (IND) analysis set N=603 in full (OP/MA) analysis set**
Induction phase	
Gender	
Male	

Subgroup	ESK-NS + OAD N=779 in full (IND) analysis set N=603 in full (OP/MA) analysis set
Mean (SD) CFB to endpoint (IND)	–15.8 (9.21) (n=283)
Female Mean (SD) CFB to endpoint (IND)	–16.7 (8.48) (n=473)
Age group	
18–44 years Mean (SD) CFB to endpoint (IND)	–17.5 (8.15) (n=218)
45–64 years Mean (SD) CFB to endpoint (IND)	–16.1 (8.81) (n=386)
65–74 years Mean (SD) CFB to endpoint (IND)	–15.0 (9.35) (n=135)
≥75 years Mean (SD) CFB to endpoint (IND)	–18.4 (9.35) (n=17)
Baseline MADRS total score	
≤31 Mean (SD) CFB to endpoint (IND)	–14.8 (7.90) (n=431)
>31 Mean (SD) CFB to endpoint (IND)	–18.4 (9.41) (n=325)
Number of previous treatment failures in the current episode of depression (induction phase)	
2 Mean (SD) CFB to endpoint (IND)	–17.1 (8.20) (n=450)
≥3 Mean (SD) CFB to endpoint (IND)	–15.4 (9.46) (n=306)
Baseline (IND) functional impairment (SDS)	
Not impaired (0–3) Mean (SD) CFB to endpoint (IND)	–10.3 (9.56) (n=6)
Mild (4–11) Mean (SD) CFB to endpoint (IND)	–14.6 (8.78) (n=27)
Moderate (12–19) Mean (SD) CFB to endpoint (IND)	–14.2 (9.40) (n=142)
Marked (20–26) Mean (SD) CFB to endpoint (IND)	–17.5 (8.02) (n=365)
Extreme (27–30) Mean (SD) CFB to endpoint (IND)	–16.2 (9.79) (n=147)

Subgroup	ESK-NS + OAD N=779 in full (IND) analysis set N=603 in full (OP/MA) analysis set
Race	
Black Mean (SD) CFB to endpoint (IND)	–19.3 (9.63) (n=15)
White Mean (SD) CFB to endpoint (IND)	–16.3 (8.66) (n=641)
Other Mean (SD) CFB to endpoint (IND)	–16.1 (9.28) (n=100)
Class of OAD	
SNRI Mean (SD) CFB to endpoint (IND)	–17.2 (8.30) (n=390)
SSRI Mean (SD) CFB to endpoint (IND)	–15.6 (9.14) (n=365)
Dose of ESK-NS	
28 mg Mean (SD) CFB to endpoint (IND)	–16.6 (7.95) (n=37)
56 mg Mean (SD) CFB to endpoint (IND)	–17.0 (8.26) (n=328)
84 mg Mean (SD) CFB to endpoint (IND)	–16.8 (8.56) (n=368)
Optimisation/maintenance phase	
Gender	
Male Mean (SD) CFB (OP/MA) to endpoint (OP/MA)	0.5 (8.24) (n=219)
Female Mean (SD) CFB (OP/MA) to endpoint (OP/MA)	0.2 (8.06) (n=384)
Age group	
18–44 years Mean (SD) CFB (OP/MA) to endpoint (OP/MA)	–0.2 (7.24) (n=183)
45–64 years Mean (SD) CFB (OP/MA) to endpoint (OP/MA)	0.1 (8.05) (n=294)
65–74 years Mean (SD) CFB (OP/MA) to endpoint (OP/MA)	1.6 (8.85) (n=113)
≥75 years Mean (SD) CFB (OP/MA) to endpoint (OP/MA)	3.3 (12.95) (n=13)

Subgroup	ESK-NS + OAD N=779 in full (IND) analysis set N=603 in full (OP/MA) analysis set
Baseline MADRS total score	
≤31 Mean (SD) CFB (OP/MA) to endpoint (OP/MA)	0.4 (7.24) (n=348)
>31 Mean (SD) CFB (OP/MA) to endpoint (OP/MA)	0.2 (9.20) (n=255)
Number of previous treatment failures in the current episode of depression (induction phase)	
2 Mean (SD) CFB (OP/MA) to endpoint (OP/MA)	–0.1 (7.71) (n=375)
≥3 Mean (SD) CFB (OP/MA) to endpoint (OP/MA)	1.1 (8.72) (n=228)
Baseline (IND) functional impairment (SDS)	
Not impaired (0–3) Mean (SD) CFB (OP/MA) to endpoint (OP/MA)	–0.3 (8.26) (n=4)
Mild (4–11) Mean (SD) CFB (OP/MA) to endpoint (OP/MA)	0.7 (7.88) (n=22)
Moderate (12–19) Mean (SD) CFB (OP/MA) to endpoint (OP/MA)	–0.4 (7.61) (n=105)
Marked (20–26) Mean (SD) CFB (OP/MA) to endpoint (OP/MA)	–0.2 (7.63) (n=314)
Extreme (27–30) Mean (SD) CFB (OP/MA) to endpoint (OP/MA)	3.3 (9.12) (n=95)
Race	
Black Mean (SD) CFB (OP/MA) to endpoint (OP/MA)	–0.3 (5.19) (n=13)
White Mean (SD) CFB (OP/MA) to endpoint (OP/MA)	0.1 (8.29) (n=520)
Other Mean (SD) CFB (OP/MA) to endpoint (OP/MA)	1.8 (7.15) (n=70)
Class of OAD	
SNRI Mean (SD) CFB (OP/MA) to endpoint (OP/MA)	0.5 (7.65) (n=324)
SSRI Mean (SD) CFB (OP/MA) to endpoint (OP/MA)	0.2 (8.65) (n=279)

Subgroup	ESK-NS + OAD N=779 in full (IND) analysis set N=603 in full (OP/MA) analysis set
Dose of ESK-NS	
28 mg Mean (SD) CFB (OP/MA) to endpoint (OP/MA)	–0.1 (5.86) (n=20)
56 mg Mean (SD) CFB (OP/MA) to endpoint (OP/MA)	–0.9 (8.07) (n=278)
84 mg Mean (SD) CFB (OP/MA) to endpoint (OP/MA)	1.5 (8.15) (n=298)

Abbreviations: CFB, change from baseline; ESK-NS, esketamine nasal spray; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; IND, induction phase; MA, maintenance phase; MADRS, Montgomery-Asberg Depression Rating Scale; OAD, oral antidepressant; OP, optimisation phase; SD, standard deviation; SDS, Sheehan Disability Scale; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Overall summary of AEs

Table 47. Overall summary of AEs reported during the induction (full [IND] analysis set), optimisation/maintenance (full [OP/MA] analysis set), and follow-up (follow-up analysis set) phases of SUSTAIN-2

	ESK-NS + OAD
Induction phase, n (%)	**N=779**
AE	653 (83.8)
AE possibly related to nasal spray drug[a]	586 (75.2)
AE possibly related to OAD[a]	177 (22.7)
AE leading to death	0
≥1 serious AE	17 (2.2)
AE leading to nasal spray drug being withdrawn	53 (6.8)
AE leading to OAD being withdrawn	20 (2.6)
Optimisation/maintenance phase, n (%)	**N=603**
AE	516 (85.6)
AE possibly related to nasal spray drug[a]	402 (66.7)
AE possibly related to OAD[a]	110 (18.2)
AE leading to death	2 (0.3)
≥1 serious AE	38 (6.3)
AE leading to nasal spray drug being withdrawn[b]	23 (3.8)
AE leading to OAD being withdrawn[b]	14 (2.3)
Follow-up phase, n (%)	**N=357**
AE	55 (15.4)

	ESK-NS + OAD
AE possibly related to nasal spray drug[a]	9 (2.5)
AE possibly related to OAD[a]	5 (1.4)
AE leading to death	0
≥1 serious AE	8 (2.2)
AE leading to OAD being withdrawn[b]	1 (0.3)

Abbreviations: AE, adverse event; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; MedDRA, Medical Dictionary for Regulatory Activities; OAD, oral antidepressant.
[a] Study drug relationships of possible, probable, and very likely were included in this category.
[b] An AE that started in the previous phases and resulted in discontinuation in the follow-up phase was counted as treatment-emergent in the previous phase.
Note: Incidence was based on the number of patients experiencing ≥1 AE, not the number of events.
Note: AEs were coded using MedDRA version 20.0.

AEs reported in ≥5% of patients

Table 48. AEs reported in ≥5% of patients (all enrolled analysis set) during the induction and optimisation/maintenance phases of SUSTAIN-2

	ESK-NS + OAD (N=802)
Total number of patients with an AE, n (%)	723 (90.1)
Nervous system disorders, n (%)	528 (65.8)
Dizziness	264 (32.9)
Headache	200 (24.9)
Somnolence	134 (16.7)
Dysgeusia	95 (11.8)
Hypoaesthesia	95 (11.8)
Sedation	71 (8.9)
Dizziness postural	67 (8.4)
Paraesthesia	58 (7.2)
Psychiatric disorders, n (%)	384 (47.9)
Dissociation	221 (27.6)
Anxiety	72 (9.0)
Insomnia	63 (7.9)
Gastrointestinal disorders, n (%)	373 (46.5)
Nausea	201 (25.1)
Vomiting	87 (10.8)
Hypoaesthesia oral	73 (9.1)
Diarrhoea	60 (7.5)
Infections and infestations, n (%)	279 (34.8)
Viral upper respiratory tract infection	82 (10.2)

	ESK-NS + OAD (N=802)
Urinary tract infections	65 (8.1)
influenza	43 (5.4)
General disorders and administration site conditions, n (%)	187 (23.3)
Fatigue	63 (7.9)
Musculoskeletal and connective tissue disorders, n (%)	154 (19.2)
Back pain	41 (5.1)
Investigations, n (%)	143 (17.8)
Blood pressure increased	75 (9.4)
Ear and labyrinth disorders, n (%)	126 (15.7)
Vertigo	88 (11.0)
Eye disorders, n (%)	105 (13.1)
Vision blurred	60 (7.5)

Abbreviations: AE, adverse event; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; MedDRA, Medical Dictionary for Regulatory Activities; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray.
Note: Incidence was based on the number of patients experiencing ≥1 AE, not the number of events.
Note: AEs were coded using MedDRA version 20.0.

Appendix D. Non-clinical SLR hand search details

Table 49. Non-clinical SLR hand search details

Source	Date searched	Search details	Additional information	Search terms
Conference proceedings				
Anxiety and Depression Association of America Conference 2019	24/05/2019			MDD
				Major depressive disorder
				TRD
				Treatment-resistant
Anxiety and Depression Association of America Conference 2018	31/10/18			MDD
				Major depressive disorder
				TRD
				Treatment-resistant
Anxiety and Depression Association of America Conference 2017	31/10/18			MDD
				Major depressive disorder
				TRD
				Treatment-resistant
Anxiety and Depression Association of America Conference 2016	31/10/18			MDD
				Major depressive disorder
				TRD
				Treatment-resistant
International Conference on Management of Depression 2019	24/05/2019			MDD
				Major depressive disorder
				TRD
				Treatment-resistant

Source	Date searched	Search details	Additional information	Search terms
International Conference on Management of Depression 2018	31/10/18			MDD
				Major depressive disorder
				TRD
				Treatment-resistant
International Conference on Management of Depression 2017	31/10/18			MDD
				Major depressive disorder
				TRD
				Treatment-resistant
International Conference on Management of Depression 2016	31/10/18			MDD
				Major depressive disorder
				TRD
				Treatment-resistant
American Psychiatry Association Annual Meeting 2019	23/05/2019	Searched annual poster proceedings via: https://www.psychiatry.org/psychiatrists/search-directories-databases/library-and-archive		MDD
				Major depressive disorder
				TRD
				Treatment-resistant
American Psychiatry Association Annual Meeting 2018	1/10/18	Searched annual poster proceedings via: https://www.psychiatry.org/psychiatrists/search-directories-	Ctrl + F search term within the poster proceedings document.	Major depressive disorder
				MDD
				Treatment-resistant

Source	Date searched	Search details	Additional information	Search terms
		databases/library-and-archive Link to 2018 poster proceedings: file:///C:/Users/CharlotteFleming/Downloads/Poster-Proceedings%20(1).pdf		TRD
American Psychiatry Association Annual Meeting 2017	1/10/18	Searched annual poster proceedings via: https://www.psychiatry.org/psychiatrists/search-directories-databases/library-and-archive Link to 2017 poster proceedings: file:///C:/Users/CharlotteFleming/Downloads/Poster-Proceedings.pdf	Ctrl + F search term within the poster proceedings document.	Major depressive disorder
				MDD
				Treatment-resistant
				TRD
American Psychiatry Association Annual Meeting 2016	5/10/18	Searched annual poster proceedings via: https://www.psychiatry.org/psychiatrists/search-directories-databases/library-and-archive Link to annual new research posters: file:///C:/Users/CharlotteFleming/Downloads/am_newresearch_2016%20(1).pdf	Ctrl + F search term within the poster proceedings document.	Major depressive disorder
				MDD
				Treatment-resistant
				TRD
European Congress of Psychiatry 2019	23/05/2019	Searched: https://www.europsy.net/ecp-congress-programmes/		Major depressive disorder
				MDD
				Treatment-resistant
				TRD

Source	Date searched	Search details	Additional information	Search terms
European Congress of Psychiatry 2018	05/11/2018	Previous congresses: https://epa-congress.org/2018/useful-links/previous-congresses#.W-Bhi5P7SUk Online abstract book from Journal of European Psychiatric Association 2018: https://epa-congress.org/2018/programme-submission/abstract-book-2018#.W-BiS5P5CUk	Ctrl + F search term within the poster proceedings document.	Major depressive disorder
				MDD
				Treatment-resistant
				TRD
European Congress of Psychiatry- Italy 2017	06/11/2018	Online abstract book for 2017: https://epa-congress.org/2017/2017-abstract-book-(2)/2017-abstract-book#.W-FcLJP5CUl	Ctrl + F search term within the poster proceedings document.	Major depressive disorder
				MDD
				Treatment-resistant
				TRD
European Congress of Psychiatry- Spain 2016	06/11/2018	Online abstract book for 2016: https://epa-abstracts-2016.elsevierdigitaledition.com/index.html	Ctrl + F search term within the poster proceedings document.	Major depressive disorder
				MDD
				Treatment-resistant
				TRD
The Royal College of Psychiatrists International Congress 2019	24/05/2019			Major depressive disorder
				MDD
				Treatment-resistant
				TRD
The Royal College of Psychiatrists International Congress 2018	06/11/2018			Major depressive disorder
				MDD

Source	Date searched	Search details	Additional information	Search terms
				Treatment-resistant
				TRD
The Royal College of Psychiatrists International Congress 2017	06/11/2018			Major depressive disorder
				MDD
				Treatment-resistant
				TRD
The Royal College of Psychiatrists International Congress 2016	06/11/2018			Major depressive disorder
				MDD
				Treatment-resistant
				TRD
WPA World Congress of Psychiatry 2019	23/05/2019			Major depressive disorder
				MDD
				Treatment-resistant
				TRD
WPA World Congress of Psychiatry 2018	06/11/2018			Major depressive disorder
				MDD
				Treatment-resistant
				TRD
WPA World Congress of Psychiatry 2017	06/11/2018			Major depressive disorder
				MDD
				Treatment-resistant

Source	Date searched	Search details	Additional information	Search terms
				TRD
WPA World Congress of Psychiatry – South Africa 2016	06/11/2018	Link to download page for all abstracts from 2016, segregated by 5 topics: https://www.wpacapetown2016.org.za/index.php/sessions-abstracts/download-abstracts Link to 'cultural, religious care' abstracts: https://www.wpacapetown2016.org.za/images/Pdf/WPA-2016-Abstracts-PSY_TH.pdf	Ctrl + F search term within the poster proceedings document.	Major depressive disorder
				MDD
				Treatment-resistant
				TRD
		Link to 'integrated care' abstracts: https://www.wpacapetown2016.org.za/images/Pdf/WPA-2016-Abstracts-_INT.pdf	Ctrl + F search term within the poster proceedings document.	Major depressive disorder
				MDD
				Treatment-resistant
				TRD
		Link to 'neuroscience' abstracts: https://www.wpacapetown2016.org.za/images/abstracts/WPA-2016-Abstracts-NS.pdf	Ctrl + F search term within the poster proceedings document.	Major depressive disorder
				MDD
				Treatment-resistant
				TRD
		Link to 'psychotherapy' abstracts: https://www.wpacapetown2016.org.za/images/Pdf/WPA-2016-Abstracts-PSY_TH.pdf	Ctrl + F search term within the poster proceedings document.	Major depressive disorder
				MDD
				Treatment-resistant
				TRD

Source	Date searched	Search details	Additional information	Search terms
		Link to 'social involvement' abstracts: https://www.wpacapetown2016.org.za/images/Pdf/WPA-2016-Abstracts_SOC.pdf	Ctrl + F search term within the poster proceedings document.	Major depressive disorder
				MDD
				Treatment-resistant
				TRD
ISPOR Europe 2019 Denmark	23/05/2019			Major depressive disorder
				MDD
				Treatment-resistant
				TRD
ISPOR US 2019 New Orleans	23/05/2019			Major depressive disorder
				MDD
				Treatment-resistant
				TRD
ISPOR Europe 2018- Barcelona, Spain -2018	23/05/2019	https://tools.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp	Search feature using 'abstract' setting.	Major depressive disorder
				MDD
				Treatment-resistant
				TRD
ISPOR 2018- Baltimore, MD, USA- 2018	23/05/2019	https://tools.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp	Search feature using 'abstract' setting.	Major depressive disorder
				MDD
				Treatment-resistant
				TRD
ISPOR 20th Annual European Congress- Glasgow, Scotland- 2017	23/05/2019	https://tools.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp	Search feature using 'keyword' and 'abstracts' setting.	Major depressive disorder
				MDD

Source	Date searched	Search details	Additional information	Search terms
				Treatment-resistant
				TRD
ISPOR 22nd Annual International Meeting – Boston, MA, USA- 2017	23/05/2019	https://tools.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp	Search feature using 'keyword' and 'abstracts' setting.	Major depressive disorder
				MDD
				Treatment-resistant
				TRD
ISPOR 19th Annual European Congress –Vienna, Austria- 2016	23/05/2019	https://tools.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp	Search feature using 'keyword' and 'abstracts' setting.	Major depressive disorder
				MDD
				Treatment-resistant
				TRD
ISPOR 21st Annual International Meeting – Washington, USA – 2016	23/05/2019	https://tools.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp	Search feature using 'keyword' and 'abstracts' setting.	Major depressive disorder
				MDD
				Treatment-resistant
				TRD
ISPOR 18th Annual European Congress- Milan, Italy – 2015	23/05/2019	https://tools.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp	Search feature using 'keyword' and 'abstracts' setting.	Major depressive disorder
				MDD
				Treatment-resistant
				TRD
ISPOR 20th Annual International Meeting – Philadelphia, PA, USA - 2015	23/05/2019	https://tools.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp	Search feature using 'keyword' and 'abstracts' setting.	Major depressive disorder
				MDD
				Treatment-resistant
				TRD

Source	Date searched	Search details	Additional information	Search terms
HTA agencies – hand searching for clinical studies				
NICE	30/05/2019	https://www.nice.org.uk/guidance/published?type=ta&title=major%20dep Also searched: https://www.nice.org.uk/guidance/published?type=ta&title=major%20dep	Search bar, filtered for technology appraisal guidance. Evidence was reviewed for each 'hit'.	Major depressive disorder
				MDD
				Treatment-resistant depression
				TRD
SMC	30/05/2019	https://www.scottishmedicines.org.uk/	Search bar	Major depressive disorder
				MDD
				Treatment-resistant
				TRD
PBAC	30/05/2019	Public Summary Documents by product: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/public-summary-documents-by-product	NA	NA
CADTH	30/05/2019	https://cadth.ca/	Search bar, filtered for reports and HTA.	Major depressive disorder
				MDD
				Treatment-resistant
				TRD
NCPE	30/05/2019	http://www.ncpe.ie/	Search bar	Major depressive disorder
				MDD
				Treatment-resistant
				TRD
HTA agencies- hand searching for relevant economic reviews/ cost report/ HSUV + QoL reports				

Source	Date searched	Search details	Additional information	Search terms
NICE	23/05/2019	https://www.nice.org.uk/	Search bar, filtered for technology appraisal guidance.	Major depressive disorder
NICE	30/08/2018	https://www.nice.org.uk/	Search bar, filtered for technology appraisal guidance.	Major depressive disorder
SMC	23/05/2019	https://www.scottishmedicines.org.uk/	Search bar	major depressive disorder
SMC	30/08/2018	https://www.scottishmedicines.org.uk/	Search bar	major depressive disorder
PBAC	23/05/2019	Public Summary Documents by product: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/public-summary-documents-by-product	NA	NA
PBAC	30/08/2018	Public Summary Documents by product: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/public-summary-documents-by-product	Searched by product	NA
CADTH	23/05/2019	https://cadth.ca/	Search bar, filtered for reports and HTA	major depressive disorder
CADTH	30/08/2018	https://cadth.ca/	Search bar, filtered for reports and HTA	major depressive disorder
NCPE	23/05/2019	http://www.ncpe.ie/	Search bar	major depressive disorder

Source	Date searched	Search details	Additional information	Search terms
NCPE	30/08/2018	http://www.ncpe.ie/	Search bar	major depressive disorder
Additional sources – hand searching for relevant economic reviews/ cost report/ HSUV + QoL reports				
CEA registry	24/05/2019	http://healtheconomics.tuftsmedicalcenter.org/cear2n/search/search.aspx	Search bar, filtered for 'methods'	major depressive disorder
CEA registry	24/05/2019	http://healtheconomics.tuftsmedicalcenter.org/cear2n/search/search.aspx	Search bar, filtered for 'ratios'	major depressive disorder
CEA registry	24/05/2019	http://healtheconomics.tuftsmedicalcenter.org/cear2n/search/search.aspx	Search bar, filtered for 'utility weights'	major depressive disorder
CEA registry	31/08/2018	http://healtheconomics.tuftsmedicalcenter.org/cear4/home.aspx	Search bar	major depressive disorder
EconPapers within RePEC	24/05/2019	https://econpapers.repec.org/scripts/search.pf	Advanced search feature, title and keyword search	"major depressive disorder"
EconPapers within RePEC	31/08/2018	https://econpapers.repec.org/scripts/search.pf	Advanced search feature, title and keyword search	"major depressive disorder"
INAHTA	24/05/2019	http://www.inahta.org/	Search bar	major depressive disorder
INAHTA	31/08/2018	http://www.inahta.org/	Search bar	major depressive disorder
NIHR HTA	24/05/2019	https://www.crd.york.ac.uk/CRDWeb/	Search facility using MeSH search option. Tick boxes 'DARE' 'NHD EED' HTA'.	"major depressive disorder"
NIHR HTA	31/08/2018	https://www.crd.york.ac.uk/CRDWeb/	Search facility	"major depressive disorder"

Source	Date searched	Search details	Additional information	Search terms
ICER	24/05/2019	https://icer-review.org/	Search bar	major depressive disorder
ICER	31/08/2018	https://icer-review.org/	Search bar	major depressive disorder
Ad hoc	Multiple	Reference lists, google scholar	NA	NA
EuroQoL website	24/05/2019	Search for EQ-5D publications: https://euroqol.org/search-for-eq-5d-publications/	Advanced search using 'abstract' and 'title' filter; sort by date.	major depressive disorder
ScHARRHUD	24/05/2019	https://www.scharrhud.org/index.php?recordsN1&m=search	Search feature	major depressive disorder OR MDD in abstract.

Appendix E. 18th October 2018 advisory board notes

TRD clinical advisory board **18 Oct 2018**

Summary

An advisory board was conducted to gain clinical opinion on the esketamine nasal spray clinical trial programme and how the drug would likely be used in clinical practice in patients with treatment resistant depression (TRD), including likely positioning and considering the observation requirements. The insights from the advisory board, together with responses from the pre-meeting questionnaire, have been used to guide the assumptions and approach considered in the NICE submission (with attendee permission). Attendees were asked if their input could be used anonymously to support the NICE submission. The respondents agreed that this would be acceptable.

Advisory board attendees:

Name
Psychiatrist
Professor in mental health and psychiatrist†
Professor in mental health and GP
Psychiatrist
Psychiatrist
Professor in Mental Health
Psychiatrist

†This clinician was unable to attend the advisory board but completed a separate questionnaire.

Meeting objectives and agenda

Objective: The objective of the advisory board was to validate the clinical assumptions for the UK Health Technology Appraisal submissions for esketamine nasal spray with regards to:

- Current and expected future treatment patterns for patients with TRD.
- The clinical value and interpretation of esketamine nasal spray phase 3 data.
- The expected duration of treatment with esketamine nasal spray in clinical practice.

Meeting agenda

09:30	Welcome and tea/coffee
09:45	Introductions and objectives
10:00	Presentation: Esketamine nasal spray phase 3 results and target profile summary overview
10:30	Q & A: What further information is required in relation to the clinical trials to aid participation in this advisory board?
11:00	Tea/coffee break
11:15	Q & A: How can the clinical trials be interpreted in relation to overall efficacy of esketamine nasal spray versus placebo nasal spray? (Part 1)
12:15	Lunch break
12:45	Q & A: How can the clinical trials be interpreted in relation to overall efficacy of esketamine nasal spray versus placebo nasal spray? (Part 2)
13:30	Q&A: What is the current and potential future treatment pathway for TRD and what are the relevant comparators for esketamine nasal spray?
14:30	Coffee/tea break
14:45	Q&A: What are the likely observation requirements for esketamine nasal spray in clinical practice and how can they be defined?
16:00	Summary of advisory board & close
16:30	Meeting ends

Summary

Key recommendation from the advisory board

- Further investigate the placebo effect by identifying other studies ideally in depression which have included a placebo arm with a novel mode of action. The aim of this would be to compare the size of the active comparator/placebo effect with other studies in mental health.

Efficacy of esketamine nasal spray

Key takeaway from discussions with advisers:

- The effect in the active comparator arm of the TRANSFORM-2 study is higher than the treatment effect of OADs shown in other clinical trials in the TRD population, and higher than in NHS clinical practice.
- Treatment adjustment of the TRANSFORM-2 active comparator arm is justified.

- Clinicians noted the pronounced treatment effect in the active comparator arm (newly initiated OAD plus placebo nasal spray) and highlighted that this would not usually be seen with an OAD, particularly so soon (Day 2) after treatment initiation (usually a treatment effect with OADs is not seen for at least 2 weeks).

- The attendees agreed that the treatment effect in the active comparator arm is not reflective of expected outcome of OADs in patients with TRD in clinical practice. The

clinicians agreed that the pronounced treatment effect in the active comparator arm is likely due to:

1. the novel treatment administration,
2. the anticipation of receiving esketamine nasal spray treatment, and
3. the intensive management approach (twice weekly 1-1 interaction with an HCP for >2 hours).

- Clinicians noted that similar effects have been seen in studies comparing ECT with sham ECT, and with TMS where patients have daily nurse interactions, showing that the amount of time spent in contact with HCPs can have a considerable impact on the treatment effect.

Treatment duration

Key takeaway from discussions with advisers:

- The largest proportion of patients with TRD (~80%) will discontinue esketamine nasal spray treatment if recovery is achieved.
- A small proportion of patients with TRD, the ones who are at high risk of relapse, will continue treatment with esketamine nasal spray for up to two years.
- Clinicians will motivate the most severe patients with TRD who failed all possible lines of AD treatment to continue treatment with esketamine nasal spray plus OAD if it is effective in these patients.

- The clinicians agreed that once a treatment is working in the TRD population, it is difficult to take patients off the treatment, because both physicians and patients will be reluctant to stop a treatment to which the patient is responding, at least in the short-term.
- Clinician consensus was that the most severe patients with TRD who failed all possible lines of AD treatment and who had achieved remission when using esketamine nasal spray + OAD should be motivated to continue esketamine nasal spray + OAD for an indefinite period.
- When clinicians were reminded of the logistics associated with esketamine nasal spray treatment (i.e. visits to the clinic for approx. 1 hour and 10 minutes every week or every other week) and it was explained that for HTA purposes it was necessary to get real-life estimates (instead of aspirational) and a timeframe for treatment, the clinicians agreed that:
    - The largest proportion of patients with TRD (~80%) will discontinue esketamine nasal spray treatment if recovery is achieved.
    - A small proportion of patients with TRD (~20%), the ones who are at high risk of relapse, will continue treatment with esketamine nasal spray for up to two years.

Subsequent treatments

- Potential treatments after esketamine nasal spray include augmentation therapy.
- One clinician indicated that ECT would be considered as a next step after esketamine nasal spray if the patient failed to respond or had a relapse.

Administration and observation costs

- Observation requirements did not seem to be a major concern for the clinicians.
- There was a high level of agreement with regard to the amount of time that administration (10 minutes) and monitoring (maximum 90 minutes) will take.
- Self- administration of esketamine nasal spray would need to be monitored by a qualified nurse.
- A physician would need to be accessible but not necessarily present, in case of an emergency.
- Due to the safety profile of esketamine nasal spray, the clinicians agreed that the ratio of healthcare professional (nurse) to patients could be increased in the maintenance phase from 1:8 to 1:20.

Current treatment pathway for TRD and relevant comparators for esketamine nasal spray

- Numerous treatment options were proposed for 1st, 2nd, and 3rd line TRD indicating the heterogeneity of the patient population. Treatment choice may be driven by presentation/symptoms.
- Clinicians may consider restarting the treatment algorithm if there is evidence that patients are non-compliant or not taking their medication correctly (applies to approximately 15% of patients).
- Treatment decisions are multifactorial in this patient group and will consider the treatments already given and the efficacy and side effect profile of subsequent treatments.
- The treatments agreed to be the most likely comparators to esketamine nasal spray (in order of ranking) were vortioxetine, augmentation therapy, serotonin, and noradrenaline re-uptake inhibitors (e.g. venlafaxine and duloxetine) and other ADs (e.g., agomelatine, mirtazapine, reboxetine, and non-reversible mono-amine oxidase inhibitors [such as phenelzine]).
- Several clinicians indicated that they would choose esketamine nasal spray before ECT.
- Psychological therapies (e.g. CBT) may also be provided to patients with TRD if they are responding to treatment.

Future esketamine nasal spray treatment dosing

- If there was a partial response to esketamine nasal spray, they would increase the dose to the maximum and increase to once weekly if not already done and potentially optimise the oral treatment.
- They noted that in a patient with severe depression even a 30% response is significant and will make a big difference to their quality of life.

Grouping of oral antidepressants

- Clinicians agreed that, based on available evidence, it is appropriate to consider the effectiveness of SSRI and SNRIs to be similar.
- One clinician indicated that it would be appropriate to conclude that all different oral antidepressant drug classes are of similar effectiveness.

MDD and TRD treatment response in patients ≥65 years

- The participants agreed that younger adults (aged 18–64 years) with TRD on average experience a greater magnitude of treatment response to OADs than older adults (aged ≥65 years) with TRD.
    - This may be due to duration of MDD, higher number of previous episodes and higher number of comorbidities.

Appendix F. 4th June 2019 advisory board notes

TREATMENT RESISTANT DEPRESSION HTA ADVISORY BOARD

Royal College of General Practitioners, London, 4th June 2019

SUMMARY REPORT

ATTENDEES

Panel
Health Economist
Professor of Psychiatry
Psychiatrist
Professor of Medical Statistics
Professor in Mental Health
Professor of Psychiatry

MEETING OBJECTIVES AND AGENDA

09:15	*Welcome and coffee/tea*
09:30	Introductions and objectives for the day
09:45	Presentation: Esketamine nasal spray phase 3 results and target profile summary overview
10:00	Q & A: What further information is required in relation to the clinical trials to aid participation in this advisory board?
10.15	Presentation: Esketamine nasal spray in TRD Cost Effectiveness model
10.30	Q & A: What are the optimal clinical inputs/assumptions in the cost effectiveness model (part 1)
11:00	*Coffee/tea break*
11:15	Q & A: What are the optimal clinical inputs/assumptions in the cost effectiveness model (part 2)
12:45	*Lunch break*
13.15	Presentation: The proposed indirect comparative approach for esketamine nasal spray for the acute and maintenance phase
13:30	Q & A: How will the indirect comparative approach for esketamine nasal spray for the acute phase be interpreted?
14:30	*Coffee/tea break*
14:45	Q & A: How will the indirect comparative approach for esketamine nasal spray for the maintenance phase be interpreted?
15:45	Wrap up and close

16:00	*Meeting ends*

SUMMARY POINTS

- There was general agreement upon the approaches suggested by Janssen to inform the economic model, given the absence of evidence and large amount of uncertainty in this area.

Key recommendations from HTA advisory board:

- The rationale for the adjustment of the TRANSFORM-2 active comparator arm was considered appropriate. Suggest using unadjusted in the base case and active comparator arm treatment adjustment as a scenario, mainly due to the non-robust methodology (Posternak) applied.
- Suggest further clarification regarding the role of the phase 3 open label long-term studies in informing treatment duration.
- Agreed that the evidence suggests that esketamine nasal spray has a different mechanism of action to currently available therapies, however it was suggested to be less assertive about exact mechanism of action and clarify that it is the proposed hypothesis.
- Suggest alternative approach to estimating the cost of administration within the healthcare setting, such as a group approach in an open treatment setting rather than individual patients in cubicles.
- Suggest presenting a scenario- or subgroup-analysis with the TRANSFORM-3 data, rather than pooling the TRANSFORM-2/3 due to differences in the patient population.

This summary report captures the key points raised at Janssen's advisory board for esketamine nasal spray in TRD held on 4th June 2019. A brief summary of the conclusions from the discussion is provided for each discussion topic. Where similar points were raised in different sessions, there has been an attempt to collate them in the relevant section of the report for a more logical flow and to minimise repetition.

FULL NOTES

Janssen explained the proposed hypothesis for the mechanism of action (MoA) of esketamine nasal spray

- Feedback was to be less assertive on the hypothesis of MoA, and frame that this is still a hypothesis (one out of currently six hypothesises).
- It was fed back rather to show the difference in MoA compared to current therapies, using the objective empirical evidence as rationale (e.g. time scale of effect, pharmacology is very different).

- Ultimately, it was agreed that esketamine nasal spray (NS) is not directly working through monoaminergic mechanism, which existing therapies target.

Time to recovery: Janssen presented the concepts of remission and recovery, and specifically the reduced rate of recurrence when in the recovery state versus relapse in the remission state

- Clinicians explained the concepts of remission vs recovery are recognised in clinical practice and based on their understanding of the natural history of the disease.
- It was fed back that the Judd study 1998 (US) and Pakal study provided important information relating to the natural history of the disease.
- Judd et al 1998 data show that the presence of residual symptoms is important, even if in remission and recovery. Publication shows that difference in relapse rates between asymptomatic recovery and residual recovery. For people who have residual symptoms, median 68 weeks to relapse compared to 231 weeks for those without residual symptoms.

Assumptions regarding time to recovery in the economic model

Key assumptions presented by Janssen regarding treatment duration:

- Esketamine nasal spray is continued whilst patients remain in the response health state
- For those in remission, treatment is continued until 9 months when recovery is reached. This is because the recurrence rate is lower after 9 months of treatment in SUSTAIN-1.

- Advisors generally agreed with the proposed approach and all assumptions as presented during the meeting appeared to be reasonable to the extent of individual advisors' expert knowledge.
- Advisors agreed that the proposed approach to use the license wording (at least 6 months) as a priori data and use curves from the SUSTAIN-1 data to support the modelling assumptions appeared reasonable.

Treatment duration

- Clinical experts were not clear on the inclusion of the wording for recommendation of 6 months duration of treatment in the SmPC (which is included in other OAD treatment SmPCs, such as vortioxetine and paroxetine).
- Clinical consensus on the average duration of treatment to define recovery was not reached, (e.g. 6 months=recovery) due to inter patient variability.
- It was recommended to include scenarios with different treatment durations for esketamine nasal spray, and different stopping rules, and ensure alignment to expected clinical practice.
- It was advised that Janssen clearly communicate any rationale for not using the open label long term study to inform the treatment duration.

Key assumptions included in the model:

- Once reaching recovery, approximately 35% of patients who had been in continuous remission for 9 months discontinue. It is assumed these patients have a lower risk of relapse.
- The proportion of patients at lower risk of relapse at the recovery time point (35%) is taken from the proportion of patients in SUSTAIN-1, who are have experienced their first or second MDD episode
- After recovery is reached, patients face a 25% monthly risk of discontinuing treatment, so that by 2 years, only 1% remain on treatment
- Recurrence rates are non-treatment specific

Assumptions regarding esketamine nasal spray treatment discontinuation

- All advisors generally agree with the assumptions for the base case regarding discontinuation of treatment and regarded them as reasonable assumptions.
- Discontinuation of treatment due to transitioning into a recovery health state is not assessed during the SUSTAIN-1 trial, as patients were continued on treatment until relapse.
- It was suggested that perhaps the biggest determinant for patient continuation or discontinuation beyond 9 months in remission is patient acceptability and budget pressures for the treatment administration.

Over 65 population (TRANSFORM-3)

- The health economist recommended against pooling TRANSFORM-2 (TF-2) and TRANSFORM-3 (TF-3) data due to fundamental differences in population (co-morbidities and age etc).
- It was suggested to reference to the average age of patients with TRD from real world data to reassure that TF-2 is the most relevant information for the decision problem.

Janssen explained the rationale for adjusting the short term clinical data (TRANSFORM-2)

Janssen provided the rationale for adjusting the active comparator arm of the TF-2 data:

- Due to the frequency and duration of HCP visits, the placebo intranasal device with bitter taste, high patient expectation

- Advisors agreed with the proposed rationale for the approach and believe that there is a strong clinical rationale for the adjustment.
- It was explained the placebo effect is well recognised in depression.

Proposed methodology for adjustment in the active comparator arm

- Although the rationale for the adjustment in the active comparator arm is understood, there were concerns with the robustness of the methodology of the adjustment.

COST EFFECTIVENESS MODEL DISCUSSION POINTS

Definition of health states: (MDE, Response, Remission, Recovery)

- Advisors agreed with the health states included in the economic model.
- It was thought there would be a need to explain the mixture of absolute and relative definitions of health states to ensure they are mutually exclusive.

Model structure:

- It was suggested a clinical transition from the remission health state to the response health state would improve face validity of the model.
- Clinical advisors explained that in clinical practice when initiating esketamine nasal spray, for some patients who show a partial response to OAD, clinicians would consider keeping the same OAD and augment with esketamine NS rather than switching to a new OAD, as per the license.

Episodic vs lifetime approach

- All experts agreed that the episodic approach is the right approach for the model. The rationale is provided below:
    - TRD is defined on an episodic basis, defined on basis of resistance to acute treatment.
    - There are large data gaps for a lifetime model.
    - A lifetime model with many uncertainties would not be a useful model for decision making.

Data source to inform the maintenance efficacy of the OAD comparator

- Advisors were satisfied with the rationale for not using SUSTAIN-1 for OAD, due to the design of the trial. Advisors agreed with the rationale and approach for using STAR*D.
- Advisors observed that it would be a similar argument to adjusting for the short term active comparator arm, as the TRANSFORM-2 trial is not the best data source to model OAD efficacy.

Utility data

- The health economist agreed with using TRANSFORM-2 as the data source for utilities for the health states in the base case.

Time horizon

- Advisors agreed with the provided rationale for using the 5 year time horizon
- A 5 year time horizon is able to capture as much benefit of esketamine NS as possible, whilst avoiding modelling a future MDE episode.

Sources of data to inform the subsequent treatments in the model

The following sources of efficacy data for the treatment sequencing approach were proposed:

- STAR*D to inform efficacy of subsequent treatment lines (4th line, 5th line, 6th line)
- Edwards et al, 2013 for non-specific treatment phase

- Overall, given the little data available, these sources were agreed to be appropriate.
- It was agreed that a basket of treatments makes sense for the downstream treatment.
- For the non-specific treatment phase, it was agreed that Edwards 2013 provides reasonable data, given that it represents 7th/ 8th/ 9th/10th line etc and not only 7th line.
- A further rationale proposed by advisors is that Edwards 2013 was published subsequent to STAR*D, therefore the clinical opinion uses the information from STAR*D into account when estimating efficacy .

Health state cost

- Janssen proposed to use the results of an unpublished UK cost study to inform the health state costs.
- It was advised to compare the UK TRD cost study results with the costs of TRD in the literature. (E.g. mean annual total service costs for patients with TRD were £4388 (McCrone, 2017), which covered all health states of patients (MDE, response, remission, relapse)). However, there is no other study that reports the data per health state.
- Advisors were aware that patients with TRD are very costly and estimated that the costs of the MDE state may be an underestimation of the true costs of TRD patients.

Administration assumptions

- Advisors suggested an alternative method of costing where the cost per session (6 people), is estimated based on the staff required for the supervision and monitoring.
- Advisors suggested a band 5 minimum nurse would be required to supervise the self-administration. Two nurses would be required to be present for release of a controlled drug (at least 1 qualified = band 5).
- Clinical advisors with experience of using esketamine nasal spray are planning on having a divider between patients allowing 6 patients to be monitored at any one time, and a doctor being present in the building for clinical support.
- Advisors suggested that monitoring of this kind happens already in group setting e.g. clozapine clinic.
- It was agreed that a doctor would be present initially after launch, and for modelling purposes, it was reasonable to exclude the need for a clinician being present, once confidence in the administration increased.
- It was advised that Band 5 nurses would be the most likely to supervise self-administration and band 4 to monitor patients. It is unlikely that Band 6 and above would be involved on a day to day basis (unless short staffed etc).

Administration logistics for esketamine nasal spray

- Clinical advisors suggested that community health teams and CRHT more credible than being administered in GP practices (after explaining that self-administration would not be cost-effective in a patient's home).
- Clinical advisors expect to only monitor blood pressure prior to self-administration, if there are symptoms present and at end of the monitoring period.

NMA approach

Summary of the approach for the indirect comparison:

- There was no comparable maintenance treatment data available.
- There are limited comparable acute treatment data, with high heterogeneity.
- In summary, the NMA did not generate comparative data suitable for CEA model inputs.

Advisors agreed with the proposed approach to undertake an NMA and present the results, although present it to be not robust for input into the cost effectiveness model.

In the absence of a feasible network including 2-6-week outcomes, the criteria were extended for 2-8-week outcomes.

Appendix G. Markov trace data

Table 50. Markov trace background data

Cycle	Year	MDE (%)	Response (%)	Remission (%)	Recovery (%)	Proportion (%) receiving ESK-NS	ESK-NS monthly frequency	Mean devices per session
0	0.000	100	0	0	0	100.00000	7.40	2.5285714
1	0.077	31	17	52	0	69.31000	3.04	2.605
2	0.153	34	13	53	0	65.67040	3.04	2.605
3	0.230	38	10	52	0	62.17880	3.04	2.605
4	0.307	41	7	51	0	58.83968	2.68	2.605
5	0.383	44	6	50	0	55.65524	2.68	2.605
6	0.460	47	4	48	0	52.62449	2.68	2.605
7	0.537	50	3	47	0	49.74465	2.67	2.605
8	0.613	53	2	45	0	47.01171	2.67	2.605
9	0.690	55	2	43	0	44.42082	2.67	2.605
10	0.767	58	1	9	31	30.88682	2.67	2.605
11	0.843	59	1	7	32	23.25547	2.67	2.605
12	0.920	60	1	5	33	17.51013	2.67	2.605
13	0.997	62	1	4	33	13.18457	2.67	2.605
14	1.073	63	0	3	33	9.92784	2.67	2.605
15	1.150	64	0	2	33	7.47578	2.67	2.605
16	1.227	65	0	2	32	5.62951	2.67	2.605
17	1.303	66	0	1	32	4.23930	2.67	2.605
18	1.380	67	0	1	31	3.19250	2.67	2.605
19	1.457	68	0	1	30	2.40425	2.67	2.605
20	1.533	69	0	1	30	1.81068	2.67	2.605
21	1.610	70	0	0	29	1.36369	2.67	2.605
22	1.687	71	0	0	28	1.02708	2.67	2.605
23	1.763	71	0	0	28	0.77358	2.67	2.605
24	1.840	72	0	0	27	0.58266	2.67	2.605
25	1.916	73	0	0	26	0.43888	2.67	2.605
26	1.993	74	0	0	25	0.33058	2.67	2.605
27	2.070	74	0	0	25	0.24902	2.67	2.605
28	2.146	75	0	0	24	0.18758	2.67	2.605
29	2.223	76	0	0	23	0.14131	2.67	2.605

Cycle	Year	MDE (%)	Response (%)	Remission (%)	Recovery (%)	Proportion (%) receiving ESK-NS	ESK-NS monthly frequency	Mean devices per session
30	2.300	76	0	0	23	0.10645	2.67	2.605
31	2.376	77	0	0	22	0.08020	2.67	2.605
32	2.453	77	0	0	21	0.06042	2.67	2.605
33	2.530	78	0	0	21	0.04552	2.67	2.605
34	2.606	79	0	0	20	0.03430	2.67	2.605
35	2.683	79	0	0	20	0.02584	2.67	2.605
36	2.760	80	0	0	19	0.01947	2.67	2.605
37	2.836	80	0	0	18	0.01467	2.67	2.605
38	2.913	81	0	0	18	0.01105	2.67	2.605
39	2.990	81	0	0	17	0.00833	2.67	2.605
40	3.066	82	0	0	17	0.00628	2.67	2.605
41	3.143	82	0	0	16	0.00473	2.67	2.571
42	3.220	82	0	0	16	0.00356	2.67	2.571
43	3.296	83	0	0	15	0.00269	2.67	2.571
44	3.373	83	0	0	15	0.00202	2.67	2.571
45	3.450	84	0	0	15	0.00153	2.67	2.571
46	3.526	84	0	0	14	0.00115	2.67	2.571
47	3.603	84	0	0	14	0.00087	2.67	2.571
48	3.680	85	0	0	13	0.00065	2.67	2.571
49	3.756	85	0	0	13	0.00049	2.67	2.571
50	3.833	85	0	0	13	0.00037	2.67	2.571
51	3.910	86	0	0	12	0.00028	2.67	2.571
52	3.986	86	0	0	12	0.00021	2.67	2.571
53	4.063	86	0	0	12	0.00016	2.67	2.571
54	4.140	87	0	0	11	0.00012	2.67	2.571
55	4.216	87	0	0	11	0.00009	2.67	2.571
56	4.293	87	0	0	11	0.00007	2.67	2.571
57	4.370	87	0	0	10	0.00005	2.67	2.571
58	4.446	88	0	0	10	0.00004	2.67	2.571
59	4.523	88	0	0	10	0.00003	2.67	2.571
60	4.600	88	0	0	9	0.00002	2.67	2.571
61	4.676	88	0	0	9	0.00002	2.67	2.571
62	4.753	89	0	0	9	0.00001	2.67	2.571

Cycle	Year	MDE (%)	Response (%)	Remission (%)	Recovery (%)	Proportion (%) receiving ESK-NS	ESK-NS monthly frequency	Mean devices per session
63	4.830	89	0	0	9	0.00001	2.67	2.571
64	4.906	89	0	0	8	0.00001	2.67	2.571
65	4.983	89	0	0	8	0.00001	2.67	2.571

Abbreviations: ESK-NS, esketamine nasal spray; MDE, major depressive episode.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Esketamine for treatment-resistant depression [ID1414]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	

2. Name of organisation	SANE
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	SANE is a leading UK mental health charity set up in 1986 to improve the quality of life for anyone affected by mental illness. Our three main aims are to raise awareness and combat stigma about mental illness, educating and campaigning to improve mental health services; to promote and host research into the causes and more effective treatments for mental illness; and to provide guidance and emotional support for people with mental health problems, their families and carers, through our helpline, SANEline, Textcare and other services. The organisation receives no government funding, and 86% of income is from voluntary sources (individuals and legacies) 59%, grants from charitable trusts and foundations 28%, and companies and other organisations 13%. Funding from pharmaceutical companies in the financial years 2014/15 to 2018/19 was as follows:

Company	14/15	15/16	16/17	17/18	18/19	TOTAL
Lundbeck Ltd	0	15,000.00	0	1,000	0	16,000
Celgene	0	0	0	0	25,000.00	25000
Janssen	0	20,000	0	5,000	0	25,000
Otsuka Pharmaceuticals	0	30	270	9,850	600	10750
						76,750

	SANE does not have members. There are 24 members of staff, some part-time, and around 80 volunteers who work on SANEline and other services. We interact with people affected by depression and other mental health conditions, and their carers and families, through our services, our online SANE Community, our website and social media.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.
5. How did you gather information about the experiences of patients and carers to include in your submission?	We drew on what we know to be the experiences of people affected by depression who have called our helpline, SANEline, and used our other services for patients and carers, or with whom have otherwise been in contact. We have also drawn on an online survey funded by Janssen and carried out by Synergy Healthcare Research (Synergy) in May and June 2019. This survey was undertaken in order to understand the impact of treatment-resistant depression (TRD) among patients and carers in the UK; to identify patient and carer perspectives on the nature of TRD as a distinct condition with unique challenges; to understand the journey to diagnosis, referral and treatment from patient and carer perspectives; and to identify needs for increased support to patients and carers. The survey results will be used to inform materials on major depressive disorder for patients and carers, and an awareness campaign for patients, carers and health professionals, in partnership with Janssen. The survey invited responses from patients and carers in cases where the patient had not responded sufficiently to at least two different anti-depressants prescribed to treat the current depressive episode and was continuing to experience depressed mood and/or loss of interest or pleasure in almost all activities, up to five symptoms in total. It excluded patients with bipolar disorder, schizophrenia or schizoaffective disorder; the carers were immediate family members or friends and excluded professional care givers. 100 patients and 90 carers responded to the survey.
Living with the condition	
6. What is it like to live with the condition? What do carers	In our experience, those living with the condition – both patients and carers -- are impacted heavily in most areas of their lives. For those with the condition, there is a loss of hope that it can improve, or that any treatments might be helpful or effective.

experience when caring for someone with the condition?	In our survey, patients experience a wide range of symptoms every day or nearly every day, and 94% feel that others do not understand what it is like to experience depression. **80% of patients report having had suicidal thoughts in the previous 12 months, but only 51% of carers are aware of these.** 89% of patients report TRD as having a major impact on their quality of life, with 93% experiencing a loss of interest or pleasure in all or almost all activities most of the day. 86% feel fatigued, 82% have difficulty concentrating; 78% feel worthless and 75% have trouble sleeping. TRD has an impact on social life (81%), relationships with friends (70%) and physical health (58%). Over 9 out of 10 carers report that looking after someone with TRD impacts on their own quality of life, leaving them feeling drained or exhausted and affecting their relationships and mental health. The above may be epitomised by some of the open responses from individuals when describing TRD. For example, *"You feel guilty for being the person that you don't want to be, you're down and unhappy and in turn this affects performance at work, at home and can have negative impacts on relationships. The self-harm, suicidal thoughts and feeling of dread combined with emptiness and emotional turmoil take their toll."* *"Feeling utterly desolate. Total shame and embarrassment. Lack of interest in anything……Trying to explain my situation to friends and family."* A sense of hopelessness was a consistent theme: *"Knowing you'd have more potential if not for the illness, but not being able to act on it, making it more frustrating and upsetting."* 84% of patients report TRD having an impact on work, with 45% having to stop work completely. Many report having not told work colleagues about their diagnosis, and those taking time off work due to the condition lost a mean 20 days' work in the last 3 months. Just over half of patients (54%) report a negative financial impact, affecting their ability to pay rent or a mortgage. Carers also report TRD affecting their work or study performance (43%) and having a negative financial impact (47%). 37% have had to take time off work or study, and 9% have had to stop work or study completely. In 14% of cases, they have been affected in their ability to pay rent or a mortgage.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	In the survey, elevated mood is regarded by both patients and carers as the most significant benefit of taking antidepressants. However, 92% report side effects, most significantly increased fatigue and insomnia, and side effects impact on the quality of life of 84% of patients. 56% of patients and carers regard their treatment as ineffective, with only 57% believing the benefits of antidepressants outweigh the side-effects. Of the 74% of TRD patients offered access to treatments other than medication, only 10% initially found Cognitive Behavioural Therapy (CBT), talking therapy or counselling to be very effective. Over a third (35%) of TRD patients stopped feeling the benefits of non-drug therapy within a month of the treatment ending.
8. Is there an unmet need for patients with this condition?	While patients receive support and care in a variety of ways, for many, unmet needs are for better information, earlier diagnosis; earlier access to non-drug treatments and specialist help, in particular earlier help from psychiatrists; and better support from HCPs in relation to medication, condition management and everyday living. Our survey found that not all patients and carers feel they fully understand what depression is, with11% feeling they understand it not very well or not at all well. Only 21% of patients and carers feel they have a good understanding of what causes depression. While both groups are most likely to have gained information or support from healthcare professionals (HCPs), 25% report not having received it from an HCT. Fewer than half of patients and carers regard HCPs as the most useful source of information about depression, and many patients and carers do not feel their doctor provides the right amount of information about depression or its treatment. Only around a third of patients contact a doctor within 6 months of first experiencing symptoms of depression, and fewer than 50% of patients are diagnosed with depression within 4 weeks of first consulting their doctor. Most people are initially diagnosed with depression by their GP, with the majority (55%) reporting their doctor described their condition as being “depression and anxiety”. Of those given a diagnosis of depression, 14 % were diagnosed as having Major Depressive Disorder and 7% TRD. While 92% of patients and carers have seen a GP and 57% a counsellor, only 52% have seen a psychiatrist. Patients take a mean 3 years to see a psychiatrist after their initial diagnosis of depression, and more than a third wait 4 months or longer to change antidepressant after telling a doctor it is ineffective. While 74% of patients have been offered non-drug treatment, over 1 in 4 were only offered this over a year after initial diagnosis. At the time of

	the survey, only 23% of patients were still receiving non-drug treatment, and of those no longer receiving non-drug treatment, 59% had stopped receiving it over a year before. Most patients report trying to hide the effects of depression and feel psychiatrist referral is too slow. Patients would like additional support from HCPs in managing TRD, and carers of those with TRD would like increased physical and emotional support from HCPs, around medication and patients' management of their condition, and around everyday living. Most patients (72%) see their GP most frequently in connection with depression and see a primary care HCP once every 2-3 months on average. Although most (57%) see a secondary care HCP during a year, 43% do not. While 36% of carers report having a written treatment plan for managing depression, only 12% of patients report having one. Less than 1 in 10 of patients with a treatment plan are very satisfied with it. Fewer than 1 in 6 patients are very happy with the support provided by the HCP they see most frequently, and only 2 in 10 feel their HCP understands what they are going through very well. While just over half of patients and carers (56%) are aware of Electroconvulsive Therapy (ECT) as a therapy, only 5% of patients have been offered it. 3 out of 10 of those offered it would have liked more information provided by their doctor. Patients and carers expressed a desire for increased treatment options and better access to treatment, mentioning such things as easier access to appointments, reduced waiting times and early referrals for treatment, together with longer appointment times, annual check-ups, 24/7 support and long-term counselling. They would like to see the same GP every time and receive more listening, empathy and understanding from GPs. They would like better communication and consistency of advice between HCPs, explanation of treatment choices and support for patient choice. Carers would like to be listened to and asked about their own wellbeing.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	As this drug is not licensed in the UK, we are not in a position to give a view on this, and we do not have information from any patients who have taken part in clinical trials. But from what is known about the drug, we think the advantage that would be seen by patients and carers is the fact that it shows an improvement in depressive symptoms in as little as 24 hours after the first dose, as compared with other types of antidepressant medication. Patients with TRD have not been able to respond to existing medications, which also take longer to have an effect

	in alleviating symptoms. The fact that the drug, if licensed, would be expected to be administered in a clinical setting might also be considered an advantage compared with existing medications because of the structured setting and the contact with healthcare practitioners. Patients responding to our survey would like additional support from HCPs in managing their condition, and 43% report not seeing a secondary care HCP during a year. Overall, given the damaging impact of TRD on the lives of patients and carers, we think both groups would see this technology being beneficial if it would result in alleviation of depressive symptoms to the extent that the patient could achieve a better quality of life and resume a more normal existence and relationship with the outside world.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Some patients and carers might see as a disadvantage the fact that the technology would be expected to be administered in a clinical setting, initially twice weekly, for a period of up to two hours. This could be seen as inconvenient for those patients who would have to travel to a clinic and incur costs. There is also the issue of disassociation in the first two hours of the technology being administered, meaning that it would be likely that carers would need to be involved. Patients with other mental health conditions, such as agoraphobia, which made it difficult to leave the house, would see the need to receive the treatment in a clinical setting as a significant disadvantage and barrier. Also, some patients might have concerns about the possible stigma associated with being seen to attend a mental health facility. These problems might be overcome if community nurses were enabled to deliver the technology in people's homes.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	We believe that a group of patients that might benefit more from the technology than others are those with suicidal ideation for whom urgent alleviation of symptoms was desirable. This could apply especially where ECT would not be not appropriate for a person in a particular group of patients, for example, those who suffer from epilepsy, or older people; where it could not be accessed urgently enough; or where a patient would be too anxious or afraid to undergo the procedure.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Groups of people who would have difficulties using the technology without assistance would be those whose condition, for example, paraplegia, would not allow them to lean their head far enough back for the nasal spray to be administered, and those without the manual dexterity to administer it themselves. Other groups who might have difficulty in using the technology are those with mobility problems who would need assistance in attending a clinic, and those for whom the treatment might need to be administered outside a clinic, for example, patients in a care or nursing home or hospital where it would not be appropriate or feasible for them to be taken to a clinic. Patients living in isolated rural communities might also experience difficulty in accessing the technology because of the need to have it delivered in a clinical setting. Some patients might be caused anxiety by the need for the technology to be administered in a clinical setting, or might not find the side effects acceptable, for example, the dissociation that can result in the first two hours after administration. Patients who had a religious or cultural difficulty with taking antidepressant treatment might not find the technology acceptable, but the objection would be likely to apply equally to existing antidepressant treatment. The association of the technology with the recreational drug ketamine might also present a difficulty for some patients and carers.

	However, it is estimated that up to two thirds of patients receiving antidepressant medication in tablet form (all existing medications) are non-compliant to some degree, and for those with TRD, this could exacerbate their condition. Delivery of this new technology in a clinical setting could help non-compliant TRD patients, provided there were no barriers to accessing a clinic or those barriers could be overcome by a community nurse visiting the patient at home. Evidence relating to difficulties experienced by people in taking antidepressant medication could help the committee to identify any potential difficulties in relation to this new technology.
Other issues	
13. Are there any other issues that you would like the committee to consider?	This is an innovative technology in the treatment of depression. It has a significantly different mechanism of working from existing antidepressants, acting on the NDMA pathway, and is administered via a nasal spray under clinical supervision. These two features make it significantly different from other treatments for depression. For patients with treatment-resistant depression who have not responded to existing antidepressant treatments, the treatment offers the potential for improved compliance with medication; the alleviation of symptoms that could result in a much improved quality of life for patients and carers; and greater help in preventing suicide in those patients with suicidal ideation as a result of their condition.
Key messages	

14. In up to 5 bullet points, please summarise the key messages of your submission:

- TRD can have a very detrimental effect on all areas of the lives of patients and carers, including the mental health of carers.
- Patients experience a wide range of symptoms almost daily, and 80 % report suicidal thoughts in the previous 12 months.
- Side effects of existing antidepressants affect the quality of life of 84% of patients, and 56% of patients and carers regard them as ineffective.
- For patients with TRD there is a loss of hope that any treatments might be helpful or effective.
- 84% of patients and 43% of carers report a negative impact on work or study, and both groups experience a negative financial impact.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Esketamine for treatment-resistant depression [ID1414]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**R. Hamish McAllister-Williams**
2. Name of organisation	**Newcastle University and** **Cumbria, Northumberland, Tyne and Wear NHS FT**

3. Job title or position	**Professor of Affective Disorders and Hon. Consultant Psychiatrist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To maximise symptom control, reduce risks e.g. of suicide, reduce risk of relapse and optimise psychosocial functioning and quality of life.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The accepted definition of "response" in the treatment of depression (e.g. as recognised by EMEA and FDA) is a ≥ 50% improvement in depression symptom severity as assessed using a recognised scale (e.g. HDRS, MADRS, QIDS etc). Remission is defined on a scale specific basis as minimal depressive symptoms.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Very much so. Unfortunately a significant minority of patients fail to show a response (as defined above) despite multiple serial trials of currently available medication, psychotherapy or neurostimulatory treatment.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	There is an entire NICE Guideline on the management of depression. It is not possible to summarise it here. Treatment modalities include pharmacotherapy (antidepressants plus augmentation options), psychosocial interventions (e.g. cognitive behavioural therapy, exercise) and neurostimulatory treatments (e.g. ECT, TMS and VNS).
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes. NICE CG90. In addition, in the UK, the British Association for Psychopharmacology guidelines are very influential since they provide clearer and more detailed guidance on the use of medication than in NICE CG90. These are published (Cleare et al. J Psychopharmacol. 2015 May;29(5):459-525)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is significant variation in the way that individual GPs manage depression, and the relative weight they give to different modalities of treatment. In secondary care, there are massive difference in the treatments used by psychiatrists – some of this evidence based, much of it not. Audits and research frequently identify issues. For example a recent finding that 72% of people in primary care who are on an antidepressant to which they are not responding have been on this same drug for more than a year (Wiles N et al. (2018) *Br J Gen Pract* 68:e673-e681). This suggests that these people aren't really on any pathway, whether or not there is supposedly one there. The issue is that patients who have treatment resistant depression feel intensely hopeless due to a) this being a core symptom of depression and b) the fact that they had not responded to a number of treatments. Why, when they are feeling so hopeless, would they go back to their GP to seek further treatment? If they are not proactively followed up, they fall out of contact.
• What impact would the technology have on the current pathway of care?	It would provide a potential extra medication option with a totally different mechanism of action. It may also help with regards the acute management of suicide risk.

11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No. The treatment has to be given in a hospital location with patients monitored for 2 hours afterwards. This is clearly very different to patients being prescribed an SSRI that they take at home.
• How does healthcare resource use differ between the technology and current care?	Facilities and staff will be required to provide the treatment in a safe environment and monitor patients in the subsequent two hours or so.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care in a variety of settings. Potentially in time , after experience of using the treatment, an important question is whether the treatment could be administered to patients in their own home under the supervision of a Crisis and Home Treatment Team.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Significant investment in training and staff to be able to administer the treatment. It is potentially possible that there would NOT need to be significant investment in infrastructure since it may be possible to identify various places within existing building to administer treatment (e.g. ECT clinics, wards, day hospitals etc)
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Potentially yes.

• Do you expect the technology to increase length of life more than current care?	Yes. The evidence to date is that the drug has a specific anti-suicidal effect dissociable from its antidepressant effect. In addition, evidence more generally suggests that the successful treatment of depression leads to a reduction in all cause mortality.
• Do you expect the technology to increase health-related quality of life more than current care?	In patients not responsive to current treatment – yes.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes. Patients with treatment resistant depression. Possibly an alternative to ECT
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	More difficult than current medication. Has to be administered under supervision, with monitoring for 2 hours afterwards. However, this is less difficult than giving ECT which may be the alternative for these patients.

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	It is extremely difficult to precisely define groups of depressed patients who might be more appropriate for one treatment or another. This will largely be based on failure to respond to previous treatments. However, there is vast differences in views as to how many treatments should be failed, what constitutes a failure (e.g. in terms of doses needed to have been tried), whether intolerance counts, whether psychotherapy or e.g. ECT counts. Rules could be employed around depression rating scale changes required for ongoing treatment. Perhaps the most important rule is probably that all patients receiving treatment be entered on a registry to try to prevent “doctor or clinic shopping”. This has been documented to have happened in the USA with the use of iv ketamine. It may be easier to address the issue in the NHS, but this does not preclude patients receiving treatment in private clinics outside of the NHS in addition to NHS treatment.
16. Do you consider that the use of the technology will	Reduction in suicide risk.

result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. Novel mechanism of action. Possible alternate treatment to ECT. Only treatment currently available that appears to have an acute anti-suicidal effect in patients with depression.
• Is the technology a 'step-change' in the management of the condition?	Yes. (excluding the use of IV ketamine which is very sparsely available in the UK)
• Does the use of the technology address any particular unmet need of the patient population?	Yes. Lack of response. Additionally it is much easier to administer than IV ketamine.

18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Adverse effects tend to be very short lived. There is a concern around the use of the treatment in the longer term. It is not known, for example, how many courses of treatment are acceptable per year. It is also not known, if the treatment is fully available on an as needed basis, how frequently patients will seek course of treatment.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	No. The treatment was given far earlier in the treatment pathway than is likely in current UK practice. In general it is not recommended to change two treatments at the same time. The esketamine studies required patients to go onto a new conventional antidepressant at the same time as starting the course of esketamine.
• If not, how could the results be extrapolated to the UK setting?	Hard to say. Response rates are likely to be lower in patients who have failed more treatments before receiving esketamine.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Mood, suicidality, quality of life. Yes.
• If surrogate outcome measures were used, do they adequately predict	

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	There remains a lingering question regarding balder issues is patients have repeated course, or manage to obtain courses from multiple sources.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatment(s)?	No
22. How do data on real-world experience compare with the trial data?	I am not aware of real-world data on esketamine. Real world data of the use of IV ketamine, if anything, is better than the esketamine trials.
Equality	

23a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not that I am aware of.
23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. In clinical practice, what measures are used to define 'moderate to severe' depression?	Most of the time it is simple clinical impression. ICD-11 criteria for depression uses a simple symptom count to define this. The most robust way is to use a scale to assess depression severity (e.g. PHQ-9, QIDS, HDRS, MADRS). This is recommended, but rarely done in practice.
25. What is considered to be an adequate response to antidepressant treatment?	This is a strange question. What is adequate from a patient's perspective is likely to be very different to a doctor's or a health service managers perspective. "Adequate" also implies that there is some level of improvement, less than back to normal levels of functioning, that is OK. This is not the goal of treatment. The goal should be full remission of symptoms, since this is associated with a significant decreased relapse rate, and functional improvement only occurs after full remission. The reality is that a significant minority of

	patients struggle to attain full remission. It is these patients, as much as those who show no response to current antidepressants, who could potentially benefit from esketamine. **NB – a patient can show a response (≥ 50% improvement in depression rating scale score) and STILL have moderate to severe depression.**

Key messages

26. In up to 5 bullet points, please summarise the key messages of your statement.

- This is a potentially exciting new therapeutic option with a novel mechanism of action
- In addition to treating depression, the drug appears to have specific and dissociable anti-suicidal effects
- Its use does require in hospital administration with brief monitoring
- Whether the administration is seen as being more or less burdensome/expensive than current treatment depends upon what it is compared. It is more burdensome that standard antidepressants, but less so than ECT. Its use is likely to be at this interphase.
-

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NICE National Institute for Health and Care Excellence

Patient expert statement

Esketamine for treatment-resistant depression [ID1414]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Are you (please tick all that apply):	✓ a patient with the condition? a carer of a patient with the condition? a patient organisation employee or volunteer? other (please specify):
3. Name of your nominating organisation	
4. Did your nominating organisation submit a submission?	yes, they did no, they didn't ✓ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	yes, I agree with it no, I disagree with it I agree with some of it, but disagree with some of it other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	
7. How did you gather the information included in your statement? (please tick all that apply)	✓ I have personal experience of the condition I have personal experience of the technology being appraised ✓I have other relevant personal experience. Please specify what other experience: ✓ Being treated with Ketamine via IM and IV for over a year for Treatment Resistant Depression. I am drawing on others' experiences. Please specify how this information was gathered:

Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with Treatment Resistant Depression is challenging for a number of reasons. As the name suggests it doesn't respond to typical depression treatments and therefore is a chronic condition to be managed. It brings with it a sense of hopelessness which affects all areas of your health and life. It can make other mental health conditions and physical health conditions harder to manage e.g. contributing to the chronic pain cycle. When new treatments come along it is easy to fall into a trap of thinking 'this will be the thing which fixes my depression' and then if it doesn't it exacerbates the depression thus maintaining a cycle of hopelessness. It can be an unhelpful cycle and means that anticipation and hope for new treatments needs to be managed and supported. I think that there also can be a sense of helplessness/hopelessness from those around you as it can be difficult for them to know how to help. There can be a sense of uncertainty for carers 'is this a bad day or a better day?' The condition changes the person suffering from it and leads to a toll or 'black shadow' over them and also those around them. There can be expectations from professionals as to how carers should be coping or acting with this difficult condition.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	In my experience it has been difficult to access the support I need. It is hard to access long term support as a lot of resources are time limited. It would be helpful to have a holistic bio-psycho-social approach but that is a model which isn't always imbedded within services so instead there is a focus and reliance on medication and less on the psychological and social factors which have caused/maintained the condition, such as looking at coping strategies and talking therapy.
10. Is there an unmet need for patients with this condition?	I believe the unmet need is a consistent offer of long term support in secondary care, be that psychological therapy or support and monitoring.

Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	My experience of Ketamine is that it provides ‘breathing space’ as the dissociation acts as distance between you and your thoughts which helpful and can be used to achieve positive change. It lifts my mood (temporarily) enabling me to socialise more easily, to think more clearly and challenge unhelpful thoughts and to sleep better. I have been able to use the opportunity of a lifted mood Ketamine provides to do things which have helped such as attending social events. The distance between my thoughts and my low mood has helped me manage them better. I feel that if I could have access to psychological therapy (I am on a 12 month waiting list) then I would be able to use the opportunity Ketamine brings more constructively to work on cognitive and behavioural changes with specialist support. I have found the regular contact with the clinic helpful as the staff monitor my mood (through online questionnaires) and have got to know me and offer support whilst I am taking the ketamine.

Disadvantages of the technology

12. What do patients or carers think are the disadvantages of the technology?	The lift in your mood is temporary and last around 24-48 hours. It's important that you use the improvement in your mood constructively and as an opportunity, i.e through doing something which will improve your quality of life such as challenging your thoughts, socialising, creating positive memories. It helps to have therapeutic support to be able to do this as when you have been severely depressed for a long time it is hard to know how to cope with an improvement. Likewise it is important that you are prepared that it is temporary otherwise it will lead into an unhelpful cycle of feeling low, feeling a bit better, then feeling more low as you no longer feel better. I feel that ketamine and esketamine would work better with psychological therapy alongside so that it can be used to help create cognitive and behavioural changes which can be made and maintained. Ketamine is not a miracle it is a tool which if worked with can help you. I have found it helpful to think that it provides an opportunity to work on your depression rather than a holiday away from it. It has a complexity to it as it is not as straight forward as other medications that you can take and just wait to work you need to work with it. The dissociative side effects need to be managed, these can feel distressing and can make you feel anxious. There needs to be supervision at a clinic for two hours so that you have access to support if needed and so that you can be monitored, especially when you first take it. I have found that every time I have the ketamine treatment my experience of it is different (I have been on it once/twice a week for over a year). There has always been a baseline of some dissociation but sometimes it is very physical (feeling spaced out, dizzy, sedated, nauseous, blurred vision, harder to think/speak, sensitivity to noise and light) other times it is more psychological (hallucinating, feeling unreal, dreamlike, sensory disturbances) other times it is both of these combined. It is hard to predict how the experience will be. It is helpful therefore to have nurses at the clinic who understand this and get to know you and the support you will need. Side effect wise after my Ketamine IM I am dizzy, often nauseous, spaced out, dissociated, unsteady. As outlined above I sometimes hallucinate which can feel distressing. After the treatment, you are unable to drive and therefore need someone to collect you. My experience is that I feel spaced out and more tired for the rest of the day, I often have a headache.

Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Continued from last question: It can paradoxically be difficult to feel a bit better for a while as it is only temporary. It can feel challenging to have an experience of feeling less depressed as it gives you a taste of what life could be like if you were feeling a bit better and then it goes away. 13. If the patient has had difficult and distressing experiences with dissociation in the past then they may need extra support to be able to manage the dissociative experiences the medication can cause. This may mean psychological therapy or specialist therapeutic support. I found it helpful to learn coping strategies to use during the treatment, such as listening to music on headphones, visual cues for reassurance such as items with positive memories from home (to help ground me) and having a nurse sit with me if I get distressed. If the patient has been severely depressed for a long time then they may need additional support to manage their mood changing as outlined above.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	People with additional physical health conditions may require additional support, e.g. after treatment can be more exhausted and need further rest.

Other issues	
15. Are there any other issues that you would like the committee to consider?	There is a risk that if the patient feels a benefit from esketamine (after feeling severely depressed for a long time) that they may seek out ketamine or further esketamine (for instance from private providers) that is one of the reasons that a form of central regulation and monitoring of dosage would help promote safe prescribing. As using ketamine/esketamine for depression is relatively new are the long term effects for using the medication in this way fully known? The long term cognitive effects of 'Spravato' have not been evaluated beyond a year (from Spravato's prescribing information)

Key messages

16. In up to 5 bullet points, please summarise the key messages of your statement:

- It is important that hope/hopelessness and anticipation is managed in terms of new treatments for Treatment Resistant Depression
- The medication provides an opportunity which needs to be engaged with to be effective and to make sustained changes. I strongly feel this would work better with accompanying psychological support/therapy due to the complexity of the treatment.
- For safety I think it is important that there is a form of central regulation for the medication which monitors dosage and manages the potential risks of patients seeking different types of the medication from other sources

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NICE National Institute for Health and Care Excellence

NHS commissioning expert statement

Esketamine for treatment-resistant depression [ID1414]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. Your response should not be longer than 10 pages.

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- Your response should not be longer than 10 pages.

About you	
1. Your name	**J Peter Pratt**
2. Name of organisation	**NHS England**

3. Job title or position	**Former Head of MH & LD medicines strategy NHSE/NHSI (to July 2019) – now supporting NHSE specialised commissioning (pharmacy) in an advisory capacity**
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? ☐ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? **x**☐ other (please specify): Former Head of MH & LD medicines strategy NHSE/NHSI – now supporting NHSE specialised commissioning (pharmacy) in an advisory capacity
Current treatment of the condition in the NHS	
5. Are any clinical guidelines used in the treatment of the condition, and if so, which?	I expect /hope that the update of NICE depression in adults [GID-CGWAVE0725] will include reference to the place of this treatment – which links to the outcome of the TA
6. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across	Management of depression and TRD in adults is well defined , but the use of this technology is likely to sit outside of the current pathways due to 1) It will be a schedule 2 controlled drug 2) The need for administration in a health care setting 3) The need for appropriate post dose monitoring following administration 4) The need to use in combination with a “new” antidepressant

the NHS? (Please state if your experience is from outside England.)	5) Uncertainty about "duration" of a course of treatment and the number of repeated "courses" over time.(i.e will esketamine use become "lifelong" treatment for some people?) 6) (note points 2 & 3 could apply to the provision of ECT) I note the FDA has approved the use of this treatment in the US – but approval was not a unanimous decision by the approval committee
7. What impact would the technology have on the current pathway of care?	It is likely to require amendment/adjustments to take account of the issues highlighted in 6) above.
The use of the technology	
8. To what extent and in which population(s) is the technology being used in your local health economy?	It is very difficult to predict the likely uptake of this technology – using a definition of treatment resistant depression (TRD) as a failure to response to an adequate trial of 2 antidepressants could indicate the potential for a substantial number of people beingconsidered to be "eligible" . Current guidelines include the use of combination treatments and/or ECT as options for TRD. It will be important to clarify and define the point at which a person is deemed to be eligible for consideration of this technology in relation to the established treatment options for TRD. The complexity of use (as highlighted in 6) above is likely to limit the use if additional staffing and "premises" need to be established in order to administer the technology.
9. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	As highlighted in 8) above the place of esketamine in relation to combination treatments – including non-pharmacological interventions - and/or ECT is not clear. Local clinical judgements are likely to vary with some clinicians adoption a low threshold for use – and others adopting a very high threshold for use
• How does healthcare resource use differ	"If" the technology is considered safe, effective and cost effective - this could offer an alternative to in-patient admission – or "out of area treatment" – However most MH services are not well established to

between the technology and current care?	offer health care settings where esketamine administration and post dose monitoring can be undertaken in line with the proposal for use. Adoption of the use of esketamine nasal spray will require adjustments in the configuration of services for people with TRD.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This technology is not appropriate for use in primary care. The outcome of the TA review will be critical in determining whether this should be a "specialist clinic" intervention only – or an intervention available to mental health secondary care services in general. On the basis of the information available to me, I would suggest that if the intervention is given a positive TA - then the uncertainty about facilities as well as safety, efficacy and appropriate use , would indicate restriction to use specialist clinics only.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Suitable premises for administration and post dose monitoring Adequate staffing for administration and post dose monitoring Adequate storage, transportation, disposal and monitoring facilities in relation to the controlled drug status of this drug Adequate "medical" equipment to deal with the immediate management of any post dose medical complications Given the specialist nature of this intervention there will be no option to transfer care to primary care under any local "shared care" treatment agreements. Therefore the acquisition costs, pus all associated costs of administration and monitoring etc. will fall on the secondary care mental health service – whether that be as part of "normal" care or as a "specialist service" established within a mental health service. TRD services are not commissioned nationally as part of specialised commissioning arrangements and the "tariff" system does not apply. The "block contract" nature of funding secondary mental health care would create a substantial financial burden on mental health trusts if this technology was given a positive outcome.

	The drug and associated administration and monitoring costs would not be affordable within the current drug budgets allocated within mental health trusts (Estimated to be around £200 – £250million across all MH trusts in England) If this drug was given a positive TA without any additional financial uplift to support its use, the block contract /funding mechanisms would mean that Mental health trusts/CCG's would have to divert funding away from other services to make the drug available in line with the TA funding rules
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	It will be important to establish clear guidance on the duration of treatment and/or the number of courses of treatment an individual could/should receive over a period of time. Systems must be in place to guard against the unintended or inappropriate "drift" into long term/continuous treatment.
10. What is the outcome of any evaluations or audits of the use of the technology?	You may be aware that this drug is currently under consideration by the MHRA for an EAMS process for use in patients with major depressive disorder at immediate risk of suicide. It will be important for the NHS to manage any potential drift in use across and between the different indications of TRD and management of suicide risk. I understand that the company intends to use the EAMS process to collect audit type data relating to use in the NHS if it receives a positive EAMS opinion from MHRA.
Equality	
11a. Are there any potential equality issues that should be taken into account when considering this treatment?	It is important to ensure adequate safeguards against diversion, as well as "equity of access" to this treatment for people who may also be part of the criminal justice system.

11b. Consider whether these issues are different from issues with current care and why.	

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Esketamine for treatment-resistant depression

Produced by Kleijnen Systematic Reviews Ltd (KSR)

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None.

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Commercial in confidence (CiC) data are highlighted in blue throughout the report.
Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors
Robert Wolff acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Nigel Armstrong acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Titas Buksnys and Steve Ryder acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Debra Fayter and Stephanie Swift acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Caro Noake critiqued the search methods in the submission and contributed to the writing of the report. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AAP	Atypical antipsychotic
ACP	American College of Physicians
AD	Antidepressant
AE	Adverse event
AiC	Academic in confidence
ANCOVA	Analysis of covariance
APA	American Psychiatry Association
Aug	Augmentation
BSC	Best supportive care
CBT	Cognitive behavioural therapy
C-SSRS	Columbia-Suicide Severity Rating Scale
CADTH	Canadian Agency for Drugs and Technologies in Health
CDSR	Cochrane Database Systematic Reviews
CEA	Cost effectiveness analysis
CFB	Change from baseline
CG	Clinical guideline
CGI-S	Clinical Global Impression – Severity
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CiC	Commercial in confidence
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
DARE	Database of Abstracts of Reviews of Effects
DBS	Deep brain stimulation
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – Fifth edition
DSU	Decision Support Unit
EBM	Evidence-based medicine
epCS	Epidural cortical stimulation
ECT	Electroconvulsive therapy
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-3L	European Quality of Life-5 Dimensions – 3 levels
EQ-5D-5L	European Quality of Life-5 Dimensions – 5 levels
ERG	Evidence Review Group
ESK	Esketamine
ESK-NS	Esketamine nasal spray
EU	European Union
EUCTR	European Union Clinical Trials Register
FAS	Full analysis set
GAD-7	Generalised Anxiety Disorder – 7-item scale
GAD	Generalised anxiety disorder
GP	General practitioner
HAM-D	Hamilton Depression Rating Scale
HCP	Healthcare professional
HCRU	Healthcare resource use
HDRS	Hamilton Depression Rating Scale
HR	Hazard ratio
HRQoL	Health-related quality of life
HSI	Health status index
HTA	Health technology assessment
IDMC	Independent data monitoring committee
ICER	Incremental cost effectiveness ratio

ICTRP	International Clinical Trials Registry Platform
INAHTA	International Network of Agencies for Health Technology Assessment
IND	Induction phase
IQR	Interquartile range
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IWRS	Interactive web response system
KM	Kaplan–Meier
KSR	Kleijnen Systematic Reviews
LS	Least squares
LYG	Life years gained
MA	Maintenance phase
MADRS	Montgomery-Åsberg Depression Rating Scale
MAOI	Monoamine oxidase inhibitor
MDD	Major depressive disorder
MDE	Major depressive episode
MECIR	Methodological Expectations of Cochrane Intervention Reviews
MeDRA	Medical Dictionary for Regulatory Activities
MeSH	Medical subject headings
NA	Not applicable
NCPE	National Centre for Pharmacoeconomics
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
nortrip	Nortriptyline
NR	Not reported
NRI	Norepinephrine reuptake inhibitor
NS	Nasal spray
OAD	Oral antidepressant
OC	Observed cases
OP	Optimisation phase
OR	Odds ratio
PAS	Patient access scheme
PBAC	Pharmaceutical Benefits Advisory Committee
PBO	Placebo
PBO-NS	Placebo nasal spray
PGI-S	Patient Global Impression – Severity
PHQ-9	Patient Health Questionnaire – 9 questions
PRIMA	Preliminary Independent Model Advice
PSA	Probabilistic sensitivity analyses
PSS	Personal social services
PWC-WS	Physicians Withdrawal Checklist- Withdrawal Symptoms- subscale
QALY	Quality-adjusted life year
QIDS	Quick Inventory of Depressive Symptomatology
QLDS	Quality of life in depression scale
RCT	Randomised controlled trial
RePEc	Research papers in economics
SAD	Seasonal affective disorder
SAE	Serious adverse events
SARI	Serotonin antagonist and reuptake inhibitor
SD	Standard deviation
SDS	Sheehan disability scale
SLaM	South London and Maudsley
SLR	Systematic literature review
SMC	Scottish Medicine Consortium

SNRI	Serotonin–norepinephrine reuptake inhibitor
SR	Systematic review
SSRI	Selective serotonin reuptake inhibitor
TA	Technology appraisal
TADS	Tavistock adult depression study
TAU	Treatment as usual
TCA	Tricyclic antidepressant
TeCA	Tetracyclic antidepressant
TMS	Transcranial magnetic stimulation
TRD	Treatment-resistant depression
UK	United Kingdom
US	United States (of America)
USA	United States of America
VNS	Vagal nerve stimulation
WHO	World Health Organization
WPA	World Psychiatric Association
WTP	Willingness-to-pay
XR	Extended release

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1. Executive summary

1.1 Critique of the decision problem in the company's submission

The final scope issued by the National Institute for Health and Care Excellence (NICE) defined the decision problem as follows:

- Adults with treatment-resistant depression (TRD)
- Esketamine nasal spray (ESK-NS) in addition to established clinical management
- Comparators including
    - Selective serotonin reuptake inhibitors (SSRIs)
    - Tricyclic antidepressants (TCAs)
    - Monoamine oxidase inhibitors (MAOIs)
    - Serotonin–norepinephrine reuptake inhibitors (SNRIs)
    - Vortioxetine
    - Combination or augmentation treatments (with lithium or an antipsychotic)
    - Electroconvulsive therapy (ECT)
    - Best supportive care (BSC)
- Outcomes of interest
    - Response to treatment (including response rate and time to response)
    - Relapse (including relapse rate and time from remission to relapse)
    - Severity of depression
    - Cognitive dysfunction
    - Remission of symptoms
    - Anxiety
    - Sleep quality
    - Hospitalisation
    - Functioning and associated disability
    - Mortality
    - Adverse effects of treatment (including adverse effects of treatment discontinuation)
    - Health-related quality of life (HRQoL)

Regarding the population, the evidence presented in the company submission (CS) was broadly in line with the NICE scope. However, there are some important discrepancies with the scope, which include the specification of moderate to severe depression. Also, the main clinical and cost effectiveness evidence was of questionable applicability to those in the age group 65 years and above, although the company did perform some mitigatory adjustment to the cost effectiveness model, see section 1.3.

The intervention defined and presented in the CS was ESK-NS co-administered with a newly initiated oral antidepressant (OAD). This is in line with the expected label indication (*"ESK-NS in combination with an SSRI or SNRI for treatment resistant major depressive disorder in adults who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode"*).

The comparators in the decision problem of the CS were in line with the NICE scope. However, the company suggested adding mirtazapine, a tetracyclic OAD, to the list of comparators. Subsequently, mirtazapine was a comparator in network meta-analyses (NMAs) presented in the CS.

The outcomes investigated in the CS reflected the NICE scope. However, some outcomes were not reported for the main trials in the CS, namely cognitive dysfunction, hospitalisation and sleep quality.

No patient access scheme (PAS) was presented in the CS. Given the method of administration of ESK-NS requiring supervision by a healthcare professional, it will be important to ensure that access to healthcare support will not inappropriately discriminate against individuals for whom geography may pose a challenge.

1.2 Summary of clinical effectiveness evidence submitted by the company

The CS and response to clarification provided sufficient details for the Evidence Review Group (ERG) to appraise the searches for eligible studies. A good range of resources were searched and the majority of searches were well documented making them transparent and reproducible. Additional searches of HTA agencies, clinical trials registries and conference proceedings were reported. However, the ERG was concerned about the language bias of restricting searches to English language only as this is not in line with current best practice.

Six studies formed the evidence base for ESK-NS. Four of these were randomised controlled trials (TRANSFORM-1, TRANSFORM-2, TRANSFORM-3, SUSTAIN-1) and two were open label extension studies (SUSTAIN-2, SUSTAIN-3). The two main trials which informed the economic modelling were TRANSFORM-2 and SUSTAIN-1.

TRANSFORM-2 enrolled adults with a history of non-response to at least two antidepressants in the current episode with one antidepressant assessed prospectively while SUSTAIN-1 assessed maintenance of effect (prevention of relapse). Both trials compared ESK-NS plus a newly initiated OAD to a newly initiated OAD plus placebo and both involved flexible dosing of 56 mg/ 84 mg of ESK-NS. ESK-NS was given for four weeks in TRANSFORM-2 and patients were either followed-up for 24 weeks or joined SUSTAIN-1. SUSTAIN-1 also enrolled patients directly who had not taken part in TRANSFORM-2. In SUSTAIN-1, ESK-NS was given until relapse or trial termination.

In TRANSFORM-2, ESK-NS + OAD in comparison to placebo nasal spray (PBO-NS) + OAD showed a statistically significant reduction on the Montgomery-Åsberg Depression Rating Scale (MADRS) at day 28 (difference in least squares means -4.0, 95% confidence interval (CI) -7.31 to -0.64). Of note, there are differences between the type of OAD for remission rates after 28 days, e.g. within the SSRI group: sertraline (odds ratio (OR) 1.38, 95% CI 0.26 to 7.22) vs. escitalopram (OR 4.71, 95% CI 1.08 to 20.63). The trial also showed differences in response rate and remission rate, respectively, between the two groups. Other reported outcomes were in favour of the intervention (see Table 1.1).

In SUSTAIN-1, the percentage of relapse was lower in the ESK-NS + OAD (stable remitters: 26.7%, stable responders: 25.8%) group in comparison to participants receiving PBO-NS + OAD (45.3% and 57.6%, respectively). The trial also showed time to relapse to be in favour of the intervention group for both, stable remitters (hazard ratio (HR) 0.49, 95% CI 0.29 to 0.84) and stable responders (HR 0.30, 95% CI 0.16 to 0.55). Other reported outcomes were in favour of the intervention (see Table 1.2).

In the induction phase of TRANSFORM-2, more adverse events were observed in patients treated with ESK-NS + OAD compared to those receiving PBO-NS + OAD (85.2% vs. 60.6%, see Table 1.3). In SUSTAIN-1 more adverse events were seen in the ESK-NS + OAD group in the maintenance phase (82.2% vs. 45.5%) and the follow-up phase (11.0% vs. 7.8%), see Table 1.4. Potential adverse events, especially psychiatric disorders (47.8% vs. 19.3% in TRANSFORM-2), need to be considered before considering ESK-NS as a treatment option for patients with TRD.

The main limitation of these trials in terms of this appraisal is that they only included patients aged 18 to 64 years of age. Furthermore, the trials in the CS excluded patients with moderate/severe alcohol abuse according to Diagnostic and Statistical Manual of Mental Disorders – Fifth edition (DSM-5)

criteria. The committee will need to consider whether evidence in the CS on effectiveness and safety of ESK-NS can be generalised to those with a dual diagnosis of depression and alcohol misuse.

The trials in the CS also excluded patients who had suicidal/homicidal ideation/intent within six months prior to screening per the investigator's clinical judgements and/or based on Columbia-Suicide Severity Rating Scale (C-SSRS) or a history of suicidal behaviour in the 12 months prior to screening. Again, the committee will need to consider if the evidence in the CS on effectiveness and safety of ESK-NS can be generalised to this vulnerable population.

As discussed in section 1.3, the ERG noted a lack of clarity on dosing in the included trials which might impact on the generalisability of these trials.

Furthermore, the ERG noticed the short-term nature of the trials which is a concern, especially for safety-related outcomes. SUSTAIN-3, when reported in full, should give a fuller picture of any potential longer-term risks with ESK-NS including those related to withdrawing from treatment.

The company stated that the NMA was not considered sufficiently robust to inform the cost effectiveness analysis (CEA). The ERG could run the NMA and obtained results which were very close to those provided by the company so they have no concerns about the NMA analysis methods. However, the main concerns about the NMA results are due to the clinical and methodological differences between the studies included in each network.

Table 1.1: Summary of efficacy results of TRANSFORM-2

Outcome	ESK-NS + OAD	OAD + PBO-NS
MADRS[a,b]		
Change from baseline (observed cases)		
MMRM (difference in LS means, SE, 95% CI)[d]	-4.0 (1.69, -7.31 to -0.64)	
Onset of clinical response (FAS)		
Generalised Cochran-Mantel-Haenszel test[e]	OR 1.79 (95% CI 0.57 to 5.67)	
Response and remission (observed cases)		
Response rate[f]	69.3%	52.0% (unadjusted)[g]
		34.0% (adjusted)[g]
Remission rate[h]	52.5%	31.0% (unadjusted)[g]
		18.0% (adjusted)[g]
CGI-S (observed cases)[i]		
MMRM (difference in LS means, SE, 95% CI)[d]	-0.4 (0.17, -0.72 to -0.04)	
PHQ-9 (observed cases)[i]		
MMRM (difference in LS means, SE, 95% CI)[d]	-2.4 (0.88, -4.18 to -0.69)	
GAD-7 (observed cases)[j]		
ANCOVA (difference in LS means, SE, 95% CI)[k]	-1.0 (0.67, -2.35 to 0.28)	

Outcome	ESK-NS + OAD	OAD + PBO-NS
SDS (observed cases)[l]		
MMRM (difference in LS means, SE, 95% CI)[b]	-4.0 (1.17, -6.28 to -1.64)	
EQ-5D (observed cases)[b,m]		
Change from baseline to day 28 (mean, SD)	N=104, 0.310 (0.2191)	N=100, 0.235 (0.2525)
Other outcomes defined in the final scope		
Cognitive dysfunction	NR	NR
Hospitalisation	NR	NR
Sleep quality	NR	NR

Based on Tables 7, 19, 21, 23, 24, 26, 45 and Figure 15 of the CS as well as the CSR

[a] Related to response, severity of depression, and remission; [b] Used in the economic model; [c] = Table 19 of the CS reported this as "109". Error corrected by the ERG; [d] Change from baseline was the response variable and fixed effect model terms for treatment, day, country, class of OAD (SNRI or SSRI), treatment-by-day, and baseline value were covariates; [e] Adjusted for region and class of OAD (SNRI or SSRI); [f] ≥50% reduction from baseline in MADRS total score; [g] See details in section 5.2.6.1; [h] MADRS total score of ≤12; [i] Related to severity of depression; [j] Related to anxiety; [k] Change from baseline was the response variable and treatment, country, class of OAD (SNRI or SSRI), and baseline GAD-7 value were covariates; only ANCOVA reported; [l] Related to functioning and associated disability; [m] = Related to health-related quality of life

ANCOVA = analysis of covariance; CGI-S = Clinical Global Impression; CI = confidence interval; CS = company submission; CSR = clinical study report; EQ-5D = European Quality of Life-5 Dimensions; ERG = Evidence Review Group; ESK = esketamine; FAS = full analysis set; GAD-7 = Generalised Anxiety Disorder – 7-item scale; HR = hazard ratio; LS = least squares; MADRS = Montgomery-Åsberg Depression Rating Scale; MMRM = mixed-effects model using repeated measures; NR = not reported; NS = nasal spray; OAD = oral antidepressant; OR = odds ratio; PBO = placebo; PHQ-9 = Patient Health Questionnaire – 9 questions; SD = standard deviation; SDS = Sheehan Disability Scale; SE = standard error; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

Table 1.2: Summary of efficacy results of SUSTAIN-1

Outcome	ESK-NS + OAD	OAD + PBO-NS
Time to relapse		
Stable remitters[a]		
Time to relapse	HR 0.49 (95% CI 0.29 to 0.84)	
Stable responders[b]		
Time to relapse	HR 0.30 (95% CI 0.16 to 0.55)	
MADRS (LOCF)[c,d]		
Change from baseline		
ANCOVA (difference in LS means, SE, 95% CI)[e]	Stable remitters[a]: -5.2 (1.82, -8.7 to -1.58)	
	Stable responders[b]: -7.4 (1.95, -11.30 to -3.55)	
Response/remission		
Responder at end of maintenance phase[f]	Stable remitters[a]: 67/89 (75.3%)	Stable remitters[a]: 48/86 (55.8%)
	Stable responders[b]: 41/62 (66.1%)	Stable responders[b]: 20/59 (33.9%)
Remitter at end of maintenance phase[f]	Stable remitters[a]: 58/89 (65.2%)	Stable remitters[a]: 36/86 (41.9%)

Outcome	ESK-NS + OAD	OAD + PBO-NS
	Stable responders[b]: 29/62 (46.8%)	Stable responders[b]: 15/59 (25.4%)
CGI-S (LOCF)[g]		
ANCOVA (difference in LS means, SE, 95% CI)[e]	Stable remitters[a]: P value 0.055[h]	
	Stable responders[b]: P value 0.002[h]	
PHQ-9 (LOCF)[g]		
Change from baseline		
ANCOVA (difference in LS means, SE, 95% CI)[e]	Stable remitters[a]: -2.4 (0.90, -4.20 to -0.65)	
	Stable responders[b]: -3.0 (0.93, -4.87 to -1.18)	
Response/remission		
Responder at end of maintenance phase	Stable remitters[a]: 72/89 (80.9%)	Stable remitters[a]: 57/86 (66.3%)
	Stable responders[b]: 48/61 (78.7%)	Stable responders[b]: 40/58 (69.0%)
Remitter at end of maintenance phase	Stable remitters[a]: 51/89 (57.3%)	Stable remitters[a]: 38/86 (44.2%)
	Stable responders[b]: 23/61 (37.7%)	Stable responders[b]: 12/58 (20.7%)
GAD-7 (LOCF)[i]		
ANCOVA (difference in LS means, SE, 95% CI)[e]	Stable remitters[a]: -1.7 (0.72, -3.12 to -0.28)	
	Stable responders[b]: -1.1 (0.72, -2.56 to 0.31)	
SDS (LOCF)[g]		
Change from baseline		
ANCOVA (difference in LS means, SE, 95% CI)[e]	Stable remitters[a]: -2.9 (1.30, -5.51 to -0.38)	
	Stable responders[b]: -4.7 (1.31, -7.30 to -2.10)	
Response/remission		
Responder at end of maintenance phase[f]	Stable remitters[a]: 58/83 (69.9%)	Stable remitters[a]: 43/78 (55.1%)
	Stable responders[b]: 42/60 (70.0%)	Stable responders[b]: 23/53 (43.4%)
Remitter at end of maintenance phase[f]	Stable remitters[a]: 48/83 (57.8%)	Stable remitters[a]: 30/78 (38.5%)
	Stable responders[b]: 25/60 (41.7%)	Stable responders[b]: 11/53 (20.8%)
EQ-5D (HIS score)[h]		
Change from baseline to end of maintenance phase (mean, SD)[f]	Stable remitters[a]: N=88, -0.067 (0.1180)	Stable remitters[a]: N=86, -0.096 (0.1484)
	Stable responders[b]: N=61, -0.023 (0.0753)	Stable responders[b]: N=58, -0.073 (0.1383)
Other outcomes defined in the final scope		
Cognitive dysfunction	NR	NR
Hospitalisation	NR	NR

Outcome	ESK-NS + OAD	OAD + PBO-NS
Sleep quality	NR	NR

Based on Tables 7, 8, 27, 28, 29, 30 of the CS

[a] Patients who were in stable remission at the end of the optimisation phase and who received at least 1 dose of intranasal study drug and 1 dose of OAD during the maintenance phase; [b] Patients who were stable responders (who were not stable remitters) at the end of the optimisation phase and who received at least 1 dose of intranasal study drug and 1 dose of OAD during the maintenance phase; [c] Related to relapse, severity of depression, and remission; [d] Used in the economic model; [e] Change from baseline was the response variable and treatment, country, and baseline value were covariates; [f] Variable duration (until relapse or study termination); [g] Related to severity of depression; [h] No further information reported, [i] Related to anxiety

ANCOVA = analysis of covariance; CGI-S = Clinical Global Impression; CI = confidence interval; CS = company submission; EQ-5D = European Quality of Life-5 Dimensions; ESK = esketamine; GAD-7 = Generalised Anxiety Disorder – 7-item scale; HSI = health status index; HR = hazard ratio; LOCF = last observation carried forward; LS = least squares; MADRS = Montgomery-Åsberg Depression Rating Scale; NR = not reported; NS = nasal spray; OAD = oral antidepressant; PBO = placebo; PHQ-9 = Patient Health Questionnaire – 9 questions; SD = standard deviation; SDS = Sheehan Disability Scale; SE = standard error

Table 1.3: Safety results of TRANSFORM-2

	ESK-NS + OAD	OAD + PBO-NS
Induction phase, n (%)	**N=115**	**N=109**
Overall summary		
AE	98 (85.2)	66 (60.6)
AE possibly related to nasal spray drug[a]	90 (78.3)	39 (35.8)
AE possibly related to OAD[a]	39 (33.9)	26 (23.9)
AE leading to death	1 (0.9)	0
≥1 serious AE	1 (0.9)	1 (0.9)
AE leading to nasal spray drug being withdrawn[b]	8 (7.0)	1 (0.9)
AE leading to OAD being withdrawn[b]	4 (3.5)	0
Follow-up phase, n (%)	**N=34**	**N=52**
Overall summary		
AE	9 (26.5)	12 (23.1)
AE possibly related to nasal spray drug[a]	0	1 (1.9)
AE possibly related to OAD[a]	1 (2.9)	3 (5.8)
AE leading to death	0	0
≥1 serious AE	1 (2.9)	0
AE leading to OAD being withdrawn[b]	0	0

Based on Tables 37 and 38 of the CS

Notes: 1) Incidence was based on the number of patients experiencing ≥1 AE, not the number of events; 2) AEs were coded using MedDRA version 20.0

[a] Study drug relationships of possible, probable, and very likely were included in this category; [b] An AE that started in the double-blind induction phase and resulted in discontinuation in the follow-up phase was counted as treatment-emergent in the double-blind induction phase; [redacted]

AE = adverse event; CS = company submission; ESK = esketamine; MedDRA = Medical Dictionary for Regulatory Activities; NS = nasal spray; OAD = oral antidepressant; PBO = placebo

Table 1.4: Safety results of SUSTAIN-1 (overall)

	Induction phase	Optimisation phase	Maintenance phase		Follow-up phase	
	ESK-NS + OAD (N=437)	ESK-NS + OAD (N=455)	ESK-NS + OAD (N=152)	OAD + PBO-NS (N=145)	ESK-NS + OAD during any phase (N=481)	OAD + PBO-NS for all phases (N=64)
AE, n (%)	336 (76.9)	335 (73.6)	125 (82.2)	66 (45.5)	53 (11.0)	5 (7.8)
AE possibly related to nasal spray drug, n (%)[a]	301 (68.9)	281 (61.8)	106 (69.7)	37 (25.5)	7 (1.5)	0
AE possibly related to OAD, n (%)[a]	71 (16.2)	61 (13.4)	13 (8.6)	9 (6.2)	3 (0.6)	0
AE leading to death, n (%)	0	0	0	0	0	0
≥1 serious AE, n (%)	13 (3.0)	11 (2.4)	4 (2.6)	1 (0.7)	3 (0.6)	0
AE leading to nasal spray drug being withdrawn, n (%)	22 (5.0)	5 (1.1)	4 (2.6)	3 (2.1)	NA[b]	NA[b]
AE leading to OAD being withdrawn, n (%)[c]	8 (1.8)	2 (0.4)	3 (2.0)	0	0[c]	0[c]

Based on Table 39 of the CS

Notes: 1) Incidence was based on the number of patients experiencing ≥1 AE, not the number of events; 2) AEs were coded using MedDRA version 20.0

[a] Study drug relationships of possible, probable, and very likely were included in this category; [b] Patients did not receive nasal spray during the follow-up phase; [c] An AE that started in the induction phase and resulted in discontinuation in a subsequent phase was counted as treatment-emergent in the induction phase.

AE = adverse event; CS = company submission; ESK = esketamine; MedDRA = Medical Dictionary for Regulatory Activities; NA = not applicable; NS = nasal spray; OAD = oral antidepressant; PBO = placebo

1.3 Summary of the key issues in the cost effectiveness evidence

Given that the NICE scope has no upper age limit, the ERG considers that a new version of the base-case model, submitted at the clarification stage should be used as an updated company base-case. It includes acute response and remission transition probabilities and utilities for major depressive episode (MDE), response and remission/recovery states from both TRANSFORM-2 and TRANSFORM-3, weighted by percentage in each age group such that if set to 0% for age >65 years one gets the same result as in the original base-case. This forms the starting point for the ERG base-case.

Regarding the intervention, ESK-NS + OAD, the ERG is concerned with the lack of clarity on dosing in TRANSFORM-2 and TRANSFORM-3 trials plus the complex dose changes in SUSTAIN-1 and SUSTAIN-2, which mean that it is difficult to know how applicable to clinical practice the transition probabilities estimated from the trials would be. The ERG recognises that adopting a mix of OADs as concomitant and comparator treatment is not ideal, given possible differences in effectiveness between individual OADs. There is the possibility that ESK-NS might be cost effective in combination with one OAD and not another. However, the ERG did not have the data to implement the required variation in all parameter estimates required for the model. The ERG is convinced that the limitations of the NMA are sufficient to exclude any other comparator except in a scenario analysis. However, the applicability to clinical practice of results would be highest in those patients who might be switched to one of the OADs prescribed in the trials. The ERG could find no errors or violations of modelling convention in the model. The only other key issues, which were substantial, were addressed as matters of judgement as much as was feasible by the ERG in forming the ERG base-case (issues 1 to 5) and three additional scenarios (issues 6 to 8):

1) Time horizon: although a lifetime time horizon is usually required, the company base case of five years in the company base case is longer than that in the previous appraisal in a similar population, technology appraisal (TA) 367. The ERG discovered that 20 years appeared to be the minimum to ensure no continued difference in cost or quality-adjusted life years (QALYs) in the model, see section 5.2.5.

2) Adjustment for placebo effect to the acute response or remission transition probabilities only for the comparator. This introduces a bias in favour of ESK-NS + OAD. The ERG considers that the company made a case for stating that some of the placebo response might be due to the effect of additional clinic visits in the trials, but is not convinced that this is the only factor and that it could only apply to ESK-NS + OAD in clinical practice, see section 5.2.6.1.

3) Discontinuation for reasons other than loss of efficacy. There was a lack of evidence to support there being no loss of efficacy on discontinuing ESK-NS and remaining only on OAD. [redacted]

4) Effect on mortality of ESK-NS + OAD. There was an absence of evidence for a treatment effect on mortality and no such treatment effect was applied in TA367, see section 5.2.6.7.

5) Cost of clinic visit for ESK-NS + OAD based on patient to nurse ratio of 1:6. This was believed by the ERG to be implausible in clinical practice. [redacted]

6) The considerable difference between ESK-NS + OAD and OAD in the loss of response and relapse transition probabilities. There was a lack of comparative evidence to inform these parameters, the

values being derived from different sources. Such a difference is also inconsistent with the judgement of the committee in TA367, see section 5.2.6.2.

7) The probabilities of response and remission at each line of subsequent therapy appeared to be too low when considering how they were implemented in the model and by comparison to the values in what was purported to be the data source, i.e. the STAR*D trial. There was also a lack of clarity in the method of calculation of these probabilities. It also seemed to be inconsistent with the method recommended by the committee in TA367, see sections 5.2.6.4 and 5.2.6.5.

8) Although the ERG is not convinced that the placebo response is explained entirely by the effect of additional clinic visits in the trials, it does consider that it is reasonable to attribute some of the effect on response and remission to be attributable to the extra clinic sessions. Therefore, it might be that the correct comparator should be OAD plus additional clinic sessions.

Searches were undertaken to identify economic evaluations and United Kingdom (UK) based resource use and HRQoL evidence. The CS provided sufficient details for the ERG to appraise the searches. An extensive range of databases and additional resources was searched.

1.4 Summary of the ERG's preferred assumptions and resulting ICER

The ERG base-case was created based on the preferred assumptions of the ERG regarding the issues 1) to 5), as listed in section 1.3. The results are shown in Table 1.5.

Table 1.5: ICER resulting from ERG's preferred assumptions (cumulative effect)

Preferred assumption		Section in ERG report	Cumulative ICER £/QALY
	Company base-case using 'adults and elderly' model		£7,699
1	Time horizon 20 years	5.2.5	£4,774
2	No adjustment for placebo effect to OAD Acute response or remission transition probabilities	5.2.6.1	£12,743
3	No discontinuation for reasons other than loss of efficacy	5.2.6.3	£53,254
4	No effect on mortality of ESK-NS + OAD	5.2.6.7	£55,478
5	Cost of clinic visit for ESK-NS + OAD based on patient to nurse ratio of 1:1	5.2.8.2	£62,566

ERG = Evidence Review Group; ESK = esketamine; ICER = incremental cost effectiveness ratio; NS = nasal spray; OAD = oral antidepressant; QALY = quality-adjusted life year

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

Two scenario analyses were created and added to the ERG base-case, based on the preferred assumptions of the ERG regarding issues 6) and 7), as listed in section 1.3. A further scenario was a response to the idea that the placebo effect might be the result of extra clinic visits, the cost for which should be equal in both the intervention and the comparator. The results are shown in Table 1.6.

Table 1.6: Exploratory analyses undertaken by the ERG (non-cumulative)

ERG assumption		Section in ERG report	ICER £/QALY
5	ERG's base-case using 'adults and elderly' model		£62,566
6	No difference between ESK-NS + OAD and OAD in the loss of response and relapse transition probabilities	5.2.6.2	£97,396
7	A decrease in response and remission was applied at each line of subsequent therapy (including BSC) by multiplying the values for OAD by a factor equal to the ratio of values in Step 3 versus Step 4 in STAR*D. These ratios are: 13.7/13.0 and 16.8/16.3 for remission and response respectively. Values estimated by the company from STAR*D were, for loss response, 22.2% for first line TRD and 22.8% for second line TRD and, for relapse, of 6.8% for first line TRD and 12.8% for second line TRD.	5.2.6.4, 5.2.6.5	£148,650
8	Cost of clinic visits for OAD set equal to that for ESK-NS + OAD	5.2.8.3	£53,911

BSC = best supportive care; ERG = Evidence Review Group; ESK = esketamine; ICER = incremental cost effectiveness ratio; NS = nasal spray; OAD = oral antidepressant; QALY = quality-adjusted life year, TRD = treatment-resistant depression

In conclusion, the result of the adjustments to the company base-case produced an ERG base-case with an ICER that was considerably higher that the company base-case, i.e. £62,566 instead of £7,699. Scenario analyses showed it could be as low as £53,911 and as high as £148,650. The approach taken to form the ERG base-case contrasts very strongly with the assumptions made in the CS, which at every stage enhanced the treatment effect on the basis of unclear justification, i.e. no or very little comparative evidence and rather opaque exposition. In particular, no data were provided to support the lack of impact on effectiveness of discontinuing ESK and all of the evidence to inform the company base case came from differential data sources for the intervention and the comparator beyond the acute phase. Despite a request for clarification, it remains unclear why more data from the SUSTAIN studies could not have been used to inform the relapse and loss of response rates for OAD.

Finally, the method of estimating all transition probabilities beyond the acute phase is unclear, both the precise data used from SUSTAIN-1 to inform those for ESK-NS + OAD and the calculations used to transform the data from STAR*D to inform those for OAD.

2. Background

2.1 Introduction

In this report, the Evidence Review Group (ERG) provides a review of the evidence submitted by Janssen in support of esketamine nasal spray (ESK-NS), trade name SPRAVATO®, for patients with treatment-resistant depression (TRD). In this section, the critique of the company's description of the underlying health problem and the overview of current service provision is outlined. The information is taken from section B.1.3 of the company submission (CS) with subsections referenced as appropriate.[1] The ERG also received a submission from the United Kingdom (UK) mental health charity SANE which presented the views of those with TRD.[2] The views were largely taken from a survey of 100 patients and 90 carers where patients had not responded to at least two different anti-depressants in the current depressive episode.

2.2 Critique of company's description of underlying health problem

The underlying health problem of this appraisal is TRD which the company described as '*major depressive disorder (MDD) that has not responded to at least two different treatments with OADs* [oral antidepressants] *in the current moderate to severe depressive episode*'.[1]

The company described MDD (also known simply as 'depression') as a '*severely debilitating and potentially life-threatening psychiatric disorder. MDD is characterised by recurrent episodes of persistent low mood and / or loss of interest or pleasure in (almost) all activities*'.[1] The accompanying symptoms as '*profound sleep disturbance, fatigue, change in appetite/weight, agitation or slowness of speech/action, diminished concentration, decreased libido, inability to enjoy life, and feelings of worthlessness*'.[1] The CS provided details of the diagnosis and the psychological, physical and social symptoms of MDD and TRD.

Regarding burden of disease, the company stated that '*around 3% of the UK population, about 2 million people are affected by MDD at any given time*'.[1] The CS identified that there could be over 130,000 patients in the UK who do not achieve remission with currently available OADs and therefore have TRD. The company further stated that '*the total estimated societal burden of TRD is £3.9 billion, the majority of which (80%) is due to carer burden and lost productivity*'[1] and that depression '*can develop at any age, but disproportionally effects* [sic] *people of working age*'.[1]

The company made several statements to illustrate the seriousness and impact on patients of TRD in relation to non-TRD: '*Episodes of depression in patients with TRD are typically three times longer than in patients with non-treatment resistant MDD* [CS reference 37] *and are associated with increased all-cause mortality* [CS reference 38]*, mainly due to a seven times increased risk of suicide relative to MDD* [CS reference 39].[1] The company added that '*at least 30% of patients with TRD attempt suicide at least once during their lifetime*'.[1]. In the survey conducted by SANE, 80% of patients reported having had suicidal thoughts in the previous 12 months.[2]

In the CS, the company further stated that '*The impact of TRD on patient health-related quality of life (HRQoL) is profound; patients with TRD have around 35% greater reductions in HRQoL compared with non-treatment resistant MDD, and report impairment in HRQoL in the range of metastatic cancer or acquired blindness* [CS reference 40].'[1] In the survey by SANE, 89% of patients reported TRD as having a major impact on their quality of life with 93% having a loss of interest or pleasure in all or almost all activities most of the day.[2]

The company described the negative impact on work activity of TRD. The survey by SANE commented that 45% of those with TRD had to stop work completely.[2]

The company concluded that '*there is a large unmet need for a safe, well-tolerated treatment with a rapid onset of action and durable efficacy*'.[1] This was supported by the SANE submission which stated that just 56% of patients and carers considered their current treatment to be effective and that 57% believed the benefits of antidepressants outweighed the adverse effects.[2]

ERG comment: The company provided a good overview of the underlying health problem of treatment-resistant depression, illustrating the seriousness of the condition and its impact on patients and their families. The ERG checked the references provided to support the statements in the CS. In general, these were appropriately referenced. However, some points should be noted:

- The ERG noted that TRD was not explicitly defined in the National Institute for Health and Care Excellence (NICE) scope and, as mentioned in the CS, is not consistently defined in clinical practice. The definition used by the company ('*major depressive disorder (MDD) that has not responded to at least two different treatments with OADs in the current moderate to severe depressive episode*')[1] reflects the expected licence for ESK-NS as well as the European Medicines Agency (EMA) guidance and therefore appears reasonable.[3]
- The ERG could not verify the estimate of 130,000 people with TRD, but given differences in the definition of TRD, this will be difficult to determine with certainty. The estimated societal burden of TRD of £3.9 billion was taken from a retrospective analysis of service use and costs of 129 Tavistock Adult Depression Study (TADS) patients.[4] In current (2015/16) prices the authors stated that costs would be approximately £25,000 per person. The authors acknowledged that costs in their study were higher than other studies using a different definition of TRD.
- The statement that those with TRD are at seven times increased risk of suicide relative to MDD was based on a Medicare analysis of with 4,639 patients with TRD and 7,524 with managed depression.[5] In this study, 7% of those with TRD and 1% with managed depression made a suicide attempt or self-inflicted injury. Although those with TRD are at increased risk of suicide, the exact difference between groups should be treated with some caution. In this context, it is important to note that in the main trials of this submission the following patients were excluded: '*Suicidal ideation/intent within 6 months prior to screening per the investigator's clinical judgements and/or based on C-SSRS* [Columbia-Suicide Severity Rating Scale]*, or a history of suicidal behaviour in the 12 months prior to screening*'[1]
- The company stated that '*in clinical practice semi-structured interviews are usually used to diagnose and monitor the level of depressive symptoms. Scoring systems for depression are rarely used in NHS* [National Health Service] *clinical practice*'.[1] The clinical trials for ESK-NS used the clinician-reported Montgomery-Åsberg Depression Rating Scale (MADRS) and the patient-reported outcome Patient Health Questionnaire-9 questions (PHQ-9) to measure the severity of depressive episodes. The company reported that '*feedback from NICE early scientific advice was that "the MADRS score is appropriate to measure outcomes in the ESK-NS clinical trials"*'.[1]

2.3 Critique of company's overview of current service provision

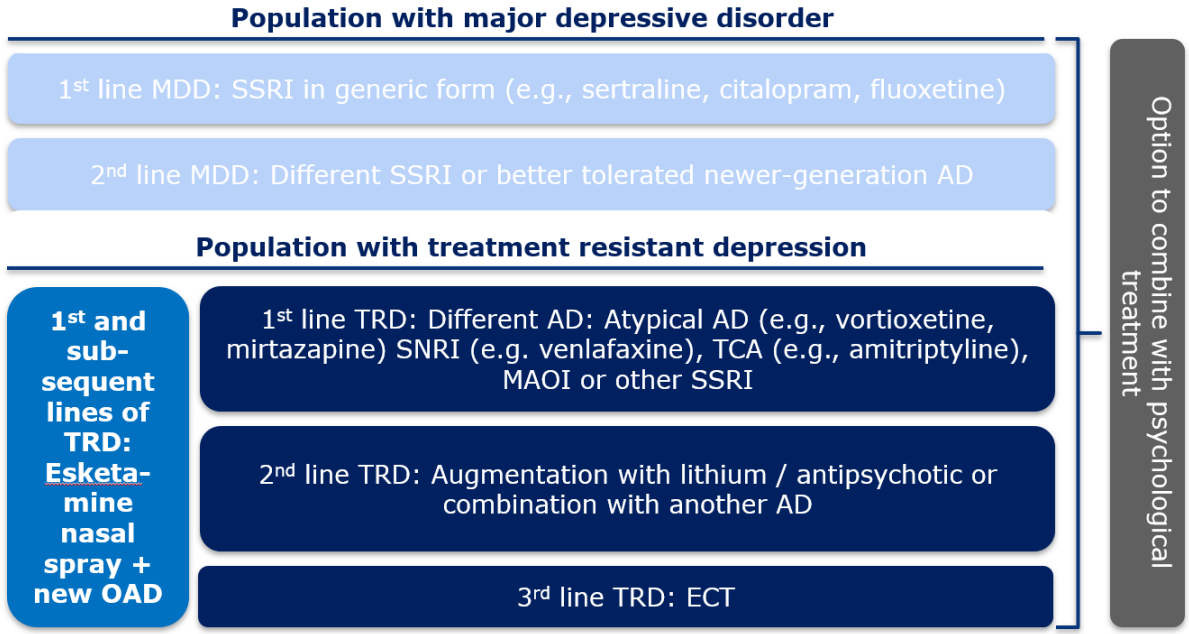
The company correctly stated that there are no UK guidelines specific to TRD. The main relevant guideline is NICE clinical guideline CG90 which covers the recognition and management of depression in adults.[6] This guideline along with that of the British Association for Psychopharmacology were

described in the CS.[7] The company also referenced American Psychiatry Association (APA) Practice Guidelines for the treatment of Patients with Major Depressive Disorder.[8]

Currently, the first-line treatment for MDD is an OAD, typically a selective serotonin reuptake inhibitor (SSRI). After four weeks, if response is inadequate or due to patient preference, a switch to another OAD is recommended. NICE recommends initially a different SSRI or a better tolerated newer-generation antidepressant but recognises the weakness of the evidence of any advantage switching either within or between classes. NICE subsequently advises an antidepressant of a different pharmacological class that may be less well tolerated, for example venlafaxine, a tricyclic antidepressant (TCA) or an monoamine oxidase inhibitor (MAOI).[6]

It is at this third-line and beyond (or first-line treatment-resistant and beyond) that ESK-NS is to be placed and should be taken alongside a new OAD according to the CS, see Figure 2.1.[1] In response to request for clarification, the company advised that the label indication is expected to change to ESK-NS in combination with an SSRI or SNRI for treatment-resistant major depressive disorder in adults who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode.[3] At this stage, ESK-NS is a comparator for other treatments including atypical antidepressants (ADs), serotonin–norepinephrine reuptake inhibitor (SNRI), TCA, MAOI or other SSRI and for augmentation with either lithium or other antipsychotic and electroconvulsive therapy (ECT).

Figure 2.1: Proposed future MDD and TRD treatment pathway



Based on Figure 6 of the CS[1]
AD = antidepressant; ECT = electroconvulsive therapy; MAOI = monoamine oxidase inhibitor; MDD = major depressive disorder; NICE = National Institute for Health and Care Excellence; OAD = oral antidepressant; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; TRD = Treatment-resistant depression

The company summarised the currently used treatments for patients with TRD and their limitations. The problem of delay in response to OADs (four to six weeks) was particularly highlighted by the company. In this context, the CS described ESK-NS as having a '*unique mechanism of action which results in a rapid onset of action (within 24 hours)*'.[1]

Regarding the introduction of ESK-NS, the company noted that 'i*t is expected to diminish the need for combination and augmentation strategies in addition to invasive non-pharmacological treatments that are associated with an increased side effect burden in later lines*'.[1]

The CS advised that 'd*uring and after ESK-NS administration at each treatment session, patients should be monitored for sedation and dissociation until the patient is stable and ready to leave the clinic based upon clinical judgement. While ESK-NS could potentially be used in all lines of treatment, the suitability should be addressed by a specialist in mental health and the setting needs to be appropriate to allow for the required observation and monitoring period*'.[1]

The company highlighted geographic access as a consideration in relation to equality.

ERG comment: The overview of the current pathway for TRD, presented in the CS, was appropriate. The pathway shows that there are a number of possible comparators. The ERG noted in particular that a NICE appraisal of vortioxetine has been conducted (technology appraisal (TA) 367) and that vortioxetine is recommended for adults with major depressive episodes whose condition has responded inadequately to two OADs within the current depressive episode, see Figure 2.1.[9] The company were unable to conduct a direct or indirect comparison of ESK-NS and vortioxetine to inform the decision problem.

NICE recommends that for relapse prevention patients who respond to treatment should continue to take their OAD for at least six months after remission. For those at high risk of relapse, OAD should be continued for at least two years with a re-evaluation to assess if maintenance should continue.[6]

The company was asked to provide a breakdown of how long people in clinical practice might be expected to take esketamine in an acute phase and in the maintenance phase. In response, the company stated that 'i*n the acute treatment phase, patients are expected to receive ESK-NS + OAD for 4 weeks, and patients who do not respond and / or reach remission at that time point are expected to discontinue treatment*'.[3] They further stated that '*SUSTAIN-1 data on relapse among stable remitters indicated that a patient with TRD needed to be in relapse-free remission for 36 weeks (approximately nine months) to achieve recovery. (…) Once entering the maintenance phase, a benefit of ESK-NS is that it can be discontinued while patients can still receive OAD for recurrence prevention. A total of 35.4% of patients were assumed to stop ESK-NS immediately upon achieving recovery (…) For the remainder of patients, treatment with ESK-NS + OAD will be continued during the maintenance phase and discontinued over time. Based on UK expert opinion, a 4-week discontinuation risk of 25% for ESK-NS + OAD was used during recovery. (…) Patients who achieve response (without remission) are assumed to continue ESK-NS + OAD as long as they are in the response health state and have not reached remission, as they are assumed to be at high risk of relapse'*.[3] The company stated that their assumptions were discussed with UK clinical experts and considered to be representative of clinical practice. The implications of these assumptions are discussed within this report.

The company advised that suitability for ESK-NS should be addressed by a specialist in mental health. However in the CS, the company stated that *'only an estimated 10% of patients with TRD are referred to specialist mental health services (generally those deemed to be at risk of suicide)*'.[1] Furthermore the survey by SANE commented that just over a half of respondents had been seen by a psychiatrist with an average of a three year wait.[2]

Administration of ESK-NS requires observation by a healthcare professional due to potential adverse effects and driving is not permitted until the next day after a restful sleep. This has implications for resourcing and for patients. Implications of resourcing are discussed within this report. In terms of

patients, the ERG received the following information from the mental health charity SANE in their submission: '*The main advantage of the administration method would be contact with healthcare practitioners who might be able to give additional support in managing the patient's depression and encourage greater compliance with medication. The disadvantages to patients include the costs of travel and the time involved and difficulties in accessing clinic for patients such as those with mobility problems, agoraphobia or those in a care home. Further disadvantages could be the risk of disassociation after administration thus requiring input from carers*'.[2]

3. Critique of company's definition of decision problem

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the CS and rationale	Rationale if different from the final NICE scope	ERG comment
Population	Adults with treatment-resistant depression	The population would be more appropriately defined as: *"Adults with treatment resistant MDD who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode"*.	The proposed wording reflects the expected population in the marketing authorisation.	In line with the scope. However, trial results might not be applicable regardless of severity. Also, the trials in the economic model included only those aged 18 to 64 years. The trials in the CS excluded patients with moderate/severe alcohol abuse according to DSM-5 criteria. The trials in the CS also excluded patients who had suicidal/ homicidal ideation/intent within 6 months prior to screening per the investigator's clinical judgements and/or based on C-SSRS or a history of suicidal behaviour in the 12 months prior to screening.
Intervention	ESK-NS in addition to established clinical management	ESK-NS co-administered with a newly initiated OAD.	In response to clarification, the company advised that the label indication is expected to change to *'ESK-NS in combination with an SSRI or SNRI, is indicated for adults with treatment-resistant major depressive disorder, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode'*.[3]	In line with the scope. However, the potential impact of a number of issues of applicability discussed within this report. These include the effectiveness of different types of OADs, the complex dosing of ESK-NS and the assumption that at some point patients can discontinue ESK-NS with no reduction in efficacy.

	Final scope issued by NICE	Decision problem addressed in the CS and rationale	Rationale if different from the final NICE scope	ERG comment
Comparator(s)	• SSRIs • TCAs • MAOIs • SNRIs • Vortioxetine • Combination or augmentation treatments (with lithium or an antipsychotic) • ECT • Best supportive care	As per the scope, plus the tetracyclic OAD mirtazapine.	Mirtazapine is currently not included in the final scope. Mirtazapine should be included as a comparator as two retrospective database analyses conducted by 1) King's College London, using secondary data from the South London and Maudsley (SLaM) Trust, and 2) IQVIA, using *Longitudinal Patient Data,* a primary care prescription data set, which show that mirtazapine is amongst the five most frequently prescribed treatments for TRD.[10, 11] NICE stated in their early scientific advice in 2013 and at the NICE Scoping Workshop for ESK-NS in TRD held on 17 September 2018 that RWE will determine which comparators are the most relevant ones.[12] Figure 5 [of the CS] shows the most frequently used OAD therapies for TRD in the UK. Of the list of comparators in the final scope, it shows that SSRIs, TCAs, SNRIs, and mirtazapine are the most relevant comparators.	The trials included in the CS compared ESK-NS + OAD + placebo and OAD. The implications of adjustments made for the high placebo response are discussed within this report.
Outcomes	• Response to treatment (including response rate and time to response)	As per the scope, with the addition of the impact of ESK-NS on indirect costs and carer HRQoL.	TRD-associated disability has been associated with substantial indirect costs. In a systematic literature review, Johnston et al. 2019[13] found that increasing treatment resistance	

	Final scope issued by NICE	Decision problem addressed in the CS and rationale	Rationale if different from the final NICE scope	ERG comment
	• Relapse (including relapse rate and time from remission to relapse) • Severity of depression • Cognitive dysfunction • Remission of symptoms • Anxiety • Sleep quality • Hospitalisation • Functioning and associated disability • Mortality • Adverse effects of treatment (including adverse effects of treatment discontinuation) • HRQoL		was associated with higher costs, reduced HRQoL and decreased health status.[13] In addition, McCrone et al. 2018 showed that 80% of the total UK society burden of TRD was due to lost productivity and carer burden.[14] NICE CG90 states that *"depression incurs significant non-healthcare costs such as social service costs, direct costs to patients and their families, and lost productivity costs due to morbidity or premature mortality"*.[6] Consideration of the wider indirect cost impact is in line with NICE social values which state that: *"Decisions about whether to recommend interventions should not be based on evidence of their relative costs and benefits alone. NICE must consider other factors when developing its guidance, including the need to distribute health resources in the fairest way within society as a whole"*.[15] Additionally, the feedback from NICE at the early scientific advice meeting was that *"Workplace productivity and occupational functioning should not currently be included in the base-case of the economic model however such data*	

	Final scope issued by NICE	Decision problem addressed in the CS and rationale	Rationale if different from the final NICE scope	ERG comment
			could be presented as supporting evidence".[12]	
Subgroups to be considered	If evidence allows the following subgroups will be considered by severity of the condition in people with treatment-resistant depression. In addition, the clinical and cost effectiveness of ESK-NS may be considered in different positions in the treatment pathway.	No subgroup analyses based on level of severity at baseline or ESK-NS in different positions in the treatment pathway.	There is insufficient comparative evidence to evaluate the effectiveness of ESK-NS by level of severity or positioning in the treatment pathway. Therefore, ESK-NS plus OAD has been considered in the full label population, as per the clinical trials and anticipated license indication.	Some subgroup data on severity of disease were provided in response to the request for clarification, see section 4.2.6.
Special considerations including issues related to equity or equality		In relation to equality, Janssen would like to highlight geographic access as a key consideration. Additionally, there may be an equality consideration for patients aged ≥65 years.		The ERG agrees that, given the method of administration of ESK-NS requiring supervision by a healthcare professional, it will be important to ensure that access to healthcare support will not inappropriately discriminate against individuals for whom geography may pose a challenge. The main trials included only those aged 18 to 64 years. The main trials in the economic model included only those aged 18 to 64 years.

Based on Table 1 of the CS[1]

C-SSRS = Columbia-Suicide Severity Rating Scale; CG = clinical guideline; CS = company submission; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders – Fifth edition; ECT = electroconvulsive therapy; ERG = Evidence Review Group; ESK-NS = esketamine nasal spray; HRQoL = health-related quality of life; MAOI = monoamine oxidase inhibitor; MDD = major depressive disorder; NICE = National Institute for Health and Care Excellence; OAD = oral antidepressant; RWE = real-world evidence; SLaM = South London and Maudsley; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCAs = tricyclic antidepressants; TRD = treatment-resistant depression; UK = United Kingdom

3.1 Population

The population defined in the scope is adults with treatment-resistant depression, i.e. people who do not respond to at least two therapies. The population is broadly consistent with the NICE scope and the expected marketing authorisation.[3, 16] However, the scope does not specify severity. Also, subgroup analysis reveals that severity as measured by functional impairment in terms of Sheehan Disability Scale (SDS) does seem to have an impact on the effectiveness of ESK + OAD (see Appendix E of the CS).[17]

The two main trials which informed the economic modelling were TRANSFORM-2 and SUSTAIN-1. TRANSFORM-2, an acute treatment study, enrolled adults with a history of non-response to at least two antidepressants in the current episode with one antidepressant assessed prospectively. SUSTAIN-1 assessed maintenance of effect (prevention of relapse).

The main limitation of these trials in terms of this appraisal is that they only included patients aged 18 to 64 years of age. A four-week trial in adults aged 65 and over (TRANSFORM-3) was included in the CS only as supporting evidence and did not inform the economic model. The ERG was, therefore, concerned as to the relevance of evidence to the older population. The company was asked to clarify if they considered the trials to be applicable to patients aged 65 years and over. In response, the company presented results of patients aged 65 to 74 years from TRANSFORM-3 showing them to be similar in magnitude to those in the younger adult population; the lower effect noted in those aged 75 years and over was considered to be an artefact of the low number of patients (n=22).[3] However, for response and remission, the results for TRANSFORM-3 were much lower. Day 28 risks of remission and response (ESK + OAD vs. OAD + PBO-NS) were: 69.3% vs. 52.0% and 52.5% vs. 31.0% for TRANSFORM-2. For TRANSFORM-3 these were: 27.0% vs. 13.3% and 17.5% vs. 6.7%, respectively. As can be seen, the risk differences were also lower for TRANSFORM-3 suggesting that, although ESK + OAD was still effective, its effectiveness was not only lower in absolute terms, but lower relative to OAD. The dose of ESK was also lower in TRANSFORM-3. Indeed, whilst the company argued that TRANSFORM-2 was representative of the population in the scope, they also argued in Section B 3.5.1 of the CS that TRANSFORM-2 and TRANSFORM-3 could not be pooled, partly because of differential efficacy which they explained in terms of difference in age and dose.[1] On this basis, the ERG questions the applicability of TRANSFORM-2 to the whole population. Also, there is no equivalent study to SUSTAIN-1 in the older age group by which comparisons might be made. SUSTAIN-2 included older patients, but relapse was not measured and no separate subgroup analysis was provided.[1, 17]

The company also submitted a new version of the base-case model to include acute response and remission transition probabilities and utilities for MDE, response and remission/recovery states from both TRANSFORM-2 and TRANSFORM-3, weighted by percentage in each age group such that if set to 0% for age >65 years one gets the same result as in the original base-case. Section 5.2.3 discusses this in more detail.

The trials in the CS excluded patients with moderate/severe alcohol abuse according to Diagnostic and Statistical Manual of Mental Disorders – Fifth edition (DSM-5) criteria. The committee will need to consider whether evidence in the CS on effectiveness and safety of ESK-NS can be generalised to those with a dual diagnosis of depression and alcohol misuse.

The trials in the CS also excluded patients who had suicidal/homicidal ideation/intent within six months prior to screening per the investigator's clinical judgements and/or based on C-SSRS or a history of suicidal behaviour in the 12 months prior to screening. Again, the committee will need to consider if

the evidence in the CS on effectiveness and safety of ESK-NS can be generalised to this vulnerable population.

3.2 Intervention

The intervention in the NICE scope is ESK-NS in addition to established clinical management. In the trials ESK-NS is co-administered with a newly initiated OAD according to the expected licence. According to the CS, a Committee for Medicinal Products for Human Use (CHMP) positive opinion is expected in September 2019 with marketing authorisation anticipated to be granted by the European Commission in November 2019.[1] The anticipated indication was given in the CS is as follows:

- ESK-NS is indicated for treatment-resistant major depressive disorder in adults who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode.
- ESK-NS must be co-administered with a newly initiated OAD therapy.

In response to request for clarification, the company advised that the label indication is expected to change to ESK-NS in combination with an SSRI or SNRI for treatment-resistant major depressive disorder in adults who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode.[3] In the main trials TRANSFORM-2 and SUSTAIN-1 over 60% were prescribed a SNRI and the remainder a SSRI. The OAD as assigned by the investigator could be one of four: duloxetine, escitalopram, sertraline or venlafaxine XR. The company also confirmed that no OADs are contraindicated with ESK-NS. However, when ESK-NS is to be given with MAOIs blood pressure may be increased and would require close monitoring.[3]

The company stated that '*ESK-NS comes as a single-use device that delivers a total of 28 mg of esketamine in two sprays (one spray per nostril). ESK-NS is self-administered and is to be used under the supervision of a healthcare professional. One device (for a 28 mg dose), two devices (for a 56 mg dose), or three devices (for an 84 mg dose), are to be used, with a five-minute interval between each nasal spray self-administration'*.[1]

The company provided the following information on dosing:

'Induction phase dosing: In weeks 1–4, patients start on 56 mg (<65 years) or 28 mg (≥65 years) on Day 1. Subsequent doses are 56 or 84 mg twice a week. Dose adjustments should be made based on efficacy and tolerability. Evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine need for continued treatment.

Maintenance phase dosing: It is recommended to maintain the dose the patient receives at the end of the induction phase in the maintenance phase. In weeks 5-8, 56 mg or 84 mg once weekly. From Week 9, 56 mg or 84 mg every 2 weeks or once weekly.

The need for continued treatment should be re-examined periodically'.[1]

The issue of how well dosing in the trials might reflect dosing in clinical practice is discussed in section 5.2.4.

The company did not use the TRANSFORM-1 trial in the economic modelling of this submission. This trial was similar to TRANSFORM-2 in that ESK-NS + OAD were compared to OAD + PBO-NS twice weekly for four weeks. However the company stated that '*ESK-NS was administered as a fixed dose which is not in line with the expected licence*'.[1]

The company stated that after depressive symptoms improve, treatment is recommended for at least six months. The ERG asked the company to provide a breakdown of how long people in clinical practice might be expected to take esketamine in an acute phase and in the maintenance phase.[18] In response, the company stated that '*in the acute treatment phase, patients are expected to receive ESK-NS + OAD for 4 weeks, and patients who do not respond and / or reach remission at that time point are expected to discontinue treatment*'.[3] The response further stated that '*SUSTAIN-1 data on relapse among stable remitters indicated that a patient with TRD needed to be in relapse-free remission for 36 weeks (approximately nine months) to achieve recovery (...) Once entering the maintenance phase, a benefit of ESK-NS is that it can be discontinued while patients can still receive OAD for recurrence prevention. A total of 35.4% of patients were assumed to stop ESK-NS immediately upon achieving recovery (...) For the remainder of patients, treatment with ESK-NS + OAD will be continued during the maintenance phase and discontinued over time. Based on UK expert opinion, a 4-week discontinuation risk of 25% for ESK-NS + OAD was used during recovery.* (…) *Patients who achieve response (without remission) are assumed to continue ESK-NS + OAD as long as they are in the response health state and have not reached remission, as they are assumed to be at high risk of relapse*'.[3] The company stated that their assumptions were discussed with UK clinical experts and considered representative of clinical practice. The implications of these assumptions are discussed within this report, see section 5.2.6.2. The company's advisory board agreed that '*the largest proportion of patients with TRD (~80%) will discontinue esketamine nasal spray treatment if recovery is achieved. A small proportion of patients with TRD (~20%), the ones who are at high risk of relapse, will continue treatment with esketamine nasal spray for up to two years*'.[3]

A key difference between ESK-NS and other antidepressants is that, although it is self-administered, this needs to be done under the supervision of a healthcare professional. The company stated that *'during and after ESK-NS administration at each treatment session, patients should be observed for sedation and dissociation until the patient is stable based on clinical judgment. In the SUSTAIN-2 trial, approximately 60% of individuals were ready to leave after 1 hour, with approximately 95% ready to leave after 90 minutes'*.[1] The company's own advisors agreed that '*self- administration of esketamine nasal spray would need to be monitored by a qualified nurse. A physician would need to be accessible but not necessarily present, in case of an emergency*'.[3]

In addition to this supervision patients will need to be aware that after taking ESK-NS according to the CS '*driving is not permitted until the next day after a restful sleep*'.[1]

The company acknowledged the potential of ESK-NS for abuse, misuse, and diversion due to its similar pharmacologic profile to ketamine. They stated that the controlled distribution model was intended to limit diversion. They further stated that *'during clinical development trials of ESK-NS, the percentage of nasal spray kits that were not returned from the clinical sites was 0.004% (5 of 141,561 kits)'* and that *'there were no reports of overdose, drug abuse, or confirmed diversion of drug product across the clinical development programme'*.[1]

3.3 Comparators

The main trials in this appraisal compared ESK-NS + OAD to placebo nasal spray (PBO-NS) and OAD. The company submission stated that "*efficacy estimates (response and remission) for the OAD + PBO-NS arm of the TRANSFORM-2 trial were high compared with other studies in TRD*" and on this basis the response rate was adjusted down for PBO-NS.[1] The company attributed this to the high number of clinic visits.

The ERG is concerned that any placebo effect (due to clinic visits or for any other reason) was likely to be present in both trial arms. Therefore, only removing the placebo effect for OAD + PBO while not removing it for ESK would likely overestimate the ESK treatment benefit. The company was asked to use the unadjusted estimates of response for OAD + PBO-NS for the model base case or perform the same adjustment to ESK-NS + OAD.[18] The company provided these data which are detailed in this report, see section 4.2.5 for these results and section 5.2.6.1 for a detailed discussion of this issue.[3]

3.4 Outcomes

The NICE final scope listed the following outcomes:

- Response to treatment (including response rate and time to response)
- Relapse (including relapse rate and time from remission to relapse)
- Severity of depression
- Cognitive dysfunction
- Remission of symptoms
- Anxiety
- Sleep quality
- Hospitalisation
- Functioning and associated disability
- Mortality
- Adverse effects of treatment (including adverse effects of treatment discontinuation)
- Health-related quality of life (HRQoL)

The outcomes investigated in the CS reflected the scope. However, some outcomes defined in the final scope issued by NICE were not reported for the main trials in the CS, namely cognitive dysfunction, hospitalisation and sleep quality.

3.5 Other relevant factors

No patient access scheme was presented in the CS. The ERG agrees that, given the method of administration of ESK-NS requiring supervision by a healthcare professional, it will be important to ensure that access to healthcare support will not inappropriately discriminate against individuals for whom geography may pose a challenge.

4. Clinical effectiveness

4.1 Critique of the methods of review(s)

4.1.1 Searches

Appendix D of the CS[17] reported search methods for two systematic literature reviews (SLRs):

- Systematic literature review of acute management of patients with TRD
- Systematic literature review of ongoing maintenance treatment of patients with TRD

Section D1.1 of the CS details a systematic search of the literature used to identify evidence reporting on the efficacy and safety of esketamine and its comparators. Searches were undertaken on 14 July 2017 and updated on 10 May 2019. A summary of the sources searched is provided in Table 4.1.

Table 4.1: Data sources for the clinical effectiveness systematic review for the acute management of patients with TRD

Resource	Host/Source	Date Range	Date searched
Electronic databases			
Medline	OVID	1990-2017/07/14	14/7/17 (Updated 10/5/19)
Epub ahead of print[a]			
Medline In-Process & Other Non-Indexed Citations			
Medline Daily Update			
Embase		1990-2017/07/14	
PsycINFO		1990-2017/07/14	
Cochrane CENTRAL	EBM Reviews via OVID	Up to 14th July 2017	
CDSR			
DARE			
HTA Database			
ACP Journal Club			
Cochrane clinical answers			
Cochrane methodology register			
NHS EED			
Conference proceedings[b]			
Anxiety and Depression Association of America Conference		2016-2019	31/10/18 (updated 24/5/19) Unable to access abstracts
International Conference on Management of Depression		2016-2019	31/10/18 (updated 24/5/19) Unable to access abstracts

Resource	Host/Source	Date Range	Date searched
American Psychiatry Association Annual Meeting		2016-2019	1/11/18 (updated 23/5/19)
European Congress of Psychiatry		2016-2019	5-6/11/18 (updated 23/5/19)
The Royal College of Psychiatrists International Congress		2016-2019	6/11/18 (updated 24/5/19) Unable to access abstracts
WPA World Congress of Psychiatry		2016-2019	6/11/18 (updated 23/5/19) Unable to access abstracts for 2017-19
ISPOR (USA/Europe)		2016-2019	23/5/19
HTA agencies[b]			
NICE, SMC, PBAC, CADTH, NCPE			30/05/2019
Trials registries[b]			
ClinicalTrials.gov			Not reported
EUCTR			Not reported
WHO ICTRP			10/5/19

[a] Whilst Medline epub ahead of print was included in the resources listed for the 2019 update, it was unclear if it had been included in the original searches; [b] Studies identified were considered for inclusion in either the acute or maintenance treatment categories, respectively
ACP = American College of Physicians; CADTH = Canadian Agency for Drugs and Technologies in Health; CDSR = Cochrane Database Systematic Reviews; DARE = Database of Abstracts of Reviews of Effects; EBM = evidence-based medicine; EED = Economic Evaluation Database; EUCTR = European Union Clinical Trials Register; HTA = Health Technology Assessment; ICTRP = International Clinical Trials Registry Platform; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NCPE = National Centre for Pharmacoeconomics; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicine Consortium; TRD = treatment-resistant depression; USA = United States of America; WHO = World Health Organization; WPA = World Psychiatric Association

Section D1.2 of the CS details a systematic search of the literature used to identify evidence reporting on the efficacy and safety of therapies used in the maintenance treatment of TRD.[17] Searches were undertaken on 01 February 2017 and updated on 23 May 2019. A summary of the sources searched is provided in Table 4.2 below.

Table 4.2: Data sources for the clinical effectiveness systematic review for the ongoing maintenance of patients with TRD

Resource	Host/Source	Date Range	Date searched
Electronic databases			
Medline	OVID	1946-2017/02/1	1st Feb 2017 (Updated 23/5/19)
Epub ahead of print*			
Medline In-Process & Other Non-Indexed Citations*			
Medline Daily Update*			

Resource	Host/Source	Date Range	Date searched
Embase		1974-2017/01/30	
Cochrane CENTRAL	EBM Reviews via OVID	Up to 2017/02/1	
CDSR			
DARE			
HTA Database			
ACP Journal Club			
Cochrane clinical answers			
Cochrane methodology register			
NHS EED			

* Whilst listed in the 2019 update searches, it was not clear from reporting whether these additional Medline in process resources were included in the original searches.
CDSR = Cochrane Database Systematic Reviews; DARE = Database of Abstracts of Reviews of Effects; EBM = evidence-based medicine; EED = Economic Evaluation Database; HTA = Health Technology Assessment; NHS = National Health Service; TRD = treatment-resistant depression

ERG comment:

- During clarification, the company confirmed that both sets of searches (Tables 4.1 and 4.2) were screened for papers relevant to both SLRs: *"…during screening for either the acute or maintenance treatment SLRs, any studies that were potentially relevant for inclusion in the other review were flagged and assessed for eligibility"*.[3]
- The selection of databases searched was comprehensive, and the majority of searches were clearly reported and reproducible. The database name, host and date searched were provided. An extensive range of resources additional to database searching were included in the SLR to identify further relevant studies and grey literature. Missing data regarding the clinical trials registry searches were queried at clarification.[18] The ERG noted that searches were reported in sections D1.1 and 1.2 for Clinical Trials.gov and the EU Clinical Trials registry and asked for full details of all search dates and search strategies used.[18] In their response, the company failed to provide full details for the searches listed above but instead provided search dates and strategy for an additional search of the WHO ICTRP (World Health Organization - International clinical trials registry platform).[3] Although this omission may affect reproducibility, it is unlikely to affect the overall recall of results.
- The ERG noted that a randomised controlled trial (RCT) filter was applied to the Cochrane library searches. The MECIR (Methodological Expectations of Cochrane Intervention Reviews) Manual advises *"…do not use filters in pre-filtered databases e.g. do not use a randomized trial filter in CENTRAL or a systematic review filter in DARE"*.[19] The inclusion of these filters may result in unnecessarily restricting the results retrieved. However, given the breadth of the searches reported, this is unlikely to have impacted on the overall recall of results.
- There were some limitations with the use of MeSH indexing terms in the Embase search for acute management of TRD. Although some automated mapping between indexing terms does take place it is possible that relevant Emtree indexing terms were not included in the search, and potentially relevant records could have been missed. Given the additional use of free text terms this is unlikely to have affected the overall recall of results.
- The ERG was concerned that limiting the searches reported in sections D1.1 and 1.2 to English language may have introduced potential language bias.[17] Current best practice states that *"whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication"*.[20]

- Whilst not reported in the submission, the company confirmed that reference checking was performed as part of both the original and update searches.[3]
- The ERG noted that the strategies in section D1.2 (Ongoing maintenance treatment of patients with TRD) appeared to include a reduced interventions facet compared with that used in section D1.1 for acute treatment, further to this not all of the drugs listed in Table 5 of the CS (Eligibility criteria) appeared in the strategies (missing drugs included reboxetine, butriptyline, clomipramine etc.). Whilst there were some limited free text terms for the drug types of interest (see Embase strategy line #72), the ERG was unsure of the rationale behind this decision and what impact it may have had on the overall recall of results. Whilst this omission was not directly addressed in their response, the company did clarify that both sets of searches reported in section D were screened for papers relevant to both SLRs.[3] Without rerunning the searches, the ERG is unable to confirm what impact this may have had on the overall recall of results, however this approach may have mitigated against some loss of recall.
- The ERG queried whether any additional searches were conducted for non-RCTs, in response the company reported that *"an SLR was conducted (December 2018) interrogating the same electronic databases as the clinical SLRs. A bespoke search strategy using a validated search filter to identify observational studies was employed"*.[3] Full search strategies were provided for the resources listed in Table 4.3.
- The company confirmed at clarification that the searches reported in sections D1.1 and 1.2 were intended the inform section B2.10 (adverse events).[3] While the searches outlined would have retrieved some relevant information in these areas, the addition of a trials filter may have resulted in relevant references being missed. Guidance by the Centre for Reviews and Dissemination (CRD) recommends that if searches have been limited by a study design filter, additional searches should be undertaken to ensure that adverse events that are long-term, rare or unanticipated are not missed.[21] The searches for observational studies sent at clarification may have mitigated against this loss of recall, although it is unclear whether these searches were screened for adverse events.

Table 4.3: List of resources for which full search strategies were provided

Resource	Host/Source	Date Range	Date searched
Electronic databases			
Medline	OVID	1990-2018/12/17	18/12/18
Epub ahead of print			
Medline In-Process & Other Non-Indexed Citations			
Medline Daily Update			
Embase		1990- 2018/12/17	
Cochrane CENTRAL	EBM Reviews via OVID	Up to 2018/12/17	
CDSR			
DARE			
HTA Database			
ACP Journal Club			
Cochrane clinical answers			
Cochrane methodology register			
NHS EED			

Resource	Host/Source	Date Range	Date searched
PsycINFO	OVID	1990- 2018/12/wk2	19/12/18
ACP = American College of Physicians; CDSR = Cochrane Database Systematic Reviews; DARE = Database of Abstracts of Reviews of Effects; EBM = evidence-based medicine; EED = Economic Evaluation Database; HTA = Health Technology Assessment; NHS = National Health Service			

4.1.2 Inclusion criteria

The company reported on two different SLRs performed to identify evidence reporting on data relevant for: 1) the acute management of patients with TRD; and 2) the ongoing maintenance treatment of patients with TRD.

Population:

For the acute management SR, the company reported that the population of interest was adults (18 years or older) with TRD (defined as unipolar MDD with failure to respond to ≥2 antidepressant treatment regimens of adequate dose and duration *in the current episode*). However, due to inconsistent reporting in this research field, the definition of current or prior episode was not used as an inclusion or exclusion criteria for study selection. A step-wise procedure was used at the full-text screening stage. At first pass, studies that included patients with ≥1 treatment failure were included, with no exclusions as to whether treatment failures occurred during the current or prior episode in anticipation of subgroup results for the required ≥2 treatment failure population. However, no information was provided as to how or at what stage of the process the second (or more) pass selection process was applied. This was not the population defined in the scope, which had a broader definition of *'adults with treatment-resistant depression'*.[16] The company justified their use of this narrower population by indicating that this reflects the expected marketing authorisation of esketamine.

For the ongoing maintenance SR, the company reported that the population of interest was adults (18 years or older) with TRD (by any definition). This was a broader population than reported for the acute management SR, and was in line with the scope.

Interventions and comparators:

For the acute management SR, the company included all the classes of medications indicated in the scope (SSRIs, TCAs, MAOIs, SNRIs, vortioxetine, augmentation treatments (with anti-psychotics), combination treatments (with lithium), electroconvulsive therapy (ECT) and best supportive care (BSC). They also included three additional classes of comparators that were not specified in the scope: SARIs (serotonin antagonist and reuptake inhibitors; trazodone), NRIs (norepinephrine reuptake inhibitor; reboxetine) and TeCAs (tetracyclic antidepressants; amoxapine, maprotiline, mianserin, mirtazapine, setiptiline). Several of these are not considered common OAD medications in the UK, and as such the inclusion of such comparators may skew any resulting data away from the standard UK perspective.

For the ongoing maintenance SR, the company included all the classes of medications indicated in the scope (SSRIs, SNRIs, TCAs, MAOIs, vortioxetine, augmentation treatments (with anti-psychotics), augmentation treatments (with lithium), ECT and BSC. They also included two additional classes of comparators that were not specified in the scope: SARIs (trazodone) and NRIs; and also included no therapy as a comparator. The company did not include TeCAs, amoxapine, maprotiline, mianserin or septiptiline, which were named drugs included in the acute management SR.

Outcomes:

For the acute management SR, the company included depressive symptoms (based on change in any depression rating scale, such as Hamilton Depression Rating Scale (HAM-D) or Montgomery-Åsberg Depression Rating Scale (MADRS)), response rate, relapse rate, remission rate, time to response, time to remission, mortality and discontinuation due to adverse events, all of which were in line with the scope.

Additionally, the CS included recurrence rate, suicide behaviour/ attempts and suicidal ideation. Conversely, the company failed to include some outcomes specified in the scope, namely cognitive dysfunction, anxiety, sleep quality, hospitalisation, functioning and associated disability, adverse events related to treatment discontinuation and HRQoL.

Studies that reported only on adverse events were excluded under the inclusion/exclusion criteria of the systematic review, which means that some relevant studies may have been missed. In the decision problem, the company also state that they have included two additional outcomes: impact of ESK-NS on costs and carer-related HRQoL. These outcomes did not appear to have been included nor identified within the framework of the SR.

For the ongoing maintenance systematic review, the company included: depressive symptoms (based on change in one of five named depression rating scales: MADRS, Quick Inventory of Depressive Symptomatology (QIDS-SR14), Clinical Global Impression – Severity (CGI-S), Patient Global Impression – Severity (PGI-S) and HAMD/HDRS), onset of clinical response, remission, relapse and HRQoL (PHQ9 and Quality of Life in Depression Scale (QLDS)), all of which were in line with the scope. They additionally included: recurrence, discontinuation, discontinuation due to adverse events, European Quality of Life-5 Dimensions (EQ-5D) and health resource utilisation information. However, the company failed to include some outcomes specified in the scope, namely response rate, time from remission to relapse, cognitive dysfunction, anxiety, sleep quality, hospitalisation, functioning and associated disability, mortality, adverse events and adverse events related to treatment discontinuation.

Study design:

For the acute management SR, the company only included RCTs that reported on the efficacy and safety of acute interventions with ≤4 weeks of follow-up data. This restriction based on follow-up time was considered by the ERG to be inappropriate. While several of the company's own trials reported a core treatment period of four weeks, the maintenance and post-treatment follow-up phases are much longer than this (up to 24 weeks), and therefore other trials with longer follow-up periods may represent relevant comparator datasets.

For the ongoing maintenance SR, the company only included RCTs with either >4 weeks of treatment or maintenance treatments >4 weeks or treatment explicitly for relapse prevention (presumably of any duration, since this was not specified).

Study selection:

Across both SRs, two reviewers were involved in study selection, and any discrepancies were resolved by the intervention of a third reviewer. This was considered sufficient to minimise bias in study selection. In the ongoing maintenance SR, studies were restricted based on language (only English language studies were included), meaning relevant studies may have been missed. The company was asked to clarify why a date limit of 1990 had been applied to searching/screening for the systematic review.[18] The response stated that this was '*based on internal clinical expert opinion that TRD-related publications started in the early 1990s. The 1990 date limit was therefore applied to ensure that the*

current standard of depression treatment was captured'.[3] No references were supplied to support this perspective. It is not normally recommended in systematic reviews to set arbitrary date limits in case relevant studies are missed.

4.1.3 Critique of data extraction

No information was provided on the number of reviewers involved in the data extraction process, therefore reviewer error and bias cannot be ruled out.

4.1.4 Quality assessment

Quality was assessed for the two RCTs that informed the economic model (TRANSFORM-2 and SUSTAIN-1) and two further RCTs (TRANSFORM-1 and TRANSFORM-3) using the NICE recommended tool.[22] This was considered a sufficient tool to use.

The open-label extension study, SUSTAIN-2, was assessed using a different set of signalling questions to the four RCTs, which was appropriate given the difference in study design; however, the company did not report the tool that was used. It appeared to the ERG that most of the signalling questions were based on a reporting guideline rather than a risk of bias assessment, and as such, this was probably an inappropriate tool to use.

No information was provided on the number of reviewers who were involved in the quality assessment, therefore reviewer error and bias cannot be ruled out.

4.1.5 Evidence synthesis

The company performed a feasibility assessment of the n=68 citations (Figure 1 and Figure 2 in Appendix D[17]) identified by their acute phase systematic literature searches and concluded that limited NMA could be conducted.

The company also performed a feasibility assessment of the n=49 citations (Figure 3 and Figure 4 in Appendix D[17]) identified by their maintenance phase systematic literature searches, and concluded that a network meta-analysis could not be conducted. However, it was not clear why this was the case, and no supporting network diagrams or study details were provided. Further details of the NMA are provided in section 4.4.

4.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Details of included studies

Six studies formed the evidence base for ESK-NS (Table 4.4). Four of these were randomised controlled trials (TRANSFORM-1, TRANSFORM-2, TRANSFORM-3, SUSTAIN-1) and two were open label extension studies (SUSTAIN-2, SUSTAIN-3).[1]

Table 4.4: Summary of clinical effectiveness evidence for esketamine

	TRANSFORM-1	TRANSFORM-2	TRANSFORM-3	SUSTAIN-1	SUSTAIN-2	SUSTAIN-3
In economic model	No	Yes	No	Yes	No	No
Rationale for use/non-use in economic model	ESK-NS was administered as a fixed dose which is not in line with the anticipated licence	ESK-NS was administered via flexible dosing in line with the anticipated licence	Patients aged ≥65 years, who, for tolerability reasons, were started on an initial dose of 28 mg ESK-NS which is below the minimum effective dose of 56 mg	ESK-NS was administered via flexible dosing in line with the anticipated licence	A non-comparative study primarily designed to assess long-term safety (with minimal efficacy data)	An ongoing, non-comparative study primarily designed to assess long-term safety (with minimal efficacy data). Only interim data are available
Study design	Randomised, double-blind, parallel-group, active-controlled, Phase 3				Open-label, long-term, Phase 3	
Population	Adults (aged 18–64 years) with recurrent or single-episode TRD		Adults (aged ≥65 years) with recurrent or single-episode TRD	Adults (aged 18–64 years) with recurrent or single-episode TRD. Patients either directly entered the study or transferred from TRANSFORM-1/2 (having completed double-blind induction phase and demonstrated treatment response at end of 4-week double-blind induction phase of these transfer studies)	Adults (aged ≥18 years) with recurrent or single-episode TRD	

	TRANSFORM-1	TRANSFORM-2	TRANSFORM-3	SUSTAIN-1	SUSTAIN-2	SUSTAIN-3
Intervention	Fixed dose ESK-NS (56 mg OR 84 mg) twice weekly for 4 weeks (starting dose for all patients: 56 mg) PLUS newly initiated OAD	Flexibly-dosed ESK-NS (56 mg/84 mg) twice weekly for 4 weeks (starting dose for all patients: 56 mg) PLUS newly initiated OAD	Flexibly-dosed ESK-NS (28 mg/56 mg/84 mg) twice weekly for 4 weeks (starting dose for all patients: 28 mg) PLUS newly initiated OAD	Flexibly-dosed ESK-NS (SUSTAIN-1: 56 mg/84 mg; SUSTAIN-2/3: 28 mg/56 mg/84 mg in patients aged ≥65 years) twice weekly, weekly, or every other week (depending on efficacy and tolerability) until relapse or study termination PLUS newly initiated OAD		
Comparator	Newly initiated OAD plus PBO-NS twice weekly for 4 weeks			Newly initiated OAD plus PBO-NS twice weekly, weekly, or every other week (depending on efficacy and tolerability) until relapse or study termination	NA	

Based on Table 7 of the CS[1]
CS = company submission; ESK-NS = esketamine nasal spray; NA = not applicable; OAD = oral antidepressant; PBO-NS = placebo nasal spray; TRD = treatment-resistant depression

ERG comment*:* The company included two trials in the economic model (TRANSFORM-2, SUSTAIN-1) and these two alongside the TRANSFORM-3 and SUSTAIN-2 trials will be discussed in this section. The remaining trials TRANSFORM-1 (the fixed dosing study) and the ongoing non-comparative study SUSTAIN-3 will be discussed briefly in sections 4.2.8 and 4.2.9, respectively.

The two trials included in the initial economic model were TRANSFORM-2 and SUSTAIN-1, see Table 4.5. These were randomised, double-blind controlled trials targeting adults aged 18 to 64 years with recurrent or single episode depression. Both trials compared ESK-NS plus a newly initiated OAD to a newly initiated OAD plus placebo and both involved flexible dosing of 56 mg/ 84 mg of ESK-NS. ESK-NS was given for four weeks in TRANSFORM-2 and patients were either followed up for 24 weeks or joined SUSTAIN-1. SUSTAIN-1 also enrolled patients directly who had not taken part in TRANSFORM-2. In SUSTAIN-1, ESK-NS was given until relapse or trial termination.

The focus of the two trials was also different. TRANSFORM-2 aimed to treat patients with TRD in the acute phase of depression. Hence in TRANSFORM-2 the primary outcome was response as measured by the change in the 10-item clinician administered MADRS total score from baseline to the end of the four-week double-blind induction phase. SUSTAIN-1 aimed to delay relapse of depressive symptoms in patients with TRD who were in stable remission. The primary outcome for this trial was relapse defined as the time between patient randomisation into the maintenance phase and the first documentation (earliest date) of a relapse event (based on MADRS) during the maintenance phase among patients in stable remission (based on MADRS) at the end of the optimisation phase following treatment with ES-NS plus an OAD. Further outcomes in each trial relevant to the appraisal are given in Table 4.5.

TRANSFORM-2 enrolled 227 patients whereas SUSTAIN-1 enrolled 705 patients. See Table 4.5 for further details of the methodology of the two trials.

Table 4.5: Summary of study methodology for RCTs included in economic model

	TRANSFORM-2	**SUSTAIN-1**
Study objective	To evaluate the efficacy, tolerability and safety of flexibly-dosed ESK-NS (56 mg/ 84 mg) plus a newly initiated OAD (ESK-NS + OAD) versus a newly initiated OAD plus PBO-NS (OAD + PBO-NS) for the treatment of TRD in adults aged 18–64 years	To evaluate the efficacy, tolerability and safety of flexibly-dosed ESK-NS (56 mg/84 mg) plus a newly initiated OAD (ESK-NS + OAD) versus a newly initiated OAD + PBO-NS in delaying relapse of depressive symptoms in adults aged 18–64 years with TRD who are in stable remission following an induction (4 weeks) and optimisation (12 weeks) course of ESK-NS plus an OAD
No of patients	227	705
Study phases	Screening/prospective observational phase: • 4 weeks • Antidepressant taper period: ≤3 weeks (optional) • Double-blind induction phase: 4 weeks	**Direct-entry patients only:** • Screening/prospective observational phase, with an optional taper of ≤3 weeks for OAD(s): 4 weeks • Open-label induction phase: 4 weeks

	TRANSFORM-2	SUSTAIN-1
	• Follow-up phase: ≤24 weeks (only for those patients ineligible or unwilling to participate in subsequent long-term study SUSTAIN-1 following double-blind induction phase)	**Direct-entry and transferred-entry (from TRANSFORM-1/2) responder patients:** • Optimisation phase: 12 weeks (open-label for direct-entry patients, double-blind for transferred-entry patients) • Maintenance phase: variable duration (until relapse or study termination) • Follow-up phase: 2 weeks
Outcomes	• **Response (MADRS)** • Severity of depression (MADRS, CGI-S, PHQ-9) • **Remission (MADRS)** • Anxiety (GAD-7) • Functioning and associated disability (SDS) • Mortality (Safety outcome) • **Adverse effects of treatment (including adverse effects of treatment discontinuation)** • **Health-related quality of life (EQ-5D)**	• **Relapse (MADRS)** • Severity of depression (MADRS, CGI-S, PHQ-9) • Remission (MADRS) • Anxiety (GAD-7) • Functioning and associated disability (SDS) • Mortality (Safety outcome) • **Adverse effects of treatment (including adverse effects of treatment discontinuation)** • Health-related quality of life (EQ-5D)
Based on Tables 6 and 7 of the CS[1] Outcomes marked in bold are used in the model. CGI-S = Clinical Global Impression – Severity; EQ-5D = European Quality of Life-5 Dimensions; ESK-NS = esketamine nasal spray; GAD-7 = Generalised Anxiety Disorder – 7-item scale; MADRS = Montgomery-Åsberg Depression Rating Scale; OAD = oral antidepressant; PBO-NS = placebo nasal spray; PHQ-9 = Patient Health Questionnaire – 9 questions; RCT = randomised controlled trial; SDS = Sheehan Disability Scale; TRD = treatment-resistant depression		

ERG comment: The main trials in the CS and the economic model were randomised. Evidence is available for both acute treatment of treatment-resistant depression and for maintenance of effect after remission.

The above trials included only patients aged 18 to 64 years. A separate trial of those aged 65 and over with different dosing (TRANSFORM-3) and an open-label trial in adults aged 18 years or over (SUSTAIN-2) were initially not included in the model but are described below.

In response to clarification, the company advised that the label indication is expected to change to ESK-NS in combination with an SSRI or SNRI for treatment-resistant major depressive disorder in adults who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode.[3] This reflects the trials where patients received either a SNRI or SSRI in conjunction with ESK-NS.

The company was asked to justify the use of the MADRS and PHQ-9 scales to determine depression severity. The PHQ-9 definition of response used was defined as ≥50% reduction from baseline in the PHQ-9 total score. A patient was defined as a responder at any given time point if the percentage improvement (decrease) in MADRS total score from baseline was ≥50%. A patient was defined as being

in remission at any time point if their MADRS total score was ≤12. The ERG noted that in technology appraisal 367 (TA367), remission was defined as MADRS total score of 10 or less.[9] The company stated that the difference was to account for the fact that remote raters were used instead of face-to-face raters.[3] Remote raters were used as the dissociative effects of ESK-NS might have resulted in unblinding if face-to-face MADRS raters were used.

The two main trials not included in the initial economic model were TRANSFORM-3 and SUSTAIN-2.

TRANSFORM-3 (138 participants) was a randomised, double-blind controlled trial targeting adults aged 65 years or over with recurrent or single episode depression. TRANSFORM-3 compared ESK-NS plus a newly initiated OAD to a newly initiated OAD plus placebo (28 mg/56 mg/84 mg) twice weekly for four weeks (starting dose for all patients: 28 mg). This lower dosage reflected the older population in the trial. Patients were either followed-up for two weeks or joined SUSTAIN-2.

SUSTAIN-2 (802 participants) also enrolled patients directly who had not taken part in TRANSFORM-3. SUSTAIN-2 was a one year long non-comparative study to assess long-term safety and tolerability of ESK-NS with selected efficacy outcomes also evaluated.

Further details of the methodology of the two trials are presented in Table 4.6.

A discussion of the role of TRANSFORM-3 in the economic model can be found in section 5.2. As SUSTAIN-2 was an open label study with no comparator, it is most useful as supporting evidence for longer-term safety outcomes.

Table 4.6: Summary of study methodology for TRANSFORM-3 and SUSTAIN-2

Trial no. (acronym)	**ESKETINTRD3005 (TRANSFORM-3)**	**ESKETINTRD3004 (SUSTAIN-2)**

Study objective	• To evaluate the efficacy of flexibly-dosed esketamine nasal spray plus a newly initiated OAD (ESK-NS + OAD) versus a newly initiated OAD plus placebo nasal spray (OAD + PBO-NS) for the treatment of TRD in elderly adults aged ≥65 years
	• To evaluate the safety and tolerability of each treatment regimen
		• To evaluate the long-term safety and tolerability of flexibly-dosed esketamine nasal spray plus a newly initiated OAD (ESK-NS + OAD) in adults aged ≥18 years with TRD, with special attention to the following:
		  • Potential effects on cognitive function
		  • Potential treatment-emergent symptoms of cystitis and/or lower urinary tract symptoms
		  • Potential withdrawal and/or rebound symptoms following cessation of esketamine treatment

Number of patients enrolled	N=138	N=802
Study phases	• Screening/prospective observational phase: 4 weeks • Antidepressant taper period: ≤3 weeks (optional) • Double-blind induction phase: 4 weeks	Direct-entry patients only: • Screening phase: 4 weeks Direct-entry and transferred-entry (from TRANSFORM-3) non-responder[a] patients only: • Open-label induction phase: 4 weeks

Trial no. (acronym)	ESKETINTRD3005 (TRANSFORM-3)	ESKETINTRD3004 (SUSTAIN-2)
	• Follow-up phase: • **TRANSFORM-3:** 2 weeks (only for those patients ineligible or unwilling to participate in subsequent long-term safety study SUSTAIN-2 following double-blind induction phase)	Direct-entry and transferred-entry (from TRANSFORM-3) responder[a] patients: • Optimisation/maintenance phase: 48 weeks • Follow-up phase: 4 weeks
Reported outcomes specified in the decision problem[b]	• Response (MADRS) • Severity of depression (MADRS, CGI-S, PHQ-9) • Remission (MADRS) • Anxiety (GAD-7) • Functioning and associated disability (SDS) • Mortality (Safety outcome) • Adverse effects of treatment (including adverse effects of treatment discontinuation) • Health-related quality of life (EQ-5D)	• Response (MADRS, PHQ-9) • Severity of depression (MADRS, CGI-S, PHQ-9) • Remission (MADRS, PHQ-9) • Anxiety (GAD-7) • Functioning and associated disability (SDS) • Mortality (Safety outcome) • Adverse effects of treatment (including adverse effects of treatment discontinuation) • Health-related quality of life (EQ-5D)
Based on Table 74 of the CS[1] [a] Response was defined as a ≥50% reduction from baseline in the MADRS total score; [b] Severity of depressive symptoms assessed using the MADRS score CGI-S = Clinical Global Impression – Severity; EQ-5D = European Quality of Life-5 Dimensions; ESK-NS + OAD = esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; GAD-7 = Generalised Anxiety Disorder – 7-item scale; MADRS = Montgomery-Åsberg Depression Rating Scale; OAD = oral antidepressant; OAD + PBO-NS = newly initiated oral antidepressant plus placebo nasal spray; PHQ-9 = Patient Health Questionnaire – 9 questions; SDS = Sheehan Disability Scale; TRD = treatment-resistant depression		

4.2.2 Statistical analysis of the studies included in the economic model

Table 4.7 summarises details on the statistical analysis for TRANSFORM-2 and SUSTAIN-1. These trials are used in the economic model.

Table 4.7: Statistical analysis of TRANSFORM-2 and SUSTAIN-1

	TRANSFORM-2	SUSTAIN-1
Sample size, power calculation	The maximum sample size planned was calculated assuming a treatment difference for the double-blind induction phase of 6.5 points in MADRS total score between ESK-NS + OAD and the OAD + PBO-NS arms, an SD of 12, a one-sided significance level of 0.025, and a drop-out rate of 25%. The treatment difference and SD used in this calculation were based on results of Panel A of the ESKETINTRD2003 study and on clinical judgment.	The maximum number of relapses (in patients with stable remission) required was 84, which would provide 90% power to detect a hazard ratio of 0.493 at the one-sided significance level of 0.025 for a fixed-sample design to detect superiority of ESK-NS plus an OAD over OAD plus PBO-NS in delaying relapse of depressive symptoms in patients with TRD who were in stable remission.

	TRANSFORM-2	SUSTAIN-1
	About 98 patients were required to be randomised to each treatment group to achieve 90% power using a fixed design assuming no interim analysis.	Calculation of sample size assumed that the time to the first relapse follows an exponential distribution, with a median time of 6 months for an OAD plus PBO-NS and 12.17 months for ESK-NS plus an OAD (corresponding 6-month relapse rates: 50% for OAD plus PBO-NS and 28.95% for ESK-NS plus an OAD). Accounting for assumptions made for accrual period and rate, maximum study duration, and dropout rate, a total of approximately 211 patients in stable remission needed to be randomised (1:1) to obtain 84 relapses.
Interim analysis for sample size re-estimation or stopping for futility	An interim analysis was planned to re-estimate sample size or to stop the study due to futility. Due to recruitment dynamics, a sample size re-estimation was not recommended after the study started, and the interim analysis was removed from the planned analyses in the second protocol amendment.	To evaluate the assumptions used in the sample size calculation, relapse rates were to be monitored sequentially during the maintenance phase. In particular, a two-stage group sequential design was adopted, with one interim analysis to be performed when at least 33 relapse events had occurred in stable remitters with at least 30 relapses from patients treated with ESK-NS plus an OAD in the optimisation phase. The interim analysis was conducted according to a separate statistical analysis plan. The IDMC reviewed the interim analysis results and made a recommendation to either stop the study for efficacy or provide the sample size adjustment based on the rules defined in the interim analysis statistical analysis plan.
Statistical testing sequence and levels of significance	A fixed sequence, serial gatekeeping procedure was applied to adjust for multiplicity and to strongly control type I error across the primary and the three key secondary efficacy endpoints. Testing of the endpoints was performed sequentially in the following order: change in MADRS total score, onset of clinical response by Day 2 (24 hours), change in SDS total score, and change in PHQ-9 total score. Testing of the endpoints was performed sequentially in the order indicated above and were considered statistically significant at the one-sided 0.025 level only if the endpoint was individually significant at the one-sided 0.025 level	A two-stage group sequential design, with one interim analysis was adopted as described above. In either case of stopping at the interim analysis or continuing with sample size re-estimation, control of overall type I error would thereby be maintained. The final efficacy analysis was performed at a significance level of 0.046 (two-sided). If the result of the final efficacy analysis was significant ($Z_f \geq 1.998$), ESK-NS plus an OAD would be declared superior to an OAD plus PBO-NS in delaying relapse.

	TRANSFORM-2	SUSTAIN-1
	and previous endpoints in the hierarchy were significant at the one-sided 0.025 level.	
Hypothesis objective	The hypothesis for TRANSFORM-2 was that, in adult patients with TRD, switching from a failed OAD to ESK-NS plus a newly initiated OAD would be superior to switching to a newly initiated OAD treatment (active comparator) plus PBO-NS in improving depressive symptoms.	ESK-NS plus an OAD is more effective than treatment with an OAD plus PBO-NS in delaying relapse of depressive symptoms in patients with TRD in stable remission.
Statistical analysis (primary outcome)	The primary endpoint was: • Change from baseline to Day 28 in the MADRS total score reported as the difference in treatment means. The primary analysis was based on the full analysis set and the MADRS total scores collected during the double-blind induction phase. Different analysis methods were used dependent on the regulatory needs of specific regions: ANCOVA (EU) and MMRM (non-EU). ***ANCOVA*** Change from baseline in MADRS total score at Day 28 of the double-blind induction phase was analysed based on LOCF data. The model included factors for treatment, country, and class of OAD (SNRI or SSRI), and baseline MADRS total score as a covariate. ***MMRM*** Change from baseline in MADRS total score at Day 28 of the double-blind induction phase was analysed based on observed data. The model included baseline MADRS total, and treatment, class of OAD (SNRI or SSRI), day, day-by-treatment interaction, and country as fixed effects. The within-patient covariance between visits was estimated via an unstructured variance-covariance matrix.	The primary endpoint was: Time to relapse during the maintenance phase, while on their initially randomised treatment. The primary analysis was based on the full (stable remitters) analysis set and relapse (based on MADRS total score, defined in Table 10 of the CS) collected during the maintenance phase. The treatment groups were compared using the weighted log-rank test. Time to relapse was summarised (number of events, number of censored patients and quartiles of time to relapse). The cumulative distribution function of the time to relapse was estimated by the Kaplan-Meier method.
Statistical analysis (key secondary outcomes)	• Analysis of the proportion of patients showing onset of clinical response by Day 2 (24 hours) that was maintained for the duration of the double-blind induction phase in the ESK-NS plus an OAD arm versus the OAD plus PBO-NS arm was planned using a Cochran-Mantel-Haenszel chi square test adjusting for country and class of antidepressant (SSRI or SNRI).	• For time to relapse in stable responders (who were not stable remitters), time to relapse was summarised and the cumulative distribution function of time to relapse was estimated by the Kaplan-Meier method. The difference in time to relapse between treatment groups was evaluated using a two-sided log-

	TRANSFORM-2	SUSTAIN-1
	• Change from baseline in SDS total score and change from baseline in PHQ-9 total score at Day 28 in the double-blind induction phase were analysed using the same models described for the primary efficacy analysis.	rank test and the hazard ratio and 95% CI were estimated based on the Cox proportional hazards model with treatment as a factor. • For MADRS, PHQ-9, CGI-S, GAD-7, and SDS, change from baseline (for the maintenance phase) at each visit, including observed case and LOCF data, were analysed using the ANCOVA model with factors for treatment and country and baseline score as covariates. The proportion of patients with response and remission based on MADRS, PHQ-9 or SDS were summarised over time.
Data management, patient withdrawals	**Imputation for missing timepoints:** For endpoints using ANCOVA, the LOCF method was applied to the MADRS total score, SDS total score, PHQ-9 total score, and CGI-S for the double-blind induction phase. The last post-baseline observation during the double-blind induction phase was carried forward as the endpoint for that phase. In addition to the observed cases and the endpoint assessments, the LOCF values were created for intermediate post-baseline timepoints as well.	**Imputation for missing timepoints:** For the MADRS, CGI-S, PHQ-9, GAD-7 and SDS, both observed case and LOCF values were determined for the induction, optimisation and maintenance phases. The last post-baseline observation during each phase was carried forward as the "Endpoint." In addition to the observed cases and endpoint assessment, the LOCF values were created for intermediate post baseline timepoints.
	Imputation for missing items: For MADRS total score, if two or more items were missing, no imputation was performed, and the total score was left missing. Otherwise, the total score was calculated as a sum of the non-missing items multiplied by the ratio of the maximum number of items (i.e., 10) to the number of non-missing items. For all other scales where multiple items were summed to create a total, if any item of the scale was missing at a visit, the total score for that scale at that visit was left blank.	

Based on Table 17 of the CS[1]

ANCOVA = analysis of covariance; CGI-S = Clinical Global Impression – Severity; CI = confidence interval; CS = company submission; ESK = esketamine; EU = European Union; GAD-7 = Generalised Anxiety Disorder – 7-item scale; IDMC = independent data monitoring committee; LOCF = last observation carried forward; MADRS = Montgomery-Åsberg Depression Rating Scale; MMRM = Mixed-Effects Model using Repeated Measures; NS = nasal spray; OAD = oral antidepressant; PBO = placebo; PHQ-9 = Patient Health Questionnaire – 9 questions; SD = standard deviation; SDS = Sheehan Disability Scale; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TRD = treatment-resistant depression

ERG comment: The ERG has no concerns regarding the appropriateness of the statistical methods described in Table 4.7.

4.2.3 Trial inclusion criteria and participant characteristics

Details of the full inclusion criteria for TRANSFORM-2 and SUSTAIN-1 are provided in section B.2.3.4 of the CS and for TRANSFORM-3 and SUSTAIN-2 in Appendix M3 and are not reproduced in this report.[1, 17]

ERG comment: The ERG notes the following in relation to these inclusion criteria:

- TRANSFORM-2 and SUSTAIN-1 only included patients aged 18 to 64 years of age. TRANSFORM-3 was conducted in patients aged over 65 years only. SUSTAIN-2 included a wider age range but was an open label trial. TRANSFORM-3 was included in the CS only as supporting evidence and did not inform the economic model. The ERG was, therefore, concerned as to the relevance of evidence to the older population. The company was asked to clarify if they considered the trials to be applicable to patients aged 65 years and over.[18] The company presented results of patients aged 65 to 74 years from TRANSFORM-3 showing them to be similar in magnitude to those in the younger adult population. The lower effect noted in those aged 75 years and over was considered to be an artefact of the low number of patients (n=22).[3]
- The trials in the CS excluded patients with moderate/severe alcohol abuse according to DSM-5 criteria. The committee will need to consider whether evidence in the CS on effectiveness and safety of ESK-NS can be generalised to those with a dual diagnosis of depression and alcohol misuse.
- The trials in the CS also excluded patients who had suicidal/homicidal ideation/intent within six months prior to screening per the investigator's clinical judgements and/or based on C-SSRS or a history of suicidal behaviour in the 12 months prior to screening. Again, the committee will need to consider if the evidence in the CS on effectiveness and safety of ESK-NS can be generalised to this vulnerable population.
- In the trials, the patients had to be adherent to current OAD treatment (without adjustment in dosage) throughout screening/prospective observational phases. In clinical practice patients may not adhere to OAD medication, i.e. this might limit the generalisability of the findings.
- The trials excluded patients who had not responded to an adequate course of treatment with ECT in the current major depressive episode. This appears to be in line with the proposed pathway for ESK-NS. The committee will need to consider if ESK-NS is likely to be offered to patients who have not responded to ECT.
- Details of selected baseline characteristics across the four main trials (TRANSFORM-2, SUSTAIN-1, TRANSFORM-3 and SUSTAIN-2) are shown in Table 4.8.

Table 4.8: Selected demographic baseline characteristics of the main trials: TRANSFORM-2, SUSTAIN-1, TRANSFORM-3 and SUSTAIN-2

Characteristic	TRANSFORM-2 (N=223)	SUSTAIN-1 (N=705)	TRANSFORM-3 (N=138)	SUSTAIN-2 (N=802)
Age, mean years (SD)	45.7 (11.89)	46.1 (11.10)	70.0 (4.52)	52.2 (13.69)
Age category, n (%)				
18–44 years	94 (42.2)	292 (41.4)	NA	225 (28.1)
45–64 years	129 (57.8)	413 (58.6)	NA	399 (49.8)
65–74 years	NA		116 (84.7)	159 (19.8)
≥74 years	NA		21 (15.3)	19 (2.4)
Sex, n (%)				
Male	85 (38.1)	248 (35.2)	52 (38.0)	300 (37.4)
Female	138 (61.9)	457 (64.8)	85 (62.0)	502 (62.6)
Race, n (%)				
American Indian or Alaskan Native	NA	1 (0.1)	NA	
Asian	2 (0.9)	3 (0.4)	NA	81 (10.1)
Black or African American	11 (4.9)	31 (4.4)	NA	15 (1.9)
White	208 (93.3)	635 (90.1)	130 (94.9)	686 (85.5)
Multiple	2 (0.9)	4 (0.6)	4 (2.9)	8 (1.0)
Not reported	NA	9 (1.3)	2 (1.5)	4 (0.5)
Other	NA	22 (3.1)	NA	8 (1.0)
Unknown	NA		1 (0.7)	
Employment status, n (%)[a]				
Any type of employment	131 (58.7)	448 (63.5)	24 (17.5)	450 (56.1)
Any type of unemployment	69 (30.9)	180 (25.5)	8 (5.8)	175 (21.8)
Other	23 (10.3)	77 (10.9)	105 (76.6)	177 (22.1)
Region, n (%)				
Europe	134 (60.1)	411 (58.3)	59 (43.1)	322 (40.1)

Characteristic	TRANSFORM-2 (N=223)	SUSTAIN-1 (N=705)	TRANSFORM-3 (N=138)	SUSTAIN-2 (N=802)
North America	89 (39.9)	195 (27.7)	70 (51.1)	147 (18.3)
Other	NA	99 (14.0)	8 (5.8)	333 (41.5)
Class of OAD, n (%)				
SNRI	152 (68.2)	440 (62.9)	61 (44.5)	407 (50.8)
SSRI	71 (31.8)	259 (37.1)	76 (55.5)	394 (49.2)
OAD, n (%)				
Duloxetine	121 (54.3)	323 (46.2)	48 (35.0)	251 (31.3)
Escitalopram	38 (17.0)	128 (18.3)	50 (36.5)	237 (29.6)
Sertraline	32 (14.3)	130 (18.6)	25 (18.2)	157 (19.6)
Venlafaxine XR	32 (14.3)	118 (16.9)	14 (10.2)	156 (19.5)
MADRS total score, mean (SD)	37.1 (5.67)	37.9 (5.50)	35.2 (6.16)	31.4 (5.39)
PHQ-9 total score, mean (SD)	20.3 (3.68)	19.9 (4.18)	17.5 (5.65)	17.3 (5.01)
Screening C-SSRS lifetime, n (%)[b]				
No event	126 (56.5)	407 (57.7)	73 (54.1)[j]	474 (59.3)
Suicidal ideation	74 (33.2)	193 (27.4)	43 (31.9)[j]	203 (25.4)
Suicidal behaviour	23 (10.3)	105 (14.9)	19 (14.1)[j]	123 (15.4)
Screening C-SSRS past 6 or 12 months, n (%)				
No event	151 (67.7)	499 (70.8)	86 (63.7)	583 (72.9)
Suicidal ideation (past 6 months)	71 (31.8)	205 (29.1)	48 (35.6)	215 (26.9)
Suicidal behaviour (past 12 months)	1 (0.4)[c]	1 (0.1)	1 (0.7)	2 (0.3)
Duration of current episode, mean weeks (SD)	114.6 (157.96)	132.2 (209.18)	215.8 (341.71)	160.5 (261.80)
Number of previous antidepressant medications, n (%)[d]	[e]			
2	136 (61.0)	248 (57.7)	68 (49.6)	452 (58.0)
3	53 (23.8)	111 (25.8)	34 (24.8)	182 (23.4)

Characteristic	TRANSFORM-2 (N=223)	SUSTAIN-1 (N=705)	TRANSFORM-3 (N=138)	SUSTAIN-2 (N=802)
4	20 (9.0)	39 (9.1)	17 (12.4)	83 (10.7)
≥5	9 (4.0)	20 (4.7)	7 (5.1)	49 (6.3)
Number of major depressive episodes including current episode, n (%)				
1	29 (13.0)	83 (11.8)	18 (13.1)	111 (13.9)
2–5	159 (71.3)	454 (64.5)	86 (62.8)	534 (66.7)
6–10	31 (13.9)	122 (17.3)	20 (14.6)	121 (15.1)
>10	4 (1.8)	45 (6.4)	13 (9.5)	35 (4.4)

Based on Tables 12 and 13 of the CS[1] and Tables 77 and 78 of the CS appendices[17]

[a] Any type of employment included: any category containing "employed," sheltered work, housewife or dependent husband, and student. Any type of unemployment included: any category containing "unemployed." Other included: retired and no information available; [b] C-SSRS category: No event = 0; Suicidal ideation = 1, 2, 3, 4, 5; Suicidal behaviour = 6, 7, 8, 9, 10; [c] Due to a data collection error, one patient in TRANSFORM-2 reported suicidal behaviour in the 12 months prior to screening. The suicidal behaviour for this patient actually occurred more than 12 months prior to screening.; [d] Referring to the number of antidepressant medications with non-response (defined as ≤25% improvement in MGH-ATRQ) taken for ≥6 weeks during the current episode; [e] All of the five patients not accounted for in this baseline measure TRANSFORM-2 were determined to have failed at least two OADs based on other data in the database

C-SSRS = Columbia – Suicide Severity Rating Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; NA = not applicable; OAD = oral antidepressant; PHQ-9 = Patient Health Questionnaire – 9 questions; SD = standard deviation; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

In line with the different age inclusion criteria, the mean age of patients in TRANSFORM-2 and SUSTAIN-1 was approximately 46 years (52 years in SUSTAIN-2) compared to 70 years in TRANSFORM-3. Both male and female participants were represented across the trials and women formed over 60% of the population in the trials. Most participants (85.5% to 94.9%) identified as white. Most participants were employed (56.1% to 63.5%) except for TRANSFORM-3 where most participants were not of working age. Trial participants were mainly from Europe in TRANSFORM-2 (60.1%) and SUSTAIN-1 (58.3%) and from North America in TRANSFORM-3 (51.1%).

ERG comment: The larger number of women in the trials reflects the higher prevalence of women with depression. The ERG notes that Black and Asian people appear to be underrepresented across the two trials.

The company stated that '*neither TRANSFORM-2 or* [sic] *SUSTAIN-1 enrolled any patients in the UK. (One UK patient was enrolled in the supporting trial, TRANSFORM-3, and 12 UK patients were enrolled in the long-term safety study, SUSTAIN-2). Although subgroup analyses conducted on the primary outcomes in TRANSFORM-2 and SUSTAIN-1 did suggest minor effects of patient region, country, and/or ethnicity on ESK-NS treatment response, drawing conclusions from these results is cautioned due to the small numbers of patients in these subgroups and the resulting wide confidence intervals*'.[1] The lack of UK patients in the main trials included in the economic model is a limitation particularly given the mode of delivery of this intervention. There is a lack of evidence in how well ESK-NS might work in the NHS setting.

ESK-NS patients across the trials received either a SNRI or SSRI. In TRANSFORM-2 and SUSTAIN-1, used in the model, most patients (68.2% and 62.9% respectively received a SNRI). The most frequently prescribed OAD in these trials was duloxetine (54.3% and 46.2%, respectively). Patients had an average score on MADRS of 37.1 in TRANSFORM-2 and 37.9 in SUSTAIN-1 indicating severe depression. Over 40% had a lifetime score on C-SSRS indicating suicide ideation or behaviour. As mentioned before, the trials in the CS excluded patients who had suicidal/homicidal ideation/intent within six months prior to screening per the investigator's clinical judgements and/or based on C-SSRS or a history of suicidal behaviour in the 12 months prior to screening. For most patients (approximately 87%) this was not their first major depressive episode. Most patients had received two prior OADs in this episode (61% and 57.7% in TRANSFORM-2 and SUSTAIN-1, respectively).

ERG comment: The committee will need to consider how well the OADs prescribed as co-interventions across these trials reflect those prescribed at this stage of the pathway in the NHS setting.

There is evidence available in the trials on those given ESK-NS after over two previous OADs to inform later stages of the proposed pathway, but participant numbers are smaller. Across the trials between 49.6% and 61.1% had received two previous OADs. The committee is referred to the subgroup analysis described in section 4.2.6.

4.2.4 Risk of bias assessments of included trials

The company's quality assessment of the two ESK-NS trials supporting the economic model used the NICE recommended tool.[22] The quality assessment was reported in the main submission and in the appendices of the CS and is shown in Table 4.9 for TRANSFORM-2 and SUSTAIN-1 and in Tables 4.10 and 4.11 for TRANSFORM-3 and SUSTAIN-2, respectively.[1, 17] The open-label extension study, SUSTAIN-2, was assessed using a different set of signalling questions to the four RCTs, but the

company did not report the tool that was used. As stated in section 4.1.4, it was not clear how many reviewers were involved in the quality assessment process.

ERG comment: All three RCTs (TRANSFORM-2 and -3 and SUSTAIN-1) were judged by the company to have met all of the relevant quality criteria. The ERG re-assessed the studies against the specified criteria and agrees that the RCTs were well conducted with appropriate procedures of randomisation and allocation concealment.

However, the question regarding the blinding of care providers, participants and outcome assessors has been answered in the affirmative (i.e. that all three populations were adequately blinded). The ERG queries whether blinding (specifically of care providers and participants) could be maintained in a clinical situation where the dissociative effects of the esketamine intervention were so much more overt than the comparator that they required the use of remote, independent raters to assess the primary outcome.

The ERG agrees that the observational study (SUSTAIN-2) met all of the relevant criteria on the tool used for assessment by the company. However, it appeared to the ERG that most of the signalling questions were based on a reporting guideline rather than a risk of bias assessment, and as such, this was probably an inappropriate tool to use. Although SUSTAIN-2 appeared to be a well conducted observational study, it is a non-comparative open-label study and as such will be open to bias. It is best viewed as supporting evidence for ESK-NS and indeed the company did not include it in economic modelling stating that its primary aim was to assess long-term safety.

Table 4.9: Company quality assessment of TRANSFORM-2 and SUSTAIN-1

	TRANSFORM-2	SUSTAIN-1
Was randomisation carried out appropriately?	Yes. Patients were randomised in a 1:1 ratio based on a computer-generated randomisation schedule prepared before the study by or under the supervision of the sponsor.	Yes. At the start of the maintenance phase patients were randomised in a 1:1 ratio based on a computer-generated randomisation schedule prepared before the study under the supervision of the sponsor.
Was the concealment of treatment allocation adequate?	Yes. IWRS was used to assign a unique treatment code, which dictated the treatment assignment and matching medication kits for the patient.	Yes. An IWRS was used to assign a unique treatment code, which dictated the treatment assignment and matching medication kits for the patient.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Demographics and disease characteristics were balanced between the groups. Randomisation was balanced by using randomly permuted blocks (block size=4) and was stratified by country and class of OAD (SNRI or SSRI) initiated in the double-blind induction phase.	Yes. Demographics and disease characteristics were balanced between the groups. Both randomisations were balanced by using randomly permuted blocks (block size=4) and were stratified by country.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes. This was a double-blind study. The IWRS was used to manage study agent inventory while ensuring that no one at the site had to be unblinded. The investigator was not provided with the treatment randomisation codes. The investigators and the site personnel were blinded to the treatment assignment until all patients completed study participation through the follow-up phase. To maintain the blinding of intranasal study medication, the esketamine and placebo intranasal devices were indistinguishable (via use of a bittering agent added to the placebo solution to simulate the taste of the intranasal solution with active drug). To ensure an unbiased efficacy evaluation, independent, remote (by phone), blinded MADRS raters were used to assess the antidepressant treatment response.	Yes. This was a double-blind study. The IWRS was used to manage study agent inventory while ensuring that no one at the site had to be unblinded. The investigator was not provided with the unique treatment randomisation codes. The blind was not to be broken until all patients completed the study and the database was finalised. To maintain the blinding of intranasal study medication, the esketamine and placebo intranasal devices were indistinguishable (via use of a bittering agent added to the placebo solution to simulate the taste of the intranasal solution with active drug). To ensure an unbiased efficacy evaluation, independent, remote (by phone), blinded MADRS raters were used to assess the antidepressant treatment response.
Were there any unexpected imbalances in drop-outs between groups?	No. The overall drop-outs were generally well-balanced between treatment arms.	No. The overall drop-outs during the randomised maintenance phase were generally well-balanced between treatment arms and the primary reasons for treatment discontinuation were also well-balanced between treatment arms.

	TRANSFORM-2	SUSTAIN-1
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. Based on the clinical study report all outcomes are reported in detail	No. Based on the clinical study report all outcomes are reported in detail.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Efficacy analyses in the double-blind induction phase were performed on the FAS, defined as all randomised patients who received at least 1 dose of intranasal study medication and 1 dose of OAD medication. The safety analysis set was defined as all randomised patients who received at least 1 dose of intranasal study medication or 1 dose of OAD medication. For the MADRS, if 2 or more items were missing, no imputation was performed and the total score was left missing. For all other scales where multiple items were summed to create a total, if any item of the scale was missing at a visit, the total score for that scale at that visit was left blank.	Yes. There were 2 FAS defined for the maintenance phase: • Full (stable remitters): used to perform primary and secondary efficacy evaluations on randomised patients who were in stable remission at the end of the optimisation phase and who received at least 1 dose of intranasal study drug and 1 dose of OAD during the maintenance phase. • Full (stable responders): used to perform secondary efficacy evaluations on randomised patients who were stable responders (who were not stable remitters) at the end of the optimisation phase and who received at least 1 dose of intranasal study drug and 1 dose of OAD during the maintenance phase. For the MADRS, if 2 or more items were missing, no imputation was performed, and the total score was left missing. For all other scales where multiple items were summed to create a total, if any item of the scale was missing at a visit, the total score for that scale at that visit was considered missing.
Based on Table 18 of the CS[1] CS = company submission; FAS = full analysis set; IWRS = interactive web response system; MADRS = Montgomery-Åsberg Depression Rating Scale; OAD = oral antidepressant; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor		

Table 4.10: Company quality assessment of TRANSFORM-3

	TRANSFORM-3
Was randomisation carried out appropriately?	Yes. Central randomisation was implemented. Patients were randomised in a 1:1 ratio based on a computer-generated randomisation schedule prepared before the study by or under the supervision of the sponsor.

	TRANSFORM-3
Was the concealment of treatment allocation adequate?	Yes. An IWRS was used to assign a unique treatment code, which dictated the treatment assignment and matching medication kits for the patient.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Demographics and disease characteristics were balanced between the groups. Randomisation was balanced by using randomly permuted blocks (block size=4) and was stratified by country and class of oral antidepressant (SNRI or SSRI) initiated in the double-blind induction phase.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes. This was a double-blind study. The IWRS was used to manage study agent inventory while ensuring that no one at the site had to be unblinded. The investigator was not provided with randomisation codes. Randomisation codes were disclosed fully only after the study was completed and the clinical database was closed. To maintain the blinding of intranasal study medication, the esketamine and placebo intranasal devices were indistinguishable (via use of a bittering agent added to the placebo solution to simulate the taste of the intranasal solution with active drug). To ensure an unbiased efficacy evaluation, independent, remote (by telephone), blinded MADRS raters were used to assess the antidepressant treatment response
Were there any unexpected imbalances in drop-outs between groups?	No. The overall drop-outs were generally well-balanced between treatment arms and the primary reasons for treatment discontinuation were also well-balanced between treatment arms.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. Based on the clinical study report all outcomes are reported in detail.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Efficacy analyses in the double-blind induction phase were performed on the FAS, defined as all randomised patients who received at least 1 dose of intranasal study medication and 1 dose of oral antidepressant medication. The safety analysis set was defined as all randomised patients who received at least 1 dose of intranasal study medication or 1 dose of oral antidepressant medication. For the MADRS, if 2 or more items were missing, no imputation was performed and the total score was left missing. For all other scales where multiple items were summed to create a total, if any item of the scale was missing at a visit, the total score for that scale at that visit was considered missing.

Based on Table 50 of the CS[1]
CS = company submission; FAS = full analysis set; IWRS = interactive web response system; MADRS = Montgomery-Åsberg Depression Rating Scale; OAD = oral antidepressant; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

Table 4.11: Company quality assessment of SUSTAIN-2

	SUSTAIN-2
Was the hypothesis/aim/objective of the study clearly stated?	Yes, the objective was to evaluate the long-term safety and tolerability of flexibly-dosed esketamine nasal spray plus a newly initiated oral anti-depressant in adults aged ≥18 years with treatment resistance depression.
Was the study conducted prospectively?	Yes, this was an open-label prospective study to investigate the long-term safety and tolerability of esketamine.
Were the cases collected in more than one centre?	Yes, patients were enrolled at multiples sites across Europe, South America and Asia.
Were patients recruited consecutively?	Yes, the study recruited both direct entry and transferred entry subjects from a previous study (ESKEINTRD3005), based on clearly defined eligibility criteria.
Were the characteristics of the patients included in the study described?	Yes, demographics and baseline disease characteristics were reported for patients in the study.
Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes. Exclusion criteria were clearly stated for direct entry patients. For transferred entry, patients had to have completed the double-blind induction phase of ESKEINTRD3005.
Did patients enter the study at a similar point in the disease?	Yes. All patients (direct-entry and transferred-entry) had TRD, defined as non-response to at least 2 OADs.
Was the intervention of interest clearly described?	Yes, all of the most relevant characteristics of esketamine were reported (including dosage, frequency, duration and administration methods). Details for the induction and optimisation/maintenance phases were clearly defined.
Were additional interventions (co-interventions) clearly described?	Yes, all patients received one of four OADs from 2 classes, with dosing according to local prescribing guidelines.
Based on Table 51 of the CS[1] CS = company submission; OAD = oral antidepressant; TRD = treatment-resistant depression	

4.2.5 Main efficacy results

Tables 4.12 and 4.13 summarise the efficacy results of TRANSFORM-2 and SUSTAIN-1, the RCTs used to inform the economic model. Tables 4.14 and 4.15 summarise the efficacy results of TRANSFORM-3 and SUSTAIN-2 which the CS included as supporting evidence.

Table 4.12: Summary of efficacy results of TRANSFORM-2

Outcome	ESK-NS + OAD	OAD + PBO-NS
MADRS[a,b]		
Change from baseline (observed cases)		
Baseline (mean, SD)	N=114, 37.0 (5.69)	N=109, 37.3 (5.66)
Day 28 (mean, SD)	N=101, 15.5 (10.67)	N=100, 20.6 (12.70)
Change from baseline to day 28 (mean, SD)	N=101, -21.4 (12.32)	N=100[c], -17.0 (13.88)
MMRM (difference in LS means, SE, 95% CI)[d]	-4.0 (1.69, -7.31 to -0.64)	
Onset of clinical response (FAS)		
Achieved onset of clinical response by day 2 (n, %)	N=114, 9 (7.9%)	N= 109, 5 (4.6%)
Generalised Cochran-Mantel-Haenszel test[e]	OR 1.79 (95% CI 0.57 to 5.67)	
Response and remission (observed cases)		
Response rate[f]	69.3%	52.0% (unadjusted)[g]
		34.0% (adjusted)[g]
Remission rate[h]	52.5%	31.0% (unadjusted)[g]
		18.0% (adjusted)[g]
CGI-S (observed cases)[i]		
Baseline (mean, SD)	NR	NR
Day 28 (mean, SD)	NR	NR
Change from baseline to day 28 (mean, SD)	N=101, -2.1 (1.33)	N=97, -1.6 (1.38)
MMRM (difference in LS means, SE, 95% CI)[d]	-0.4 (0.17, -0.72 to -0.04)	
PHQ-9 (observed cases)[i]		
Baseline (mean, SD)	N=114, 20.2 (3.63)	N=109, 20.4 (3.74)
Day 28 (mean, SD)	N=104, 7.3 (5.74)	N=100, 10.2 (7.68)
Change from baseline to day 28 (mean, SD)	N=104, -13.0 (6.42)	N=100, -10.2 (7.80)
MMRM (difference in LS means, SE, 95% CI)[d]	-2.4 (0.88, -4.18 to -0.69)	
GAD-7 (observed cases)[j]		
Baseline (mean, SD)	N=114, 13.2 (5.12)	N=109, 13.1 (4.83)
Day 28 (mean, SD)	N=110, 5.2 (5.46)	N=102, 6.2 (5.17)

Outcome	ESK-NS + OAD	OAD + PBO-NS
Change from baseline to day 28 (mean, SD)	N=110, -7.9 (6.12)	N=102, -6.8 (5.75)
ANCOVA (difference in LS means, SE, 95% CI)[k]	-1.0 (0.67, -2.35 to 0.28)	
SDS (observed cases)[l]		
Baseline (mean, SD)	N=111, 24.0 (4.07)	N=104, 24.2 (4.38)
Day 28 (mean, SD)	N=86, 10.1 (7.71)	N=86, 14.8 (9.07)
Change from baseline to day 28 (mean, SD)	N=86, -13.6 (8.31)	N=85, -9.4 (8.43)
MMRM (difference in LS means, SE, 95% CI)[b]	-4.0 (1.17, -6.28 to -1.64)	
EQ-5D (observed cases)[b,m]		
Baseline (mean, SD)	N=114, 0.530 (0.2081)	N=109, 0.501 (0.2143)
Day 28 (mean, SD)	N=104, 0.843 (0.1407)	N=100, 0.732 (0.2325)
Change from baseline to day 28 (mean, SD)	N=104, 0.310 (0.2191)	N=100, 0.235 (0.2525)
Difference in LS means, SE, 95% CI	NR	NR
Other outcomes defined in the final scope		
Cognitive dysfunction	NR	NR
Hospitalisation	NR	NR
Sleep quality	NR	NR

Based on Tables 7, 19, 21, 23, 24, 26, 45 and Figure 15 of the CS as well as the CSR[1, 23]

[a] Related to response, severity of depression, and remission (Table 4.5); [b] Used in the economic model; [c] = Table 19 of the CS reported this as "109". Error corrected by the ERG; [d] Change from baseline was the response variable and fixed effect model terms for treatment, day, country, class of OAD (SNRI or SSRI), treatment-by-day, and baseline value were covariates; [e] Adjusted for region and class of OAD (SNRI or SSRI); [f] ≥50% reduction from baseline in MADRS total score; [g] See details in section 5.2.6; [h] MADRS total score of ≤12; [i] Related to severity of depression (Table 4.5); [j] Related to anxiety (Table 4.5); [k] Change from baseline was the response variable and treatment, country, class of OAD (SNRI or SSRI), and baseline GAD-7 value were covariates; only ANCOVA reported; [l] Related to functioning and associated disability (Table 4.5); [m] = Related to health-related quality of life (Table 4.5)

ANCOVA = analysis of covariance; CGI-S = Clinical Global Impression; CI = confidence interval; CS = company submission; CSR = clinical study report; EQ-5D = European Quality of Life-5 Dimensions; ERG = Evidence Review Group; ESK = esketamine; FAS = full analysis set; GAD-7 = Generalised Anxiety Disorder – 7-item scale; HR = hazard ratio; LS = least squares; MADRS = Montgomery-Åsberg Depression Rating Scale; MMRM = mixed-effects model using repeated measures; NR = not reported; NS = nasal spray; OAD = oral antidepressant; OR = odds ratio; PBO = placebo; PHQ-9 = Patient Health Questionnaire – 9 questions; SD = standard deviation; SDS = Sheehan Disability Scale; SE = standard error; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

Table 4.13: Summary of efficacy results of SUSTAIN-1

Outcome	ESK-NS + OAD	OAD + PBO-NS
Time to relapse		
Stable remitters[a]		
Number of relapses	24/90 (26.7%)	39/86 (45.3%)
Time to relapse	HR 0.49 (95% CI 0.29 to 0.84)	

Outcome	ESK-NS + OAD	OAD + PBO-NS
Stable responders[b]		
Number of relapses	16/62 (25.8%)	34/59 (57.6%)
Time to relapse	HR 0.30 (95% CI 0.16 to 0.55)	
MADRS (LOCF)[c,d]		
Change from baseline		
Change from baseline to end of maintenance phase (mean, SD)[e]	Stable remitters[a]: N=89, 7.5 (11.59)	Stable remitters[a]: N=86, 12.5 (13.63)
	Stable responders[b]: N=62, 4.4 (11.38)	Stable responders[b]: N=59, 11.4 (12.00)
ANCOVA (difference in LS means, SE, 95% CI)[f]	Stable remitters[a]: -5.2 (1.82, -8.7 to -1.58)	
	Stable responders[b]: -7.4 (1.95, -11.30 to -3.55)	
Response/remission		
Responder at beginning of maintenance phase	Stable remitters[a]: 90/90 (100.0%)	Stable remitters[a]: 86/86 (100.0%)
	Stable responders[b]: 62/62 (100.0%)	Stable responders[b]: 59/59 (100.0%)
Responder at end of maintenance phase[e]	Stable remitters[a]: 67/89 (75.3%)	Stable remitters[a]: 48/86 (55.8%)
	Stable responders[b]: 41/62 (66.1%)	Stable responders[b]: 20/59 (33.9%)
Remitter at beginning of maintenance phase	Stable remitters[a]: 90/90 (100.0%)	Stable remitters[a]: 85/86 (98.8%)
	Stable responders[b]: 37/62 (59.7%)	Stable responders[b]: 38/59 (64.4%)
Remitter at end of maintenance phase[e]	Stable remitters[a]: 58/89 (65.2%)	Stable remitters[a]: 36/86 (41.9%)
	Stable responders[b]: 29/62 (46.8%)	Stable responders[b]: 15/59 (25.4%)
CGI-S (LOCF)[g]		
Change from baseline to end of maintenance phase (median, range)[e]	Stable remitters[a]: N=89, 0.0 (-3 to 4)	Stable remitters[a]: N=86, 1.0 (-2 to 5)
	Stable responders[b]: N=62, 0.0 (-2 to 4)	Stable responders[b]: N=58, 1.0 (-3 to 5)
ANCOVA (difference in LS means, SE, 95% CI)[f]	Stable remitters[a]: P value 0.055[h]	
	Stable responders[b]: P value 0.002[h]	
PHQ-9 (LOCF)[g]		
Change from baseline		
Change from baseline to end of maintenance phase (mean, SD)[e]	Stable remitters[a]: N=89, 3.3 (5.58)	Stable remitters[a]: N=86, 5.9 (7.09)
	Stable responders[b]: N=61, 1.7 (5.02)	Stable responders[b]: N=58, 4.7 (5.48)
ANCOVA (difference in LS means, SE, 95% CI)[f]	Stable remitters[a]: -2.4 (0.90, -4.20 to -0.65)	
	Stable responders[b]: -3.0 (0.93, -4.87 to -1.18)	

Outcome	ESK-NS + OAD	OAD + PBO-NS
Response/remission		
Responder at beginning of maintenance phase	Stable remitters[a]: 88/90 (97.8%)	Stable remitters[a]: 86/86 (100.0%)
	Stable responders[b]: 60/62 (96.8%)	Stable responders[b]: 56/59 (94.9%)
Responder at end of maintenance phase	Stable remitters[a]: 72/89 (80.9%)	Stable remitters[a]: 57/86 (66.3%)
	Stable responders[b]: 48/61 (78.7%)	Stable responders[b]: 40/58 (69.0%)
Remitter at beginning of maintenance phase	Stable remitters[a]: 83/90 (92.2%)	Stable remitters[a]: 76/86 (88.4%)
	Stable responders[b]: 25/62 (40.3%)	Stable responders[b]: 32/59 (54.2%)
Remitter at end of maintenance phase	Stable remitters[a]: 51/89 (57.3%)	Stable remitters[a]: 38/86 (44.2%)
	Stable responders[b]: 23/61 (37.7%)	Stable responders[b]: 12/58 (20.7%)
GAD-7 (LOCF)[i]		
Change from baseline to end of maintenance phase (mean, SD)[e]	Stable remitters[a]: N=89, 2.2 (4.45)	Stable remitters[a]: N=86, 4.0 (5.93)
	Stable responders[b]: N=61, 1.4 (3.76)	Stable responders[b]: N=58, 2.6 (4.26)
ANCOVA (difference in LS means, SE, 95% CI)[f]	Stable remitters[a]: -1.7 (0.72, -3.12 to -0.28)	
	Stable responders[b]: -1.1 (0.72, -2.56 to 0.31)	
SDS (LOCF)[g]		
Change from baseline		
Change from baseline to end of maintenance phase (mean, SD)[e]	Stable remitters[a]: N=82, 4.7 (7.34)	Stable remitters[a]: N=77, 7.2 (10.44)
	Stable responders[b]: N=58, 2.2 (6.63)	Stable responders[b]: N=53, 6.8 (7.64)
ANCOVA (difference in LS means, SE, 95% CI)[f]	Stable remitters[a]: -2.9 (1.30, -5.51 to -0.38)	
	Stable responders[b]: -4.7 (1.31, -7.30 to -2.10)	
Response/remission		
Responder at beginning of maintenance phase	Stable remitters[a]: 84/89 (94.4%)	Stable remitters[a]: 74/84 (88.1%)
	Stable responders[b]: 45/60 (75.0%)	Stable responders[b]: 48/57 (84.2%)
Responder at end of maintenance phase[e]	Stable remitters[a]: 58/83 (69.9%)	Stable remitters[a]: 43/78 (55.1%)
	Stable responders[b]: 42/60 (70.0%)	Stable responders[b]: 23/53 (43.4%)
Remitter at beginning of maintenance phase	Stable remitters[a]: 72/89 (80.9%)	Stable remitters[a]: 63/84 (75.0%)

Outcome	ESK-NS + OAD	OAD + PBO-NS
	Stable responders[b]: 28/60 (46.7%)	Stable responders[b]: 30/57 (52.6%)
Remitter at end of maintenance phase[e]	Stable remitters[a]: 48/83 (57.8%)	Stable remitters[a]: 30/78 (38.5%)
	Stable responders[b]: 25/60 (41.7%)	Stable responders[b]: 11/53 (20.8%)
EQ-5D (HSI score)[h]		
Start of maintenance phase (mean, SD)	Stable remitters[a]: N=90, 0.925 (0.0440)	Stable remitters[a]: N=86, 0.918 (0.0422)
	Stable responders[b]: N=62, 0.877 (0.0664)	Stable responders[b]: N=59, 0.875 (0.0796)
End of maintenance phase (mean, SD)[e]	Stable remitters[a]: N=88, 0.857 (0.1275)	Stable remitters[a]: N=90, 0.822 (0.1442)
	Stable responders[b]: N=61, 0.855 (0.0880)	Stable responders[b]: N=58, 0.802 (0.1292)
Change from baseline to end of maintenance phase (mean, SD)[f]	Stable remitters[a]: N=88, -0.067 (0.1180)	Stable remitters[a]: N=86, -0.096 (0.1484)
	Stable responders[b]: N=61, -0.023 (0.0753)	Stable responders[b]: N=58, -0.073 (0.1383)
Other outcomes defined in the final scope		
Cognitive dysfunction	NR	NR
Hospitalisation	NR	NR
Sleep quality	NR	NR

Based on Tables 7, 8, 27, 28, 29, 30 of the CS[1]

[a] Patients who were in stable remission at the end of the optimisation phase and who received at least 1 dose of intranasal study drug and 1 dose of OAD during the maintenance phase; [b] Patients who were stable responders (who were not stable remitters) at the end of the optimisation phase and who received at least 1 dose of intranasal study drug and 1 dose of OAD during the maintenance phase; [c] Related to relapse, severity of depression, and remission (Table 4.5); [d] Used in the economic model; [e] Variable duration (until relapse or study termination); [f] Change from baseline was the response variable and treatment, country, and baseline value were covariates; [g] Related to severity of depression (Table 4.5); [h] No further information reported, [i] Related to anxiety (Table 4.5)

ANCOVA = analysis of covariance; CGI-S = Clinical Global Impression; CI = confidence interval; CS = company submission; EQ-5D = European Quality of Life-5 Dimensions; ESK = esketamine; GAD-7 = Generalised Anxiety Disorder – 7-item scale; HR = hazard ratio; HSI = health status index; LOCF = last observation carried forward; LS = least squares; MADRS = Montgomery-Åsberg Depression Rating Scale; NR = not reported; NS = nasal spray; OAD = oral antidepressant; PBO = placebo; PHQ-9 = Patient Health Questionnaire – 9 questions; SD = standard deviation; SDS = Sheehan Disability Scale; SE = standard error

Table 4.14: Summary of efficacy results of TRANSFORM-3

Outcome	ESK-NS + OAD	OAD + PBO-NS
MADRS		
Change from baseline (observed cases)		
Baseline (mean, SD)	N=72, 35.5 (5.91)	N=65, 34.8 (6.44)
Day 28 (mean, SD)	N=63, 25.4 (12.70)	N=60, 28.7 (10.11)
Change from baseline to day 28 (mean, SD)	N=63, -10.0 (12.74)	N=60, -6.3 (8.86)

Outcome	ESK-NS + OAD	OAD + PBO-NS
MMRM (difference in LS means, SE, 95% CI)[a]	-3.6 (NR, -7.20 to -0.07)	
Response and remission (observed cases)		
Response rate	17/63 (27.0%)	8/60 (13.3%)
Remission rate	11/63 (17.5%)	4/60 (6.7%)
CGI-S (observed cases)		
Baseline (mean, SD)	N=72, 5.1 (0.76)	N=65, 4.8 (0.80)
Day 28 (mean, SD)	N=64, 3.9 (1.33)	N=60, 4.3 (1.20)
Change from baseline to day 28 (mean, SD)	N=64, -1.2 (1.30)	N=60, -0.5 (1.03)
MMRM (difference in LS means, SE, 95% CI)[a]	-0.7 (0.21, -1.10 to -0.27)	
PHQ-9 (observed cases)		
Baseline (mean, SD)	N=72, 17.6 (4.99)	N=65, 17.4 (6.33)
Day 28 (mean, SD)	N=64, 11.6 (7.04)	N=57, 13.5 (6.81)
Change from baseline to day 28 (mean, SD)	N=64, -6.4 (7.24)	N=57, -4.1 (6.36)
MMRM (difference in LS means, SE, 95% CI)[a]	-2.8 (1.16, -5.08 to -0.48)	
GAD-7 (observed cases)		
Baseline (mean, SD)	NR	NR
Day 28 (mean, SD)	NR	NR
Change from baseline to day 28 (mean, SD)	NR	NR
ANCOVA (difference in LS means, SE, 95% CI)	NR	
SDS (observed cases)		
Change from baseline		
Baseline (mean, SD)	N=45, 21.8 (5.90)	N=44, 22.9 (4.74)
Day 28 (mean, SD)	N=36, 14.3 (9.33)	N=37, 19.2 (7.25)
Change from baseline to day 28 (mean, SD)	N=29, -7.5 (8.24)	N=37[b], -3.8 (5.57)
MMRM (difference in LS means, SE, 95% CI)[a]	-4.6 (1.82, -8.21 to -0.94)	
Response and remission		
Response rate	15/44 (34.1%)	10/44 (22.7%)
Remission rate	7/44 (15.9%)	2/44 (4.5%)
EQ-5D (observed cases)		
Baseline (mean, SD)	N=72, 0.581 (0.2258)	N=65, 0.635 (0.2276)
Day 28 (mean, SD)	N=65, 0.658 (0.2608)	N=59, 0.680 (0.1918)
Change from baseline to day 28 (mean, SD)	N=65, 0.086 (0.2674)	N=59, 0.041 (0.2074)

Outcome	ESK-NS + OAD	OAD + PBO-NS
Difference in LS means, SE, 95% CI	NR	NR
Other outcomes defined in the final scope		
Cognitive dysfunction	NR	NR
Hospitalisation	NR	NR
Sleep quality	NR	NR

Based on Tables 30 to 35 of the response to request for clarification[3]

[a] Change from baseline was the response variable and fixed effect model terms for treatment, day, country, class of OAD (SNRI or SSRI), treatment-by-day, and baseline value were covariates; [b] Table 32 of the response to request for clarification[3] reported this as "85". Error corrected by the ERG

CGI-S = Clinical Global Impression; CI = confidence interval; EQ-5D = European Quality of Life-5 Dimensions; ERG = Evidence Review Group; ESK = esketamine; GAD-7 = Generalised Anxiety Disorder – 7-item scale; LS = least squares; MADRS = Montgomery-Åsberg Depression Rating Scale; MMRM = mixed-effects model using repeated measures; NR = not reported; NS = nasal spray; OAD = oral antidepressant; PBO = placebo; PHQ-9 = Patient Health Questionnaire – 9 questions; SD = standard deviation; SDS = Sheehan Disability Scale; SE = standard error; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

Table 4.15: Summary of efficacy results of SUSTAIN-2

Outcome	ESK-NS + OAD
MADRS	
Change from baseline (LOCF)	
Baseline (mean, SD)	N=779, 31.2 (5.29)
End of induction (mean, SD)	N=756, 14.8 (8.83)
Change from baseline to end of induction (mean, SD)	N=756, -16.4 (8.76)
Response/remission (observed cases)	
Responder at beginning of induction	NR
Responder at end of induction	581/688 (84.4%)
Remitter at beginning of induction	NR
Remitter at end of induction	349/688 (50.7%)
CGI-S (LOCF)	
Baseline (median, range)	N=779, 5.0 (1 to 7)
End of induction (median, range)	N=763, 3.0 (1 to 7)
Change from baseline to end of induction (median, range)	N=763, -2.0 (-6 to 2)
PHQ-9 (LOCF)	
Baseline (mean, SD)	N=779, 17.3 (5.00)
End of induction (mean, SD)	N=746, 8.4 (5.80)
Change from baseline to end of induction (mean, SD)	N=746, -8.9 (6.67)
GAD-7 (LOCF)	
Baseline (mean, SD)	N=771, 11.3 (5.45)
End of induction (mean, SD)	N=732, 5.3 (NR)
Change from baseline to end of induction (mean, SD)	N=724, -5.9 (5.85)

Outcome	ESK-NS + OAD
SDS (LOCF)	
Change from baseline	
Baseline (mean, SD)	N=709, 22.2 (5.45)
End of induction (mean, SD)	N=648, 12.8 (7.89)
Change from baseline to end of induction (mean, SD)	N=626, -9.3 (7.86)
Response/remission	
Responder at beginning of induction	NR
Responder at end of induction	295/571 (51.7%)
Remitter at beginning of induction	NR
Remitter at end of induction	132/571 (23.1%)
EQ-5D (HSI score)	
Start of induction (mean, SD)	N=779, 0.601 (0.2056)
End of induction (mean, SD)	N=745, 0.792 (0.1725)
Change from baseline to end of induction phase (mean, SD)	N=745, 0.190 (0.2138)
Other outcomes defined in the final scope	
Cognitive dysfunction	NR
Hospitalisation	NR
Sleep quality	NR

Based on Tables 39 to 45 of the response to request for clarification[3]

CGI-S = Clinical Global Impression; EQ-5D = European Quality of Life-5 Dimensions; ESK = esketamine; GAD-7 = Generalised Anxiety Disorder – 7-item scale; HSI = health status index; LOCF = last observation carried forward; MADRS = Montgomery-Åsberg Depression Rating Scale; NR = not reported; NS = nasal spray; OAD = oral antidepressant; PBO = placebo; PHQ-9 = Patient Health Questionnaire – 9 questions; SD = standard deviation; SDS = Sheehan Disability Scale

ERG comment: Tables 4.12 and 4.13 summarise the efficacy results of TRANSFORM-2 and SUSTAIN-1, respectively, which are the RCTs used to inform the economic model. However, some outcomes defined in the final scope issued by NICE have not been reported in the CS, namely cognitive dysfunction, hospitalisation and sleep quality (see Table 3.1).[1]

Both of these trials report on a number of outcomes, however, it should be noted that according to Table 7 of the CS (see Table 4.5), only response and remission based on MADRS (TRANSFORM-2) and relapse (SUSTAIN-1) are used in the economic model.[1]

In TRANSFORM-2 (Table 4.12), ESK-NS + OAD in comparison to PBO-NS + OAD showed a statistically significant reduction of MADRS at day 28 (difference in LS means -4.0, 95% CI -7.31 to 5.67). The trial also showed differences in response rate and remission rate, respectively, between the two groups. For the control arm of the trial, adjusted and unadjusted estimates are reported. As discussed in section 3.3, the ERG prefers the use of unadjusted estimates. Other reported outcomes (CGI-S, PHQ-9, GAD-7, SDS and EQ-5D) were in favour of the intervention (see Table 4.12 for details).

SUSTAIN-1 reported results separately for participants considered stable remitters (defined as *"patients who were in stable remission at the end of the optimisation phase and who received at least 1 dose of intranasal study drug and 1 dose of OAD during the maintenance phase"*) and stable responders (defined as *"patients who were stable responders (who were not stable remitters) at the end*

of the optimisation phase and who received at least 1 dose of intranasal study drug and 1 dose of OAD during the maintenance phase"). As shown in Table 4.13, the percentage of relapse was lower in the ESK-NS + OAD (stable remitters: 26.7%, stable responders: 25.8%) group in comparison to participants receiving PBO-NS + OAD (45.3% and 57.6%, respectively). The trial also showed time to relapse to be in favour of the intervention group for both, stable remitters (HR 0.49, 95% CI 0.29 to 0.84) and stable responders (HR 0.30, 95% CI 0.16 to 0.55). Other reported outcomes (CGI-S, PHQ-9, GAD-7, SDS and EQ-5D) were in favour of the intervention (see Table 4.13 for details). However, it should be noted that these results are based on last observation carried forward (LOCF) which fails to acknowledge uncertainty in the imputed values and results, typically, in confidence intervals that are too narrow.[24]

The results for TRANSFORM-2 and SUSTAIN-1 are in line with those of TRANSFORM-3 and SUSTAIN-2 which have been summarised in Tables 4.14 and 4.15.

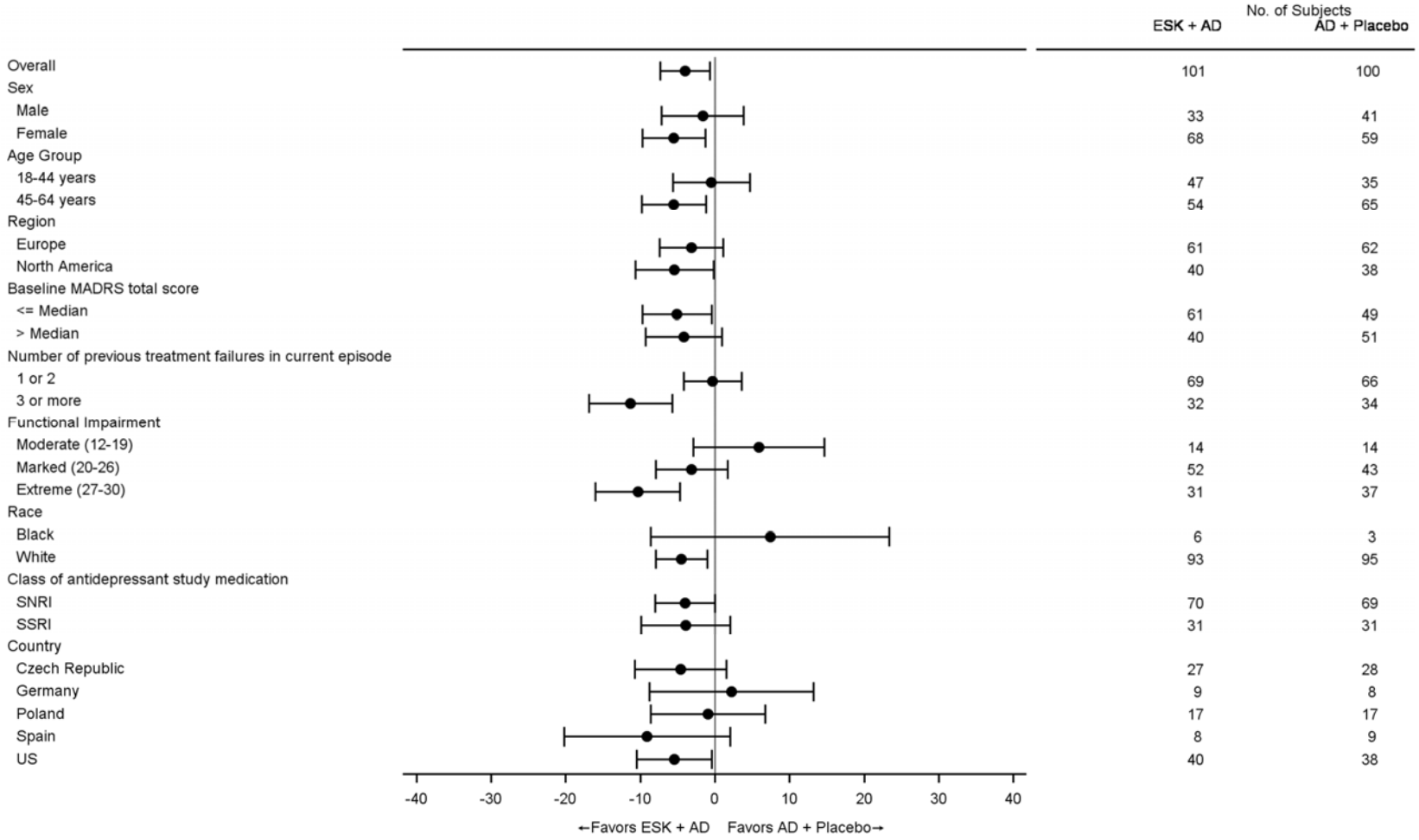
4.2.6 Subgroup analysis

Table 8 of the CS[1] listed pre-planned subgroups for TRANSFORM-2 and SUSTAIN-1:

- *Gender; race (White, Black, Other); country; number of previous treatment failures in current episode (based on MGH-ATRQ); class of OAD study medication (SNRI or SSRI)*
- *Functional impairment based on baseline SDS total score: not impaired (0–3), mild (4–11), moderate (12–19), marked (20–26), extreme (27–30)*
- *Age group (18–44 years, 45–64 years)*
- *Region (North America, Europe, Other)*
- *Baseline MADRS total score (≤/> median) (TRANSFORM-2 only)*
- *Consented protocol (pre-/post-protocol amendment 4) (SUSTAIN-1 only)*
- *Study entry route (direct-entry, transferred-entry) (SUSTAIN-1 only)*
- *OAD (duloxetine, escitalopram, sertraline, venlafaxine XR) (SUSTAIN-1 only)*

Figure 4.1 shows the differences by subgroup for TRANSFORM-2 in a forest plot. Table 4.16 gives further details. Based on information received in response to the request for clarification, Table 4.16 also includes details on unadjusted response and remission rates by OAD class and type as well as by disease severity.[3] Similarly, a forest plot for SUSTAIN-1 is presented in Figure 4.2 (no further details were provided).

Figure 4.1: Forest plot of LS mean treatment difference (95% CI) in change in MADRS total score from baseline to Day 28 by subgroup (MMRM; full analysis set) – TRANSFORM-2



Based on Figure 15 of the CS appendices[17]

AD = antidepressant; CI = confidence interval; CS = company submission; ESK = esketamine; LS = least squares; MADRS = Montgomery-Åsberg Depression Rating Scale; MMRM = mixed-effects model using repeated measures; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; US = United States (of America)

Table 4.16: MADRS total score: change from baseline to the end of induction by subgroup (observed cases MMRM and LOCF ANCOVA; full analysis set) – TRANSFORM-2

Subgroup	ESK-NS + OAD N=114	OAD + PBO-NS N=109
Gender		
Male		
Mean (SD) CFB to Day 28 (OC)	–20.5 (11.85) (n=33)	–18.3 (13.19) (n=41)
Diff in LS means (SE; 95% CI) (MMRM)[a]	–1.7 (2.80; –7.17 to 3.86)	
Mean (SD) CFB to endpoint (LOCF)	–17.9 (13.92) (n=39)	–17.1 (13.95) (n=46)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	–2.2 (2.65; –7.45 to 3.01)	
Female		
Mean (SD) CFB to Day 28 (OC)	–21.9 (12.61) (n=68)	–16.1 (14.38) (n=59)
Diff in LS means (SE; 95% CI) (MMRM)[a]	–5.5 (2.13; –9.71 to –1.31)	
Mean (SD) CFB to endpoint (LOCF)	–20.4 (13.42) (n=73)	–15.7 (14.53) (n=63)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	–4.4 (2.09; –8.52 to –0.26)	
Age group		
18–44 years		
Mean (SD) CFB to Day 28 (OC)	–23.1 (11.01) (n=47)	–2.5 (12.64) (n=35)
Diff in LS means (SE; 95% CI) (MMRM)[a]	–0.5 (2.62; –5.64 to 4.69)	
Mean (SD) CFB to endpoint (LOCF)	–20.7 (13.14) (n=54)	–22.0 (13.05) (n=40)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	–0.6 (2.52; –5.53 to 4.41)	
45–64 years		
Mean (SD) CFB to Day 28 (OC)	–20.0 (13.30) (n=54)	–14.0 (13.69) (n=65)
Diff in LS means (SE; 95% CI) (MMRM)[a]	–5.5 (2.19; –9.82 to –1.18)	
Mean (SD) CFB to endpoint (LOCF)	–18.5 (14.01) (n=58)	–13.0 (13.95) (n=69)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	–4.8 (2.13; –8.99 to –0.58)	
Region		
Europe		
Mean (SD) CFB to Day 28 (OC)	–22.3 (12.83) (n=61)	–19.4 (13.93) (n=62)
Diff in LS means (SE; 95% CI) (MMRM)[a]	–3.2 (2.16; –7.42 to 1.09)	
Mean (SD) CFB to endpoint (LOCF)	–20.1 (14.08) (n=68)	–18.2 (14.63) (n=65)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	–2.9 (2.18; –7.18 to 1.42)	
North America		
Mean (SD) CFB to Day 28 (OC)	–20.1 (11.54) (n=40)	–13.1 (13.07) (n=38)
Diff in LS means (SE; 95% CI) (MMRM)[a]	–5.4 (2.66; –10.69 to –0.18)	
Mean (SD) CFB to endpoint (LOCF)	–18.7 (12.90) (n=44)	–13.5 (13.31) (n=44)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	–4.6 (2.68; –9.88 to 0.66)	
Baseline MADRS total score		
≤37		
Mean (SD) CFB to Day 28 (OC)	–17.7 (11.17) (n=61)	–12.6 (12.75) (n=49)

Subgroup	ESK-NS + OAD N=114	OAD + PBO-NS N=109
Diff in LS means (SE; 95% CI) (MMRM)[a]	–5.1 (2.36; –9.74 to –0.43)	
Mean (SD) CFB to endpoint (LOCF)	–16.2 (12.35) (n=65)	–11.3 (12.84) (n=55)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	–5.7 (2.33; –10.27 to –1.10)	
>37		
Mean (SD) CFB to Day 28 (OC)	–27.2 (11.90) (n=40)	–21.2 (13.72) (n=51)
Diff in LS means (SE; 95% CI) (MMRM)[a]	–4.2 (2.59; –9.27 to 0.94)	
Mean (SD) CFB to endpoint (LOCF)	–24.2 (13.97) (n=47)	–21.4 (13.90) (n=54)
Diff in LS means (SE; 95% CI) (ANCOVA)[b]	–1.5 (2.54; –6.54 to 3.45)	
Number of previous treatment failures in the current episode of depression (induction phase)		
2[c]		
Mean (SD) CFB to Day 28 (OC)	–20.4 (11.91) (n=59)	–21.0 (12.89) (n=64)
Diff in LS means (SE; 95% CI) (MMRM)[d]	0.5 (2.08; –3.60 to 4.59)	
Mean (SD) CFB to Day 28 (LOCF)	–19.0 (12.54) (n=64)	–19.8 (13.61) (n=70)
Diff in LS means (SE; 95% CI) (ANCOVA)[d]	–0.1 (2.06; –4.15 to 3.98)	
≥3		
Mean (SD) CFB to Day 28 (OC)	–22.7 (12.77) (n=38)	–10.3 (12.95) (n=35)
Diff in LS means (SE; 95% CI) (MMRM)[d]	–11.5 (2.70; –16.85 to –6.22)	
Mean (SD) CFB to Day 28 (LOCF)	–19.9 (15.02) (n=44)	–10.3 (13.33) (n=38)
Diff in LS means (SE; 95% CI) (ANCOVA)[d]	–9.1 (2.65; –14.30 to –3.84)	
Disease severity		
Remission		
Moderate (MADRS total score at baseline 18-34) (n=65)	56.25	30.30
	OR 2.96 (95% CI 1.07 to 8.20)	
Severe (MADRS total score at baseline >34) (n=136)	50.72	31.34
	OR 2.26 (95% CI 1.12 to 4.54)	
Response		
Moderate (MADRS total score at baseline 18-34) (n=65)	59.38	36.36
	OR 2.56 (95% CI 0.94 to 6.96)	
Severe (MADRS total score at baseline >34) (n=136)	73.91	59.70
	OR 1.91 (95% CI 0.93 to 3.95)	
Functional impairment (assessed by SDS)		
Mild (SDS: 4–11)		
Mean (SD) CFB to Day 28 (OC)	–22.0 (-) (n=1)	–9.0 (-) (n=1)
Diff in LS means (SE; 95% CI) (MMRM)[e]	–15.6 (17.00; –49.07 to 17.97)	
Mean (SD) CFB to endpoint (LOCF)	–22.0 (-) (n=1)	–9.0 (-) (n=1)
Diff in LS means (SE; 95% CI) (ANCOVA)[f]	–10.5 (17.37; –44.77 to 23.74)	
Moderate (SDS: 12–19)		
Mean (SD) CFB to Day 28 (OC)	–14.9 (11.25) (n=14)	–22.8 (13.62) (n=14)

Subgroup	ESK-NS + OAD N=114	OAD + PBO-NS N=109
Diff in LS means (SE; 95% CI) (MMRM)[e]	5.9 (4.45; –2.89 to 14.64)	
Mean (SD) CFB to endpoint (LOCF)	–13.9 (11.50) (n=15)	–19.8 (14.13) (n=17)
Diff in LS means (SE; 95% CI) (ANCOVA)[f]	1.4 (4.37; –7.24 to 10.01)	
Marked (SDS: 20–26)		
Mean (SD) CFB to Day 28 (OC)	–20.8 (11.88) (n=52)	–16.8 (13.27) (n=43)
Diff in LS means (SE; 95% CI) (MMRM)[e]	–3.1 (2.44; –7.96 to 1.67)	
Mean (SD) CFB to endpoint (LOCF)	–18.4 (13.53) (n=58)	–16.9 (13.30) (n=45)
Diff in LS means (SE; 95% CI) (ANCOVA)[f]	–2.7 (2.43; –7.47 to 2.10)	
Extreme (SDS: 27–30)		
Mean (SD) CFB to Day 28 (OC)	–26.2 (12.16) (n=31)	–14.8 (14.88) (n=37)
Diff in LS means (SE; 95% CI) (MMRM)[e]	–10.3 (2.87; –16.00 to –4.66)	
Mean (SD) CFB to endpoint (LOCF)	–24.3 (13.68) (n=35)	–13.9 (15.65) (n=41)
Diff in LS means (SE; 95% CI) (ANCOVA)[f]	–7.6 (2.84; –13.22 to –2.03)	
Race		
Black		
Mean (SD) CFB to Day 28 (OC)	–16.8 (9.60) (n=6)	–18.3 (17.21) (n=3)
Diff in LS means (SE; 95% CI) (MMRM)[g]	7.4 (8.13; –8.63 to 23.41)	
Mean (SD) CFB to endpoint (LOCF)	–16.8 (9.60) (n=6)	–17.6 (16.89) (n=5)
Diff in LS means (SE; 95% CI) (ANCOVA)[h]	4.3 (7.38; –10.22 to 18.86)	
White		
Mean (SD) CFB to Day 28 (OC)	–21.8 (12.41) (n=93)	–17.0 (13.99) (n=95)
Diff in LS means (SE; 95% CI) (MMRM)[g]	–4.5 (1.76; –7.96 to –1.03)	
Mean (SD) CFB to endpoint (LOCF)	–19.7 (13.79) (n=104)	–16.2 (14.30) (n=102)
Diff in LS means (SE; 95% CI) (ANCOVA)[h]	–3.8 (1.69; –7.11 to –0.44)	
Other		
Mean (SD) CFB to Day 28 (OC)	–18.0 (19.80) (n=2)	–16.5 (9.19) (n=2)
Diff in LS means (SE; 95% CI) (MMRM)[g]	–5.5 (12.25; –29.69 to 18.62)	
Mean (SD) CFB to endpoint (LOCF)	–18.0 (19.80) (n=2)	–16.5 (9.19) (n=2)
Diff in LS means (SE; 95% CI) (ANCOVA)[h]	–8.6 (12.19; –35.59 to 15.46)	
Class of OAD		
SNRI		
Mean (SD) CFB to Day 28 (OC)	–22.0 (11.99) (n=70)	–18.1 (13.88) (n=69)
Diff in LS means (SE; 95% CI) (MMRM)[i]	–4.0 (2.04; –8.02 to 0.03)	
Mean (SD) CFB to endpoint (LOCF)	–20.8 (12.92) (n=76)	–17.0 (14.40) (n=75)
Diff in LS means (SE; 95% CI) (ANCOVA)[j]	–4.0 (1.97; –7.87 to –0.11)	
SSRI		
Mean (SD) CFB to Day 28 (OC)	–20.1 (13.13) (n=31)	–14.6 (13.81) (n=31)
Diff in LS means (SE; 95% CI) (MMRM)[i]	–3.9 (3.04; –9.91 to 2.08)	

Subgroup	ESK-NS + OAD N=114	OAD + PBO-NS N=109
Mean (SD) CFB to endpoint (LOCF)	–16.8 (14.72) (n=36)	–14.8 (13.97) (n=34)
Diff in LS means (SE; 95% CI) (ANCOVA)[j]	–2.3 (2.90; –8.03 to 3.38)	
Type of OAD		
Day 28 Remission rates (%)		
SSRI	51.61 (n=36)	25.81 (n=34)
	OR 3.07 (95% CI 1.05 to 8.93)	
Sertraline	33.33 (n=15)	26.67 (n=16)
	OR 1.38 (95% CI 0.26 to 7.22)	
Escitalopram	63.16 (n=21)	26.67 (n=17)
	OR 4.71 (95% CI 1.08 to 20.63)	
SNRI	52.86 (n=76)	33.33 (n=75)
	OR 2.24 (95% CI 1.13 to 4.45)	
Duloxetine	50.00 (n=59)	32.73 (n=61)
	OR 2.06 (95% CI 0.95 to 4.47)	
Venlafaxine XR	62.50 (n=17)	33.33 (n=15)
	OR 3.33 (95% CI 0.76 to 14.58)	
Day 28 Response rates (%)		
SSRI	67.74 (n=36)	45.16 (n=34)
	OR 2.55 (95% CI 0.91 to 7.17)	
Sertraline	58.33 (n=15)	33.33 (n=16)
	OR 2.80 (95% CI 0.58 to 13.48)	
Escitalopram	73.68 (n=21)	53.33 (n=17)
	OR 2.45 (95% CI 0.58 to 10.33)	
SNRI	70.00 (n=76)	55.07 (n=75)
	OR 1.90 (95% CI 0.95 to 3.82)	
Duloxetine	70.37 (n=59)	60.00 (n=61)
	OR 1.58 (95% CI 0.72 to 3.51)	
Venlafaxine XR	68.75 (n=17)	40.00 (n=15)
	OR 3.30 (95% CI 0.75 to 14.47)	
Country		
Czech Republic		
Mean (SD) CFB to Day 28 (OC)	–26.8 (10.78) (n=27)	–21.8 (15.34) (n=28)
Diff in LS means (SE; 95% CI) (MMRM)[k]	–4.6 (3.11; –10.72 to 1.54)	
Mean (SD) CFB to endpoint (LOCF)	–24.8 (13.25) (n=29)	–21.8 (15.34) (n=28)
Diff in LS means (SE; 95% CI) (ANCOVA)[l]	–3.7 (3.21; –10.00 to 2.65)	
Germany		
Mean (SD) CFB to Day 28 (OC)	–10.2 (12.43) (n=9)	–13.5 (9.09) (n=8)
Diff in LS means (SE; 95% CI) (MMRM)[k]	2.2 (5.60; –8.81 to 13.25)	

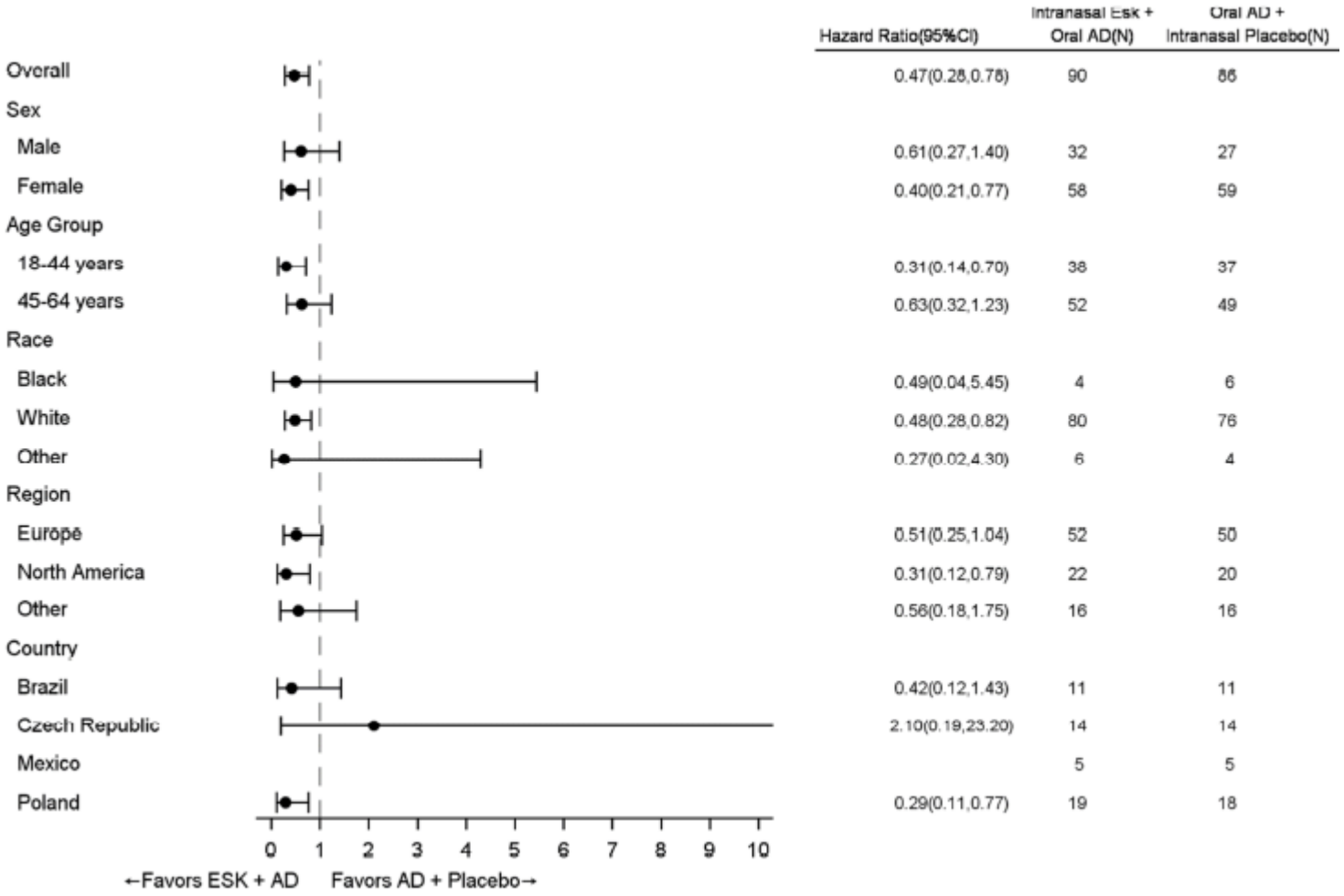
Subgroup	ESK-NS + OAD N=114	OAD + PBO-NS N=109
Mean (SD) CFB to endpoint (LOCF)	–9.2 (12.15) (n=10)	–10.1 (10.96) (n=10)
Diff in LS means (SE; 95% CI) (ANCOVA)[l]	–0.6 (5.42; –11.30 to 10.07)	
Poland		
Mean (SD) CFB to Day 28 (OC)	–24.8 (9.59) (n=17)	–23.6 (8.48) (n=17
Diff in LS means (SE; 95% CI) (MMRM)[k]	–0.9 (3.89; –8.57 to 6.78)	
Mean (SD) CFB to endpoint (LOCF)	–21.6 (12.12) (n=20)	–21.7 (11.42) (n=18)
Diff in LS means (SE; 95% CI) (ANCOVA)[l]	0.8 (3.94; –6.93 to 8.60)	
Spain		
Mean (SD) CFB to Day 28 (OC)	–15.5 (16.04) (n=8)	–9.1 (16.09) (n=9)
Diff in LS means (SE; 95% CI) (MMRM)[k]	–9.1 (5.63; –20.18 to 2.00)	
Mean (SD) CFB to endpoint (LOCF)	–13.8 (15.86) (n=9)	–9.1 (16.09) (n=9)
Diff in LS means (SE; 95% CI) (ANCOVA)[l]	–9.4 (5.75; –20.71 to 1.96)	
United States		
Mean (SD) CFB to Day 28 (OC)	–20.1 (11.54) (n=40)	–13.1 (13.07) (n=38)
Diff in LS means (SE; 95% CI) (MMRM)[k]	–5.5 (2.56; –10.52 to –0.44)	
Mean (SD) CFB to endpoint (LOCF)	–18.7 (12.90) (n=44)	–13.5 (13.31) (n=44)
Diff in LS means (SE; 95% CI) (ANCOVA)[l]	–4.6 (2.58; –9.72 to 0.46)	

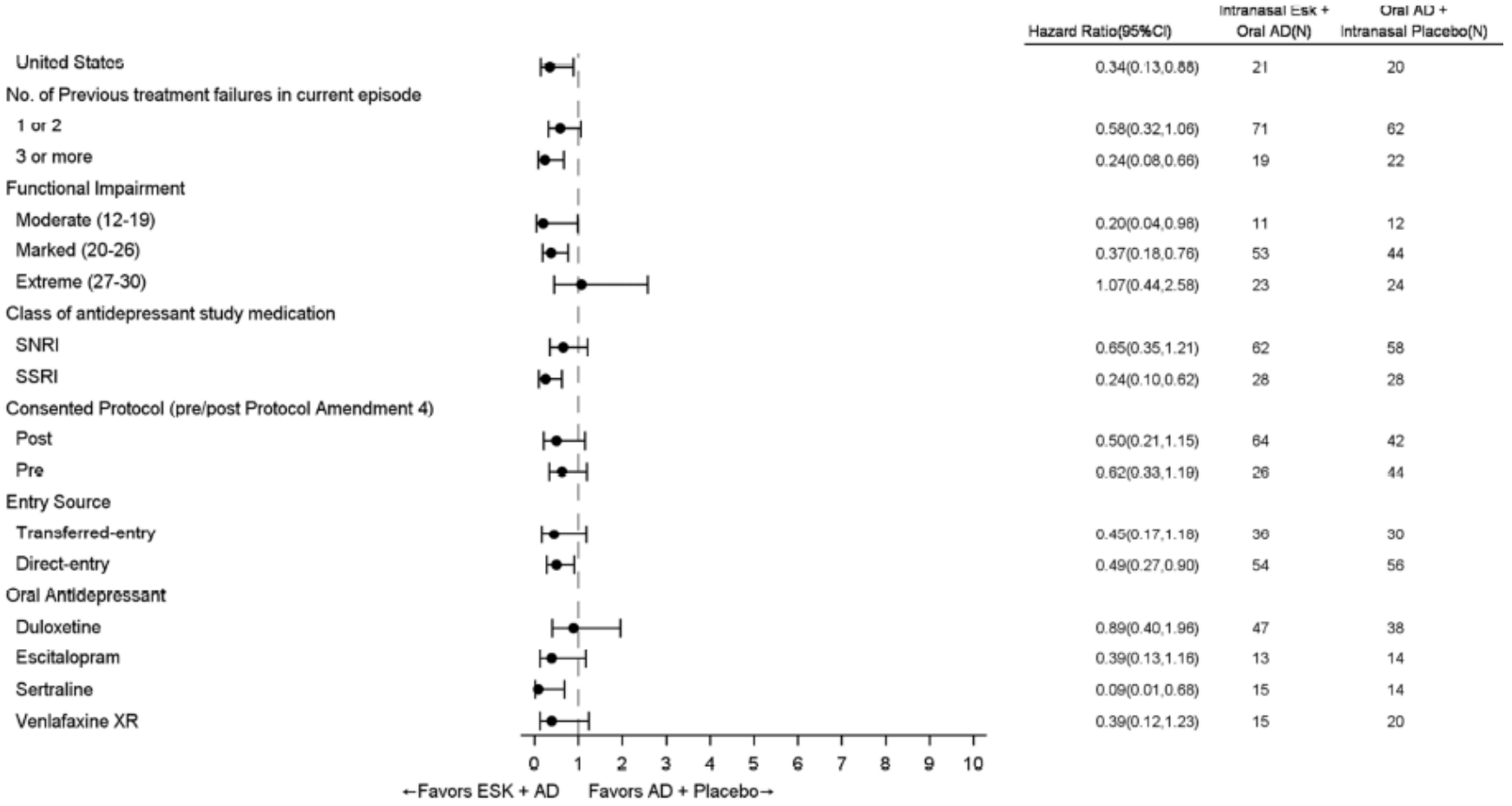
Based on Table 52 of the CS appendices[19] and Tables 3 and 8 of the response to the request for clarification[3]

[a] Fixed effect model adjusted for treatment, day, country, OAD (SNRI or SSRI), sex, treatment-by-day, treatment-by-sex, treatment-by-day-by-sex, and baseline value; [b] Adjusting for treatment, country, OAD , treatment-by-sex, and baseline MADRS value were covariates; [c] The minimum number of prior OADs to which patients could have not responded to at the beginning of induction was two since patients had to demonstrate non-response to one OAD during the screening/prospective observation phase; [d] Fixed effect model adjusted for treatment, day, country, OAD, number of previous treatment failures in current episode, treatment-by-day, treatment-by-number of previous treatment failures in current episode, treatment-by-day-by-number of previous treatment failures in current episode, and baseline value; [e] Fixed effect model adjusted for treatment, day, country, OAD , functional impairment, treatment-by-day, treatment-by-functional impairment, treatment-by-day-by-functional impairment, and baseline value; [f] Adjusted for treatment, country, OAD , functional impairment, treatment-by-functional impairment, and baseline value; [g] Fixed effect model adjusted for treatment, day, country, OAD , race, treatment-by-day, treatment-by-race, treatment-by-day-by-race, and baseline value; [h] Adjusted for treatment, country, OAD , race, treatment-by-race, and baseline MADRS value; [i] Adjusted for treatment, day, country, OAD, treatment-by-day, treatment-by- OAD, treatment-by-day-by- OAD, and baseline value; [j] Adjusted for treatment, country, OAD , treatment-by- OAD, and baseline MADRS value; [k] Adjusted for treatment, day, country, OAD, treatment-by-day, treatment-by-country, treatment-by-day-by-country, and baseline value; [l] Adjusted for treatment, country, OAD , treatment-by-country, and baseline MADRS value

ANCOVA = analysis of covariance; CFB = change from baseline; CI = confidence interval; CS = company submission; Diff = difference; ESK-NS = esketamine nasal spray; LS = least squares; MADRS = Montgomery-Åsberg Depression Rating Scale; MMRM = mixed-effects model using repeated measures; OAD = oral antidepressant; OC = observed cases; OR = odds ratio; SD = standard deviation; SDS = Sheehan Disability Scale; SE = standard error; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

Figure 4.2: Forest plot of LS mean treatment difference (95% CI) in change in MADRS total score from baseline to Day 28 by subgroup (MMRM; full analysis set) – SUSTAIN-1





Based on Figure 16 of the CS appendices[17]

AD = antidepressant; CI = confidence interval; CS = company submission; ESK = esketamine; LS = least squares; MADRS = Montgomery-Åsberg Depression Rating Scale; MMRM = mixed-effects model using repeated measures; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

ERG comment: Due to the small numbers of participants in each arm, any differences in the subgroup analyses need to be interpreted with some caution.

A visual inspection of TRANSFORM-2 (Figure 4.1) indicate some differences between gender, number of previous treatment failures in current episode, functional impairment, and race. Furthermore, the advantage of esketamine compared to the control group seems bigger in remission rather than relapse, see Table 4.16 for details. Of note, there are differences between the type of OAD for remission rates after 28 days, e.g. within the SSRI group: sertraline (odds ratio (OR) 1.38, 95% CI 0.26 to 7.22) vs. escitalopram (OR 4.71, 95% CI 1.08 to 20.63). This might indicate a clinically relevant limitation of the basket approach used in the economic model.

No relevant differences were noted when visually inspecting the forest plot provided for SUSTAIN-1, replicated in Figure 4.2. However, no further details were provided, preventing a closer examination.

4.2.7 Safety results

Safety results for TRANSFORM-2 (Table 4.17) and SUSTAIN-1 (Tables 4.18 and 4.19), the trials used in the economic model, are reported below. Furthermore, safety results for TRANSFORM-3 (Table 4.20) and SUSTAIN-2 (Tables 4.21 and 4.22) are presented.

Table 4.17: Safety results of TRANSFORM-2

	ESK-NS + OAD	OAD + PBO-NS
Induction phase, n (%)	**N=115**	**N=109**
Overall summary		
AE	98 (85.2)	66 (60.6)
AE possibly related to nasal spray drug[a]	90 (78.3)	39 (35.8)
AE possibly related to OAD[a]	39 (33.9)	26 (23.9)
AE leading to death	1 (0.9)	0
≥1 serious AE	1 (0.9)	1 (0.9)
AE leading to nasal spray drug being withdrawn[b]	8 (7.0)	1 (0.9)
AE leading to OAD being withdrawn[b]	4 (3.5)	0
AEs reported in ≥5% of patients		
Nervous system disorders, n (%)	**72 (62.6)**	**39 (35.8)**
Dysgeusia	28 (24.3)	13 (11.9)
Dizziness	24 (20.9)	5 (4.6)
Headache	23 (20.0)	19 (17.4)
Somnolence	15 (13.0)	7 (6.4)
Paraesthesia	13 (11.3)	1 (0.9)
Dizziness postural	8 (7.0)	1 (0.9)
Hypoaesthesia	8 (7.0)	1 (0.9)
Psychiatric disorders, n (%)	**55 (47.8)**	**21 (19.3)**
Dissociation[c]	30 (26.1)	4 (3.7)
Anxiety	12 (10.4)	5 (4.6)
Insomnia	11 (9.6)	5 (4.6)

	ESK-NS + OAD	OAD + PBO-NS
Gastrointestinal disorders, n (%)	**52 (42.5)**	**26 (23.9)**
Nausea	30 (26.1)	7 (6.4)
Vomiting	11 (9.6)	2 (1.8)
Diarrhoea	10 (8.7)	10 (9.2)
Dry mouth	9 (7.8)	3 (2.8)
Hypoaesthesia oral	9 (7.8)	1 (0.9)
Paraesthesia oral	9 (7.8)	1 (0.9)
Ear and labyrinth disorders, n (%)	**34 (29.6)**	**6 (5.5)**
Vertigo	30 (26.1)	3 (2.8)
General disorders and administration site conditions, n (%)	**30 (26.1)**	**13 (11.9)**
Feeling drunk	9 (7.8)	1 (0.9)
Fatigue	5 (4.3)	6 (5.5)
Respiratory, thoracic and mediastinal disorders, n (%)	**24 (20.9)**	**15 (13.8)**
Throat irritation	9 (7.8)	5 (4.6)
Nasal discomfort	8 (7.0)	2 (1.8)
Eye disorders, n (%)	**18 (15.7)**	**3 (2.8)**
Vision blurred	14 (12.2)	3 (2.8)
Investigations, n (%)	**14 (12.2)**	**4 (3.7)**
Blood pressure increased	11 (9.6)	0
Follow-up phase, n (%)	**N=34**	**N=52**
Overall summary		
AE	9 (26.5)	12 (23.1)
AE possibly related to nasal spray drug[a]	0	1 (1.9)
AE possibly related to OAD[a]	1 (2.9)	3 (5.8)
AE leading to death	0	0
≥1 serious AE	1 (2.9)	0
AE leading to OAD being withdrawn[b]	0	0

Based on Tables 37 and 38 of the CS[1]

Notes: 1) Incidence was based on the number of patients experiencing ≥1 AE, not the number of events; 2) AEs were coded using MedDRA version 20.0

[a] Study drug relationships of possible, probable, and very likely were included in this category; [b] An AE that started in the double-blind induction phase and resulted in discontinuation in the follow-up phase was counted as treatment-emergent in the double-blind induction phase; [redacted]

AE = adverse event; CS = company submission; ESK = esketamine; MedDRA = Medical Dictionary for Regulatory Activities; NS = nasal spray; OAD = oral antidepressant; PBO = placebo

Table 4.18: Safety results of SUSTAIN-1 (overall)

	Induction phase	Optimisation phase	Maintenance phase		Follow-up phase	
	ESK-NS + OAD (N=437)	ESK-NS + OAD (N=455)	ESK-NS + OAD (N=152)	OAD + PBO-NS (N=145)	ESK-NS + OAD during any phase (N=481)	OAD + PBO-NS for all phases (N=64)
AE, n (%)	336 (76.9)	335 (73.6)	125 (82.2)	66 (45.5)	53 (11.0)	5 (7.8)
AE possibly related to nasal spray drug, n (%)[a]	301 (68.9)	281 (61.8)	106 (69.7)	37 (25.5)	7 (1.5)	0
AE possibly related to OAD, n (%)[a]	71 (16.2)	61 (13.4)	13 (8.6)	9 (6.2)	3 (0.6)	0
AE leading to death, n (%)	0	0	0	0	0	0
≥1 serious AE, n (%)	13 (3.0)	11 (2.4)	4 (2.6)	1 (0.7)	3 (0.6)	0
AE leading to nasal spray drug being withdrawn, n (%)	22 (5.0)	5 (1.1)	4 (2.6)	3 (2.1)	NA[b]	NA[b]
AE leading to OAD being withdrawn, n (%)[c]	8 (1.8)	2 (0.4)	3 (2.0)	0	0[c]	0[c]

Based on Table 39 of the CS[1]

Notes: 1) Incidence was based on the number of patients experiencing ≥1 AE, not the number of events; 2) AEs were coded using MedDRA version 20.0

[a] Study drug relationships of possible, probable, and very likely were included in this category; [b] Patients did not receive nasal spray during the follow-up phase; [c] An AE that started in the induction phase and resulted in discontinuation in a subsequent phase was counted as treatment-emergent in the induction phase.

AE = adverse event; CS = company submission; ESK = esketamine; MedDRA = Medical Dictionary for Regulatory Activities; NA = not applicable; NS = nasal spray; OAD = oral antidepressant; PBO = placebo

Table 4.19: Safety results of SUSTAIN-1 (AEs reported in ≥5% of patients)

	ESK-NS + OAD	OAD + PBO-NS
Induction phase (Safety [IND] analysis set)	**N=437**	**NA**
Total number of patients with an AE, n (%)	**336 (76.9)**	**-**
Nervous system disorders, n (%)	**248 (56.8)**	**-**
Dizziness	97 (22.2)	-
Dysgeusia	90 (20.6)	-
Somnolence	65 (14.9)	-
Headache	60 (13.7)	-
Paraesthesia	48 (11.0)	-
Sedation	44 (10.1)	-
Dizziness postural	33 (7.6)	-
Hypoaesthesia	30 (6.9)	-
Psychiatric disorders, n (%)	**163 (37.3)**	**-**
Dissociation	82 (18.8)	-
Anxiety	31 (7.1)	-
Gastrointestinal disorders, n (%)	**150 (34.3)**	**-**
Nausea	94 (21.5)	-
Hypoaesthesia oral	32 (7.3)	-
Vomiting	29 (6.6)	-
Ear and labyrinth disorders, n (%)	**108 (24.7)**	**-**
Vertigo	99 (22.7)	-
Respiratory, thoracic and mediastinal disorders, n (%)	**88 (20.1)**	**-**
Nasal discomfort	29 (6.6)	-
Throat irritation	26 (5.9)	-
Eye disorders, n (%)	**63 (14.4)**	**-**
Vision blurred	45 (10.3)	-
Investigations, n (%)	42 (9.6)	-
Blood pressure increased	34 (7.8)	-
Optimisation phase (Safety [OP] analysis set)	**N=455**	**NA**
Total number of patients with an AE, n (%)	**335 (73.6)**	**-**
Nervous system disorders, n (%)	**212 (46.6)**	**-**
Dysgeusia	79 (17.4)	-
Somnolence	63 (13.8)	-
Dizziness	61 (13.4)	-
Headache	57 (12.5)	-
Dizziness postural	26 (5.7)	
Hypoaesthesia	24 (5.3)	-
Paraesthesia	24 (5.3)	-

	ESK-NS + OAD	OAD + PBO-NS
Psychiatric disorders, n (%)	**136 (29.9)**	**-**
Dissociation	73 (16.0)	-
Gastrointestinal disorders, n (%)	**116 (25.5)**	**-**
Nausea	48 (10.5)	-
Hypoaesthesia oral	34 (7.5)	-
Ear and labyrinth disorders, n (%)	**101 (22.2)**	**-**
Vertigo	91 (20.0)	-
Respiratory, thoracic and mediastinal disorders, n (%)	**73 (16.0)**	**-**
Nasal discomfort	26 (5.7)	-
Investigations, n (%)	**47 (10.3)**	**-**
Blood pressure increased	26 (5.7)	-
Eye disorders, n (%)	46 (10.1)	-
Vision blurred	30 (6.6)	-
Maintenance phase (Safety [MA] analysis set)	**N=152**	**N=145**
Total number of patients with an AE, n (%)	**125 (82.2)**	**66 (45.5)**
Nervous system disorders, n (%)	**83 (54.6)**	**30 (20.7)**
Dysgeusia	41 (27.0)	10 (6.9)
Somnolence	32 (21.1)	3 (2.1)
Dizziness	31 (20.4)	7 (4.8)
Headache	27 (17.8)	14 (9.7)
Paraesthesia	11 (7.2)	0
Dizziness postural	10 (6.6)	3 (2.1)
Sedation	10 (6.6)	1 (0.7)
Hypoaesthesia	9 (5.9)	0
Psychiatric disorders, n (%)	**60 (39.5)**	**15 (10.3)**
Dissociation	35 (23.0)	0
Anxiety	12 (7.9)	5 (3.4)
Confusional state	9 (5.9)	0
Gastrointestinal disorders, n (%)	**53 (34.9)**	**11 (7.6)**
Nausea	25 (16.4)	1 (0.7)
Hypoaesthesia oral	20 (13.2)	0
Vomiting	10 (6.6)	1 (0.7)
Paraesthesia oral	8 (5.3)	1 (0.7)
Ear and labyrinth disorders, n (%)	**43 (28.3)**	**9 (6.2)**
Vertigo	38 (25.0)	8 (5.5)
Eye disorders, n (%)	**32 (21.1)**	**1 (0.7)**
Vision blurred	24 (15.8)	1 (0.7)
Diplopia	9 (5.9)	0

	ESK-NS + OAD	OAD + PBO-NS
Infections and infestations, n (%)	**32 (21.1)**	**25 (17.2)**
Viral upper respiratory tract infection	11 (7.2)	12 (8.3)
Respiratory, thoracic and mediastinal disorders, n (%)	**29 (19.1)**	**11 (7.6)**
Nasal discomfort	11 (7.2)	4 (2.8)
Throat irritation	8 (5.3)	1 (0.7)
Investigations, n (%)	**19 (12.5)**	**10 (6.9)**
Blood pressure increased	10 (6.6)	5 (3.4)

Based on Table 40 of the CS[1]

Notes: 1) Incidence was based on the number of patients experiencing ≥1 AE, not the number of events; 2) AEs were coded using MedDRA version 20.0

[a] Study drug relationships of possible, probable, and very likely were included in this category; [b] Patients did not receive nasal spray during the follow-up phase; [c] An AE that started in the induction phase and resulted in discontinuation in a subsequent phase was counted as treatment-emergent in the induction phase.

AE = adverse event; CS = company submission; ESK = esketamine; IND = induction phase; MA = maintenance phase; MedDRA = Medical Dictionary for Regulatory Activities; NA = not applicable; NS = nasal spray; OAD = oral antidepressant; OP = optimisation phase; PBO = placebo

Table 4.20: Safety results of TRANSFORM-3

	ESK-NS + OAD	OAD + PBO-NS
Induction phase, n (%)	**N=72**	**N=65**
Overall summary		
AE	51 (70.8)	39 (60.0)
AE possibly related to nasal spray drug[a]	42 (58.3)	22 (33.8)
AE possibly related to OAD[a]	13 (18.1)	11 (16.9)
AE leading to death	0	0
≥1 serious AE	3 (4.2)	2 (3.1)
AE leading to nasal spray drug being withdrawn[b]	4 (5.6)	2 (3.1)
AE leading to OAD being withdrawn[b]	1 (1.4)	1 (1.5)
AEs reported in ≥5% of patients		
Total number of patients with an AE, n (%)	51 (70.8)	39 (60.0)
Psychiatric disorders, n (%)	26 (36.1)	11 (16.9)
Dissociation	9 (12.5)	1 (1.5)
Dysphoria	4 (5.6)	0
Insomnia	4 (5.6)	3 (4.6)
Anxiety	2 (2.8)	5 (7.7)
Nervous system disorders, n (%)	24 (33.3)	16 (35.8)
Dizziness	15 (20.8)	5 (7.7)
Headache	9 (12.5)	2 (3.1)
Dysgeusia	4 (5.6)	3 (4.6)
Hypoaesthesia	4 (5.6)	1 (1.5)
Paraesthesia	4 (5.6)	2 (3.1)

	ESK-NS + OAD	OAD + PBO-NS
Gastrointestinal disorders, n (%)	19 (26.4)	8 (12.3)
Nausea	13 (18.1)	3 (4.6)
Hypoaesthesia oral	4 (5.6)	0
Vomiting	4 (5.6)	1 (1.5)
General disorders and administration site conditions, n (%)	14 (19.4)	8 (12.3)
Fatigue	9 (12.5)	5 (7.7)
Investigations, n (%)	14 (19.4)	6 (9.2)
Blood pressure increased	9 (12.5)	3 (4.6)
Ear and labyrinth disorders, n (%)	10 (13.9)	4 (6.2)
Vertigo	8 (11.1)	2 (3.1)
Infections and infestations, n (%)	8 (11.1)	6 (9.2)
Urinary tract infections	6 (8.3)	1 (1.5)
Follow-up phase, n (%)	**N=12**	**N=3**
Overall summary		
AE	1 (8.3)	1 (33.3)
AE possibly related to nasal spray drug[a]	0	1 (33.3)
AE possibly related to OAD[a]	1 (8.3)	0
AE leading to death	0	0
≥1 serious AE	0	0
AE leading to OAD being withdrawn[b]	0	0

Based on Tables 37 and 38 of response to request for clarification[3]

Notes: 1) Incidence was based on the number of patients experiencing ≥1 AE, not the number of events; 2) AEs were coded using MedDRA version 20.0

[a] Study drug relationships of possible, probable, and very likely were included in this category; [b] An AE that started in the double-blind induction phase and resulted in discontinuation in the follow-up phase was counted as treatment-emergent in the double-blind induction phase.

AE = adverse event; CS = company submission; ESK = esketamine; MedDRA = Medical Dictionary for Regulatory Activities; NA = not applicable; NS = nasal spray; OAD = oral antidepressant; PBO = placebo

Table 4.21: Safety results of SUSTAIN-2 (overall)

	ESK-NS + OAD
Induction phase, n (%)	**N=779**
AE	653 (83.8)
AE possibly related to nasal spray drug[a]	586 (75.2)
AE possibly related to OAD[a]	177 (22.7)
AE leading to death	0
≥1 serious AE	17 (2.2)
AE leading to nasal spray drug being withdrawn	53 (6.8)
AE leading to OAD being withdrawn	20 (2.6)
Optimisation/maintenance phase, n (%)	**N=603**
AE	516 (85.6)

	ESK-NS + OAD
AE possibly related to nasal spray drug[a]	402 (66.7)
AE possibly related to OAD[a]	110 (18.2)
AE leading to death	2 (0.3)
≥1 serious AE	38 (6.3)
AE leading to nasal spray drug being withdrawn[b]	23 (3.8)
AE leading to OAD being withdrawn[b]	14 (2.3)
Follow-up phase, n (%)	**N=357**
AE	55 (15.4)
AE possibly related to nasal spray drug[a]	9 (2.5)
AE possibly related to OAD[a]	5 (1.4)
AE leading to death	0
≥1 serious AE	8 (2.2)
AE leading to OAD being withdrawn[b]	1 (0.3)

Based on Table 47 of response to request for clarification[3]

Notes: 1) Incidence was based on the number of patients experiencing ≥1 AE, not the number of events; 2) AEs were coded using MedDRA version 20.0

[a] Study drug relationships of possible, probable, and very likely were included in this category; [b] An AE that started in the previous phases and resulted in discontinuation in the follow-up phase was counted as treatment-emergent in the previous phase

AE = adverse event; CS = company submission; ESK = esketamine; MedDRA = Medical Dictionary for Regulatory Activities; NA = not applicable; NS = nasal spray; OAD = oral antidepressant; PBO = placebo

Table 4.22: Safety results of SUSTAIN-2 (AEs reported in ≥5% of patients)

	ESK-NS + OAD (N=802)
Total number of patients with an AE, n (%)	**723 (90.1)**
Nervous system disorders, n (%)	**528 (65.8)**
Dizziness	264 (32.9)
Headache	200 (24.9)
Somnolence	134 (16.7)
Dysgeusia	95 (11.8)
Hypoaesthesia	95 (11.8)
Sedation	71 (8.9)
Dizziness postural	67 (8.4)
Paraesthesia	58 (7.2)
Psychiatric disorders, n (%)	**384 (47.9)**
Dissociation	221 (27.6)
Anxiety	72 (9.0)
Insomnia	63 (7.9)
Gastrointestinal disorders, n (%)	**373 (46.5)**
Nausea	201 (25.1)
Vomiting	87 (10.8)

	ESK-NS + OAD (N=802)
Hypoaesthesia oral	73 (9.1)
Diarrhoea	60 (7.5)
Infections and infestations, n (%)	**279 (34.8)**
Viral upper respiratory tract infection	82 (10.2)
Urinary tract infections	65 (8.1)
influenza	43 (5.4)
General disorders and administration site conditions, n (%)	**187 (23.3)**
Fatigue	63 (7.9)
Musculoskeletal and connective tissue disorders, n (%)	**154 (19.2)**
Back pain	41 (5.1)
Investigations, n (%)	**143 (17.8)**
Blood pressure increased	75 (9.4)
Ear and labyrinth disorders, n (%)	**126 (15.7)**
Vertigo	88 (11.0)
Eye disorders, n (%)	**105 (13.1)**
Vision blurred	60 (7.5)

Based on Table 48 of response to request for clarification[3]

Notes: 1) Incidence was based on the number of patients experiencing ≥1 AE, not the number of events; 2) AEs were coded using MedDRA version 20.0

[a] Study drug relationships of possible, probable, and very likely were included in this category; [b] An AE that started in the previous phases and resulted in discontinuation in the follow-up phase was counted as treatment-emergent in the previous phase.

AE = adverse event; CS = company submission; ESK = esketamine; MedDRA = Medical Dictionary for Regulatory Activities; NA = not applicable; NS = nasal spray; OAD = oral antidepressant; PBO = placebo

ERG comment: In the induction phase of TRANSFORM-2, more adverse events were observed in patients treated with ESK-NS + OAD compared to those receiving PBO-NS + OAD (85.2% vs. 60.6%, see Table 4.17). In SUSTAIN-1 more adverse events were seen in the maintenance phase (82.2% vs. 45.5%) and the follow-up phase (11.0% vs. 7.8%), see Table 4.18. Potential adverse events, especially psychiatric disorders (47.8% vs. 19.3%, see Table 4.17), need to be considered before considering ESK-NS as a treatment option for patients with TRD.

The company reported seven deaths among 1,861 patients treated with ESK-NS across the six phase 2 and 3 studies, three of which were completed suicides.[1] The company stated that, based on the severity of patients' underlying illness and the lack of a consistent pattern the suicides were considered unrelated to ESK-NS treatment. In this context it is important to note that the trials in the CS excluded patients who had suicidal/homicidal ideation/intent within six months prior to screening per the investigator's clinical judgements and/or based on C-SSRS or a history of suicidal behaviour in the 12 months prior to screening.[1] The committee will need to consider if the evidence in the CS on effectiveness and safety of ESK-NS can be generalised to this vulnerable population.

The company was asked to provide any additional data pertaining to the development of addiction or addiction-related issues (e.g. withdrawal) during any of the identified studies.[18] In response, the company stated that *'across all clinical studies there were no cases of overdose or reports of drug*

abuse. Furthermore, there were no reports from the investigational sites of any patients engaging in drug-seeking behaviour or requesting an increase in the frequency of treatment sessions (as a potential early indicator of drug-seeking behaviour)'.[3] They further clarified that '*all Phase 3 studies included the PWC-20 to systematically assess the risk of dependence with short- and long-term use of esketamine nasal spray (...) Based on the PWC-20 results, there was no evidence suggestive of a distinct withdrawal syndrome in the longer-term studies* (…) *Levels of esketamine in the circulation do not accumulate with twice-weekly or lower dosing frequency. The steady state for physical dependence is not achieved therefore a drug withdrawal is not expected, as suggested by the PWC-20 results*'.[3]

While this appears reasonable, the company did note at clarification that Physicians Withdrawal Checklist- Withdrawal Symptoms- subscale (PWC-WS) results were higher in non-responders to ESK-NS. The ERG considers that it will be important to monitor these patients as they move to further treatments.

4.2.8 Supporting evidence

TRANSFORM-1 was regarded as a supporting trial in the CS and was not been included in the base case economic model. The company stated the rationale for this decision: '*In TRANSFORM-1, with the exception of the first dose (56 mg for all patients) ESK-NS was administered at fixed doses of either 56 mg or 84 mg which is not reflective of the anticipated esketamine licence*'.[1]

A total of 346 patients aged 18 to 64 years were randomised to treatment during the double-blind induction phase with either esketamine nasal spray 56 mg (fixed dose) plus a newly initiated OAD or esketamine nasal spray 84 mg (fixed dose) plus a newly initiated OAD or a newly initiated OAD plus placebo nasal spray. Of the 346 patients randomly assigned to treatment, 315 (91%) patients completed the 28-day double-blind induction phase, and 31 (9%) patients withdrew. There was a higher early withdrawal rate in the ESK-NS-84 + OAD arm (n=19; 16.4%) compared with the ESK-NS-56 + OAD (n=6; 5.1%) and OAD + PBO-NS (n=6; 5.3%) arms. Improvement in depressive symptoms, as assessed by the change in MADRS total score from baseline to Day 28 of induction numerically favoured the ESK-NS-56 + OAD and ESK-NS-84 + OAD arms over OAD + PBO-NS. However, these improvements did not reach statistical significance.

ERG comment: As the licence for ESK-NS is expected to be for flexible dosing, it is appropriate to treat TRANSFORM-1 as supporting evidence only. However, it is important to consider the implications of the higher withdrawal rate in the higher dosage group of ESK-NS which was mainly due to adverse events or patient choice. The company stated that withdrawals in the ESK-NS-84 + OAD arm were not due to any new or dose-related safety finding, and that 11 of the 19 early withdrawal patients (58%) withdrew after their first esketamine nasal spray dose which was 56 mg as stipulated by the fixed titration study design. The withdrawal rate could explain the lack of statistically significant results, but the ERG remains concerned that TRANSFORM-1 does not provide convincing evidence of the efficacy or safety of ESK-NS.

4.2.9 Ongoing trials

The CS included details of a long-term non-comparative safety study of ESK-NS which is ongoing (SUSTAIN-3). The study population includes those who have previously participated in completed or ongoing trials, including TRANSFORM-1/2/3 and SUSTAIN-1/2. The company provided interim safety results from a cut-off of 31 December 2018 which included data from 1,140 patients treated for a mean of 13.7 months.[26] They stated that '*the interim analysis has revealed no unexpected safety findings, with a safety and tolerability profile that is consistent with the previous Phase 3 clinical*

studies'.[1] SUSTAIN-3 is expected to complete in the third quarter of 2021, when final safety and efficacy data will be available.

ERG comment: The ERG noted that there were three deaths in this SUSTAIN-3 (0.3%). These were detailed in the interim CSR as follows: '*one death during the induction phase that was caused by a SAE of completed suicide, and considered by the investigator as not related to esketamine nasal spray; two deaths during the optimization/maintenance phase: one due to a SAE of myocardial infarction, that was considered by the investigator of doubtful relationship to esketamine nasal spray, and one due to multiple injuries (accidental polytrauma), caused by being hit by an automobile while riding a bicycle, that was considered by the investigator as not related to esketamine nasal spray*'.[26] This study, when reported in full, will give a fuller picture of any potential longer-term risks with ESK-NS including those related to withdrawing from treatment.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company conducted a Bayesian NMA to assess the relative effectiveness of ESK-NS plus a newly initiated OAD versus the comparators in the NICE scope. Feasibility assessment of the studies identified in the systematic review identified that an NMA could only be conducted for the acute phase of treatment. However, the company considered the NMA of acute treatment comparisons not to be robust and it was only used to inform scenario analyses in the analysis of cost effectiveness.[1]

Nineteen trials were used to inform the network. The outcomes investigated were change from baseline in MADRS total score, response rates based on MADRS, remission rates based on MADRS and discontinuations due to adverse events. The company stated that the NMA was not considered sufficiently robust to inform the CEA so no quality assessment of the trials was performed. The trials used in the NMA are listed in Table 4.23.

Table 4.23: Overview of the 19 trials included in the best-case scenario evidence network

Trial	Inclusion criteria and study design prior to randomisation	Randomised interventions (acute phase)	N	Mean age (SD)	Male, n (%)	Mean MADRS total score (SD)	Duration of current episode, mean (SD)	Previous OAD use, n (%)	Duration of trial, weeks
ADMIRE[27] Double-blind RCT Multicentre, Japan NCT00876343.	• Adults aged 20–65 years • DSM-5 diagnosis of MDD • HAM-D-17[a] ≥18 • Duration of current episode ≥8 weeks without adequate response to 1-3 OADs of ≥6 weeks duration Patients received an SSRI/SNRI during an 8-week single blind prospective treatment phase and those with an inadequate response were randomised	Augmentation SSRI/SNRI Aripiprazole 3-5 mg/day (flexible dose)	197	38.1 (9.6)	101 (52.1)	25.3 (7.3)	17.5 (26.1) months	1; 119 (61.3%) 2; 54 (27.8%) 3; 21 (10.8%) 4+; 0 (0%)	6 (plus 28-day screening phase and 8-week prospective treatment phase)
		Augmentation SSRI/SNRI Aripiprazole 3 mg/day	194	39.2 (9.1)	124 (62.9)	25.2 (7.2)	15.7 (21.6) months	1; 130 (66.0%) 2; 53 (26.9%) 3; 14 (7.1%) 4+; 0 (0%)	
		Augmentation SSRI/SNRI Placebo	195	38.7 (9.2)	115 (59.0)	25.5 (7.4)	15.6 (16.4) months	1; 124 (63.6%) 2; 49 (25.1%) 3; 22 (11.3%) 4+; 0 (0%)	
Bauer 2013[28] Open-label, RCT Multicentre, international	• Adults aged 18–65 years • DSM-5 diagnosis of MDD • Duration of current episode ≥42 days and ≤18 months	Augmentation SSRI/SNRI + quetiapine XR (target dose 300 mg/day)	229	NR	NR	33.2 (5.34)	190.7 (119.3) days	NR	6

Trial	Inclusion criteria and study design prior to randomisation	Randomised interventions (acute phase)	N	Mean age (SD)	Male, n (%)	Mean MADRS total score (SD)	Duration of current episode, mean (SD)	Previous OAD use, n (%)	Duration of trial, weeks
NCT00789854	• MADRS ≥25 • Stage I TRD with an inadequate response to an SSRI/ venlafaxine or stage II TRD with an inadequate response to two ADs from two different classes-most recent of which must have been an SSRI or venlafaxine	Augmentation SSRI/SNRI + lithium (target plasma level 0.6-1.2 mmol/l)	221	NR	NR	32.9 (5.20)	180.3 (119.6 days)	NR	
		Switch quetiapine XR (target dose 300 mg/day)	225	NR	NR	33.70 (5.60)	175.2 (110.8) days	NR	
Berman 2007[29] Double-blind RCT Multicentre, USA	• Adults aged 18–65 years • DSM-4 diagnosis for major depressive episode that had lasted ≥8 weeks with an inadequate response 1-3 OAD trials (>6 weeks duration) • HAM-D-17[a] ≥18 All patients received SSRI/SNRI for 8 weeks in an open label prospective treatment phase; those with an incomplete response were eligible for randomisation	Augmentation SSRI/SNRI Placebo	176	44.2 (10.9)	63 (35.8)	25.9 (6.5)	43.6 (53.8) months	1; 117 (66.5%) 2; 45 (25.6%) 3; 18 (8.0%)	6 (plus 8-week prospective treatment phase)
		Augmentation SSRI/SNRI Aripiprazole 5-20 mg/day	182	46.5 (10.6)	70 (38.5)	26.0 (6.1)	38.6 (59.0) months	1; 121 (66.5%) 2; 45 (24.7%) 3; 16 (8.8%)	
Berman 2009[30] Double-blind RCT Multicentre, USA	• Adults aged 18–65 years • DSM-4 diagnosis for major depressive episode that had lasted ≥8 weeks with	Augmentation SSRI/SNRI Placebo	172	45.6 (11.3)	55 (32.0)	27.1 (5.8)	Median 17.2 (1.6-236.5) months	0; 2 (2.9%) 1; 117 (68%)	6 (plus 8-week prospective

Trial	Inclusion criteria and study design prior to randomisation	Randomised interventions (acute phase)	N	Mean age (SD)	Male, n (%)	Mean MADRS total score (SD)	Duration of current episode, mean (SD)	Previous OAD use, n (%)	Duration of trial, weeks
	an inadequate response 1-3 OAD trials (>6 weeks duration) • HAM-D-17[a] ≥18 All patients received SSRI/SNRI + placebo for 8 weeks in a single-blind label prospective treatment phase; those with an inadequate response were eligible for randomisation							2; 45 (26.2%) 3; 3 (1.7%) 4; 2 (1.2%)	treatment phase)
		Augmentation SSRI/SNRI Aripiprazole 5-20 mg/day	177	45.1 (10.6)	39 (22.0)	26.6 (5.8)	Median 18.8 (2.1-433.1) months	0; 3 (21.7%) 1; 127 (71.8%) 2; 38 (21.5%) 3; 9 (5.1%) 4; 0	
Corya 2006[31] Double-blind RCT Multicentre, 16 countries	• Adults ≥18 years • DSM-5 diagnosis of MDD, single episode or recurrent, without psychotic features • Nonresponse to of ≥6 weeks SSRI Patients received venlafaxine in an open-label 7-week lead-in phase; those displacing less than a partial response entered the double-blind taper phase and then proceeded to the 12-week double-blind phase	Switch fluoxetine 25/50 mg/day Olanzapine 6/12 mg/day	243	45.7 (10.8)	(27.5)	30 (6.8)	186 days	Mean 4.1	12-week acute phase (plus 7-week lead-in phase and 5–9-day taper phase)
		Switch olanzapine 6 or 12 mg/day	62						
		Switch fluoxetine 25 or 50mg/day	60						
		Augmentation venlafaxine	59						

Trial	Inclusion criteria and study design prior to randomisation	Randomised interventions (acute phase)	N	Mean age (SD)	Male, n (%)	Mean MADRS total score (SD)	Duration of current episode, mean (SD)	Previous OAD use, n (%)	Duration of trial, weeks
		75-375 mg/day							
		Switch fluoxetine 5 mg/day Olanzapine 1 mg/day [arm serves as a pseudo placebo]	59						
Dunner 2007[32] Open-label RCT	• Adults aged 21–65 years • Nonresponse to ≥1 course of ≥4 weeks SSRI/SNRI • MADRS ≥20 Patients were assigned a prospective open-label 6-week lead-in treatment with sertraline; those failing to respond were eligible for randomisation	Augmentation sertraline 50 mg/day-200 mg/day	20	46.3 (10.4)	(45)	30.7 (5.4)	NR	2≥ SSRI/SNRI; 65 %	8 (plus 6-week lead-in period)
		Augmentation Sertraline 50 mg/day-200 mg/day Ziprasidone 80 mg/day	22	43.1 (9.4)	(45.5)	30.2 (5.7)	NR	2≥ SSRI/SNRI; 63.6 %	
		Augmentation Sertraline, 50 mg/day-200 mg/day Ziprasidone 1600 mg/day	19	42.6 (13.3)	(52.6)	28.9 (5.4)	NR	2≥ SSRI/SNRI; 63.2 %	

Trial	Inclusion criteria and study design prior to randomisation	Randomised interventions (acute phase)	N	Mean age (SD)	Male, n (%)	Mean MADRS total score (SD)	Duration of current episode, mean (SD)	Previous OAD use, n (%)	Duration of trial, weeks
Luzny 2013[33] Open-label RCT Single centre, Czech Republic Abstract publication	• Adults aged 65+ years • Fulfil diagnostic criteria for MDD and failing prior OAD with two different OADs in monotherapy	ECT BW up to 8 electro convulsions	8	67.3 (3.9)	7	NR	NR	2; 8 (100%)	6
		Seropram (Citalopram) 20-40 mg/day	12	68.2 (4.1)	8	NR	NR	2; 12 (100%)	
Lenze 2015[34] Double-blind RCT 3 centres, USA & Canada NCT00892047	• Adults aged ≥60 years • DSM-5 diagnosis of MDD with at least moderate symptoms • MADRS ≥15 • Although prior treatment failure not explicitly stated 74% of patients were reported to have not responded to ≥1 OAD trialled during the present episode Patients were assigned to a 12-week prospective open label venlafaxine extended release-patients who did not achieve remission were eligible for randomisation	Augmentation venlafaxine Aripiprazole	91	Median 66 (IQR: 62.8, 70.5)	39 (43)	Median 24 (IQR: 18, 29)	Median 118 (IQR: 45, 364)	≥1, 73%	12 (plus 12-week prospective treatment phase)
		Augmentation venlafaxine Placebo	90	Median 65.7 (IQR: 62.8, 69.8)	39 (43)	Median 23 (IQR: 18, 26)	Median 104 (IQR: 28, 317)	≥1, 75%	
Marcus 2008[35] Double-blind RCT Multicentre, USA	• Adults aged 18–65 years • DSM-4 diagnosis of major depressive episode that lasted ≥8 weeks • Inadequate response to previous OAD (1-3 OAD trials of >6 weeks duration) Patients were assigned to an 8-week prospective single-blind treatment phase	Augmentation SSRI/SNRI Aripiprazole 5-20 mg/day	191	44.6 (11.0)	65 (34)	25.2 (6.2)	43.7 (68.0) months	1; 135 (71.1%) 2; 49 (25.8%) 3; 5 (2.6%) 4; 1 (0.5%)	6 (plus 8-week prospective treatment phase)
		Augmentation SSRI/SNRI	190	44.4 (10.7)	62 (32.6)	27.0 (5.5)	48.5 (88.8) months	1; 128 (67.7%)	

Trial	Inclusion criteria and study design prior to randomisation	Randomised interventions (acute phase)	N	Mean age (SD)	Male, n (%)	Mean MADRS total score (SD)	Duration of current episode, mean (SD)	Previous OAD use, n (%)	Duration of trial, weeks
	of SSRI/SNRI-patients who did not response were eligible for randomisation	Placebo						2; 51 (27.0%) 3; 10 (5.3%)	
Nierenberg 2003[36] Double-blind RCT Single centre, UK	• Adults aged 18–70 years • DSM-3 diagnosis of MDD • HAMD-D-17[a] ≥18 • Treatment-resistant depression defined as at least 1 but no more than 5 failed medication trials during the current episode Patients were assigned to a 6-week prospective open-label treatment phase of nortriptyline. Non-responders were eligible for randomisation	Augmentation nortriptyline Lithium	18	37.2 (8.3)	9	NR	97.3 months (111.8)	Mean failed trials during current episode 1.9 (SD 1.2)	6 (plus 6-week prospective treatment phase)
		Augmentation nortriptyline Placebo	17	39.7 911.9)	10	NR	84.5 months (94.9)	Mean during current episode 2.5 (SD 1.6)	
OPERATION[37] Double-blind RCT Multicentre, China	• Adults aged 18–65 years • MDD • Stage 2 TRD criteria described by Thase and Rush. • HRSD-17[a] ≥17	Switch venlafaxine XR 225 mg/day	50	40.5 (11.5)	NR	NR	4.7 (4.6) years	NR	8
		Switch mirtazapine, 45 mg/day	55		NR	NR	5.5 (6.6) years	NR	
		Switch paroxetine	45		NR	NR	7.5 (6.5) years	NR	
POLARIS[38] Double blind, phase III RCT	• Adults aged 18–65 years	Augmentation SSRI/SNRI Placebo	221	46.6 (11.0)	75 (33.9)	26.3 (5.3)	16.9 (35.0) months	1; 170 (78%) 2; 44 (20.2%)	6 (plus 8-week prospective

Trial	Inclusion criteria and study design prior to randomisation	Randomised interventions (acute phase)	N	Mean age (SD)	Male, n (%)	Mean MADRS total score (SD)	Duration of current episode, mean (SD)	Previous OAD use, n (%)	Duration of trial, weeks
Multicentre, international NCT01360632	• DSM-4 diagnosis of MDD, single episode or recurrent, without psychotic features of ≥8 weeks duration • Reporting an inadequate response to 1-3 OADs including the most recent drug treatment • HADRS-17[a] ≥18 Patients were assigned to an 8-week prospective single-blind placebo as an adjunctive to standard OAD (SSRI/ SNRI)-patents with an inadequate response were eligible for randomisation							3; 4 (1.8%)	treatment phase)
		Augmentation SSRI/SNRI Brexpiprazole 1 mg/day	226	45.7 (11.6)	68 (30.1)	26.7 (5.6)	18.7 (43.0) months	1; 177 (78.7%) 2; 42 (18.7%) 3; 6 (2.7%)	
		Augmentation SSRI/SNRI Brexpiprazole 3 mg/day	230	44.5 (11.2)	74 (32.2)	26.4 (5.2)	17.7 (33.0) months	1; 184 (81.4%) 2; 34 (15.0%) 3; 7 (3.1%)	
PYXIS[39] Double blind, phase III RCT Multicentre, USA, Canada and Europe NCT01360645	• Adults aged 18–65 years • DSM-5 diagnosis of MDD, single episode or recurrent, without psychotic features of ≥8 weeks duration • Reporting an inadequate response of 1-3 OADs including the most recent drug treatment • HADRS-17[a] ≥18 Patients were assigned to an 8-week prospective single-blind placebo as an adjunctive to standard OAD (SSRI/SNRI)-patents with an inadequate response were eligible for randomisation	Augmentation SSRI/SNRI Placebo	191	45.2 (11.3)	52 (28.3)	27.1 (5.6)	13.7 (17.1) months	NR	6 (plus 8-week prospective treatment phase)
		Augmentation SSRI/SNRI Brexpiprazole 2 mg/day	188	44.1 (11.6)	25 (30.9)	26.6 (5.8)	13.5 (14.2) months	NR	
Shelton 2005[40] Double blind RCT	• DSM-5 diagnosis of MDD	Switch fluoxetine 25 - 50 mg/day	146	42.5 (10.7)	(32.9)	28.5 (7.5)	NR	NR	8 (plus 7-week dose-

Trial	Inclusion criteria and study design prior to randomisation	Randomised interventions (acute phase)	N	Mean age (SD)	Male, n (%)	Mean MADRS total score (SD)	Duration of current episode, mean (SD)	Previous OAD use, n (%)	Duration of trial, weeks
Multicentre, USA and Canada	• ≥1 past treatment failure with 4 weeks of SSRI Patients entered a 7-week nortriptyline dose-escalation period to demonstrate treatment failure for eligibility for randomisation	Olanzapine 6-12 mg/day							escalation period)
		Switch olanzapine 6-12 mg/day	144	43.4 (11.0)	(35.4)	28.4 (7.4)	NR	NR	
		Switch fluoxetine 25 - 50 mg/day	142	41.7 (11.0)	(27.5)	28.4 (7.3)	NR	NR	
		Augmentation nortriptyline up to 175 mg/day	68	41.5 (10.1)	(32.4)	28.8 (6.5)	NR	NR	
STAR*D (step 3b)[41] Open-label RCT	• Eligible participants for third-step treatment entered Level 3 if they had not achieved remission or were unable to tolerate Level 2 or Level 2A treatments • Patients were not required to meet MDD criteria at the time of entry into Level 3, as long as they had MDD criteria at entry into Level 1 and had not adequately responded or been able to tolerate previous levels	Switch mirtazapine 15-60 mg/day	114	44.8 (11.6)	66 (57.9)		34.8 (70.4) months	NR	16
		Switch nortriptyline up 25-150 mg/day	121	45.1 (12.2)	59 (48.8)		32.5 (59.6) months	NR	
STAR*D (step 4)[42] Open-label RCT	• Eligible participants for fourth-step treatment entered Level 4 if they had not achieved remission or were unable	Switch tranylcypromine 10-60 mg/day	58	46.6 911.6)	25 (43.1)	NR	33.1 (67.9) months	NR	14

Trial	Inclusion criteria and study design prior to randomisation	Randomised interventions (acute phase)	N	Mean age (SD)	Male, n (%)	Mean MADRS total score (SD)	Duration of current episode, mean (SD)	Previous OAD use, n (%)	Duration of trial, weeks
	to tolerate the first-three levels of treatment	Switch venlafaxine 37.5-300 mg Mirtazapine 15-45 mg/day	51	45.3 (10.6)	28 (54.9)	NR	55.7 (92.2) months	NR	
Tanghe 1997[43] Double-blind RCT Single centre	• Hospitalised patients with therapy resistant depression • DSM-2 R criteria for MDD • Resistant to ≥2 separate OADs	Switch moclobemide 200-600 mg/day	19	43 (12)	13	41 (7)	NR	NR	4
		Switch amitriptyline up to 280 mg/day	29				NR	NR	
		Switch moclobemide 200-600 mg/day Switch amitriptyline up to 280 mg/day	20				NR	NR	
Thase 2007[44] Double-blind RCT Canada and USA	• Adults aged 18–65 years • HAM-D-17[a] ≥22 • DSM-5 diagnosis of MDD • Failure to achieve a response to an OAD (except fluoxetine) after ≥6	Augmentation fluoxetine 50 mg/day Olanzapine 6 mg/day	200	44.3 (10.2)	68 (34)	30.1 (6.7)	415.4 (555) days		6 (8-week lead-in period)

Trial	Inclusion criteria and study design prior to randomisation	Randomised interventions (acute phase)	N	Mean age (SD)	Male, n (%)	Mean MADRS total score (SD)	Duration of current episode, mean (SD)	Previous OAD use, n (%)	Duration of trial, weeks
2 concurrent identical studies (pooled results extracted) NCT00035321	weeks within the current episode of MDD Patients received fluoxetine in an 8-week open label lead-in phase to establish fluoxetine resistance	Augmentation fluoxetine 50 mg/day	206	44.6 (10.0)	78 (37.9)	29.9 (6.4)	428.6 (603.3) days		
		Switch olanzapine 6 mg/day	199	44.3 (10.8)	76 (38.2)	29.9 (6.7)	366.5 (544.4) days		
TRANSFORM-2[23, 45, 46] Double-blind Phase III RCT Multi-centre Europe and USA	• Adults aged 18–64 years • DSM-5 • MDD with no response to ≥1 but ≤5 in current episode The prospective observational phase patients take a different OAD for ≥2 weeks-non-responders eligible for randomisation	Switch SSRI (escitalopram or sertraline) or SNRI (duloxetine or venlafaxine XR) according to local prescribing guidelines (open label) Esketamine nasal spray 56 mg or 84 mg BW for 4 weeks	116	44.9 (12.58)	39 (34.2)	37.0 (5.69)	111.4 (124.28)	1; 9 (7.9%) 2; 69 (60.5%) 3; 24 (21.1%) 4; 7 (6.1%) 5; 3 (2.6%) 6; 1 (0.9%) 9; 1 (0.9%)	4
		Switch SSRI (escitalopram or sertraline) or SNRI (duloxetine or venlafaxine	111	46.4 (11.14)	46 (42.2)	37.3 (5.66)	118.0 (187.37)	1; 18 (16.5%) 2; 54 (49.5%) 3; 22 (20.2%)	

Trial	Inclusion criteria and study design prior to randomisation	Randomised interventions (acute phase)	N	Mean age (SD)	Male, n (%)	Mean MADRS total score (SD)	Duration of current episode, mean (SD)	Previous OAD use, n (%)	Duration of trial, weeks
		XR) according to local prescribing guidelines (open label) Placebo nasal spray BW for 4 weeks						4; 13 (11.9%) 5; 1 (0.9%) 6; 1 (0.9%)	

Based on Table 10 of the CS appendices[17]

[a] HAM-D may also be referred to as HAM-D-17, HRSD, HADRS-17, and HSRD in the literature. Predecessor versions of the HAM-D contained only 17 items.

AD = antidepressant; BW = bi-weekly; CS = company submission; DSM-2/3/4/5 = Diagnostic and Statistical Manual of Mental Disorders – 2/3/4/5; ECT = electroconvulsive therapy; HAM-D-17, Hamilton Depression Rating Scale 17-item; IQR = interquartile range; MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = major depressive disorder; NR = not reported; OAD = oral antidepressant; RCT = randomised controlled trial; SD = standard deviation; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TRD = treatment-resistant depression; UK = United Kingdom; USA = United States of America; XR = extended release

4.4 Critique of the indirect comparison and/or multiple treatment comparison

In the acute treatment NMA, the company included comparator therapies based on switch or augmented treatments (i.e. where patients were randomised to switch or continue with their current OAD, respectively, with or without an additional OAD). The ERG felt that studies where patients received multiple OADs were outside the scope (patients receiving esketamine in the background of a single OAD), and should therefore not be included in the network.

The NMA assumed comparability between SSRIs and SNRIs, which the company indicated was supported by subgroup analyses in TRANSFORM-2 (Appendix E and Table 3 of the clarification letter) and NICE guidance[6, 9]; this is also in line with the proposed changes to the CHMP marketing authorisation, which were stated by the company to be, *"SPRAVATO®, in combination with an SSRI or SNRI, is indicated for adults with treatment-resistant major depressive disorder, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode"*.[3] However, as noted in section 4.2.6, there are differences between the type of OAD for remission rates after 28 days, e.g. within the SSRI group: sertraline (odds ratio (OR) 1.38, 95% CI 0.26 to 7.22) vs. escitalopram (OR 4.71, 95% CI 1.08 to 20.63).

The NMA was based on a best-case scenario evidence network. Out of the 49 citations (42 trials) identified by the acute treatment SR, 19 studies were included. The remaining 23 trials were excluded due to lack of relevant outcomes or comparators, dose issues (specifically for esketamine) and being unable to be connected in the network. Of note, the SUSTAIN-1 trial, which was included in the economic analysis, was not included in the NMA which was appropriate as patients from TRANSFORM-1 and -2 could enter SUSTAIN-1 so they would not be independent trial population. TRANSFORM-3, which was not included in the economic analysis due to age and dose restrictions, was also excluded from the NMA.

Full details of the NMA methodology including the feasibility assessment, included trials and the assessment of their clinical similarity were provided in Appendix D of the company submission. NMA could be performed for acute treatments for the following outcomes: change from baseline in MADRS, MADRS response, MADRS remission and discontinuations due to AE. The NMA used standard Bayesian models as recommended in NICE DSU TSD 2.[47] WinBUGS code and some data were provided in the response to clarification but not for all the reported analyses. Change from baseline in MADRS for the base-case, response for scenario 2 and remission for scenario 1 were provided. The ERG could run the NMA and obtained results which were very close to those provided by the company so they have no concerns about the NMA analysis methods.

The main concerns about the NMA results are due to the clinical and methodological differences between the studies included in each network. This was highlighted in the submission *"clinical trial heterogeneity in terms of overall study design, inclusion criteria and patient population meant treatment comparisons could not be undertaken (in either acute or maintenance treatment settings"*.[1] However, they still performed and presented results for an acute treatment NMA but in order to perform this analysis had to relax the inclusion criteria. Relaxing the inclusion criteria by including MADRS results from more variable timepoints (four to eight weeks rather than just four weeks) increased the clinical heterogeneity of the NMA making the results less reliable as the submission states that data suggest that relative treatment effects change over time after four weeks. The submission stated that the MADRS and HAM-D scales were combined in the NMA although the clarification response indicated that this had not been done in any of the NMA. The company also reports that there were differences in the comparator arms regarding whether they were switch SSRI/SNRI or switch SSRI. Based on these

differences the ERG agrees with the company that there are considerable uncertainties in the NMA and the results should be interpreted cautiously.

A further issue of concern for the NMA is the use of the adjusted OAD + placebo arm in TRANSFORM-2 which was adjusted to account for the effect of additional clinic visits. This used results from a paper by Posternak and Zimmerman which found that additional visits increased the treatment effect for patients on placebo, and estimated the size of the reduction in HAM-D score with additional follow-up assessments.[48] The high placebo effect seen in TRANSFORM-2 was considered by clinicians to be related to the use of a nasal-spray treatment and the increased level of healthcare contact during the twice-weekly clinical visits. However, although Posternak and Zimmerman state that it was a meta-analysis, it does not report any details of the statistical methods used nor any details of the methods or results of the individual studies so it is not possible to verify whether the reported reductions in HAM-D scores were reliable. The study by Posternak and Zimmerman used HAM-D whereas the trials presented in the CS used MADRS score as the primary outcome measure so estimates of improvements in HAM-D were converted to MADRS scores using a method reported by Leucht et al.[49] The numbers applied in the adjustment were therefore based on two sets of estimates from single studies, one of which did not report any statistical methods and therefore may be unreliable.

Although the adjustment was made to the treatment effect observed for the placebo + OAD arm this was a double-blind, randomised trial so the effects of the use of a nasal-spray treatment and the increased number of visits also applied to the esketamine + OAD arm. The paper by Posternak and Zimmerman also analysed the effect of additional visits in the active treatment arm and found a similar reduction in HAM-D with one extra visit (0.76 for active treatment vs. 0.86 for placebo) and concluded that *"a comparable therapeutic effect was also found in participants receiving active medication"*.[48] Any improvements in MADRS as a result of increased clinic visits would apply to both treatment arms in the trial so the post-hoc adjustment should have been made to both the esketamine and placebo arms. Due to concerns with both, NMA and the adjusted TRANSFORM-2 results, the ERG does not consider them to be reliable sources of treatment estimates.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

The CS included a systematic review of the evidence for ESK-NS. From this review the company identified and presented evidence from six studies of ESK-NS. Four of these were randomised controlled trials (TRANSFORM-1, TRANSFORM-2, TRANSFORM-3, SUSTAIN-1) and two were open label extension studies (SUSTAIN-2, SUSTAIN-3). SUSTAIN-3 is still ongoing.

Randomised evidence is thus available for both the acute treatment of treatment-resistant depression and for maintenance of effect after remission. The two main trials included in the economic model (TRANSFORM-2 and SUSTAIN-1) were in adults aged 18 to 64 years with recurrent or single episode depression. Both trials compared ESK-NS plus a newly initiated OAD to a newly initiated OAD plus placebo and both involved flexible dosing of 56 mg/84 mg. A separate trial of those aged 65 years and over with lower dosing (TRANSFORM-3) and an open-label trial in adults aged 18 years or over (SUSTAIN-2) were included in the CS but not in the initial model. A further trial, TRANSFORM-1, was regarded as a supporting trial in the CS and was not included in the base case economic model due to its fixed rather than flexible dosing which does not reflect the expected licence for ESK-NS.

In response to clarification, the company advised that the label indication is expected to change to ESK-NS in combination with an SSRI or SNRI for treatment-resistant major depressive disorder in adults who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode.[3] This reflects the trials where patients received either a SNRI or SSRI in conjunction with ESK-NS. Most patients in the trials had received two prior OADs in this episode (61% and 57.7% in TRANSFORM-2 and SUSTAIN-1, respectively). The committee will need to consider how well the OADs prescribed as co-interventions across these trials reflect those prescribed at this stage of the pathway in an NHS setting.

The trials were multinational. However, TRANSFORM-2 and SUSTAIN-1 did not enrol any patients in the UK. One UK patient was enrolled in the supporting trial, TRANSFORM-3, and 12 UK patients were enrolled in the long-term safety study, SUSTAIN-2. The lack of UK patients in the main trials is a limitation particularly given the mode of delivery of this intervention. Therefore, there is a lack of evidence in how well ESK-NS might work in the NHS setting.

In TRANSFORM-2, ESK-NS + OAD in comparison to PBO-NS + OAD showed a statistically significant reduction on the Montgomery-Åsberg Depression Rating Scale (MADRS) at Day 28 (difference in least squares means -4.0, 95% confidence interval (CI) -7.31 to -0.64). Of note, there are differences between the type of OAD for remission rates after 28 days, e.g. within the SSRI group: sertraline (odds ratio (OR) 1.38, 95% CI 0.26 to 7.22) vs. escitalopram (OR 4.71, 95% CI 1.08 to 20.63). The trial also showed differences in response rate and remission rate, respectively, between the two groups. Other reported outcomes were in favour of the intervention (see Table 4.12).

In SUSTAIN-1, the percentage of relapse was lower in the ESK-NS + OAD (stable remitters: 26.7%, stable responders: 25.8%) group in comparison to participants receiving PBO-NS + OAD (45.3% and 57.6%, respectively). The trial also showed time to relapse to be in favour of the intervention group for both, stable remitters (hazard ratio (HR) 0.49, 95% CI 0.29 to 0.84) and stable responders (HR 0.30, 95% CI 0.16 to 0.55). Other reported outcomes were in favour of the intervention (see Table 4.13).

In the induction phase of TRANSFORM-2, more adverse events were observed in patients treated with ESK-NS + OAD compared to those receiving PBO-NS + OAD (85.2% vs. 60.6%, see Table 4.17). In SUSTAIN-1 more adverse events were seen in the maintenance phase (82.2% vs. 45.5%) and the follow-up phase (11.0% vs. 7.8%), see Table 4.18. Potential adverse events, especially psychiatric disorders (47.8% vs. 19.3% in TRANSFORM-2), need to be considered before considering ESK-NS as a treatment option for patients with TRD.

A number of other restrictions in inclusion criteria limit the generalisability of the trials to NHS practice. The trials in the CS excluded patients with moderate/severe alcohol abuse according to DSM-5 criteria. The committee will need to consider whether evidence in the CS on effectiveness and safety of ESK-NS can be generalised to those with a dual diagnosis of depression and alcohol misuse. The trials also excluded patients who had not responded to an adequate course of treatment with ECT in the current major depressive episode. This appears to be in line with the proposed pathway for ESK-NS. The committee will need to consider if ESK-NS is likely to be offered to patients who have not responded to ECT.

It is not clear if ESK-NS can reduce incidences of suicidal behaviour or if conversely there may be greater risk of suicide. The company reported seven deaths among 1,861 patients treated with ESK-NS across the six phase 2 and 3 studies, three of which were completed suicides.[1] The company stated that, based on the severity of patients' underlying illness and the lack of a consistent pattern the suicides were considered unrelated to ESK-NS treatment. In this context it is important to note that the trials in

the CS excluded patients who had suicidal/homicidal ideation/intent within six months prior to screening per the investigator's clinical judgements and/or based on C-SSRS or a history of suicidal behaviour in the 12 months prior to screening.[1] The committee will need to consider if the evidence in the CS on effectiveness and safety of ESK-NS can be generalised to this vulnerable population.

The company stated that there were no cases of overdose or reports of drug abuse across all the clinical studies. However they did note at clarification that measures of withdrawal according to PWC-WS were higher in non-responders to ESK-NS.[3] The ERG considers that it will be important to monitor these patients as they move to further treatments.

SUSTAIN-3, when reported in full, should gve a fuller picture of any potential longer-term risks with ESK-NS including those related to withdrawing from treatment.

5. Cost effectiveness

5.1 ERG comment on company's review of cost effectiveness evidence

5.1.1 Searches performed for cost effectiveness section

Appendices G, H and I of the CS detailed systematic searches of the literature used to identify cost effectiveness (appendix G), HRQoL (appendix H) and cost and healthcare resource identification, measurement and valuation studies (appendix I).[17] The same search was reported for both resource use in appendix I and cost effectiveness in appendix G, therefore the same limitations will apply. Searches were undertaken in July 2018. A summary of the sources searched is provided in Tables 5.1 and 5.2. Reference lists of included studies were checked for further relevant studies.

Table 5.1: Data sources for published cost effectiveness studies and cost and healthcare resource identification, measurement and valuation (Appendices G and I)

Resource	Host/Source	Date Range	Date Searched
Electronic databases			
Medline, Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Medline Daily	OVID	1946-Present	4/7/18 (updated 4/4/19)
Embase		1974-2018/07/03	4/7/18 (updated 4/4/19)
HTA Database	EBM Reviews via OVID	Up to 4th Quarter 2016	4/7/18
NHS EED		Up to 1st Quarter 2016	
Econlit	OVID	1886-2018/6/21	4/7/18 (updated 4/4/19)
PsycINFO	OVID	1987-2018/07/wk1	4/7/18 (updated 4/4/19)
Conference proceedings[a]			
Anxiety and Depression Association of America Conference		2016-2019	31/10/18 (updated 24/5/19) Unable to access abstracts
International Conference on Management of Depression		2016-2019	31/10/18 (updated 24/5/19) Unable to access abstracts
American Psychiatry Association Annual Meeting		2016-2019	1/11/18 (updated 23/5/19)

Resource	Host/Source	Date Range	Date Searched
European Congress of Psychiatry		2016-2019	5-6/11/18 (updated 23/5/19)
The Royal College of Psychiatrists International Congress		2016-2019	6/11/18 (updated 24/5/19) Unable to access abstracts
WPA World Congress of Psychiatry		2016-2019	6/11/18 (updated 23/5/19) Unable to access abstracts for 2017-19
ISPOR (USA/Europe)		2016-2019	23/5/19
HTA agencies[a]			
NICE, SMC, PBAC, CADTH, NCPE			30/8/18 (updated 23/5/19)
Additional resources (cost effectiveness)[a]			
CEA Registry, RePEc, INAHTA, NIHR HTA database, ICER, Google Scholar, EuroQoL website, ScHARRHUD database			31.8.18 (updated 24/5/19)

[a] Where appropriate, searches were also used to inform both HRQoL (Appendix H) and cost and healthcare resource identification, measurement and validation (Appendix I)
CADTH = Canadian Agency for Drugs and Technologies in Health; CEA = cost effectiveness analysis; EBM = evidence-based medicine; EED = Economic Evaluation Database; HTA = Health Technology Assessment; INAHTA = International Network of Agencies for Health Technology Assessment; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NCPE = National Centre for Pharmacoeconomics; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NIHR = National Institute for Health Research; PBAC = Pharmaceutical Benefits Advisory Committee; RePEc = Research Papers in Economics; SMC = Scottish Medicine Consortium; USA = United States of America; WPA = World Psychiatric Association

ERG comment:

- The majority of searches were clearly structured and documented. Missing data regarding the supplementary searches were provided at clarification.[3]
- There were limitations with the use of MeSH (Medical subject headings) indexing terms in the Embase searches. Although some automated mapping between indexing terms does take place it is possible that relevant Emtree indexing terms were not included in the search, and potentially relevant records could have been missed.

Table 5.2: Data sources for health-related quality of life studies (Appendix H)

Resource	Host/Source	Date Range	Date Searched
Electronic databases			
Medline, Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Medline Daily	OVID	2016-Present	5/7/18 (updated 4/4/19)
Embase		2016-2018/07/03	5/7/18 (updated 4/4/19)
HTA Database	EBM Reviews via OVID	2016- 2016 4th Quarter 2016	5/7/18 (updated 4/4/19)
NHS EED		2016- 2016 1st Quarter 2016	
CENTRAL		2016-2018/06	
CDSR		2016-2018/06/28	
DARE		2016- 2016 1st Quarter 2016	
PsycINFO	OVID	2016-2018/07/wk1	5/7/18 (updated 4/4/19)
CDSR = Cochrane Database Systematic Reviews; DARE = Database of Abstracts of Reviews of Effects; EBM = evidence-based medicine; EED = Economic Evaluation Database; HTA = Health Technology Assessment; NHS = National Health Service			

ERG comment:

- The majority of searches were clearly structured and documented. Missing data regarding the supplementary searches were provided at clarification.[3]
- All searches for health-related quality of life studies were limited to papers published after 2016, these searches were intended to identify any evidence published since the draft update of NICE clinical guideline CG90.[6]

5.1.2 Inclusion/exclusion criteria

The eligibility criteria used for inclusion in the economic evaluation reviews are presented in Table 5.3.

Table 5.3: Eligibility criteria for systematic review of cost-effectiveness analyses

Criteria	Include	Exclude
Population	Adult patients with MDD (with a particular focus on patients who have progressed to TRD)	Paediatric patients (<18 years), patients with related conditions (dysphoria, dysthymia, melancholia, SAD, mood disorder, GAD), and patients with comorbid depression
Intervention(s)/ comparator(s)	Antidepressant drugs, including: • Esketamine	Interventions not listed in inclusion column

Criteria	Include	Exclude
	• SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) • SNRIs (desvenlafaxine, duloxetine, levomilnacipran, milnacipran, venlafaxine) • Vortioxetine • Trazodone • Reboxetine • Tricyclics • Tetracyclics • Monoamine oxidase inhibitors • Atypical antipsychotics • Risperidone • Other pharmacological agents (agomelatine, tianeptine, lithium, amineptine, bicifadine, bupropion, lamotrigine, mazindol, sibutramine, olanzepine/fluoxetine) Augmentation and adjunctive strategies Non-pharmacological interventions, including: • Behavioural activation • CBT and other types of psychotherapy • Combined CBT + antidepressant • Deep brain stimulation • ECT • Interpersonal psychotherapy • Magnetic seizure therapy • Repetitive TMS • Transcranial direct current stimulation • Transcranial magnetic simulation • VNS	
Outcomes	Outcomes of interest included: • Model summary and structure • Sources of model inputs • Assumptions underpinning model structures • Discounting of costs and health outcomes • Total costs and health outcomes • ICERs	Outcomes not listed in inclusion column
Study design	Eligible study designs included: • Cost-utility analyses • Cost-effectiveness analyses • Cost-benefit analyses • Cost-minimisation analyses	Reviews/editorials Budget impact analyses
Territory of interest	No restriction – although primary focus was UK	-
Date of publication	Original review: no restriction	Original review: NA

Criteria	Include	Exclude
	April 2019 update: post-July 2018	April 2019 update: pre-July 2018
Language of publication	English language publications or foreign language publications with an English abstract	Foreign language publications without an English abstract
Based on Table 53 of the CS appendices[17] CBT = cognitive behavioural therapy; CS = company submission; ECT = electroconvulsive therapy; GAD = generalised anxiety disorder; ICER = incremental cost-effectiveness ratio; MDD = major depressive disorder; NA = not applicable; SAD = seasonal affective disorder; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TMS = transcranial magnetic stimulation; TRD = treatment-resistant depression; UK = United Kingdom; VNS = vagal nerve stimulation		

ERG comment: The ERG noted that interventions such as amitriptyline and mirtazapine are ignored in the SLR. All other criteria seem appropriate.

5.1.3 Conclusions of the cost effectiveness review

The electronic database searches identified a total of 3,132 citations. Following removal of 431 duplicates, 2,701 citations were screened on the basis of title and abstract. A total of 341 citations were considered to be potentially relevant and were obtained for full text review. At this stage, a further 181 citations were excluded. Hand searching yielded 20 additional relevant citations. Therefore, a total of 16 publications (economic evaluations n=12, previous HTA submissions n=4) were identified for final inclusion in the review during the original search on July 2018. The updated systematic review on April 2019 found one additional economic evaluation. However, according to the company, none of the economic evaluations identified by the SLR evaluated the cost effectiveness of ESK-NS + OAD and were therefore not directly generalisable to the NICE decision problem.

ERG comment: The ERG agrees with the conclusions of the company's cost effectiveness review.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.4: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Adverse events were not adequately included: only as a scenario analysis and assuming only a GP contact cost.
Perspective on costs	NHS and PSS	Included
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Included, although assuming a mix of treatments as comparator and comparison to separate treatments only in a scenario.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Probably inadequate as not a lifetime horizon

Element of health technology assessment	Reference case	ERG comment on company's submission
Synthesis of evidence on health effects	Based on systematic review	Included
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Included
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Included
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Included
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Included
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Included
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Included

EQ-5D = European Quality of Life-5 Dimensions; ERG = Evidence Review Group; GP = general practitioner; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = personal social services; QALY = quality-adjusted life year; UK = United Kingdom

5.2.2 Model structure

As reported in Section B 2.2.2 of the CS, the model is a state transition model with a cycle length of four weeks and, in addition to death, four health states, which are summarised in Table 5.5.[1]

Table 5.5: Health state definitions

Health state	Health state definition
MDE	Patients experience moderate to severe symptoms of major depressive disorder with a MADRS ≥28 and failed to respond to at least two different OAD treatments of adequate dosage and duration.
Response	Patients experience a 50% or greater MDD symptom improvement from patient's baseline MADRS score but did not achieve the threshold for remission (MADRS ≤12).
Remission	Associated with a period during which the patient is either symptom-free or has only minimal symptoms. The threshold used in the model for achieving remission was MADRS ≤12.
Recovery	Represents an extended asymptomatic phase, achieved after a patient remains in relapse-free remission for 36 weeks in a row (or approximately nine months).

Based on Table 42 of the CS[1]
CS = company submission; MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = major depressive disorder; MDE = major depressive episode; OAD = oral antidepressant.

Patients enter the model in the major depressive episode (MDE) health state, after having failed to achieve a *"…clinically meaningful improvement…"* (page 160, CS) after treatment with at least two OADs *"prescribed in adequate dosages for adequate time"* (page 160, CS).[1] During each four-weekly Markov cycle, patients can occupy MDE, response, remission, recovery or death health states. Transition to recovery can only occur from remission and only after nine months (36 weeks) in the remission state and then with certainty.

Cycles in the model allow for up to three subsequent treatments, switching to a new treatment following:

- a non-response to acute treatment (at four weeks),
- a loss of response i.e. relapse from the response or remission health states respectively (5–40 weeks), or
- experience a recurrence of the MDE during the recovery health state (41 weeks+).

After three subsequent treatments, patients enter the MDE state from which they can still respond or go into remission, whilst being treated with best supportive care (BSC). [redacted]

Transitions between health states are governed by treatment phase:

- **Acute phase (weeks 1 to 4):**
  - Patients remain in MDE state for one cycle. They can then:
    - Transition to response or remission,
    - Remain in MDE state, but move to subsequent treatment,
    - Remain in MDE state, but discontinue treatment, or
    - Die.
- **Continuation phase (weeks 5 to 40):**
  - Patients in the response state can:
    - Continue treatment and remain in the same health state,
    - Improve their depressive symptoms further and transition into the remission health state,
    - Lose treatment response, return to the MDE health state, and begin the next treatment in the sequence,
    - Discontinue treatment and remain in the same health state, or
    - Die.
  - Patients in the remission state can:
    - Continue treatment and remain in the same health state,
    - Enter the recovery health state after 36 weeks (approximately nine months) of relapse-free remission,
    - Relapse (i.e. return to the MDE health state) and begin the next acute treatment in the sequence,
    - Discontinue treatment and remain in the same health state, or
    - Die.
- **Maintenance phase (weeks 41+):**
  - Patients in the recovery health state could:
    - Experience a recurrence event (i.e. return to the MDE health state) and move on to the next treatment in the sequence,
    - Continue treatment and remain in the current recovery health state, or

- Die

Transition probabilities are reported in section 5.2.6 of this report.

ERG comment: The model structure seems plausible and responds appropriately to the critique in TA367.[9]

5.2.3 Population

The population was described in the CS as adults with TRD with a moderate to severe depressive episode.[1] A moderate to severe episode of TRD was assumed to have minimum duration of two years. Treatment-resistant MDD was defined as non-response to two or more OADs prescribed at an adequate dose and for an adequate duration in the current episode.

ERG comment: The population is broadly consistent with the NICE scope and the expected marketing authorisation.[16] However, there are some issues of concern, as described in section 3.1.

The company did perform a subgroup CEA for the 65 years+ age group using TRANSFORM-3 to estimate transition probabilities for remission and response (the equivalent of those from TRANSFORM-2 presented in Section 5.2.6 of the CS). They also used utilities and dosing from TRANSFORM-3, but transition probabilities beyond the acute phase appear to have come from SUSTAIN-1.

Therefore, given that the NICE scope has no upper age limit, in the clarification letter the ERG requested that the main cost effectiveness analysis (CEA), i.e. for age <65 years, informed by TRANSFORM-2 and SUSTAIN-1 be combined with that for age 65 years+, using TRANSFORM-3 as well as SUSTAIN-2. The company responded by submitting a new version of the base-case model to include acute response and remission transition probabilities and utilities for MDE, response and remission/recovery states from both TRANSFORM-2 and TRANSFORM-3, weighted by percentage in each age group such that if set to 0% for age >65 years one gets the same result as in the original base-case.[3] This forms the starting point for the ERG base-case, see Section 7.2.

5.2.4 Interventions and comparators

The intervention in the analysis was ESK-NS co-administered with a newly initiated OAD (ESK-NS + OAD), see Section B.3.2.7 of the CS).[1] As stated in Section B.3.2.11.1, ESK-NS comes as a single-use device that delivers a total of 28 mg of esketamine in two sprays (one spray per nostril). One device (for a 28 mg dose), two devices (for a 56 mg dose), or three devices (for an 84 mg dose) are to be used, with a five-minute interval between each device. The average number of sessions per week and devices per session in the acute phase were derived from TRANSFORM-2, while for subsequent time-points they were derived from SUSTAIN-1. In TRANSFORM-2 on Day 1 of the induction phase, all patients randomised to receive esketamine nasal spray started with a dose of 56 mg weekly. Thereafter, esketamine could be dosed flexibly (56 or 84 mg) based on efficacy and tolerability up until Day 15 (or Day 18 if the Day 15 treatment session did not occur). Beyond Day 15, the esketamine nasal spray dose was to remain unchanged (see Figure 1, CS).[1] The precise rules of determining efficacy and tolerability were not reported in the CS or Appendix M.[1, 17] In TRANSFORM-3, the starting dose was 28 mg which could also be increased to 84 mg by Day 25 without any specification of the precise rules.

SUSTAIN-1 had the same dosing as TRANSFORM-2 in the first four weeks for direct entry patients. These patients then joined those who had been transferred from TRANSFORM-1 and TRANSFORM-2 to enter the optimisation phase where the dose could be adjusted at either week eight or 12:

- At week eight, reduce from weekly to every other week if MADRS total score ≤12; otherwise continue weekly until week 16,
- At week 12, increase to weekly if MADRS total score was >12; otherwise continue every other week until week 16.

In SUSTAIN-1, from week 16 onwards, the following rules applied:

- At week 16, if every other week AND MADRS total score >12 then frequency was increased to weekly; otherwise continue every other week,
- At week 16, if weekly then continue for four weeks.
- At week 20 or later:
    - if weekly AND MADRS total score ≤12 for last four weeks then reduce to every other week,
    - if every other week AND MADRS total score >12 then increase to weekly,
    - otherwise continue either weekly or every other week.
- Maximum of three changes permitted such that, if a given patient was unable to sustain, improvement on every other week dosing, they were to remain on a weekly dosing regimen for the remainder of the maintenance phase.

SUSTAIN-2 had the same weekly dosing as TRANSFORM-2 (aged <65 years)/ TRANSFORM-3 (aged ≥65 years) in the first four weeks for direct-entry patients. These patients joined those who had transferred from TRANSFORM-3 and then remained on the same weekly dose for the next four weeks. For direct-entry patients only, from week nine dosing could decrease to every other week and then switch back to weekly at four-weekly intervals according to the MADRS 12 threshold. Down titration was also possible for tolerability. For those who had been transferred from TRANSFORM-3 no change in dose or frequency was allowed from week nine except a reduction for tolerability.

Neither the concomitant OAD nor the comparator OAD were specified in the CEA: instead OAD was expressed as a mix of eight OADs, according to UK market share (See Section 5.2.8.3). The company did perform a scenario analysis (See Section B.3.4.4.9) based on an NMA using data from TRANSFORM-2 of response and remission presented in Appendix D, which compared ESK-NS + OAD with various other comparators in the form of drug classes.[1, 17] Table 5.6 shows the list of comparators as well as the remission and response probabilities. The NMA was based on an adjustment for the placebo effect (see Section 5.2.6.1 for more detail on the method of estimating those for ESK-NS + OAD and OAD).

Table 5.6: Response and remission rates at the end of the acute treatment phase

Treatment	Remission, %[a]	Response (but not remission), %[b]	Remission, %[c]	Response (but not remission), %[d]
ESK-NS + OAD (Switch SSRI/SNRI)	52.48	16.83	52.48	16.83
OAD (Switch SSRI/SNRI)	17.71	4.36	30.81	8.79
Aug tricyclic (nortrip) ± PBO	22.70	4.71	37.78	9.49
Aug SSRI/SNRI + AAP	27.65	4.04	44.45	8.15

Treatment	Remission, %[a]	Response (but not remission), %[b]	Remission, %[c]	Response (but not remission), %[d]
Aug SSRI/SNRI + lithium	21.98	2.57	36.88	5.24
Aug SSRI/SNRI ± PBO	16.25	2.05	28.80	4.19
Switch tetracyclic (mirtazapine)	13.28	3.26	24.09	6.67
Switch SSRI + AAP	22.38	4.04	37.51	8.15

Based on Table 79 of the CS[1]

[a] MADRS ≤12 with adjustment for 6 clinic visits; [b] ≥50% reduction in MADRS from baseline but MADRS score >12 with adjustment for 6 clinic visits; [c] MADRS ≤12 with no adjustment; [d] ≥50% reduction in MADRS from baseline but MADRS score >12 with no adjustment

AAP = atypical antipsychotic; Aug = augmentation; CS = company submission; ESK-NS + OAD = esketamine nasal spray; MADRS = Montgomery-Åsberg Depression Rating Scale; nortrip = nortriptyline; OAD = oral antidepressant; PBO = placebo; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

For all other parameters, equivalence with OAD was assumed given that these parameters were estimated from STAR*D and the company stated that this study included OAD and other augmentation strategies in 1st and 2nd line TRD.The results of the analysis are shown in Section 6.2. The company argued that the NMA was not robust enough to include these comparators in the base-case.

No non-pharmacological treatments, such as psychological therapy, were included as comparators (without concomitant pharmacological treatment).

ERG comment: The ERG requested clarity on the criteria by which dose was determined in TRANSFORM-2 (applicable also TRANSFORM-3) to which the company responded by stating that *"the intention was to emulate real-world clinical practice, thus there was no prescriptive algorithm"*.[3, 18] The continued lack of clarity on dosing in TRANSFORM-2 and TRANSFORM-3 trials plus the complex dose changes in SUSTAIN-1 and SUSTAIN-2 mean that it is difficult to know how applicable to clinical practice the transition probabilities estimated from the trials would be (see Section 5.2.6). This basis for questionable applicability is in addition to that in terms of whether the data to inform those transition probabilities were from patients were direct-entry or transferred-entry (see Section 5.2.6).

The ERG is convinced that the limitations of the NMA (see section 4.4) are sufficient to exclude those included comparators except in a scenario analysis, although the results should be re-calculated based on the NMA results unadjusted for the placebo effect, which the company provided in response to request for clarification (see Table 5.7).[3]

The ERG recognises that adopting a mix of OADs as concomitant and comparator treatment is not ideal. Indeed, there is some evidence of variability of effectiveness between the four OADs, see section 4.2.6. There is therefore the possibility that ESK-NS might be cost-effective in combination with one OAD and not another. However, the ERG did not have the data to implement the required variation in all parameter estimates required for the model. Therefore, it seems reasonable to not differentiate between specific OADs as either an add-on to ESK or a comparator. However, applicability to clinical practice of results would be highest in those patients who might be switched to one of the OADs prescribed in the trials.

5.2.5 Perspective, time horizon and discounting

As stated in Section B.3.2.4 of the CS, the base-case time horizon was five years.[1] This was justified by all of the treatment related benefits having been accounted for, see Figures 21 and 22 of the CS which were of the Markov trace for ESK-NS + OAD and OAD + PBO-NS, respectively.[1]

As stated in Section B3.2.5 of the CS, the base-case analysis took the perspective of the National Health Service (NHS) and personal social services (PSS) in England. Both costs and outcomes (life years and QALYs) were discounted at 3.5%, in line with the NICE Guide to the Methods of Technology Appraisal 2013.[50] The impact of discounting at 0% and 6% was assessed in sensitivity analyses.

ERG comment: The ERG asked the company to justify the choice of five years as a time horizon, given that it is longer than the time horizon used in TA367 and Edwards et al. 2013, but shorter than a lifetime horizon.[9, 18, 51] The ERG also requested the company to extend the time horizon to a lifetime given that this is according to the NICE reference case and to capture the chronic recurrent or episodic nature of the condition and to account for the effect on mortality associated with suicide.[18] In response, the company presented a sensitivity analysis that showed that the incremental cost effectiveness ratio (ICER) up to a time horizon of 50 years was lower than the base-case, e.g. £4,314 at 50 years.[3] The ERG also notes that by 20 years the percentages of the cohort in the response, remission or recovery health states in the cohort treated with ESK-NS + OAD are equal to those in the cohort treated with OAD + PBO-NS. Therefore, from this point onwards there can be no further difference in cost or QALYs and thus no need to extend the time horizon beyond this point. The ERG therefore has adopted 20 years in the ERG base-case, see section 7.2).

5.2.6 Treatment effectiveness and extrapolation

5.2.6.1 Acute phase

The transition probabilities (in the form of percentages) for response and remission are presented in Table 5.7. Response and remission values were estimated from TRANSFORM-2 (see Section 4.2.5), with the adjustment then applied to the OAD + PBP-NS arm only. Response (but not remission) was calculated by subtraction.

Table 5.7: Response and remission rates at the end of the acute treatment phase

Treatment	Remission, % (SE)[a]	Response (but not remission), % (SE)[b]	Response[c]
ESK-NS + OAD	52.48% (4.97)	16.83% (3.72)	69.31%
OAD + PBO-NS (unadjusted)	31.00% (4.26)	21.00% (4.07)	52.00%
OAD + PBO-NS (adjusted for six visits[d])	18.00% (3.84)	16.00% (3.67)	34.00%

Based on Table 45 of the CS[1]

[a] MADRS ≤12; [b] ≥50% reduction in MADRS from baseline but MADRS score >12; [c] ≥50% reduction in MADRS from baseline; [d] Base-case

CS = company submission; ESK-NS = esketamine nasal spray; MADRS = Montgomery-Åsberg Depression Rating Scale OAD = oral antidepressant; PBO-NS = placebo nasal spray; SE = standard error

The company argued that an adjustment was justified because:

1. there is a positive effect on outcome in both arms of the trial due to clinic visits such that the more visits the bigger the effect

2. this positive effect would continue to be observed in clinical practice only for ESK-NS and not for standard care

The adjustment is a reduction in the rates of response and remission estimated as the effect of a reduction in the number of clinic visits from eight in the trial to two in clinical practice. The size of the adjustment was estimated in multiples steps:

1. use the lower value of 0.67 from a range of 0.67 to 0.86 estimated as the improvement in the Hamilton Depression Rating Scale (HAM-D) of an extra clinic visit. The study also showed that this effect doubled with two extra visits.
2. 0.67 HAM-D points per follow-up clinic visit was converted to MADRS using a 1-point improvement on HAM-D being equivalent to ~1.2 points improvement on MADRS. This was based on a study that showed that 10, 20 and 25 points on the HAM-D corresponded to 12, 26 and 34 points on the MADRS.

This implied an adjustment of 0.804 MADRS points per clinic visit, i.e. 0.67 * 1.2. The number of extra clinic visits in clinical practice was estimated base on there being only two as opposed to eight visits in the first four weeks i.e. the acute phase. This then implies a decrease in the MADRS of 4.842, i.e. 6 * 0.804, which was applied to each patient in order to recalculate percentage remission and response.

ERG comment: The values for ESK-NS + OAD are appropriate. Only the unadjusted values for OAD + PBO-NS are valid in comparing with ESK-NS + OAD. This is because there is insufficient reason for believing that the values observed in the TRANSFORM-2 trial in the placebo arm have been overestimated *relative to* those in the intervention arm. There are several grounds for this argument:

1. Only the *treatment effect*, i.e. the difference/contrast between intervention and comparator in an RCT is unbiased. This is the fundamental basis of having a comparator arm. The company erroneously claim that *"high placebo rates"*, i.e. the outcome in only the placebo arm make estimating the *"true relative treatment effect"* a challenge (page 17, CS).[1] However, it is precisely because of outcomes that might be changed and often inflated beyond that due to the intervention itself that a placebo control arm is included, i.e. the so-called 'placebo effect' applies to the intervention as well as the control arm. Therefore, removing this placebo effect from the control arm means that it is retained in the intervention arm. The treatment effect, i.e. the difference between intervention and comparator thus becomes biased.
2. The company argues that one explanation of the placebo effect is *"high frequency and intensity of patient-health care professional interaction due to twice-weekly visits (of considerable length)"*, although erroneously applying the term *"treatment effect"* to the outcome in only the placebo arm of the trial (page 49, CS).[1] While the ERG would agree that this explanation of the placebo effect possesses some face validity, such an effect would still apply to both arms. This is acknowledged by the company in the response to clarification.[3] However, they claim that the effect of increased clinic visits would continue in clinical practice only for ESK-NS + OAD and that therefore the outcome is only elevated beyond what would be expected in clinical practice for the placebo arm and not the ESK-NS + OAD arm. They argue, on this basis, that removing from the placebo arm does not create a bias, but instead nullifies the bias of the placebo effect in the placebo arm. This implies that the technology in the decision problem is not ESK-NS + OAD, but it is ESK-NS + OAD + 8 clinic visits and that standard care, to which it should be compared, is OAD + 2 clinic visits. However, if, as the company claim, efficacy does improve with clinic visit frequency then standard care would also be improved by increasing the number of visits from 2 to 8. Therefore, the comparator for this ESK + OAD + 8 clinic visits would be OAD + 8 clinic visits which is the comparator in the trial, thus negating the need for any adjustment.

3. The evidence for the size of the effect of number of clinic visits is weak. There is no evidence from the trial itself that the basis of the placebo effect is the number of clinic visits, since everyone receives the same number of visits in TRANSFORM-2. The evidence provided by the company is from other studies and involves questionable assumptions regarding the relationship between clinic visit number and HAM-D and between HAM-D and MADRS. It is also unclear what the number of additional clinic visits might be.
4. The evidence for the placebo effect being the result of number of clinic visits as opposed to any other source is weak. As the company state, there are other plausible explanations of the placebo effect, two of which are listed by the company: *"Use of a nasal spray delivery system leading to patient expectation of 'something novel'"* and *"High patient expectation of benefit due to the portrayal in the media of esketamine as a 'promising' new treatment option for depression"*. (page 49, CS).[1] There is no evidence that these would play any less of a role than clinic visit frequency in mediating the placebo response. The company might also argue that, just as for clinic frequency, these factors would also apply the use of esketamine in clinical practice. On this basis one might regard the intervention to be ESK-NS + OAD + 8 clinic visits + patient expectations. Of course, it would be difficult to conceive of a suitable comparator in clinical practice that comprised partly of such expectations without actually giving the drug itself. Perhaps ironically therefore, these factors might be more of a reason for an adjustment than clinic visit frequency. However, as with clinic frequency, it is impossible to estimate the size of the effect from the trial data given that it applies equally to both arms.

The conclusion of the ERG therefore is that, whilst it might be the case that some of the placebo effect, however mediated, might continue into clinical practice, it is possible to reproduce it by increasing clinic visits even without esketamine and it is impossible to have confidence as to the size of any effect that might only apply to esketamine in clinical practice. On this basis the ERG requested that the company either use the unadjusted estimates of response for OAD + PBO-NS for the model base-case or perform the same adjustment to ESK-NS + OAD to which the company responded that a scenario had been presented without the adjustment (see Section 6.2.3.1). They also reiterated the justification employed within the CS, which has been critiqued by the ERG (as above). On this basis, the ERG base-case removes this adjustment and assumes an increase the cost of clinic visits for OAD to be identical to the monitoring cost of OAD in a scenario analysis (See Section 7.2).

5.2.6.2 Continuation and maintenance phases

Continuation phase:

The transition probabilities of response to remission are shown in Table 5.8. These were estimated by Poisson regression analysis of the SUSTAIN-1 data on patients who were initially were 'stable responders' and followed up over time to identify those who had a MADRS ≤12 for at least three of the last four weeks (three out of any four consecutive weeks during follow-up). In SUSTAIN-1, stable response was defined as a ≥50% reduction in the MADRS total score from baseline in each of the last two weeks of the optimisation phase (weeks 15 and 16) without meeting the criteria for stable remission.

Table 5.8: Four-week transition of moving from response to remission (MADRS ≤12) state

Treatment	Response to remission (SE)
ESK-NS + OAD	19.93% (4.98)
OAD + PBO-NS	12.39% (3.10)

Based on Table 46 of the CS[1]

CS = company submission; ESK-NS = esketamine nasal spray; MADRS = Montgomery-Åsberg Depression Rating Scale OAD = oral antidepressant; PBO-NS = placebo nasal spray; SE = standard error

The transition probabilities for loss of response (response to MDE) and relapse (remission to MDE in weeks 5 to 40) are shown in Table 5.9. Loss of response and relapse were stated to have been estimated from SUSTAIN-1 for ESK-NS + OAD and from STAR*D for OAD.[1]

Table 5.9: Four-week risk of relapse, loss of response and recurrence

Treatment	Relapse (SE)	Loss of response (SE)	Recurrence (SE)
ESK-NS + OAD	5.57% (4.98)	4.19% (2.55)	2.88% (1.80)
OAD + PBO-NS	9.24% (3.10)	22.43% (5.43)	2.88% (1.80)

Based on Table 47 of the CS[1]

CS = company submission; ESK-NS = esketamine nasal spray; OAD = oral antidepressant; PBO-NS = placebo nasal spray; SE = standard error

For loss of response on ESK-NS + OAD, as for response to remission, follow-up was also from then end of the optimisation phase (week 16). For relapse on ESK-NS + OAD, data from SUSTAIN-1 came from those who were 'stable remitters'. 'Stable remission' was defined as a MADRS total score of ≤12 for the last two weeks of the optimisation phase plus for at least three of the last four weeks of the optimisation phase with one excursion of the MADRS total score >12 or one missing MADRS assessment permitted at Week 13 or 14 of the optimisation phase only. Only those patients who relapsed during the first 24 weeks were counted: this corresponded to weeks 5 to 40, i.e. the continuation phase.

For loss of response on OAD, the company argued that SUSTAIN-1 could not be used because the only patients randomised to a placebo arm were those who had already been in 'stable response' or in 'stable remission' whilst on ESK-NS + OAD. Therefore, the probability was calculated as the weighted average of two risks, 22.2% for first-line TRD and 22.8% for second-line TRD, each estimated by fitting an exponential distribution to digitised Kaplan-Meier (KM) plots from STAR*D data.[3, 52] The weights were the percentages of those patients who had had two versus three or more previous treatment failures in SUSTAIN-1. The same method was used for relapse with 6.8% for first-line TRD and 12.8% for second-line TRD.[3]

Maintenance phase:
The transition probabilities for recurrence (remission to MDE in weeks 41+) are shown above in Table 5.9 (third column). For both, ESK-NS + OAD and OAD, the data pooled from both study arms of the double-blind phase of SUSTAIN-1 was used. All stable remitters who relapsed after 24 weeks of maintenance treatment (equal to 36 weeks post-acute treatment) were counted for the calculation of the recurrence rates.

ERG comment: It was unclear to the ERG how data were chosen from SUSTAIN-1 in order to estimate the transition probability of response to remission given that patients appear to enter SUSTAIN-1 from various sources, including either of the TRANSFORM-1 or TRANSFORM-2 or by direct entry. The company also specified that response and remission were defined more restrictively than in

TRANSFORM-2 in the sense that they had to have been "stable" and data were only analysed from the end of the optimisation phase (week 16). The company were therefore asked to confirm that the data sources for each of the transition probabilities appropriately reflect the starting health state, as defined by the MADRS, the treatment pathway and timing.[18] If this is not the case then they were asked to re-estimate the transition probabilities using the correct data.[18] In spite of an ERG request for clarification, the company did not provide any further details.[3, 18]

It was also unclear to the ERG why STAR*D was chosen given that at least some patients who entered SUSTAIN-1 were originally randomised to OAD + PBO-NS in TRANSFORM-1 or TRANSFORM-2. Therefore, there should have been some patients who had been observed to have lost response or relapsed whilst on OAD + PBO-NS. Indeed, the CONSORT diagram (Figure 11 in Appendix D of the CS) shows that 86 patients (including 48 from TRANSFORM-2) continued to be followed-up and, of these, 55 (33 from TRANSFORM-2) became stable remitters and responders during the optimisation phase with only one loss to follow-up beyond this phase.[17] The company did not provide any additional clarification.[3] Also, the loss or response value for OAD is much higher than those for ESK-NS + OAD, by a factor of over five, which is much higher than the relative risk in the acute phase. The company did conduct a scenario analysis (Section B.3.4.4.8) that was reported to have used SUSTAIN-1 to inform response and relapse. However, the precise data used was not clear, appearing to have been from only those patients who had received ESK-NS + OAD and then been randomised for a second time to OAD only. This contrasts very strongly with TA367, where the probability of relapse was assumed to be the same for all treatments.[9] The committee for TA367 also noted that, although STAR*D data provided the best available evidence, it might impose a poorer prognosis on patients than would be observed in the index trial.[9] The ERG believes that the problem with this submission is similar in that all ESK-NS transition probabilities have been estimated from the company trials, but that those for OAD beyond the acute phase have been estimated from a completely different source This probably incorporates a bias in favour of ESK-NS, not least because of the "placebo effect". The company in TA367 took a more conservative approach to relapse in that it assumed there to be no difference between intervention and comparator, using 14.2% from Limosin 2004 for second-line (one line prior to TRD) and 25.0% for third-line (first-line TRD) and 42.6% for fourth- (second-line TRD) and fifth-lines (third-line TRD) from STAR*D for all subsequent lines.[9] For this STA, the same values from STAR*D could be used as in TA367, but the ERG could not locate the values used in TA367 in the STAR*D paper.[53] Therefore, in a scenario, the ERG have assumed the same probability of relapse and loss of response for OAD as ESK-NS + OAD, see Section 7.2.

5.2.6.3 Discontinuation (for reasons other than loss of efficacy)

It was assumed that patients would not discontinue OAD in any phase for any reason other than lack of response. Discontinuation for any other reason from ESK-NS + OAD is presented in Table 5.10 for the acute, continuation, and maintenance phases.

Table 5.10: Risk of discontinuation following initial treatment

Comparator	Acute		Continuation		Maintenance	
	Risk	SE	Risk	SE	Risk*	SE
ESK-NS + OAD	0.00%	0.00%	1.69%	0.42%	24.89%	6.22%

Based on Table 48 of the CS[1]

* Based on assumptions

CS = company submission; ESK-NS = esketamine nasal spray; OAD = oral antidepressant; SE = standard error

Acute phase
It was assumed that patients would not discontinue ESK-NS + OAD in the acute phase for any reason other than lack of response.

Continuation phase
A discontinuation risk for other reasons was derived from SUSTAIN-1 by fitting an exponential distribution to the pooled data from the ESK-NS + OAD arm from stable responders and stable remitters. Relapse was counted as a censoring event. The estimated four-week risk was 1.69% (20% annually) and is presented in Table 5.10.

Maintenance phase
It was also assumed that 35.4% of patients were assumed to stop ESK-NS immediately upon achieving recovery, i.e. on being in the remission state after 40 weeks of treatment. This was the percentage of patients in SUSTAIN-1 who had ≤2 total number of MDD episodes, including the current episode.[54] The conceptual basis was that *"...a benefit of ESK-NS is it can be discontinued while patients can still receive OAD for recurrence prevention"* (p.175, CS).[1] For those patients who did not discontinue immediately, a four-week discontinuation risk of 25% for ESK-NS + OAD was stated to have been used during recovery. However, given that the percentage in Table 5.10 is lower than this and that Figure 24 of the CS shows the percentage remaining on ESK-NS to be 0% at two years, it appears that 24.89% was estimated in order to imply 0% at two years. These assumptions were stated by the company to have been validated by expert clinical opinion, although no reference to any report was cited. However, the minutes of an Advisory Board, dated 4th June 2019, presented as Appendix F in the response to clarification, revealed that there appeared to have been general agreement with a figure of 35% discontinuing on reaching recovery and a further 25% monthly risk.[3] Patients in the response state during the maintenance phase could not discontinue, this being justified by being *"at high risk of relapse"* (p.175, CS).[1]

The impact of discontinuation in either the continuation or the maintenance pahse was to stop incurring the cost of ESK-NS and only incur the cost of OAD whilst having no effect on QALYs (because patients were assumed to remain in the remission or recovery state until loss of response, relapse or recurrence). This was argued by the company to be conservative.

ERG comment: The ERG considers that it is reasonable to assume no discontinuation during the acute phase and the rate during the continuation phase also appears to be reasonable given that it was estimated from the trial data albeit based on an arbitrary definition of stable and choice of exponential distribution. However, the rates of discontinuation in the maintenance phase were not based on any observed data, but instead on assumptions. The company could have continued to use data from the SUSTAIN-1 study, which could have had a parametric curve fitted to extrapolate up to the time horizon. It is also not reasonable to assume that the treatment effect is maintained, i.e. no decrease in QALYs on discontinuing ESK-NS and continuing with only OAD. Indeed, the company themselves provide evidence that continuation of the treatment effect on discontinuing ESK-NS is not credible in Section B2.2 of the CS: *"...for ESK-NS, it was uncertain whether long-term treatment would be necessary as it was hypothesised that the antidepressant effect following short-term ESK-NS treatment could be maintained with an OAD alone. The maintenance study, SUSTAIN-1, however, showed this to not be the case: patients who discontinued ESK-NS demonstrated a significantly greater relapse rate than those who remained on ESK-NS..."* (p.51).[1] The ERG also question the assumption that discontinuation implies no decrease in QALYs. In the continuation phase, where the rate was estimated from the data, relapse was a censoring event, which implies that patients discontinued without relapsing. However, no evidence was presented as to the rate of relapse of those discontinuing. In the maintenance

phase, where the rate of discontinuation was assumed, it is completely opaque as to the rate of recurrence in those who have discontinued. In both phases, it is also unclear whether there might be a diminution in utility and thus a loss of QALYs even if relapse or recurrence do not occur. In the absence of any data as to the effect on relapse or recurrence or utility on discontinuation of ESK-NS, the ERG assumed no discontinuation for reasons other than loss of efficacy in the ERG base-case, see section 7.2.

5.2.6.4 Subsequent treatments

As reported in Section B.3.2.9.3, the company estimated the transition probabilities for each of three further lines of subsequent treatment (Table 5.11). They stated that they had been estimated from the STAR*D trial, as they were in TA367.[1, 9, 53] Although the final numbers were stated to have been validated by two advisory boards, it is unclear how any of the numbers reported in STAR*D were transformed to produce those in Table 5.11, other than that *"...data being converted to 4-week risks using standard formulae"* (p.177, CS).[55, 56]

The precise mix of OADs that formed subsequent treatment was not specified, but examination of the model revealed that the cost was identical to the OAD as employed in first-line treatment, see section 5.2.8.3).

Table 5.11: Health state transition probabilities – subsequent treatment

Treatment	MDE to Response*	MDE to Remission*	Response to Remission†	Loss of Response†	Relapse†	Recurrence†
TRD line 2	3.54%	0.86%	2.76%	12.79%	22.81%	2.88%
TRD line 3	2.75%	0.65%	2.76%	12.79%	22.81%	2.88%
TRD line 4	2.14%	0.49%	2.76%	12.79%	22.81%	2.88%

Based on Table 50 of the CS[1]
* Evaluated at the end of the acute phase; † Per 4-week cycle.
CS = company submission; MDE = major depressive episode; TRD = treatment-resistant depression.

ERG comment: Although the company stated that they used STAR*D, their methods were unclear and the resulting values were much lower than those in STAR*D.[53] If one assumes that TRD line 2 is equivalent to fourth-line since the onset of MDD then this might also be equivalent to Step 4 in STAR*D.[53] At this line in STAR*D, the probabilities of response and remission were reported to be 16.3% and 13.0%, which could therefore be compared to 3.54% + 0.86% (assuming that response is the sum of these two transition probabilities) and 0.86%, respectively. The company stated that values were converted to four-week risks, but it is not clear what the unconverted risks were, nor what the number of weeks for the unconverted risks was. Additionally, it is not clear what the basis of the conversion was. This is because such a conversion would only be required if the event could occur over multiple four-weekly cycles such that the cumulative risk is then equal to the unconverted one. According to the model structure, transition from MDE to either response or remission can only occur in the first cycle on starting any line of therapy. As soon as it is determined that the patient has failed to respond or remit, they then move to the next line, thus preventing any further response or remission. Of course, it might be that in STAR*D response or remission did occur later than four weeks after initiating treatment and the report of the STAR*D study does not report the mean number of weeks to response or remission, i.e. 8.3 and 7.4 respectively. Therefore, the model should allow transition from MDE to response or remission over more than one cycle. Otherwise, the full effectiveness of the treatment is underestimated. As a second-best solution the ERG assumed that all response or remission occurred in the first cycle on starting treatment in an ERG scenario, see section 7.3. This approach will overestimate the benefit and cost of treatment, but only because of the lower rate of discounting applied to the QALYs and cost due

to some response or remission occurring too early. However, given that patients were encouraged to switch treatment if no response and follow-up visits occurred every two months, it is likely that this was determined after no more than one more cycle.[53] As also recommended by the committee of TA367, a decrease in response and remission was applied at each line of therapy by multiplying the values for OAD by a factor equal to the ratio of values in Step 3 versus Step 4 in STAR*D.[9, 53] Specifically the FAD for TA367 states that *"...the Committee considered it more appropriate to apply a proportionate reduction in the rates of remission for fourth and subsequent lines of treatment, as seen in the STAR*D trial, to the remission data used for third-line treatment"* (p. 48).[9] These ratios are: 13.7/13.0 and 16.8/16.3 for remission and response, respectively. Therefore, the factors applied at second-, third- and fourth-line TRD are the ratios, the ratios to the power 2 and the ratios to the power 3 respectively.

The ERG used the same method of adjusting by line for loss of response and relapse in this ERG scenario. This was achieved by using the company estimated values, for loss of response, of 22.2% for first line TRD and 22.8% for second line TRD and, for relapse, of 6.8% for first line TRD and 12.8% for second line TRD.[3]

5.2.6.5 Best supportive care

As reported in Section B.3.2.9.4 of the CS, the company estimated the transition probabilities for the BSC treatment mix (Table 5.12). In the model, the BSC treatment phase applies to patients whose disease has failed all previous treatments (fifth-line TRD and onwards). In this phase, patients could achieve response or remission at every cycle, and those who had achieved response or remission could experience loss of response or relapse at every cycle.

The efficacy estimates (response and remission) during the BSC treatment phase were stated to have been based on the HTA monograph by Edwards 2013, which were estimated from expert UK clinical opinion based on available evidence.[51] The authors of the monograph were stated to have been contacted to confirm how clinical opinion was derived and they confirmed that the results of the STAR*D trial formed part of the available evidence considered by the clinical experts informing the Edwards 2013 publication.[51] The efficacy estimates from the study were further validated by clinical experts in June 2019.[56]

The CS then stated that standard calculations were used to convert the reported two-month probabilities to four-week probabilities. To avoid double counting, the transition probability for remission was subtracted from the probability for response to derive the transition probability for MDE to response (excluding remission) that was used in the current model.

For sensitivity analysis, a confidence interval of ±10% of the mean was assumed for all probabilities shown in Table 5.12.

The precise mix of OADs that formed subsequent treatment was not specified, but examination of the model revealed that the cost was identical to the OAD as employed in first-line treatment, see section 5.2.8.3.

Table 5.12: Health state transition probabilities – best supportive care treatment mix

Treatment	Response†,*	Remission†	Loss of Response†	Relapse†
Best supportive care treatment mix	0.83%	0.41%	10.38%	4.20%

Based on Table 51 of the CS[1]
† Per four-week cycle. * Response minus remission.

ERG comment: Transition probabilities are attributed to an HTA monograph by Edwards 2013 supplemented by methodological advice from the authors of the HTA as to how clinical opinion was derived and then further supplemented by a validation exercise and subsequent conversion of two-month probabilities to four-week probabilities.[51, 56] There is no way of validating whether the assumptions and adjustments are appropriate. Results of the STAR*D trial in terms of transition to BSC are not reported. The means of converting these non-reported two-month probabilities to four-week probabilities were also not provided. Given that the mix of drugs referred to as subsequent therapy (up to fourth-line TRD) is precisely the same as the mix referred to as BSC (fifth-line), in the absence of specific data, it seems logical to apply the same method of estimating the transition probabilities for all lines of therapy beyond first-line in the model, see section 5.2.6.4. Therefore, the factors applied for BSC are the ratios 13.7/13.0 and 16.8/16.3 for remission and response respectively, each to the power 4 in the ERG base-case, see section 7.3.

5.2.6.6 Adverse events

In TRANSFORM-2, AEs, defined as those first reported or worsening in severity after initiating study treatment, were of mild to moderate severity. There were 14 most commonly reported AEs, with incidence ≥5% and occurring more frequently in the ESK-NS + OAD over the OAD + PBO-NS arm. These include nausea/vomiting, dissociation, dizziness, headache, vertigo, dysgeusia (distortion of sense of taste), somnolence, sedation, insomnia, blurry vision, increased blood pressure, paraesthesia, hypoesthesia (reduced sense of touch or sensation), and fatigue (see section B.2.10.1.1 of the CS and Table 4.17). Over 90% of TEAEs resolved on the same day of nasal spray self-administration.[54] Patients receiving ESK-NS + OAD were monitored during self-administration and post-administration for one hour on average. It was therefore assumed that, in the base-case, there would be no cost or negative impact on quality of life associated with AEs.

For completeness, a scenario analysis including AEs was conducted based on the rates of AEs seen in TRANSFORM-2 (see Tables 37 and 38 in Section B.2.10.1.1 of the CS) and their associated disutility.[1]

ERG comment: The ERG would have preferred a more extensive search for adverse events beyond what was reported in TRANSFORM-2. Specifically, the company report adverse events from SUSTAIN-1 (see Tables 4.18 and 4.19) but do not use this evidence in the economic model. However, the ERG considers that most of the effect to AEs will be during the monitoring phase and notes that the effect of inclusion of AEs is minimal and therefore not change has been made to the ERG base-case.

5.2.6.7 Mortality

As reported in section B.3.2.9.6 of the CS, mortality effects were accounted for in the economic model based on two different sources.[1] These were all-cause mortality risk, specific to age and gender, and an excess annual mortality for TRD, associated with suicide, of 0.47% linked to the MDE health state.[57] It was assumed that half the excess mortality risk associated with suicide would still be present in the response state.

Gender and age-specific all-cause mortality were sourced from the Office of National Statistics life tables.[58] The model firstly derived a weighted mortality risk for each age. This was weighted according to the proportion of males and females in the cohort and the baseline age. The risk was applied to the number of patients alive at the beginning of the cycle in each health state:

$$n_{death\ all-cause\ cycle\ i} = n_{alive\ cycle\ i} \times p_{age},$$

where:

- i is the cycle under consideration,
- $n_{death\ all-cause\ cycle\ i}$ is the number of patients that die during cycle i, due to all-cause mortality,
- $n_{alive\ cycle\ i}$ is the number of patients alive at the beginning of cycle i, and
- p_{age} is the mortality risk (i.e. probability) at a specific age.

Additional mortality from suicide attempts was also stated to have been explicitly modelled, which was performed in two steps. First, for patients in each health state, the number of suicide attempts was calculated, and second, a proportion of these suicide attempts were considered fatal, giving the total of patients who died from suicide. The calculation was as follows: risk was applied to the number of patients alive at the beginning of the cycle in each health state:

n_(death suicide cycle i)=n_(alive cycle i) ⟦× SA⟧_hs ⟦× p⟧_fatal,

where:

i is the cycle under consideration,

n_(death suicide cycle i) is the number of patients that die during cycle i due to suicide,

n_(alive cycle i) is the number of patients alive at the beginning of cycle i,

⟦SA⟧_hs is the risk of suicide attempt (i.e., probability) at the current health state, and

p_fatal is the risk of a suicide attempt being fatal.

It is unclear how this calculation would be performed given that the risk of suicide attempt was not reported.

ERG comment: The ERG considers the use of gender and age-specific all-cause mortality tables to be appropriate but has concerns that trial-based data were ignored in favour of the results of a published meta-regression.

The meta regression itself is based on analysis of 28 small interventional studies which focus on a range of different interventions (capsulotomy, cognitive behavioural therapy (CBT), deep brain stimulation (DBS), electroconvulsive therapy (ECT), epidural cortical stimulation (epCS), ketamine, vagal nerve stimulation (VNS) and treatment as usual (TAU)). No evidence was provided to suggest that this mix of interventions is representative of standard care in the UK and no justification was made for reliance on published meta regression over trial-based evidence.

Also, an examination of the model reveals that the method described in the CS is not the way that excess mortality was incorporated. In fact, it was simply by treating the 0.47% as a hazard ratio such that the excess was independent of risk of suicide. As the ERG pointed out in the clarification letter, this appears to be methodologically correct given that the excess was estimated conditional on being depressed rather than attempting suicide, although the company did not provide any further clarification for the method stated in the CS.[3, 18, 57]

However, the main problem is the assumption by the company that risk of mortality will decrease when treating with ESK-NS, given its differential risk of response and remission. This presumes that all of

the excess mortality is removed by moving from the MDE to the remission state and half of it on moving to the response state. This is contrary to evidence of three suicides in trials all of which, whilst considered unrelated to ESK-NS treatment, occurred in patients treated with esketamine, see section 4.2.7. Also, as acknowledged by the committee, no mortality effect was included in TA367.[9] Therefore, the ERG assumed no effect on mortality of ESK-NS + OAD in the ERG base-case, see section 7.2.

5.2.7 Health-related quality of life

5.2.7.1 Health-related quality-of-life data from clinical trials

EQ-5D-5L was used to measure the quality of life of patients in the TRANSFORM-2 trial from which utility values could be derived:

- Data were retrospectively mapped to EQ-5D-3L based on the UK valuation set,[59] as described in Section B.3.2.10.2 of the CS[1].

The company suggests that this represents NICE's preference as per the NICE reference case.

Further details of the methodology used to derive the utilities are presented in Section B.3.2.10.2 of the CS.

ERG comment: The use of HRQoL (and utility) data reported directly from patients is in line with the NICE reference case. Mapping of European Quality of Life-5 Dimensions – 3 levels (EQ-5D-3L) data from European Quality of Life-5 Dimensions – 5 levels (EQ-5D-5L) data is also in line with the NICE reference case. The precise method used by the company has been criticised in a report by the Decision Support Unit 2017[60] – but the latest NICE position statement on the use of EQ-5D-5L does suggest that the mapping function developed by van Hout et al.[59] should be used for reference-case analyses, for consistency with the current guide to the methods of technology appraisal.

5.2.7.2 Mapping

Individual scores from the five dimensions were used to obtain a weighted health status index using the method from van Hout and colleagues[59], described below:

- Scores from each dimension were combined to obtain a 5L profile score or health state: e.g. a score of 1 for each dimension gives a 5L profile score of 11111. Dimension scores were combined in the following order: Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression.
- Utilities for each possible profile on the EQ-5D-3L were computed using the Dolan algorithm which is specific to the UK [61].
- Patients were assigned probabilities for each possible profile on the EQ-5D-3L based on their profile on the EQ-5D-5L.
- The utility score on the EQ-5D-5L for each patient was computed as a weighted average of the utilities, where weights were the above-mentioned probabilities.

In the model, the utilities are stratified by health state. The health state QALYs at each cycle are calculated by multiplying the user-specified utility by the duration of the Markov cycle (28 days) expressed in years.

As noted above, disutility due to adverse events (AEs) was included as a scenario in the CS. For each AE included in the model, treatment-dependent inputs were used to calculate the associated utility decrements by treatment: the incidence for each AE by treatment, the duration of each event, and the

specific utility decrements of each event. The per-cycle utility decrement is calculated for all AEs and then summed to give a per-cycle AE-associated utility decrement for each treatment. This decrement is "added" to the utility only for patients on treatment during the acute phase; it is assumed that patients who are not on treatment do not experience any AEs. AEs associated with treatment are assessed only in the acute treatment phase and not in the maintenance phase, as it is assumed that patients are likely to have adapted well to the treatment by this time. The inclusion of AE-associated utility decrements is likely to be a conservative assumption, as the impact of AE on quality of life may already be captured in the utility analysis for the health states. In other words, the inclusion of AE-associated utility decrements may be double counting the impact of AEs on quality of life.

After the patient utilities (and disutilities in the scenario) were calculated, the values were aggregated across the health states for each cycle to obtain QALYs over time.

Utility scores were estimated for all the following health states in the Markov model using data from the TRANSFORM-2 study:

- Baseline/Major Depressive Episode (MDE)
- Response at four weeks/each cycle
- Remission at four weeks/each cycle
- Recovery after 36 weeks in remission

The baseline utility data were used to inform the utility score for patients in MDE.

Remission was defined as having a total MADRS score of 12 or less at week 4 (Day 28).

Response was defined as an improvement of 50% or more in total MADRS score at week 4 (day 28) compared with baseline. In the economic model the health states "remission" and "response" are mutually exclusive, meaning that patients in the health state "response" are patients who showed response, but did not reach remission.

The utility score for patients achieving recovery was assumed to be the same as the utility score for patients achieving remission at four weeks.

A set of descriptive summaries, i.e. mean, standard deviation [SD], standard error [SE], minimum, lower quartile [Q1], median, upper quartile [Q3], and maximum was computed for all the corresponding utility scores.

Utility scores were assumed to depend only on the health state of the patient, and not to be treatment-specific. Data from both treatment arms in the TRANSFORM-2 study were pooled to increase the robustness and precision of estimates. Analyses were based on observed data only and no imputation for missing data was performed. The estimates used to populate the utilities per health state in the economic model are summarised in Table 5.13.

Table 5.13: Summary of utilities used in the model (by health state)

Health State	Utility	Standard deviation	SE	Source
MDE (baseline value in TRANSFORM-2)	0.417	0.233	0.016	TRANSFORM-2
Response (value at day 28 in TRANSFORM-2)	0.764	0.123	0.020	TRANSFORM-2
Remission (assumption)	0.866	0.122	0.013	TRANSFORM-2

Health State	Utility	Standard deviation	SE	Source
Recovery (assumption)	0.866	0.122	0.013	Assumption*
Based on Table 54 of the CS[1] * Assumed to be the same as remission CS = company submission; MDE = major depressive episode; SE = standard error				

ERG comment: In its clarification letter, the ERG asked the company to explain why it did not consider using the DSU EQG (EuroQoL) method when mapping utilities from EQ-5D-5L.[18] The company responded that the method they used was consistent with the *"NICE position statement on this topic"*.[3] The ERG is satisfied with this explanation by the company.

The ERG notes that the company originally intended to use data from several trials (not just TRANSFORM-2) to generate utility values. *"Utility values for the model will be derived using the patient reported EQ5D administered during the 3 clinical trials. Other values to populate the model will be sourced from the literature. In the acute trials, the EQ5D will be administered at Days 1, 4, 8, 15, 22 of the double-blind phase as well as at the end of the study. In the maintenance trial, the EQ5D score will be collected on a monthly basis, as well as at the time of treatment discontinuation"*.[12] It is not clear why the company chose to ignore EQ5D data from the maintenance trial, SUSTAIN-1, to inform the utility values of the remission/recovery state. Page 6,348 of 11,938 of the clinical study reports for SUSTAIN-1 suggests a mean EQ-5D-5L follow up value of 0.842 (SD 0.1146). If this value could be converted into an EQ-5D-3L equivalent it could have been used in the economic model.

The ERG has been unable to validate the utility values used in the model (as set out in Table 5.13). Furthermore, comparison with a previous STA, vortioxetine for treating major depressive episodes (TA367) reveals considerable variation in baseline utility for populations with major depressive episodes, namely 0.417 in the CS and 0.54 in TA367.[1, 9] However, the ERG do not believe that there is a better source and therefore decided not to change baseline utility in the ERG base-case.

5.2.7.3 AE disutilities

Disutility due to dry mouth was obtained from Revicki et al. 1998.[62] The study reported utilities for patients in North America with MDD who had completed at least eight weeks of treatment. The disutility due to vision blurred was derived from Sullivan et al. 2006[63] which reported EQ-5D index scores for chronic conditions in the United States of America (USA), estimated from the nationally representative Medical Expenditure Panel Survey pooled from 2000–2002 with 38,678 adults.[63] Other disutilities listed in Table 5.14 were from the study by Sullivan et al. 2004[64] a cost effectiveness study of eight OADs used as initial treatment for depression in the US.

Since the AEs related to ESK-NS observed in the ESK-NS + OAD arm of TRANSFORM-2 were transient and resolved within hours, the scenario analysis conservatively assumed a duration of one day for all AEs.

Table 5.14: AE disutilities for scenario analysis

AE	Disutility (SE)
Anxiety	–0.129 (0.032)
Blood pressure increased	0.000 (0.000)
Delusional perception	0.000 (0.000)
Derealisation	0.000 (0.000)

AE	Disutility (SE)
Diarrhoea	–0.044 (0.011)
Dissociation	0.000 (0.000)
Dizziness	–0.085 (0.021)
Dizziness postural	0.000 (0.000)
Dry mouth	–0.010 (0.003)
Dysgeusia	0.000 (0.000)
Fatigue	–0.085 (0.021)
Feeling abnormal	–0.085 (0.021)
Feeling drunk	–0.085 (0.021)
Headache	–0.115 (0.029)
Hypoaesthesia	0.000 (0.000)
Hypoaesthesia oral	0.000 (0.000)
Illusion	–0.085 (0.021)
Insomnia	–0.129 (0.032)
Nasal discomfort	0.000 (0.000)
Nausea	–0.065 (0.016)
Paraesthesia	0.000 (0.000)
Paraesthesia oral	0.000 (0.000)
Somnolence	–0.085 (0.021)
Throat irritation	–0.010 (0.003)
Vertigo	–0.085 (0.021)
Vision blurred	–0.050 (0.012)
Vomiting	–0.065 (0.016)

Based on Table 55 of the CS[1]
AE = adverse event; CS = company submission; SE = standard error

ERG comment: The ERG regards the approach to estimating the values and handling of AE disutilities as reasonable.

5.2.8 Resources and costs

The cost categories included in the model were costs associated with treatment (drug acquisition costs including subsequent therapies, cost of supervision of self-administration and post-administration monitoring), costs associated with disease management (costs of OAD), and costs associated with different health states.

5.2.8.1 Resource use and costs data identified in the SLR

According to Appendix I of the CS, the SLR performed in July 2018 (with an update in April 2019) identified 19 studies that considered MDD, but only two specifically considered patients with TRD.[17] The company stated that one of the eligible UK studies was not aligned with the definitions used in this appraisal (no formal definition of resistance was provided) and the second study did not contain the data granularity required to inform the analysis, as the study did not report data per health state.

5.2.8.2 Treatment costs

The cost per a single-use device that delivers a total of 28 mg of esketamine in two sprays (one spray per nostril) is £163, equating to a cost of £326 per 56 mg dose and £489 per 84 mg dose. The average number of sessions per week and devices per session in the acute phase were estimated based on TRANSFORM-2 trial, while for subsequent time-points they were derived from SUSTAIN-1 trial. These numbers were also tested in sensitivity analysis and a plausibility limit was applied to prevent the number of ESK-NS devices being less than two (56 mg) or greater than three (84 mg). Similarly, limitation was applied to the number of sessions (no less than 0.5 and no more than 2).

The average treatment administration cost of esketamine was based on assumption that two nurses (one band 5 and one band 4) are needed for the supervision of self-administration of ESK-NS and that a cohort of six patients will be concurrently supervised. In the CS it was also mentioned that patients will be observed for 60 minutes on average and 9.57% of patients might experience a blood pressure increase which might prolong supervision of the patients. All these assumptions resulted in an average cost per patient, per administration of £30.08 (see Table 5.15).

Table 5.15: Administration and observation resource use and costs

Item	Resource use	Cost per hour	Total duration HCP is required (hours)	Number of patients in cohort	Average cost per session per patient
Administration/ preparation	1x band 4 nurse	£28	0.25	6	£30.08
	1x band 5 nurse	£37	0.25		
Supervision of self-administration	1x band 4 nurse	£28	1		
	1x band 5 nurse	£90*	1		
Monitoring post self-administration	1x band 5 nurse	£37	1.25		
Based on Table 56 of the CS[1] CS = company submission; HCP = healthcare professional					

A summary of drug acquisition and resource costs through all treatment phases in the model is presented in Table 5.16.

Table 5.16: Acquisition and resource costs associated with ESK-NS administration

Items	Acute Weeks 1–4	Continuation (relapse prevention) Weeks 5–8	Continuation (relapse prevention) Weeks 9–40	Maintenance (recurrence prevention) Week 41 onwards
Average number of sessions per week	1.850	0.992	0.711	0.675
Average number of devices per session	2.530	2.605	2.605	2.571
Drug acquisition cost per 4-week cycle	£3,051.61	£1,684.73	£1,208.42	£1,131.00

Items	Acute Weeks 1–4	Continuation (relapse prevention) Weeks 5–8	Continuation (relapse prevention) Weeks 9–40	Maintenance (recurrence prevention) Week 41 onwards
Administration and observation costs	£222.60	£119.33	£85.60	£81.17
Total cost per 4-week cycle	£3,274.21	£1,804.06	£1,294.02	£1,212.17

Based on Table 57 of the CS[1]
CS = company submission; ESK-NS = esketamine nasal spray

5.2.8.3 Comparator cost

All OADs with a market share greater than 3% of all treatments were included in the analysis. The average cost of OADS per four-week cycle was estimated using prescription cost analysis and market share information from IQVIA data (see Table 5.17).[11] For specific drugs (duloxetine, escitalopram, sertraline, and venlafaxine) the daily doses were derived from TRANSFORM-2 trial, while a mid-point of the plausible dose ranges was chosen for other OADs. The analysis resulted in weighted average cost of £4.15 per four-week cycle. Following response to clarification, the company adjusted weighted average cost and included the elderly population in the analysis of the cost. This resulted in a revised weighted average cost of £4.06. Since ESK-NS is incremental to OADs, the associated cost was equal on both sides.

Table 5.17: Weighted average OAD cost

OAD	Market share (%)	Daily dose (mg)	Average cost per mg	Average cost per 4-weeks
Amitriptyline	13.78	100.00 mg	£0.0029	£8.00
Citalopram	17.89	30.00 mg	£0.0031	£2.57
Duloxetine	5.40	59.00 mg	£0.0052	£8.54
Escitalopram	2.42	18.15 mg	£0.0050	£2.56
Fluoxetine	13.38	40.00 mg	£0.0026	£2.93
Mirtazapine	19.66	30.00 mg	£0.0027	£2.28
Sertraline	18.53	129.70 mg	£0.0005	£1.71
Venlafaxine	8.94	210.17 mg	£0.0017	£10.12
Weighted average cost per 4 weeks				£4.15

Based on Table 58 of the CS[1]
CS = company submission; OAD = oral antidepressant

5.2.8.4 Health state costs

Resource use in the MDE, relapse, recurrence, and recovery states were based on a retrospective chart review of medical records of patients with TRD, since TRANSFORM-2, SUSTAIN-1 and the published literature have not reported such information.

The retrospective chart review included data from 295 patients with TRD in the UK from both primary and secondary care. Data were collected from nine GPs and 30 psychiatrists and provided information on numbers of GP visits, psychiatrist visits, psychotherapies, psychiatric hospitalisations (general ward/psychiatric hospital), A&E visits, length of stay when hospitalised, antidepressant treatment

history (including dosing, duration, line of therapy, adherence), other psychiatric medications prescribed (anxiolytics, hypnotics, and antipsychotics), ECT, medical devices, AEs, management of AEs, and suicides. The full report was made available for the ERG on 28 August 2019.

Health resource use costs, excluding drug treatment costs, for four-week cycle are shown in Table 5.18. The costs for response and remission, according to the CS, were based on a conservative assumption which is biased against ESK-NS, as patients in the OAD arm spend greater time in the response state, and it might be expected that patients in response have greater healthcare resource use (HCRU) costs compared with patients in remission.

Table 5.18: List of health states and associated costs in the economic model

Health states	Value (95% CI)
MDE	£980.08 (761.48, 1,198.67)
Response	£164.46 (102.81, 226.11)
Remission	£164.46 (102.81, 226.11)
Recovery	£83.75 (47.97, 119.53)
Based on Table 59 of the CS[1] CI = confidence interval; CS = company submission; MDE = major depressive episode	

5.2.8.5 Adverse event related costs

Adverse events related cost were not included in the base-case analysis. The company justified this assumption based on TRANSFORM-2 trial, where most AEs were transient and resolved during the post-administration observation phase. Only the cost of a GP contact (at £37 per contact) for all ESK-NS-associated AEs was considered in a scenario analysis.

ERG comment:

a) The assumption applied in the model that six patients will be concurrently supervised during self-administration seems to be not realistic. The ERG asked the company to conduct an additional sensitivity analysis for average cost per session, where the number of patients in a clinic varies between plausible levels. In the response to clarification, the company agreed to assess the impact on the average administration cost per session per patient of varying the number of patients seen in a clinic at any one time. The sensitivity analysis resulted in the ICER of £6,420 when patient to nurse ratio was set to 20:1 and the ICER was £9,252, when patient to nurse ratio was set to 1:1. The ERG believes that latter scenario would be the most plausible in clinical practice and should be used in the ERG base-case (see section 7.2).
b) Although there will be no adjustment to OAD for the placebo effect in the ERG base-case (See section 5.2.6.1), the ERG consider that it is reasonable to attribute some of the effect on response and remission to be attributable to the extra clinic sessions. On this basis, the correct comparator might actually be OAD plus additional clinic sessions. Therefore, the cost of clinic sessions for OAD is increased to the level for ESK-NS + OAD in an ERG scenario (see section 7.3).
c) The company, in their submission, had mentioned that at visit 8 (four weeks) a psychiatrist is required to assess response according to the pathway given. However, this cost was not included in the economic model. In the response to clarification, the company argued that this cost would cancel out in each treatment arm, since all patients, irrespective to their initial treatment, would be assessed at week 4.[3] Therefore, inclusion of the cost would not impact the base-case ICER. After the explanation provided by the company, the ERG is satisfied with this assumption.

d) The ERG received the full study of the retrospective chart review on 28 August 2019. The study describes research methods in detail, however, the ERG noted that it is unclear how monthly costs were calculated, given that information was provided only about the sources of the cost. Indeed, instead of providing information about the time period on which all the calculations were based in each health state, the company stated that the data has been standardised to a 28-day period. This shortcoming introduces an uncertainty into the findings.
e) The company did not include any cost of adverse events in their base-case analysis, given that patients in TRANSFORM-2 trial experienced only transient AEs which resolved during the post-administration observation phase. The ERG believes that this assumption is reasonable, since the cost of post-administration observation phase is included in the model. However, the ERG thinks that latter assumption only partially covers the cost of AEs. In the TRANSFORM-2 trial and in the company's submission it was reported that around 90% of TEAEs were resolved on the same day. Therefore, the ERG believes that some AEs will occur after the observation phase, but notes that the effect of inclusion of AEs is minimal and therefore not change has been made to the ERG base-case.

6. Cost effectiveness results

6.1 Company's cost effectiveness results

The base-case clinical and economic outcomes are presented in Table 6.1. Over a five-year time horizon, ESK-NS + OAD was associated with an additional 0.336 QALYs compared with OAD. The incremental drug cost for ESK-NS + OAD was £10,456; ESK-NS + OAD was estimated to have lower disease management costs, saving £8,243 compared with OAD Table 6.1. This resulted in an incremental cost difference of £2,213 and therefore a base-case incremental cost effectiveness ratio (ICER) of £6,582 per QALY.

Table 6.1: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
OAD	£48,478	4.508	2.239				
ESK-NS + OAD	£50,691	4.519	2.575	£2,213	0.011	0.336	£6,582
Based on Table 62 of the CS[1] CS = company submission; ESK-NS; ICER = incremental cost-effectiveness ratio; LYG = life years gained; OAD = oral antidepressant; QALYs = quality-adjusted life years							

ERG comment: Given that the NICE scope has no upper age limit, the ERG requested that the company conduct a cost effectiveness analysis for the whole population by adding data specific for those aged 65 years over, including TRANSFORM-3 and SUSTAIN-2 to the existing data for those aged 18-64 years. In response to this request for clarification, the company submitted a model for the combined 18–64 years and ≥65 years populations. The model includes the derived weighted averages for transition probabilities for response and relapse in the acute phase, utilities, and cost inputs of the two populations. The same model assumptions as previously submitted in the base-case model are applied. Based on the 2011 Census of the Office of National Statistics, 20.8% of patients with TRD are ≥65 years.[58] With this input, the ICER was revised to £7,699 per QALY.

6.2 Company's sensitivity analyses

6.2.1 Probabilistic sensitivity analysis

To determine the uncertainty surrounding the base-case ICERs, a probabilistic sensitivity analysis (PSA) was conducted with a total of 10,000 Monte Carlo simulations. A Beta distribution was assigned to probabilities, proportions, and utility and disutility data which take values between 0 and 1, while a Gamma distribution was assigned to costs, doses, and resource use, which take positive values and are likely to be positively skewed. Uncertainty was characterised by standard error. Results of PSA are shown in Table 6.2.

Table 6.2: Probabilistic sensitivity analysis results

Technologies	Total costs (95% CI)	Total QALYs (95% CI)	Incremental costs	Incremental LYG (95% CI)	ICER incremental (£/QALY))
OAD	£48,493 (£38,548, £59,404)	2.24 (2.10 to 2.38)			

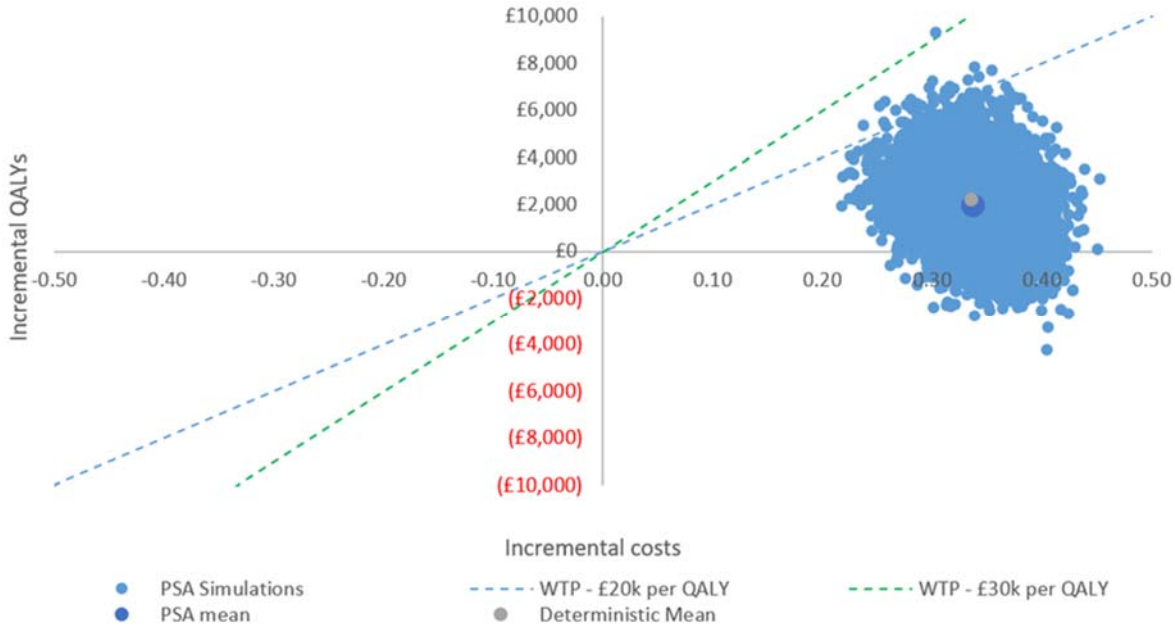
Technologies	Total costs (95% CI)	Total QALYs (95% CI)	Incremental costs	Incremental LYG (95% CI)	ICER incremental (£/QALY))
ESK-NS + OAD	£50,479 (£42,209, £59,389)	2.58 (2.43 to 2.72)	£1,987 (–£840, £4,822)	0.34 (0.27 to 0.40)	£5,903

Based on Table 63 of the CS[1]

CI = confidence interval; CS = company submission; ESK = esketamine; ICER = incremental cost-effectiveness ratio; LYG = life years gained; NS = nasal spray; OAD = oral antidepressant; QALYs = quality-adjusted life years

The incremental cost effectiveness plane and the corresponding cost effectiveness acceptability curves are shown in Figures 6.1 and 6.2.

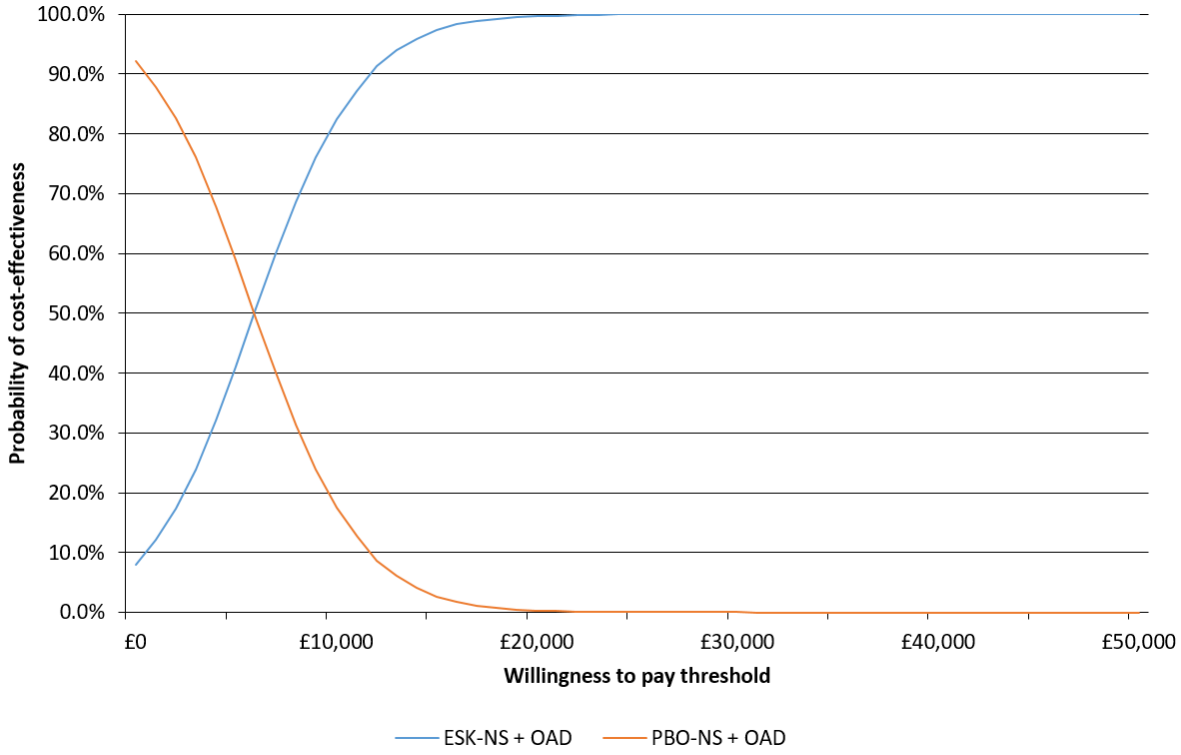
Figure 6.1: Cost effectiveness plane



Based on Figure 25 of the CS[1]

CS = company submission; PSA = probabilistic sensitivity analyses; QALY = quality-adjusted life year; WTP = willingness-to-pay

Figure 6.2: Cost effectiveness acceptability curve



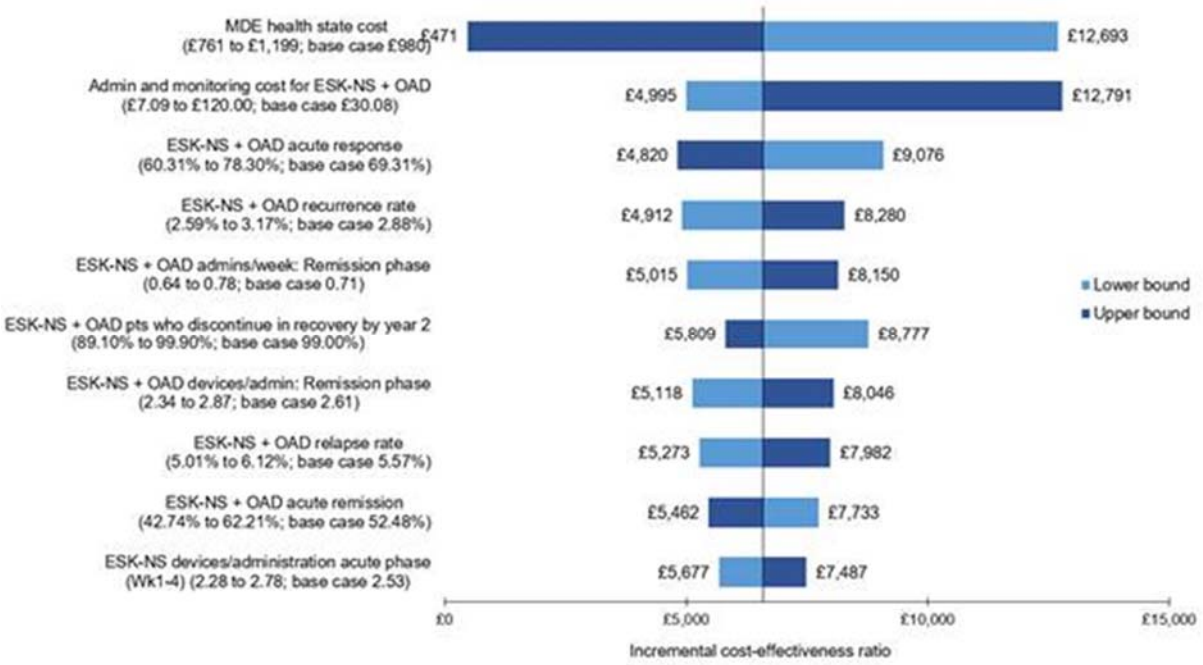
Based on Figure 25 of the CS[1]
ESK = esketamine; OAD = oral antidepressant; PBO = placebo

ERG comment: The PSA results are congruent with the deterministic analysis results and the most influential parameters (medical cost of the MDE state and the administration/observation cost associated with ESK-NS + OAD) seemed reasonable.

6.2.2 Deterministic sensitivity analysis

The results of the deterministic sensitivity analysis are shown below in the tornado diagram in Figure 6.3. All parameters were varied but the figure shows the 10 parameters with the greatest impact. Furthermore, no parameter tested in univariate sensitivity resulted in an ICER above £20,000 per QALY.

Figure 6.3: Results of univariate sensitivity analysis (tornado diagram)



Based on Figure 27 of the CS[1]

CS = company submission; ESK = esketamine; MDE = major depressive disorder; NS = nasal spray; OAD = oral antidepressant

Table 6.3: Results of univariate analysis

Variable (lower bound to upper bound; base-case value)	ICER with lower bound	ICER with upper bound
MDE health state cost (£761 to £1,199; base-case £980)	£12,693	£471
Admin and monitoring cost for ESK-NS + OAD (£7.09 to £120.00; base-case £30.08)	£4,995	£12,791
ESK-NS + OAD acute response (60.31% to 78.30%; base-case 69.31%)	£9,076	£4,820
ESK-NS + OAD recurrence rate (2.59% to 3.17%; base-case 2.88%)	£4,912	£8,280
ESK-NS + OAD administrations/week continuation phase (0.64 to 0.78; base-case 0.71)	£5,015	£8,150
ESK-NS + OAD pts who discontinue in recovery by Year 2 (89.10% to 99.90%; base-case 99.00%)	£8,777	£5,809
ESK-NS + OAD devices/administration during continuation phase (2.34 to 2.87; base-case 2.61)	£5,118	£8,046
ESK-NS + OAD relapse rate (5.01% to 6.12%; base-case 5.57%)	£5,273	£7,982
ESK-NS + OAD acute remission (42.74% to 62.21%; base-case 52.48%)	£7,733	£5,462
ESK-NS devices/administration acute phase (Wk1-4) (2.28 to 2.78; base-case 2.53)	£5,677	£7,487

Based on Table 64 of the CS[1]

CS = company submission; ESK = esketamine; ICER = incremental cost-effectiveness ratio; MDE = major depressive disorder; NS = nasal spray; OAD = oral antidepressant

6.2.3 Scenario analyses

6.2.3.1 Treatment effect adjustment

The effect of removing the adjustment for the placebo effect, consistent with the values of remission and relapse for OAD of 31.0% and 52.0% as opposed to the adjusted values of 18.0% and 34.0%, was to increase the ICER to £16,209. The company also performed analyses of combinations of various percentages of the unadjusted response and remission.

ERG comment: As explained in section 5.2.6.1, the ERG believes that the adjustment should not be made to the placebo arm of the TRANSFORM-2 trial and there is no basis for any given percentage reduction in either response of remission. This view is reflected in the ERG base-case, see section 7.2. The ERG considered sensitivity analyses to be appropriate.

6.2.3.2 Other comparators

Based on the data from the NMA, and using the data from TRANSFORM-2 adjusted for the placebo effect, as presented in section 5.2.4, the company reported the following results (Table 6.4) for a set of comparators other than those in the company trials.

In response to the request for clarification, the company also presented the results base on the NMA estimates unadjusted for the placebo effect (see section 5.2.4), which are show in Table 6.5.[3]

Table 6.4: Scenario analysis considering all comparators, adjusted for placebo effect

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline* (£/QALY)	ICER incremental (£/QALY)	ICER versus ESK-NS + OAD (£/QALY)
Aug SSRI/SNRI + AAP	£48,059	4.5089	2.2597						£8,344
Aug tricyclic (nortrip) ± PBO	£48,634	4.5081	2.2358	£576	-0.0008	-0.0240	Dominated	Dominated	£6,058
Aug SSRI/SNRI + lithium	£48,837	4.5078	2.2268	£203	-0.0003	-0.0090	Dominated	Dominated	£5,320
OAD + PBO	£49,250	4.5072	2.2090	£413	-0.0006	-0.0177	Dominated	Dominated	£3,934
Aug SSRI/SNRI ± PBO	£49,580	4.5067	2.1958	£329	-0.0004	-0.0132	Dominated	Dominated	£2,929
Switch tetracyclic (mirtazapine)	£49,865	4.5063	2.1834	£285	-0.0004	-0.0124	Dominated	Dominated	£2,108
ESK + AD	£50,691	4.5188	2.5751	£826	0.0125	0.3917	£8,344	£2,108	

Based on Table 81 of the CS[1]

* Baseline in this analysis is Aug SSRI/SNRI + AAP.

AAP = atypical antipsychotic; Aug = augmentation; ESK-NS = esketamine nasal spray; CS = company submission; ICER = incremental cost-effectiveness ratio; LYG = life years gained; nortrip = nortriptyline; OAD = oral antidepressant; PBO-NS = placebo nasal spray; PBO = placebo; QALYs = quality-adjusted life years; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

Table 6.5: Scenario analysis considering all comparators, unadjusted for placebo effect

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline* (£/QALY)	ICER incremental (£/QALY)	ICER versus ESK-NS + OAD (£/QALY)
Aug SSRI/SNRI + AAP	£45,709	4.5121	2.3569						£22,823
Aug tricyclic (nortrip) ± PBO	£46,445	4.5111	2.3261	£737	-0.0010	-0.0307	Dominated	Dominated	£17,049
Aug SSRI/SNRI + lithium	£46,804	4.5106	2.3105	£359	-0.0005	-0.0156	Dominated	Dominated	£14,686
OAD + PBO	£47,327	4.5098	2.2877	£523	-0.0008	-0.0228	Dominated	Dominated	£11,701
Aug SSRI/SNRI ± PBO	£47,870	4.5091	2.2661	£543	-0.0007	-0.0216	Dominated	Dominated	£9,124
Switch tetracyclic (mirtazapine)	£48,287	4.5085	2.2477	£416	-0.0006	-0.0184	Dominated	Dominated	£7,341
ESK + AD	£50,691	4.5188	2.5751	£2,404	0.0103	0.3274	£22,823	£7,341	

Based on Table 15 of the response to request for clarification[3]

* Baseline in this analysis is Aug SSRI/SNRI + AAP.

AAP = atypical antipsychotic; Aug = augmentation; ESK-NS = esketamine nasal spray; CS = company submission; ICER = incremental cost-effectiveness ratio; LYG = life years gained; nortrip = nortriptyline; OAD = oral antidepressant; PBO-NS = placebo nasal spray; PBO = placebo; QALYs = quality-adjusted life years; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

ERG comment: The ERG acknowledges that there are significant limitations to the NMA, as discussed in section 4.4. Also, even when the adjustment is removed, most comparators are dominated: only Aug SSRI/SNRI + AAP is not because it is the least costly. However, the ICER vs. Aug SSRI/SNRI + AAP is higher than the ICER vs. OAD and there is an unexplained discrepancy between the cost, life years and QALYs associated with OAD when OAD is the only comparator and when it is one of several. Nevertheless, the ERG has made the judgment not to include Aug SSRI/SNRI + AAP in any ERG analyses.

6.3 Model validation and face validity check

In Section B.3.6, it was stated that two independent senior health economic modellers, external to the model process, performed quality assurance, which entailed:[1]

- Review of modelling structural assumption and techniques chosen.
- Review of technical deployment (formulas, functionality).
- Review of data inputs and sources.
- Conducting extreme scenario analyses and validation of results.

The first review was conducted in 2018 and the second in 2019.

Two global advisory boards (in July 2017 and November 2018 (no citation in CS)) and two UK HTA advisory boards (in October 2018 and June 2019 (no citation in CS)) were also held to inform the development of the model.[1] [redacted].

ERG comment: It is commendable that the model has been checked and validated. [redacted]. In particular, the long-term effect of retreatment has not been incorporated. However, the ERG considers that this could be considered to be outside the scope as the population would then be at a different line of therapy. What is of more concern is the continued lack of a negative effect of discontinuation, at least for reasons other than loss of efficacy. The company provided no data to show that those who discontinued treatment, even censoring for relapse, would not demonstrate any diminution in quality of life. The CS also provided no data to support the assumption that 35.4% of patients in the recovery phase would immediately discontinue with no loss of quality of life. The ERG also believes that the simultaneous monitoring of six patients that continues to be assumed is probably not feasible in clinical practice.

7. Evidence Review Group's additional analyses

7.1 Exploratory and sensitivity analyses undertaken by the ERG

Based on all considerations discussed in section 5.2 of this report, the ERG defined a new base-case and constructed three additional scenarios on this base-case. These scenarios included multiple adjustments to the company base-case submitted with the clarification response in order to include data that is suitable for adults of any age, i.e. 'ID1414 esketamine CEM adults and elderly GB 13082019 (ACIC)'. These adjustments are subdivided into three categories (derived from Kaltenthaler 2016[65]):

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model where the ERG considers that reasonable alternative assumptions are preferred)

Fixing errors

None identified.

Fixing violations

None identified.

Matters of judgment

1) Time horizon 20 years
2) No adjustment for placebo effect to OAD Acute response or remission transition probabilities
3) No discontinuation for reasons other than loss of efficacy
4) No effect on mortality of ESK-NS + OAD
5) Cost of clinic visit for ESK-NS + OAD based on patient to nurse ratio of 1:1
6) No difference between ESK-NS + OAD and OAD in the loss of response and relapse transition probabilities
7) A decrease in response and remission was applied at each line of subsequent therapy (including BSC) by multiplying the values for OAD by a factor equal to the ratio of values in Step 3 versus Step 4 in STAR*D.[53] These ratios are: 13.7/13.0 and 16.8/16.3 for remission and response respectively. The ERG used the same method of adjusting by line for loss of response and relapse in this ERG scenario. This was achieved by using the company estimated values, for loss of response, of 22.2% for first-line TRD and 22.8% for second-line TRD and, for relapse, of 6.8% for first-line TRD and 12.8% for second-line TRD.[3]
8) Cost of clinic visit for OAD set equal to that for ESK-NS + OAD

Issues (1) to (5) are all incorporated as the ERG's preferred model assumptions and thus form the ERG base-case, the results for which are shown in Tables 7.1 and 7.2. Table 7.3 shows how the individual adjustments of (6), (7) and (8) impact additionally as scenarios on the ERG base-case.

7.2 ERG's base-case analysis

Table 7.1: ERG's base-case analysis (deterministic)

	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
OAD	145,153.86	13.278	6.678	15,298	0.000	0.246	£62,078
ESK-NS + OAD	160,452.22	13.278	6.925				

ERG = Evidence Review Group; ESK = esketamine; ICER = incremental cost effectiveness ratio, Incr. = incremental, LYG = life year gained, NS = nasal spray; OAD = oral antidepressant; QALY = quality-adjusted life year

Table 7.2: ERG's base-case: cumulative effect of each assumption

Preferred assumption		Section in ERG report	Cumulative ICER £/QALY
	Company base-case using 'adults and elderly' model		£7,699
1	Time horizon 20 years	5.2.5	£ 4,627
2	No adjustment for placebo effect to OAD Acute response or remission transition probabilities	5.2.6.1	£ 12,557
3	No discontinuation for reasons other than loss of efficacy	5.2.6.3	£ 52,872
4	No effect on mortality of ESK-NS + OAD	5.2.6.7	£ 55,027
5	Cost of clinic visit for ESK-NS + OAD based on patient to nurse ratio of 1:1	5.2.8	£ 62,078

ERG = Evidence Review Group; ESK = esketamine; ICER = incremental cost effectiveness ratio, Incr. = incremental, NS = nasal spray; OAD = oral antidepressant; QALY = quality-adjusted life year

Table 7.3: ERG's base-case analysis (probabilistic, LYs not generated)

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)
OAD	£145,471.41	6.682	£15,367	0.247	£62,141
ESK-NS + OAD	£160,838.28	6.929			

ERG = Evidence Review Group; ESK = esketamine; ICER = incremental cost effectiveness ratio, Incr. = incremental, NS = nasal spray; OAD = oral antidepressant; QALY = quality-adjusted life year

7.3 ERG's additional analyses

Table 7.4: ERG scenario analyses

ERG assumption		Section in ERG report	ICER £/QALY
5	ERG's base-case using 'adults and elderly' model	7.2	£ 62,078
6	No difference between ESK-NS + OAD and OAD in the loss of response and relapse transition probabilities	5.2.6.2	£97,396

ERG assumption		Section in ERG report	ICER £/QALY
7	A decrease in response and remission was applied at each line of subsequent therapy (including BSC) by multiplying the values for OAD by a factor equal to the ratio of values in Step 3 versus Step 4 in STAR*D.[53] These ratios are: 13.7/13.0 and 16.8/16.3 for remission and response respectively. Values estimated by the company from STAR*D were, for loss response, 22.2% for first line TRD and 22.8% for second line TRD and, for relapse, of 6.8% for first line TRD and 12.8% for second line TRD.[3]	5.2.6.4, 5.2.6.5	£ 148,376
8	Cost of clinic visits for OAD set equal to that for ESK-NS + OAD	5.2.8	£ 53,728
ERG = Evidence Review Group; ESK = esketamine; NS = nasal spray; OAD = oral antidepressant; QALY = quality-adjusted life year; TRD = treatment-resistant depression			

7.4 Conclusions of the cost effectiveness section

The company model is a state transition model with a cycle length of four weeks and, in addition to death, four health states, which are summarised in Table 5.5.[1] Patients enter the model in the major depressive episode (MDE) health state, after having failed to achieve a *"…clinically meaningful improvement…"* (page 160, CS) after treatment with at least two OADs *"prescribed in adequate dosages for adequate time"* (page 160, CS).[1] During each four-weekly Markov cycle, patients can occupy MDE, response, remission, recovery or death health states. Transition to recovery can only occur from remission and only after nine months (36 weeks) in the remission state and then with certainty. Patients can cycle through up to three subsequent treatments. After three subsequent treatments, patients enter the MDE state from which they can still respond or go into remission, whilst being treated with BSC. [redacted]

Transitions between health states are governed by treatment phase:

- Acute phase (weeks 1 to 4)
- Continuation phase (weeks 5 to 40)
- Maintenance phase (weeks 41+)

The population was described in the CS as adults with TRD with a moderate to severe depressive episode.[1] A moderate to severe episode of TRD was assumed to have minimum duration of two years. Treatment-resistant MDD was defined as non-response to two or more OADs prescribed at an adequate dose and for an adequate duration in the current episode.

The intervention in the analysis was ESK-NS co-administered with a newly initiated OAD (ESK-NS + OAD), see Section B.3.2.7 of the CS).[1] The average number of sessions per week and devices per session in the acute phase were derived from TRANSFORM-2, while for subsequent time-points they were derived from SUSTAIN-1. In TRANSFORM-2 the precise rules of determining efficacy and tolerability were not reported in the CS or Appendix M.[1, 17] In TRANSFORM-3, the starting dose was 28 mg which could also be increased to 84 mg by day 25 without any specification of the precise rules. SUSTAIN-1 had the same dosing as TRANSFORM-2 in the first four weeks for direct entry patients. These patients then joined those who had been transferred from TRANSFORM-1 and TRANSFORM-2 to enter the optimisation phase where the dose could be adjusted at either week 8 or 12. Dosing was then determined according to a complex set of rules, whereby effectiveness measured in a variety of ways that depended on number of weeks on treatment determined whether treatment was administered

weekly of fortnightly. Neither the concomitant OAD nor the comparator OAD were specified in the CEA: instead it was as a mix of eight OADs, according to market share. The company did perform a scenario analysis (see section B.3.4.4.9 of the CS) based on an NMA using data from TRANSFORM-3 of response and remission presented in Appendix D, which compared ESK-NS + OAD with various other comparators in the form of drug classes.[1, 17] For all other parameters, equivalence with OAD was assumed given that these parameters were estimated from STAR*D and the company stated that this study included OAD and other augmentation strategies in 1st and 2nd line TRD.

As stated in Section B.3.2.4 of the CS, the base-case time horizon was five years the analysis took the perspective of the NHS and PSS in England. Both costs and outcomes (life years and QALYs) were discounted at 3.5%.[1]

In terms of the effectiveness of ESK-NS + OAD versus OAD in the acute phase, response and remission values were estimated from TRANSFORM-2 with the adjustment then applied to the OAD + PBP-NS arm only. The adjustment is a reduction in the rates of response and remission estimated as the effect of a reduction in the number of clinic visits from eight in the trial to two in clinical practice, i.e. a reduction of six. In the continuation phase, the transition probabilities of response to remission were estimated by analysis of the SUSTAIN-1 data. The transition probabilities for loss of response (response to MDE) and relapse (remission to MDE in weeks 5 to 40) were stated to have been estimated from SUSTAIN-1 for ESK-NS + OAD and from STAR*D for OAD.[1] In the maintenance phase, the transition probabilities for recurrence (remission to MDE in weeks 41+) for both, ESK-NS + OAD and OAD, the data pooled from both study arms of the double-blind phase of SUSTAIN-1 was used. The effect of discontinuation for reasons other than loss of efficacy (not loss of response, relapse or recurrence) was to stop incurring the cost of ESK-NS and only incur the cost of OAD and to have no effect on QALYs because patients were assumed to remain in the remission or recovery state until loss of response, relapse or recurrence. It was assumed that patients would not discontinue OAD in any phase for any reason other than lack of response. In the acute phase, it was assumed that patients would not discontinue ESK-NS + OAD in the acute phase for any reason other than lack of response. In the continuation phase, discontinuation risk for other reasons was derived from SUSTAIN-1. In the maintenance phase, it was also assumed that 35.4% of patients were assumed to stop ESK-NS immediately upon achieving recovery, i.e. on being in the remission state after 40 weeks of treatment. This was the percentage of patients in SUSTAIN-1 who had ≤2 total number of MDD episodes, including the current episode.[56] For those patients who did not discontinue immediately, a four-week discontinuation risk of 25% for ESK-NS + OAD was stated to have been used during recovery. The company estimated the transition probabilities for each of three further lines of subsequent treatment based on evidence from STAR*D. This was also stated to be one source for the estimation, using clinical expert opinion, of the transition probabilities for the best supportive care treatment mix, i.e. for patients whose disease has failed all previous treatments (fifth-line TRD and onwards). Mortality effects were accounted for in the economic model based on two different sources. These were all-cause mortality risk, specific to age and gender, and an excess annual mortality for TRD, associated with suicide, of 0.47% linked to the MDE health state. It was assumed that half the excess mortality risk associated with suicide would still be present in the response state.

EQ-5D-5L was used to measure the quality of life of patients in the TRANSFORM-2 trial from which utility values were derived, one for each health state, MDE, response, remission and recovery, with the

latter two being assumed to be the same. Disutilities due to adverse events (AEs) were included as a scenario and values were obtained from a variety of sources.

The cost categories included in the model were costs associated with treatment (drug acquisition costs including subsequent therapies, cost of supervision of self-administration and post-administration monitoring), costs associated with disease management (costs of OAD), and costs associated with different health states. The cost per a single-use device that delivers a total of 28 mg of esketamine in two sprays (one spray per nostril) is £163, equating to a cost of £326 per 56 mg dose and £489 per 84 mg dose. The average number of sessions per week and devices per session in the acute phase were estimated based on TRANSFORM-2 trial, while for subsequent time-points they were derived from SUSTAIN-1 trial. The average treatment administration cost of esketamine was based on assumption that two nurses (one band 5 and one band 4) are needed for the supervision of self-administration of ESK-NS and that cohort of six patients will be concurrently supervised. All OADs with a market share greater than 3% of all treatments were included in the analysis. The average cost of OADS per four-week cycle was estimated using prescription cost analysis (page 170 in the CS) and market share information from IQVIA data (page 2 in the CS).[11] For specific drugs (duloxetine, escitalopram, sertraline, and venlafaxine) the daily doses were derived from TRANSFORM-2 trial, while a mid-point of the plausible dose ranges was chosen for other OADs. The analysis resulted in weighted average cost of £4.15 per four-week cycle. Since ESK-NS is incremental to OADs, the associated cost was equal on both sides. Resource use in the MDE, relapse, recurrence, and recovery states were based on a retrospective chart review of medical records of patients with TRD. Only cost of a GP contact (at £37 per contact) for all ESK-NS-associated AEs was considered in a scenario analysis.

Over a five-year time horizon, ESK-NS + OAD was associated with an additional 0.336 QALYs compared with OAD. The incremental drug cost for ESK-NS + OAD was £10,456; ESK-NS + OAD was estimated to have lower disease management costs, saving £8,243 compared with OAD. This resulted in an incremental cost difference of £2,213 and therefore a base-case incremental cost effectiveness ratio (ICER) of £6,582 per QALY. The effect of removing the adjustment for the placebo effect, consistent with the values of remission and relapse for OAD of 31.0% and 52.0% as opposed to the adjusted values of 18.0% and 34.0%, was to increase the ICER to £16,209. The company also performed analyses of combinations of various percentages of the unadjusted response and remission. Based on the data from the NMA, and using the data from TRANSFORM-2 adjusted for the placebo effect, the company conducted a scenario analysis for a set of comparators other than those in the company trials. In response to the request for clarification the company also presented the results base on the NMA estimates unadjusted for the placebo effect.

The ERG believes that the model structure seems plausible and responds appropriately to the critique in TA367.[9]

The population is broadly consistent with the NICE scope and the expected marketing authorisation.[16, 66] However, the maximum age in the trials (TRANSFORM-2 and SUSTAIN-1) used to inform the CEA, which is 64 years.[1] The ERG questions the applicability of TRANSFORM-2 to the age 65 years+ age group. It is also therefore questionable what the applicability of SUSTAIN-1 would be to the 65 years+ age group: unfortunately, there is no equivalent study in the older age group by which a comparison might be made. SUSTAIN-2 included older patients, but relapse was not measured and no separate subgroup analysis was provided.[1, 17] Therefore, given that the NICE scope has no upper age limit, in the clarification letter the ERG requested that the main cost effectiveness analysis (CEA), i.e. for age <65 years, informed by TRANSFORM-2 and SUSTAIN-1 be combined with that for age 65 years+, using TRANSFORM-3 as well as SUSTAIN-2. The company responded by submitting a new version

of the base-case model to include acute response and remission transition probabilities and utilities for MDE, response and remission/recovery states from both TRANSFORM-2 and TRANSFORM-3, weighted by % in each age group such that if set to 0% for age >65 years one gets the same result as in the original base-case.[3] This forms the starting point for the ERG base-case.

In terms of the intervention, the lack of clarity on dosing in TRANSFORM-2 and TRANSFORM-3 trials plus the complex dose changes in SUSTAIN-1 and SUSTAIN-2 mean that it is difficult to know how applicable to clinical practice the transition probabilities estimated from the trials would be. This basis for questionable applicability is in addition to that in terms of whether the data to inform those transition probabilities derived from patients were direct-entry or transferred-entry. In terms of the comparators, the ERG is convinced that the limitations of the NMA are sufficient to exclude those included comparators except in a scenario analysis. However, applicability to clinical practice of results would be highest in those patients who might be switched to one of the four OADs prescribed in the trials.

The ERG also notes that by 20 years the percentages of the cohort in the response, remission or recovery health states in the cohort treated with ESK-NS + OAD are equal to those in the cohort treated with OAD + PBO-NS. Therefore, from this point onwards there can be no further difference in cost or QALYs and thus no need to extend the time horizon beyond this point. The ERG therefore has adopted 20 years in the ERG base-case.

With regards to the effectiveness of ESK-NS +OAD versus OAD, the ERG argue that, whilst it might be the case that some of the placebo effect, however mediated, might continue into clinical practice, it is possible to reproduce it by increasing clinic visits even without esketamine and, on that basis, it is impossible to have confidence as to the size of any effect that might only apply to esketamine in clinical practice. Accordingly, the ERG base-case removes this adjustment and assumes an increase the cost of clinic visits for OAD to be identical to the monitoring cost of OAD in a scenario analysis. However, it remains unclear to the ERG how data were chosen from SUSTAIN-1 in order to estimate the transition probability of response to remission given that patients appear to enter SUSTAIN-1 from various sources, including either of the TRANSFORM-1 or TRANSFORM-2 or by direct entry. It also remains unclear to the ERG why STAR*D was chosen given that at least some patients who entered SUSTAIN-1 were originally randomised to OAD + PBO-NS in TRANSFORM-1 or TRANSFORM-2. In line with TA367 and given the absence of any comparative trial evidence, the ERG assumed there to be no difference in the loss of response and relapse transition probabilities in an ERG scenario.[9] The ERG considers that it is reasonable to assume no discontinuation during the acute phase and the rate during the continuation phase also appears to be reasonable given that it was estimated from the trial data albeit based on an arbitrary definition of stable and choice of exponential distribution. However, the rates of discontinuation in the maintenance phase were not based on any observed data, but instead on assumptions, despite the availability of SUSTAIN-1 data, which could have had a parametric curve fitted to extrapolate up to the time horizon. It is also not reasonable to assume that the treatment effect is maintained, i.e. no decrease in QALYs on discontinuing ESK-NS and continuing with only OAD. Although some continuation of effect post-discontinuation is not impossible, in the absence of any data as to the effect on relapse or recurrence or utility on discontinuation of ESK-NS, the ERG assumed no discontinuation for reasons other than loss of efficacy in the ERG base-case. To estimate the transition probabilities of subsequent therapy, although the company stated that they used STAR*D, their methods were unclear and the resulting values were much lower than those in STAR*D.[53] Given that the values from STAR*D were stated to have been adjusted to a four-weekly risk and that the model did not allow transition from MDE to response or remission over more than one cycle, the full effectiveness must have been underestimated. Given that patients were encouraged to switch treatment, if no response and

follow-up visits occurred every two months, the ERG believe it reasonable to assume that all response or remission occurred in the first cycle on starting treatment in an ERG scenario.[53] Therefore, for the ERG scenario, as also recommended by the committee of TA367, a decrease in response and remission was applied at each line of therapy by multiplying the values for OAD by a factor equal to the ratio of values in step 3 versus step 4 in STAR*D.[9, 53] The ERG used the same method of adjusting by line for loss of response and relapse in this ERG scenario. This was achieved by using the company estimated values, for loss of response, of 22.2% for first line TRD and 22.8% for second line TRD and, for relapse, of 6.8% for first line TRD and 12.8% for second line TRD.[3] Logically, the same method was used for BSC, given that BSC (fifth-line TRD) appears to be the same OAD mix as for all other lines of therapy. ERG considers that most of the effect to AEs will be during the monitoring phase and notes that the effect of inclusion of AEs is minimal and therefore not change has been made to the ERG base-case. The ERG noted that the implementation of MDE-associated mortality in the model differed from that described in the CS. However, the main problem with the estimation of mortality is the assumption by the company that risk of mortality will decrease with by treating with ESK-NS, given its differential risk of response and remission. This presumes that all of the excess mortality is removed by moving from the MDE to the remission state and half of it on moving to the response state. This also needs to be considered in the context of only three suicides in all the esketamine trials, which whilst they were considered unrelated to ESK-NS treatment, all occurred in patients treated with esketamine, see section 4.2.7). Also, as acknowledged by the committee, no mortality effect was included in TA367.[9] Therefore, the ERG assumed no effect on mortality of ESK-NS + OAD in the ERG base-case.

Although the ERG has been unable to validate the utility values used in the model, they do not believe that there is a better source and therefore there is no change to utility in the ERG base-case.

The assumption applied in the model that six patients will be concurrently supervised during self-administration seems to be not realistic. Therefore, the patient to nurse ratio is set to 1:1 in the ERG base-case. Although there will be no adjustment to OAD for the placebo effect in the ERG base-case (see section 5.2.6.1), the ERG consider that it is reasonable to attribute some of the effect on response and remission to be attributable to the extra clinic sessions. On this basis, the cost of clinic sessions for OAD is increased to the level for ESK-NS + OAD in an ERG scenario.

The result of the adjustments to the company base-case produced an ERG base-case with an ICER that was considerable higher than the company base-case, i.e. £62,078 instead of £7,699 (revised company base-case). It is important to note that this was a reflection of relatively conservative assumptions by the ERG regarding the treatment effect (difference between ESK-NS + OAD and OAD) at every stage in the model. Indeed, scenario analysis revealed that the ICER could be much higher, i.e. £148,650. Also, these assumptions were deemed, by the ERG, to be based on sound methodology, such as the removal of the placebo effect adjustment to reduce only the effectiveness of OAD in the acute phase. [redacted]. The scenarios were also aligned with opinion of the TA367 committee informed by clinical expert opinion, such as the removal of the treatment effect on relapse and loss of response and the increase in the effectiveness of subsequent therapies.[9]

In conclusion, the approach taken to form the ERG base-case and scenarios contrast very strongly with the assumptions made in the CS, which, at every stage, enhanced the treatment effect on the basis of no or very little comparative evidence and rather opaque exposition. In particular, no data were provided to support the lack of impact on effectiveness of discontinuing ESK and all of the evidence to inform the company base case came from differential data sources for the intervention and the comparator beyond the acute phase. Despite a request for clarification, it remains unclear why more data from the

SUSTAIN studies could not have been used to inform the relapse and loss of response rates for OAD. Finally, the method of estimating all transition probabilities beyond the acute phase is unclear, both the precise data used from SUSTAIN-1 to inform those for ESK-NS + OAD and the calculations used to transform the data from STAR*D to inform those for OAD.

8. End of life

According to section B.2.13.3 of the CS, this is not applicable.[1]

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Appendix 1: ERG search strategies

Additional limitations of the CS searches not covered in the main body of the report:

Clinical effectiveness

- The ERG noted an error in line combinations in both the original and update search for Embase reported in Appendix D.1.1; lines #141-144 appeared to be missing from the final combination in line #145. In their response the company confirmed that they had rerun the strategy correcting the initial error resulting in an additional 610 hits from this *"These were screened for trials investigating zotepine or ECT and no further relevant trials were identified. The 610 additional studies were excluded on the grounds of study design (n=536), intervention (n=14), population (n=13), comparator not of interest/did not influence network (n=28), and duplicate (n=19)."*[3]
- The ERG noted that no synonyms for esketamine were included in the strategies for acute management or ongoing maintenance (Appendix D), although Emtree subject headings were included. A brief search on Medline and Embase for esketamine and treatment- resistant depression with the additional terms ("s-ketamin" or "s-ketamine" or vesierra or Ketanest or Spravato) yielded no additional relevant studies.

ERG report – factual accuracy check response

Esketamine for treatment-resistant depression [ID1414]

Issue 1: Esketamine nasal spray's treatment duration

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG is not explicit about their rationale to assume no discontinuation for any other reasons than efficacy throughout all treatment phases and in particular the maintenance phase. This is contrary to the available evidence from clinical opinion and guidelines submitted in the company submission.	We wish to clarify if the ERG validated their assumption with any clinical opinion ahead of reaching their conclusions of no discontinuation for other reasons than efficacy. If this is not the case, then, the ERG report should be updated to reflect the available evidence.	The consequence of using the ERG's preferred approach is that the duration of continuous treatment with ESK-NS remains artificially inflated throughout the time horizon of the economic model, which is not aligned to the nature of the disease, recommendations in the clinical guidelines, and UK expert clinical opinion. We believe this is a factually inaccurate interpretation given the available evidence. A patient that has been stable in remission (absence of symptoms) for 4-9 months can be considered 'in recovery', and clinical guidelines recommend continuing treatment until that point. Once recovery is reached, the maintenance treatment phase aims to prevent recurrence of a new depressive episode. For a small proportion of patients who are at high risk of relapse, NICE CG90 recommends continuing treatment with OADs for up to 2	This is not a factual inaccuracy. It is essentially a difference of opinion. Whilst it is true that the company did elicit expert opinion as to the percentage of patients who might discontinue on achieving recovery, it is unclear in the minutes what the advisory board thought that the consequences might be. Indeed, there is a statement to suggest that discontinuation might actually be deleterious: "It was suggested that perhaps the biggest determinant for patient continuation or discontinuation beyond 9 months in remission is patient acceptability and budget pressures for the treatment administration." In other words, patients might actually be compelled to discontinue, the implication being that there is a concern that they might in fact relapse, thus negating the idea of discontinuation for reasons other

		years after they have reached remission. (See CS Document B, page 26 for more details). In TA367, the NICE Appraisal Committee heard from the clinical expert that, in England, about 30–50% of people experiencing their first MDE would stop treatment after 6 months, but that people experiencing a recurrent MDE would receive treatment for up to two years.	than lack of efficacy.
The following sentence needs to be amended to reflect the full assumptions in the economic model: *"For the remainder of patients, treatment with ESK-NS + OAD will be continued during the maintenance phase and discontinued"* ERG report page 25 and page 33	Proposed amendment: 'For the remainder of patients, treatment with ESK-NS +OAD will be continued during the maintenance phase and discontinued **over time. Based on UK expert opinion, a 4-week discontinuation risk of 25% for ESK-NS + OAD was used during recovery.'**	The quote from the CS may be misleading if not contextualised with the additional assumption.	The quotation has been expanded on pages 25 and 33 as requested by the company.
This following sentence needs to be amended to reflect the nature of the disease: "…chronic nature of the condition…" ERG report page 114	Proposed amendment: "… chronic **recurrent or episodic** nature of the condition…"	This sentence is a partially inaccurate description of the nature of the disease. It is well established that when remission has been achieved and sustained for a sufficient period of time, the risk of relapse falls.	Change made.

		Reaching recovery raises the possibility that treatment can be discontinued or, if treatment is continued, the aim is recurrence prevention (See CS Document B, page 174 for more details). Recurrence implies the start of a new depressive episode.	
The last sub-sentence in the following sentence is required to be deleted: "These assumptions were stated by the company to have been validated by expert clinical opinion, although no reference to any report was cited." ERG report page 119	Proposed amendment: "These assumptions were stated by the company to have been validated by expert clinical opinion"~~, although no reference to any report was cited.~~	This is a factual inaccuracy as the assumptions have been validated through the HTA advisory board held in June 2019, the minutes of which were submitted to NICE on 25th August.	Not a factual inaccuracy. The reference was not provided in the company submission. However, the ERG has added some text to recognize the advisory board minutes provided with the clarification letter response.
The sentence needs to be amended to make it factually correct: "The impact of discontinuation was to stop incurring the cost of ESK-NS and only incur the cost of OAD whilst having no effect on QALYs (because patients were assumed to remain in the remission state until loss of response, relapse or recurrence)."	Proposed amendment: "The impact of discontinuation for reasons other than loss of efficacy (not loss of response, relapse or recurrence) was ~~to stop incurring~~ **that** the cost of ESK-NS **was no longer incurred** and only ~~incur~~ the cost of OAD **was incurred** whilst having no effect on QALYs (because patients were assumed to remain in the ~~remission~~ **recovery** state	The health state description should be corrected and the possible health outcomes of patients in the recovery health state amended to make the sentence factually accurate.	A correction has been added to include the "recovery" health state.

ERG report page 119	until ~~loss of response, relapse or~~ recurrence).		
The following sentence needs to be amended to make it factually correct: "The effect of discontinuation for reasons other than loss of efficacy (not loss of response, relapse or recurrence) was to stop incurring the cost of ESK-NS and only incur the cost of OAD and to have no effect on QALYs because patients were assumed to remain in the remission state until loss of response, relapse or recurrence. ERG report page 143	Proposed amendment: "The effect of discontinuation for reasons other than loss of efficacy (not loss of response, relapse or recurrence) was ~~to stop incurring~~ **that** the cost of ESK-NS **was no longer incurred** and only ~~incur~~ the cost of OAD **was incurred** ~~and~~. **It was assumed that patients who discontinued ESK-NS for reasons other than loss of efficacy while in the recovery health state would** ~~have no effect on QALYs because patients were assumed to~~ remain in the ~~remission~~ **same** health state until ~~loss of response, relapse or~~ recurrence.	The health state description should be corrected and the possible health outcomes of patients in the recovery health state amended to make the sentence factually accurate.	A correction has been added to include the "recovery" health state.
The last sub-sentence in the following sentence is required to be deleted: "the rates of discontinuation in the maintenance phase were not based on any observed data, but instead on assumptions, despite the availability of SUSTAIN-1	Proposed amendment: "the rates of discontinuation in the maintenance phase were not based on any observed data, but instead on assumptions, ~~despite the availability of SUSTAIN-1 data~~"	The SUSTAIN-1 data is not appropriate to model rate of discontinuation in the maintenance phase. Given SUSTAIN 1 was a relapse prevention study, the objective of the study was to compare relapse between the study arms and therefore patients were not	Not a factual inaccuracy. Indeed, it is not clear that SUSTAIN-1 is unsuitable to estimate the rate of discontinuation given that patients did discontinue and, if as the company put it "…not necessarily … for reasons other than efficacy", then possibly for

data” ERG report page 145		necessarily discontinued for reasons other than efficacy in the study. It is therefore inappropriate to use SUSTAIN-1 to inform discontinuation in maintenance phase of the model. And importantly, SUSTAIN-1 data show a considerable reduction in risk of relapse after 24 weeks of maintenance therapy (corresponding to 36 weeks after the acute treatment phase) in patients from both treatment arms, indicating that patients have achieved stable remission (recovery) of the disease.	reasons other than efficacy. Also, it might be that lack of efficacy is the only reason for discontinuation.

Issue 2: The discontinuation of esketamine nasal spray in maintenance (recurrence prevention) phase

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
The following sentence needs to be amended to make it factually correct and clearer for the reader: “There was a lack of evidence to support there being no loss of efficacy on discontinuing ESK-NS and remaining only on OAD” ERG report page 19	Proposed amendment: “There **were no clinical data available** ~~was a lack of evidence~~ to support **the assumption of** there being no loss of efficacy on discontinuing ESK-NS in the **recovery health state** and remaining only on OAD. **The assumption was, however, discussed and validated by**	This is a factual inaccuracy as the assumption has been validated through the HTA advisory board held in June 2019, the minutes of which were submitted to NICE on 25th August.	Not a factual inaccuracy. It also appears that the members of the advisory board were not explicitly asked to validate the assumption of no loss of efficacy on discontinuing ESK-NS. Indeed, there is a statement to suggest that discontinuation might actually be deleterious: “It was suggested that perhaps the biggest

	four UK clinicians at an advisory board."		determinant for patient continuation or discontinuation beyond 9 months in remission is patient acceptability and budget pressures for the treatment administration." In other words, patients might actually be compelled to discontinue, the implication being that there is a concern that they might in fact relapse, thus negating the idea of discontinuation for reasons other than lack of efficacy.
"Such a difference is also inconsistent with the judgement of the committee in TA367" ERG report page 20	Proposed amendment: ~~"Such a difference is also inconsistent with the judgement of the committee in TA367"~~	The comparison with assumptions used in TA367 on discontinuation rules should be considered invalid since 1) vortioxetine is an OAD, 2) vortioxetine has not shown to be superior in efficacy versus an OAD in short-term studies, 3) the time horizon of the vortioxetine model was 24 months, and 4) vortioxetine has only been studied in a maintenance (relapse prevention) study versus a placebo in an MDD population.	Not a factual inaccuracy. It is true that ESK-NS is not an OAD. However, what this appraisal has in common with TA367 is the lack of comparative data on relapse.
The following sentence needs to be replaced to make it factually correct:	Proposed amendment: ~~"In particular, no evidence was provided to support the lack of~~	This is a factual inaccuracy as the assumption has been validated through the HTA advisory board	A change has been made to be more precise. This now reads: "In particular, no

"In particular, no evidence was provided to support the lack of impact on effectiveness of discontinuing ESK" ERG report page 21 and 146	~~impact on effectiveness of discontinuing ESK"~~ **"The assumption that patients who have received continuous treatment of ESK-NS + OAD for at least 10 months and have been in stable remission for nine months could discontinue ESK-NS (and continue OAD treatment) remained in the recovery health state was validated by four UK clinicians"**	held in June 2019, the minutes of which were submitted to NICE on 25th August.	data were provided to support the lack of impact on effectiveness of discontinuing ESK and all of the evidence to inform the company base case came from differential data sources for the intervention and the comparator beyond the acute phase."
The following sentence needs to be amended to make it factually correct: "…the assumption that at some point patients can discontinue ESK-NS with no reduction in efficacy." ERG report page 27	Proposed amendment: "…the assumption that ~~at some point~~ patients **who have received continuous treatment of ESK-NS + OAD for at least 10 months and have been in stable remission for nine months** can discontinue ESK-NS **(and continue OAD treatment) remained in the recovery health state**"	This sentence is an inaccurate description of the assumption.	Not a factual inaccuracy.
Additional information should be provided to make the following sentence reflective of the company submission and avoid erroneous conclusions from the reader:	Proposed amendment: *"..for ESK-NS, it was uncertain whether long-term* **[>4 weeks]** *treatment would be necessary as it was hypothesised that the antidepressant effect following*	The quote from the CS has been copied without any context, which would likely confuse the reader and as a result would lead to an inaccurate conclusion by the reader.	Not a factual inaccuracy.

"..for ESK-NS, it was uncertain whether long-term treatment would be necessary as it was hypothesised that the antidepressant effect following short-term ESK-NS treatment could be maintained with an OAD alone. The maintenance study, SUSTAIN-1, however, showed this to not be the case: patients who discontinued ESK-NS demonstrated a significantly greater relapse rate than those who remained on ESK-NS…" (p.51)." ERG report page 119	*short-term* **[4 weeks]** *ESK-NS treatment could be maintained with an OAD alone. The maintenance study, SUSTAIN-1, however, showed this to not be the case: patients who discontinued ESK-NS* **[after 12 weeks in stable remission or stable response]** *demonstrated a significantly greater relapse rate than those who remained on ESK-NS…"* (p.51)."		
The following sentence needs to be amended and a sentence added to make it factually correct: "In both phases, it is also unclear whether there might be a diminution in utility and thus a loss of QALYs even if relapse or recurrence do not occur. In the absence of any evidence as to the effect on relapse or recurrence or utility on discontinuation of ESK-NS" ERG report page 119	Proposed amendment: "In both phases, it is also unclear whether there might be a diminution in utility and thus a loss of QALYs even if relapse or recurrence do not occur. In the absence of any ~~evidence~~ **data** as to the effect on relapse or recurrence or utility on discontinuation of ESK-NS. **The assumption that patients who have received continuous treatment of ESK-NS + OAD for at least 10 months and have**	This is a factual inaccuracy as the assumption has been validated through the HTA advisory board held in June 2019, the minutes of which were submitted to NICE on 25th August.	Changed to be more precise.

	been in stable remission for nine months could discontinue ESK-NS (and continue OAD treatment) remained in the same health state was validated by four UK clinicians"		
The following sentence needs to be replaced to make it factually correct: "The company provided no evidence to show that those who discontinued treatment, even censoring for relapse, would not demonstrate any diminution in quality of life." ERG report page 139	Proposed replacement: **"The assumption that patients who have received continuous treatment of ESK-NS + OAD for at least 10 months and have been in stable remission for at least nine months could discontinue ESK-NS (and continue OAD treatment) remained in the same health state was based on SUSTAIN-1 data and validated by four UK clinicians**"	This is a factual inaccuracy as the assumption has been validated through the HTA advisory board held in June 2019, the minutes of which were submitted to NICE on 25th August. And importantly, SUSTAIN-1 data show a considerable reduction in risk of relapse after 24 weeks of maintenance therapy (corresponding to 36 weeks after the acute treatment phase) in patients from both treatment arms, indicating that patients have achieved stable remission (recovery) of the disease.	Changed to be more precise.
The following sentence needs to be replaced to make it factually correct: "They also provided no evidence that 35.4% of patients in the recovery phase would immediately discontinue with no	Proposed replacement: **"The assumption that 35.4% of patients who have received continuous treatment of ESK-NS + OAD for at least 10 months and have been in stable remission for nine months and were considered to**	This is a factual inaccuracy as the assumption has been validated through the HTA advisory board held in June 2019, the minutes of which were submitted to NICE on 25th August.	Changed to be more precise.

loss of quality of life." ERG report page 139	**be at low risk of relapse, could discontinue ESK-NS (and continue OAD treatment) remained in the same health state was validated by four UK clinicians**"		
The following sentence needs to be amended to make it factually correct: "Although some continuation of effect post-discontinuation is not impossible, in the absence of any evidence as to the effect on relapse or recurrence or utility on discontinuation of ESK-NS" ERG report page 145	Proposed amendment: "Although some continuation of effect post-discontinuation is not impossible, in the absence of any evidence ~~-~~as to the effect on ~~relapse or~~ recurrence or utility on discontinuation of ESK-NS"	This is a factual inaccuracy since relapse cannot take place when a patient is in the recovery health state. A relapse is a recurrence of depressive symptoms within the same depressive episode. Recurrence is the start of a new depressive episode, which can occur when a patient is in the recovery health state.	Changed to be more precise. The statement in the ERG report refers to discontinuation in both the continuation and maintenance phases.
The sentence needs to be replaced to make it factually correct: "In particular, no evidence was provided to support the lack of impact on effectiveness of discontinuing ESK" ERG report page 146	Proposed replacement: ~~"In particular, no evidence was provided to support the lack of impact on effectiveness of discontinuing ESK"~~ **"The assumption that patients who have received continuous treatment of ESK-NS + OAD for at least 10 months and have been in stable remission for nine months could discontinue ESK-NS (and continue OAD**	This is a factual inaccuracy as the assumption has been validated through the HTA advisory board held in June 2019, the minutes of which were submitted to NICE on 25th August.	See above

	treatment) remained in the recovery health state was validated by four UK clinicians"		

Issue 3: The placebo effect in the active comparator arm

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The following sentence needs to be amended: "Adjustment for placebo effect to the acute response or remission transition probabilities only for the comparator. This introduces a bias in favour of ESK-NS + OAD." ERG report page 19	Proposed amendment: "Adjustment for ~~placebo~~ **the treatment** effect to the acute response or remission transition probabilities only for the comparator ~~This introduces a bias in favour of ESK-NS + OAD"~~ **reduces the bias of OAD"**	The effect of additional clinic visits is not a placebo effect but should be considered a treatment effect. The adjustment presented in the CS is intended to reflect the effectiveness that might be achieved with OAD alone when used in NHS clinical practice and not in a randomised clinical trial (RCT) setting with six to eight more clinic visits in the first four weeks after treatment initiation than that seen in NHS clinical practice.	Not a factual inaccuracy. The 'placebo effect' is the effect on outcome observed in the trial that is additional to the effect of the studied treatment on both arms, i.e. it is not the difference in outcome between arms, which is the 'treatment effect'.
The second sentence of the following needs to be deleted: "Although the ERG is not convinced that the placebo response is explained entirely by the effect of additional clinic visits in the trials, it does consider that it	Proposed amendment: "Although the ERG is not convinced that the placebo response is explained entirely by the effect of additional clinic visits in the trials, it does consider that it is reasonable to attribute some of	OAD plus additional clinic sessions in the first four weeks after initiating treatment is not a relevant comparator since it is not a treatment option in NHS clinical practice or included in the NICE scope. This scenario would include an irrelevant comparator	Not a factual inaccuracy. The ERG is not asserting that this is part of the scope, but instead that, if additional sessions does improve health outcome, then perhaps its formal inclusion implies a different intervention to

is reasonable to attribute some of the effect on response and remission to be attributable to the extra clinic sessions. Therefore, it might be that the correct comparator should be OAD plus additional clinic sessions" ERG report page 20	the effect on response and remission to be attributable to the extra clinic sessions. ~~Therefore, it might be that the correct comparator should be OAD plus additional clinic sessions~~"	and is not appropriate for consideration.	that described in the scope. This might then imply the possibility of a comparator that is also different in a way that is equivalent to the intervention.
The following sentence needs to be amended: "Therefore, only removing the placebo effect for OAD + PBO while not removing it for ESK would likely overestimate the ESK treatment benefit. " ERG report page 34	Proposed amendment: "Therefore, only removing the ~~placebo~~ **treatment** effect for OAD + PBO while not removing it for ESK**-NS + OAD** would ~~likely over~~ **result in a more accurate** estimate **of** the ESK**-NS + OAD** treatment benefit. "	The effect of additional clinic visits is not a placebo effect but should be considered a treatment effect. The adjustment presented in the CS is intended to reflect the efficacy that might be achieved with OAD alone when used in NHS clinical practice and not in a randomised clinical trial (RCT) setting with six to eight more clinic visits in the first four weeks after treatment initiation than what is NHS clinical practice. For ESK-NS + OAD the same eight clinic visits in the first four weeks after treatment initiation will still be required in NHS clinical practice.	Not a factual inaccuracy. The 'placebo effect' is the effect on outcome observed in the trial that is additional to the effect of the studied treatment on both arms, i.e. it is not the difference in outcome between arms, which is the 'treatment effect'.
The following sentence needs to be amended to make it factually	Proposed amendment: "Any improvements in MADRS as	The adjustment presented in the CS is intended to reflect the efficacy that might be achieved	Not a factual inaccuracy. The purpose of the NMA is to

correct: "Any improvements in MADRS as a result of increased clinic visits would apply to both treatment arms in the trial so the post-hoc adjustment should have been made to both the esketamine and placebo arms." ERG report page 101	a result of increased clinic visits would apply to both treatment arms in the trial, **however the increased clinic visits is not reflective of NHS clinical practice when an OAD is initiated, but it will be when ESK-NS + OAD are initiated,** so the post-hoc adjustment should ~~have been~~ **be** made to ~~both the esketamine and~~ **only the OAD + PBO-NS** ~~placebo~~ arm~~s~~."	with OAD alone when used in NHS clinical practice and not in a randomised clinical trial (RCT) setting with six to eight more clinic visits in the first four weeks after treatment initiation than what is NHS clinical practice. For ESK-NS + OAD the same eight clinic visits in the first four weeks after treatment initiation will still be required in NHS clinical practice.	estimate the unbiased treatment effect of each comparator relative to each other and ESK-NS. Only by not applying any adjustment or by applying the adjustment equally to both arms in TRANSFORM-2 can this be achieved. There is a separate issue as to the external validity of these unbiased estimates given variation between the conditions in the trials and actual clinical practice, but this applies to all trials and the size or direction of any discrepancy is uncertain. In particular, it has not been demonstrated that such a discrepancy is explained completely by number of clinic visits or that it only applies to the TRANSFORM-2 trial.
The following sentence needs to be amended to make it factually correct: "Therefore, the comparator for this ESK + OAD + 8 clinic visits would be OAD + 8 clinic visits which is the comparator in the trial, thus negating the need for	Proposed amendment: "Therefore, the comparator for this ESK + OAD + 8 clinic visits would be OAD + 8 clinic visits which is **not reflective of NHS clinical practice** ~~the comparator in the trial~~, thus ~~negating~~ the need for ~~any~~ adjustment." This should also be amended on	OAD plus additional clinic sessions in the first four weeks after initiating treatment is not a relevant comparator since it is not a treatment option in NHS clinical practice or included in the NICE scope. This scenario would include an irrelevant comparator and is not appropriate for consideration.	Not a factual inaccuracy. The ERG is not asserting that this is part of the scope, see above for further details.

any adjustment." ERG report page 115	page 130.		
The following sentence needs to be amended to make it factually correct: "there is no basis for any given percentage reduction in either response of remission." ERG report page 136	Proposed amendment: "there is ~~no~~ **a** basis for ~~any given~~ percentage reduction in ~~either~~ response ~~of~~ **and** remission."	The clinical rationale for adjusting the treatment effect in the TRANSFORM-2 OAD + PBO-NS arm has been validated with 10 UK clinicians. The basis for quantification is mainly based on: a study undertaken by Posternak and Zimmerman. NICE CG90 describes this study as "a systematic review that provides suggestive evidence that the chance of responding to treatment with placebo is higher if monitoring is carried out more frequently in the first few weeks of treatment." Dunlop 2012 conducted a meta-analysis and found that the number of post-baseline visits was one of the significant positive predictors of clinical outcomes. • Posternak MA, Zimmerman M. Therapeutic effect of follow-up assessments on antidepressant and placebo response rates in antidepressant efficacy trials: meta-analysis. Br J Psychiatry.	Not a factual inaccuracy. Please see section 5.2.6.1 of the ERG report for the detailed argument supporting this statement.

		2007;190:287-92. • National Institute for Health and Care Excellence. Depression in adults: recognition and management (CG90). 2009. • Dunlop B.W.; Thase M.E., et al. A meta-analysis of factors impacting detection of antidepressant efficacy in clinical trials: the importance of academic sites. Neuropsychopharmacology. 2012;37,2830-6.	

Issue 4: The effectiveness of subsequent (2nd, 3rd and 4th) lines of TRD treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
It is not clear if the ERG double count remitters in their preferred approach to model subsequent treatments. "At this line in STAR*D, the probabilities of response and remission were reported to be 16.3% and 13.0%, which could therefore be compared to 3.54% + 0.86% (assuming that response is the sum of these two transition probabilities) and 0.86%, respectively."	Proposed amendment: "At this line in STAR*D, the probabilities of response and remission were reported to be 16.3% and ***3.3%*** ~~13.0%,~~ which could therefore be compared to 3.54% + 0.86% (assuming that response is the sum of these two transition probabilities) and 0.86%, respectively."	The ERG's method is not clear here, as to whether they have double counted those patients who remit as well as patients who respond. This is necessary given that these health states are mutually exclusive. This would bias the estimate of the cost-effectiveness of ESK-NS if this is the case. We suggest that this is further clarified in the ERG report.	Not a factual inaccuracy. It is reported in Table 4 of Rush 2006 that the remission and response rates were 13.0% and 16.3% respectively.

ERG report page 120			

Issue 5: The effectiveness of best supportive care

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
There is inconsistency between page 123 and page 145 in the ERG report, suggesting a possible lack of understanding of the source of data used in the CS for the BSC: ERG Report page 121: "Transition probabilities are attributed to an HTA monograph by Edwards 2013 supplemented by methodological advice from the authors of the HTA as to how clinical opinion was derived" This contrasts with the following statement on page 143, where the ERG states: "The company estimated the transition probabilities for each of three further lines of subsequent treatment based on evidence from STAR*D. This was also stated to be the source for the transition probabilities for the best	Proposed amendment: "The company estimated the transition probabilities for ***the best supportive care treatment mix i.e. for patients whose disease has failed all previous treatments (fifth-line TRD and onwards) from the HTA monograph by Edwards 2013, supplemented by methodological advice from the authors of the HTA."*** ~~each of three further lines of subsequent treatment based on evidence from STAR*D. "This was also stated to be the source for the transition probabilities for the best supportive care treatment mix, i.e. for patients whose disease has failed all previous treatments (fifth-line TRD and onwards).~~	The statement from the ERG on pg.145 is factually inaccurate. As recognised by the ERG on pg.123, transition probabilities to inform the BSC treatment phase are attributed to an HTA monograph by Edwards 2013. The Edwards et al data was further validated by clinical expert opinion at an advisory board. This presents the best source of data to inform the efficacy data in the BSC treatment phase rather than trying to extrapolate data the treatment effect from the STAR*D study.	The text in section 7.4 (page 143) has been aligned with the text on page 123 (page 124 of the revised report).

supportive care treatment mix, i.e. for patients whose disease has failed all previous treatments (fifth-line TRD and onwards)."			
On the following pages in the ERG report it is incorrectly stated that the data used to inform the BSC treatment phase of the model has not been validated. ERG report page 121 "There is no way of validating whether the assumptions and adjustments are appropriate". Similarly, the ERG states on page 121 "…validation as evidenced by Janssen data on file was not provided for the ERG"	Proposed replacements: ~~"There is no way of validating whether the assumptions and adjustments are appropriate"~~ **"Validating these assumptions with clinicians is appropriate"** ~~'validation as evidenced by Janssen data on file was not provided for the ERG'~~ **"validation as evidenced by Janssen data on file was provided to the ERG".**	Please replace these statements as these are factually inaccurate. The assumptions have been validated through an advisory board, attended by four UK clinicians, of which the minutes were previously submitted to NICE and the ERG.	The sentence about Janssen data on file has been deleted. However, it still remains unclear how these BSC parameters were estimated.

Issue 6: Effectiveness of oral antidepressants beyond the acute phase

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
The ERG state that it was not clear which data from SUSTAIN-1 was used to estimate the effectiveness beyond the acute	Proposed amendments: "Finally, the method of estimating all transition probabilities beyond	In the response to the ERG clarification questions, the following was provided as clarification (clarification	Not a factual inaccuracy. In particular, it remains unclear as to the history of the patients in SUSTAIN-1 used for the analysis

phase: "Finally, the method of estimating all transition probabilities beyond the acute phase is unclear, both the precise data used from SUSTAIN-1 to inform those for ESK-NS + OAD and the calculations used to transform the data from STAR*D to inform those for OAD." ERG Report, page 21 and page 146/7	the acute phase ~~is unclear, both the precise data used~~ are based on ~~from~~ SUSTAIN-1 to inform those for ESK-NS + OAD and the calculations used to transform the data from STAR*D to inform those for OAD."	response, submitted on 25th August): "At the end of the optimisation phase, subjects in stable remission and those with stable response were eligible to continue into the randomised, double-blind phase of SUSTAIN-1. It was the data from this treatment phase of SUSTAIN-1 that were used to inform the transition probabilities from response to remission, risk of loss of response, and risk of relapse for ESK-NS + OAD." Please see the CS Document B Section 3.2.9.2.2. for further information.	given that some came from TRANSFORM-1 some entered directly, as opposed to having come from TRANSFORM-2.
The ERG state that it was not clear which data from SUSTAIN-1 was used to estimate the effectiveness beyond the acute phase: "In spite of an ERG request for clarification, the company did not provide any further details.[3, 18]" ERG report page 118 "It was also unclear to the ERG why STAR*D was chosen given that at least some patients who	Proposed amendments: Page 118: ~~In spite of an ERG request for clarification, the company did not provide any further details~~ Page 118: "It was also unclear to the ERG why STAR*D was chosen given that at least some patients who	Janssen provided explanation in the NICE Decision Problem form, NICE Checkpoint Meeting Form, original NICE CS and further response to Clarification Questions to the ERG so these sentences are factually incorrect.	Not a factual inaccuracy. In particular, it remains unclear as to the history of the patients in SUSTAIN-1 used for the analysis given that some came from TRANSFORM-1 some entered directly, as opposed to having come from TRANSFORM-2.

entered SUSTAIN-1 were originally randomised to OAD + PBO NS in TRANSFORM 1 or TRANSFORM 2. Therefore, there should have been some patients who had been observed to have lost response or relapsed whilst on OAD + PBO NS. Indeed, the CONSORT diagram (Figure 11 in Appendix D of the CS) shows that 86 patients (including 48 from TRANSFORM 2) continued to be followed-up and, of these, 55 (33 from TRANSFORM 2) became stable remitters and responders during the optimisation phase with only one loss to follow-up beyond this phase. The company did not provide any additional clarification***[3]"*** ERG report page 118 "Despite a request for clarification, it remains unclear why more data from the SUSTAIN studies could not have been used to inform the relapse and loss of response rates for OAD. Finally, the method of estimating all transition probabilities beyond the acute phase is unclear, both the	entered SUSTAIN-1 were originally randomised to OAD + PBO NS in TRANSFORM 1 or TRANSFORM 2. Therefore, there should have been some patients who had been observed to have lost response or relapsed whilst on OAD + PBO NS. Indeed, the CONSORT diagram (Figure 11 in Appendix D of the CS) shows that 86 patients (including 48 from TRANSFORM 2) continued to be followed-up and, of these, 55 (33 from TRANSFORM 2) became stable remitters and responders during the optimisation phase with only one loss to follow-up beyond this phase. ~~The company did not provide any additional clarification~~.[3]" Page 146: ~~Despite a request for clarification, it remains unclear why more data from the SUSTAIN studies could not have been used to inform the relapse and loss of response rates for OAD. Finally, the method of estimating all transition probabilities beyond the acute phase is unclear, both the precise data used from SUSTAIN-1 to~~		

precise data used from SUSTAIN-1 to inform those for ESK-NS + OAD and the calculations used to transform the data from STAR*D to inform those for OAD." ERG report page 146	~~inform those for ESK-NS + OAD and the calculations used to transform the data from STAR*D to inform those for OAD.~~		
The problem identified above results in a factually inaccurate conclusion by the ERG, upon which the ERG takes an approach in the scenario which is not appropriate. The following sentence need amendment to make it factually accurate: "It also remains unclear to the ERG why STAR*D was chosen given that at least some patients who entered SUSTAIN-1 were originally randomised to OAD + PBO NS in TRANSFORM 1 or TRANSFORM 2. In line with TA367 and given the absence of any comparative trial evidence, the ERG assumed there to be no difference in the loss of response and relapse transition probabilities in an ERG scenario." ERG report page 145	Proposed amendment: ~~"It also remains unclear to the ERG why STAR*D was chosen given that at least some patients who entered SUSTAIN-1 were originally randomised to OAD + PBO-NS in TRANSFORM-1 or TRANSFORM-2. In line with TA367 and given the absence of any comparative trial evidence,~~ The ERG assumed there to be no difference in the loss of response and relapse transition probabilities in an ERG scenario."	The company provided a rationale in the CS and in the response to the clarification questions on why STAR*D was the most appropriate source to inform the effectiveness of OAD beyond four weeks. The company also provided comparative data from SUSTAIN-1 as a scenario analysis, see CS Document B Section B.3.4.4.8. The conclusion reached by the ERG is therefore factually inaccurate.	Not a factual inaccuracy. However, to acknowledge the scenario analysis, the following text has been inserted in Section 5.2.6.2: "The company did conduct a scenario analysis (Section B.3.4.4.8) that was reported to have used SUSTAIN-1 to inform response and relapse. However, the precise data used was not clear, appearing to have been from only those patients who had received ESK-NS + OAD and then been randomised for a second time to OAD only."

The following sentence needs to be amended to make it factually correct: "…and all of the evidence came from differential data sources for the intervention and the comparator beyond the acute phase." ERG report page 146 and page 21	Proposed amendment: ~~"…and all of the evidence came from differential data sources for the intervention and the comparator beyond the acute phase."~~	This is a factual inaccuracy and needs to be deleted. The ERG claims that differential data sources were used for data beyond the acute phase, however, a scenario was provided in the CS in Section B.3.4.4.8 where the evidence for the intervention and comparator beyond the acute phase were both derived from SUSTAIN-1.	Amended to take account of the scenario analysis in section B.3.4.4.8 of the CS.

Issue 7: The data to inform the effect on mortality

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
The following interpretation of the estimation of mortality is factually incorrect: "However, the main problem is the assumption by the company that risk of mortality will decrease when treating with ESK-NS. This presumes that all of the excess mortality is removed by moving from the MDE to the remission state and half of it on moving to the response state. This is contrary to evidence of three suicides in trials all of which	Both sentences are factually incorrect and proposed to be removed from the report: ~~"However, the main problem is the assumption by the company that risk of mortality will decrease when treating with ESK-NS. This presumes that all of the excess mortality is removed by moving from the MDE to the remission state and half of it on moving to the response state. This is contrary to evidence of three suicides in trials all of which~~	Both sentences are factually incorrect. The ESK-NS clinical development programs were not designed to provide comparative evidence on mortality (including completed suicide) between ESK-NS + OAD and OAD + PBO-NS. Completed suicides were recorded as a safety endpoint. The three completed suicides are from the trials 2003, SUSTAIN-2 and SUSTAIN-3. The completed suicide in 2003 occurred three	Not a factual inaccuracy. However, the text has been amended to provide greater clarity and context.

occurred in patients treated with esketamine” ERG report page 123 “However, the main problem with the estimation of mortality is the assumption by the company that risk of mortality will decrease with by treating with ESK-NS.” ERG report page 146	~~occurred in patients treated with esketamine”~~ “~~However, the main problem with the estimation of mortality is the assumption by the company that risk of mortality will decrease with by treating with ESK-NS.”~~	weeks after the last dose of ESK-NS during the post treatment follow-up phase. SUSTAIN-2 and SUSTAIN-3 are single arm open-label studies. Based on the severity of patients’ underlying illness, and the lack of a consistent pattern, the suicides were considered unrelated to ESK-NS treatment. As the trials do not provide comparative efficacy on completed suicide between ESK+AD and PBO+AD, we assumed additional mortality from completed suicide by health states and not by treatment arms. Additional mortality for completed suicide was assumed for patients in MDE and response (half as in MDE).	
The following statement is misleading when quoted without context: “This also needs to be considered in the context of only three suicides in all the esketamine trials, all occurring in patients treated with esketamine” ERG report page 146	The proposed amendment is below: “This also needs to be considered in the context of only three suicides in all the ~~esketamine~~ **ESK-NS** trials, all occurring in patients treated with **ESK-NS** ~~esketamine~~. **Based on the severity of patients’ underlying**	This amendment is required to contextualise the rate of completed suicides between the two arms in the clinical development programme. See Section B.2.10 of the CS for further explanation.	Not a factual inaccuracy. However, text has been added to provide this context.

	illness, and the lack of a consistent pattern, the suicides were considered unrelated to ESK-NS treatment."		

Issue 8: Incorrect interpretation of the license indication, dosing (and more clinical topics)

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
The following sentence needs to be amended to make it factually correct: "The company also specified that response and remission were defined more restrictively than in TRANSFORM-2" ERG report page 117	Proposed amendment: "The company also specified that response and remission were defined ~~more restrictively than~~ **as** in TRANSFORM-2"	The definitions of response and remission in TRANSFORM-2 and SUSTAIN-1 are the same.	Not a factual inaccuracy. However, text has been added to provide this context.
ERG report Title: ***Esketamine for treatment-related depression*** ERG report page 1 This error also occurs on page 23, page 45, page 60, page 101.	Proposed amendment: Esketamine ***nasal spray*** for treatment~~-related~~ ***resistant*** depression in each instance.	This reflects the NICE Scope and proposed licensed indication	This has now been amended.
ERG report page 2: Wolff R, Armstrong N, Ryder S, Buksnys T, Fayter D, Swift S, Worthy G, Noake C, Kleijnen J. Esketamine for ***treatment-related***	Proposed amendment: Wolff R, Armstrong N, Ryder S, Buksnys T, Fayter D, Swift S, Worthy G, Noake C, Kleijnen J. Esketamine for treatment~~-related~~ resistant depression: a Single	This reflects the NICE Scope and proposed licensed indication	This has now been amended.

depression: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2019.	Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2019.		
The ERG noted a lack of clarity on dosing in the included trials throughout the ERG report. "As discussed in section 1.3, the ERG noted a lack of clarity on dosing in the included trials which might impact on the generalisability of these trials." ERG report page 14 "The precise rules of determining efficacy and tolerability were not reported in the CS or Appendix M.[1, 17] In TRANSFORM-3, the starting dose was 28 mg which could also be increased to 84 mg by Day 25 without any specification of the precise rules." ERG report page 111 "Regarding the intervention, ESK-NS + OAD, the ERG is concerned with the lack of clarity on dosing in TRANSFORM-2 and	The relevant sentences relating to the lack of specific dosing rules should be removed from the ERG report. Page 14: ~~As discussed in section 1.3, the ERG noted a lack of clarity on dosing in the included trials which might impact on the generalisability of these trials.~~ Page 111: '~~The precise rules of determining efficacy and tolerability were not reported in the CS or Appendix M.[1, 17]~~ In TRANSFORM-3, the starting dose was 28 mg which could also be increased to 84 mg by Day 25 ~~without any specification of the precise rules.'~~ Page 19: ~~Regarding the intervention, ESK-NS + OAD, the ERG is concerned with the lack of clarity on dosing in TRANSFORM-2 and TRANSFORM-3 trials plus the complex dose changes in SUSTAIN-1 and SUSTAIN-2,~~	Table 83 in Appendix M of the CS states the ESK-NS dose titration schedule during the double-blind induction phase. As noted in the company response to the clarification questions, dose adjustments are based on efficacy and tolerability. This is aligned to the wording expected to be included in the SmPC and therefore expected use in clinical practice. The ERG is concerned that the dosing in the included trials may not be generalisable to real world clinical practice. There were no specific rules included in the TRANSFORM-2 and TRANSFORM-3 trials, so that the dosing may emulate real world clinical practice.	Not a factual inaccuracy. There remains a lack of clarity in dosing not least because there were apparently no specific rules.

TRANSFORM-3 trials plus the complex dose changes in SUSTAIN-1 and SUSTAIN-2, which mean that it is difficult to know how applicable to clinical practice the transition probabilities estimated from the trials would be." ERG report page 19 "The ERG requested clarity on the criteria by which dose was determined in TRANFORM-2 (applicable also TRANSFORM-3) to which the company responded by stating that "the intention was to emulate real-world clinical practice, thus there was no prescriptive algorithm".[3, 18] The continued lack of clarity on dosing in TRANSFORM-2 and TRANSFORM-3 trials plus the complex dose changes in SUSTAIN-1 and SUSTAIN-2 mean that it is difficult to know how applicable to clinical practice the transition probabilities estimated from the trials would be (see Section 5.2.6)." ERG report page 113	~~which mean that it is difficult to know how applicable to clinical practice the transition probabilities estimated from the trials would be.~~ Page 113: The ERG requested clarity on the criteria by which dose was determined in TRANFORM-2 (applicable also TRANSFORM-3) to which the company responded by stating that "the intention was to emulate real-world clinical practice, thus there was no prescriptive algorithm".[3, 18] ~~The continued lack of clarity on dosing in TRANSFORM-2 and TRANSFORM-3 trials plus the complex dose changes in SUSTAIN-1 and SUSTAIN-2 mean that it is difficult to know how applicable to clinical practice the transition probabilities estimated from the trials would be (see Section 5.2.6).'~~ Page 142: "~~In TRANSFORM-2 the precise rules of determining efficacy and tolerability were not reported in the CS or Appendix M~~. In TRANSFORM-3, the starting dose was 28 mg which could also		

“In TRANSFORM-2 the precise rules of determining efficacy and tolerability were not reported in the CS or Appendix M. In TRANSFORM-3, the starting dose was 28 mg which could also be increased to 84 mg by day 25 without any specification of the precise rules.” ERG report page 142 “In terms of the intervention, the lack of clarity on dosing in TRANSFORM-2 and TRANSFORM-3 trials plus the complex dose changes in SUSTAIN-1 and SUSTAIN-2 mean that it is difficult to know how applicable to clinical practice the transition probabilities estimated from the trials would be. This basis for questionable applicability is in addition to that in terms of whether the data to inform those transition probabilities derived from patients were direct-entry or transferred-entry”	be increased to 84 mg by day 25 ~~without any specification of the precise rules.”~~ Page 145: ~~In terms of the intervention, the lack of clarity on dosing in TRANSFORM-2 and TRANSFORM-3 trials plus the complex dose changes in SUSTAIN-1 and SUSTAIN-2 mean that it is difficult to know how applicable to clinical practice the transition probabilities estimated from the trials would be. This basis for questionable applicability is in addition to that in terms of whether the data to inform those transition probabilities derived from patients were direct-entry or transferred-entry’~~		

ERG report page 145			
The following sentence needs to be deleted: "No comparative data was provided for the induction phase and the optimisation phase of SUSTAIN-1" ERG report pages 13, 86, 102,	This sentence needs to be deleted: "~~No comparative data was provided for the induction phase and the optimisation phase of SUSTAIN-1"~~	The data is available in the ESKETINTRD3003 CSR, which was submitted with the CS.	This sentence has now been deleted.
The following sentence needs to be amended to make it factually accurate: "All searches for health-related quality of life studies were limited to papers published after 2016, these searches were intended to identify any evidence published since the NICE clinical guideline CG90" ERG report page 106	Proposed amendment: "All searches for health-related quality of life studies were limited to papers published after 2016, these searches were intended to identify any evidence published since the ***draft update of*** NICE clinical guideline CG90"	This statement should be amended to reflect the draft update of NICE CG90	This has now been amended.
The following sentence needs to be amended to make it factually accurate: "The company did perform a scenario analysis (see section B.3.4.4.9 of the CS) based on an NMA using data from TRANSFORM-3 of response	Proposed amendment: "The company did perform a scenario analysis (see section B.3.4.4.9 of the CS) based on an NMA using data from TRANSFORM-~~3~~***2*** of response and remission presented in Appendix D"	Incorrect trial quoted	Text has been amended.

and remission presented in Appendix D" ERG report page 143			
The following sentence needs to be amended to make it factually accurate: "equivalence with OAD was assumed given that these parameters were estimated from STAR*D and the company stated that this study included all of the comparators" ERG report page 113	Proposed amendment: "equivalence with OAD was assumed given that these parameters were estimated from STAR*D and the company stated that ~~this study included all of the comparators~~ **STAR*D included OAD and other augmentation strategies in 1st and 2nd line TRD."** This should also be amended on page143 of the ERG report: "For all other parameters, equivalence with OAD was assumed given that these parameters were estimated from STAR*D and the company stated that ~~this study included all of the comparators~~ **STAR*D included OAD and other augmentation strategies in 1st and 2nd line TRD."**	This change is necessary as the STAR*D trial included OAD and other augmentation strategies, as reported in pg.48 of the CS (Form B).	Amended accordingly.
The following sentence needs to be amended to make it factually accurate: "However, for response and remission, the results for	Proposed amendment: However, for response and remission, the **absolute** results for TRANSFORM-3 were much lower **for both arms**. Day 28	The ERG has not interpreted the results of TRANSFORM-3 correctly. The relative effectiveness of ESK-NS was greater in TRANSFORM-3, with	This is not a factual inaccuracy. It is more common to report the treatment effect in terms of the relative risk than in term of the risk difference. However, the

TRANSFORM-3 were much lower….. As can be seen, the risk differences were also lower for TRANSFORM-3 suggesting that, although ESK + OAD was still effective, its effectiveness was not only lower in absolute terms, but lower relative to OAD" ERG report page 31	risks of remission and response (ESK + OAD vs. OAD + PBO-NS) were: 69.3% vs. 52.0% and 52.5% vs. 31.0% for TRANSFORM-2. For TRANSFORM-3 these were: 27.0% vs. 13.3% and 17.5% vs. 6.7%, respectively. ~~As can be seen, the risk differences were also lower for TRANSFORM-3 suggesting that, although ESK + OAD was still effective, its effectiveness was not only lower in absolute terms, but lower relative to OAD~~ **The relative effectiveness of ESK-NS was greater in TRANSFORM-3, with more than double the risk of remission and almost triple the risk of response.**	more than double the risk of remission and almost triple the risk of response. This is significant considering the difficult to treat population which is often not studied in clinical trials.	latter is more meaningful in this case because it is the absolute values that are inputs in the cost-effectiveness model, as opposed to a relative risk plus a baseline value. Indeed, the effect of replacing the values for remission from TRANSFORM-2 with those from TRANSFORM-3 is to increase the ICER, which indicates a decrease in the effectiveness of ESK-NS, which is in turn consistent with what is shown by the risk difference.
The following sentence needs to be amended to make it factually accurate regarding the results of the TRANSFORM-1 trial: "However, these improvements did not reach statistical significance and of limited clinical value." ERG report page 87	Proposed amendment: However, these improvements did not reach statistical significance ~~and of limited clinical value.~~	Statistical significance was not achieved for the primary endpoint; nevertheless, the treatment effect (MADRS) for both esketamine/antidepressant groups exceeded what has been considered clinically meaningful for approved antidepressants versus placebo.	The proposed amendment has been made.

Issue 9: Modelling interpretation errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG suggest psychological therapy is a comparator: "No non-pharmacological treatments, such as psychological therapy, were included as comparators (without concomitant pharmacological treatment)." ERG report page 113	Proposed amendment: ***"Apart from ECT, no other*** non-pharmacological treatments~~, such as psychological therapy,~~ were included as comparators (without concomitant pharmacological treatment)."	This statement requires amendment for two reasons: Firstly, ECT, a non-pharmacological treatment, was included as a comparator. Secondly, psychological therapies were not included in the list of comparators in the final scope issued by NICE.	Not a factual inaccuracy. ECT was not included as a comparator in the cost-effectiveness analysis and best supportive care could be reasonably presumed to include psychological therapy.
The ERG misquotes the briefing provided to NICE for NICE Early Scientific Advice in 2013, and do not provide further context (i.e. the clinical development programme) upon which the advice from NICE was provided. "The ERG notes that the company originally intended to use data from several trials (not just TRANSFORM-2) to generate utility values. "Utility values for the model will be derived using the patient reported EQ5D administered during the 3 clinical	Proposed amendment: "~~The ERG notes that the company originally intended to use data from several trials (not just TRANSFORM-2) to generate utility values. "Utility values for the model will be derived using the patient reported EQ5D administered during the 3 clinical trials. Other values to populate the model will be sourced from the literature. In the acute trials, the EQ5D will be administered at Days 1, 4, 8, 15, 22 of the double-blind phase as well as at the end~~	Whilst this is a direct quote from the NICE Early Scientific Advice document, the proposed clinical trial programme submitted to NICE in 2013 differed substantially from the actual clinical development programme subsequently realised for ESK-NS five years later. As NICE state, "the advice given by NICE is based on the questions and documentation submitted, and the scientific knowledge publicly available at the time of the advice, and cannot account for future changes and developments in	Not a factual inaccuracy.

trials. Other values to populate the model will be sourced from the literature. In the acute trials, the EQ5D will be administered at Days 1, 4, 8, 15, 22 of the double-blind phase as well as at the end of the study. In the maintenance trial, the EQ5D score will be collected on a monthly basis, as well as at the time of treatment discontinuation" ERG report page 126	~~of the study. In the maintenance trial, the EQ5D score will be collected on a monthly basis, as well as at the time of treatment discontinuation"~~	scientific knowledge or regulatory requirements."	
The following sentence needs to be amended to make it factually accurate: "the ERG base-case removes this adjustment and assumes an increase the cost of clinic visits for OAD to be identical to the monitoring cost of OAD" ERG report page 145 and page 116	Proposed amendment: "the ERG base-case removes this adjustment and, ***only in a scenario,*** assumes an increase the cost of clinic visits for OAD to be identical to the monitoring cost of OAD"	This is a factual inaccuracy as the ERG base case does not include the increase in cost of clinic visits for OAD to be identical to the monitoring cost of OAD.	Corrections have been made.

Issue 10: Other typographical errors

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
ERG report page 52:	Proposed amendment:	Incorrect numbers	The data on patient characteristics for TRANSFORM-

Number of patients included in the studies are inaccurate: N=223 for TRANSFORM-2 N=137 for TRANSFORM-3	N=227 for TRANSFORM-2 N=138 for TRANSFORM-3		2 were based on Table 12 of the CS which gives the total number as 223 and percentages reflect this total. No change needed. The total for TRANSFORM-3 has been changed to 138.
ERG report page 51: "In the trials, the CS patients had to be adherent"	Proposed amendment: "In the trials, the ~~CS~~ patients had to be adherent"	Incorrect wording.	Typo corrected.
ERG report page 14 Section 1.2 Third paragraph "Furthermore, the ERG noticed the short-term nature of the terms which is a concern, especially for safety-related outcomes"	Proposed amendment: "Furthermore, the ERG noticed the short-term nature of the **terms** which is a concern, especially for safety-related outcomes" The word terms should be replaced with the word **trials.**	The incorrect word has been used.	Typo corrected.
ERG report page 24 "At this stage, ESK-NS is a comparator for other treatments including atypical antidepressants (ADs), serotonin–norepinephrine reuptake inhibitor (SNRI), TCA, MAOI or other SSRI and for lithium or other antipsychotic and electroconvulsive therapy (ECT)."	Proposed amendment: "and for ***augmentation with either*** lithium or other antipsychotic and electroconvulsive therapy (ECT)."	Incorrect wording.	Amendment made.

ERG report page 27 "ESK-NS in combination with an SSRI or SNRI for treatment resistant major depressive disorder in adults who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode". text on "intervention" row of table	Proposed amendment: In the company response to clarification questions, the company stated the label wording would likely change to: "[ESK-NS], in combination with an SSRI or SNRI, is indicated for adults with treatment-resistant major depressive disorder, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode."	The ERG have misquoted the company response to clarification questions.	The quote has now been corrected.
ERG report page 28, Table 3.1 column 4	The reference for Johnston et al 2019 has been incorrectly cited as reference 13131313 this should be reference 13.	Error with the referencing.	Now corrected.
ERG report page 31, first paragraph	The ERG correctly state that the change in MADRS from baseline is the primary efficacy outcome in TRANSFORM-1 but then proceed to describe subgroups of patients as "marked" or "extreme" which are classifications of SDS, not MADRS. Further, the ERG then proceeds to describe the point estimate for	The ERG have mixed their descriptions of MADRS and SDS endpoints as well as quoted LOCF where Janssen have presented observed cases data for the reasons outlined in Section B.2.4.3 of the company submission.	In response, the relevant section has been removed.

	"moderate" patients as being in favour of OAD + PBO-NS. While this is true based on LOCF ANCOVA analysis, the company submission, for the reasons described in Section B.2.4.3 focused on observed cases data, based on which, the point estimate for "moderate" patients favours ESK-NS, consistent with "marked" and "extreme" patients.		
ERG report page 33 "The main trials in this appraisal compared ESK-NS + OAD to placebo (PBO-NS) and OAD."	Proposed amendment: "The main trials in this appraisal compared ESK-NS + OAD to placebo **nasal spray** (PBO-NS) and OAD."	Incorrect wording.	Wording corrected.
ERG report page 39 "For the ongoing maintenance SR, the company included all the classes of medications indicated in the scope (SSRIs, SNRIs, TCAs, MAOIs, vortioxetine, augmentation treatments (with anti-psychotics), combination treatments (with lithium), ECT and BSC"	Proposed amendment: "For the ongoing maintenance SR, the company included all the classes of medications indicated in the scope (SSRIs, SNRIs, TCAs, MAOIs, vortioxetine, augmentation treatments (with anti-psychotics), ~~combination~~ **augmentation** treatments (with lithium), ECT and BSC"	Incorrect wording. Lithium treatment is considered an augmentation therapy rather than a combination therapy.	Wording amended.
ERG report page 44, paragraph 3	The ERG state the primary outcome of TRANSFORM-2 was	Incorrect wording.	Wording amended.

	relapse based on MADRS when in fact it was response based on MADRS.		
ERG report page 44, paragraph 4	The ERG state 775 patients were enrolled in SUSTAIN-1. The correct number is 705 patients.	Incorrect wording.	Typo corrected.
ERG report page 54, Table 4.8	Janssen are unsure as to why the value “7 (5.1)” is highlighted in yellow.		Highlighting has been removed.
ERG report page 61, Table 4.12	Adjusted response rate for OAD + PBO-NS is given as 34.0% but should actually be 31.0%.	Incorrect wording.	Not a factual inaccuracy. There was a discrepancy in the CS, i.e. between Figure 15 (as well as the supporting text) and Table 45. The ERG based the reported values on Table 45 of the CS, as indicated in the footer of Table 4.12
ERG report page 63, Table 4.13	N=62 for the OAD + PBO-NS stable responders population size should actually be N=59.	Incorrect wording.	Typo corrected
ERG report page 66, Table 4.14	The ERG includes GAD-7 in the list of outcomes for TRANSFORM-3 and states “NR” (i.e. not reported) in each table cell implying Janssen did not present this data when in fact GAD-7 was not an outcome that	Misleading inclusion of a trial outcome in a results table.	Not a factual inaccuracy. Some outcomes which were defined in the final scope, such as GAD-7, cognitive dysfunction, hospitalisation and sleep quality, were not measured and hence

	was assessed in TRANSFORM-3.		not reported in the trial.
ERG report page 67, Table 4.15	The rate of 84.8% for responders at the end of induction should be 84.4%.	Incorrect wording.	Typo corrected
ERG report page 67, Table 4.15	The ERG summarise only the induction phase results of SUSTAIN-2 and have omitted the optimisation/maintenance phase results, which are important since SUSTAIN-2 is a maintenance study.	Optimisation/maintenance phase data have not been included in the ERG's summary of SUSTAIN-2 results.	Not a factual inaccuracy. According to Table 7 of the CS, SUSTAIN-2 is a "non-comparative study primarily designed to assess long-term safety (with minimal efficacy data)". Therefore, the focus was on the safety data which have been reported in Tables 4.21 and 4.22 of the ERG report.
ERG report page 68, Table 4.15	The ERG report the change in HSI score from "baseline to the end of the maintenance phase". The description needs to be amended to "baseline to the end of induction."	Incorrect wording.	This has been corrected
ERG report page 13, 69, 102 "(stable remittters)"	The proposed amendment is: "(stable remittters)"	Spelling mistake.	Typos corrected.
ERG report page 72, Table 4.16	In the "disease severity" section of the subgroup analysis table, the categories should be "remission" and "response" not	Incorrect wording.	This has been corrected

	"remission and "relapse."		
ERG report page 102, paragraph 3	The 95% confidence interval –7.31 to 5.67 should actually read: –7.31 to –0.64.	Incorrect wording.	Typo corrected.
ERG report page 112 "TRANSFROM-3"	The proposed amendment is: "TRANSFORM-3"	Spelling mistake.	Typo corrected.
ERG report page 113 "TRANFORM-2"	The proposed amendment is: "TRANSFORM-2"	Spelling mistake.	Typo corrected.
ERG report page 117 and page 143 "the data pooled from both study arms of the double-blind phase of SUTSTAIN-1 was used"	The proposed amendment is: "The data pooled from both study arms of the double-blind phase of SUSTAIN-1 was used"	Spelling mistake.	Typos corrected.
ERG report pages 21, 140, 142 "These ratios are: 13.7/13.0 =and"	The proposed amendment is: "These ratios are: 13.7/13.0 and"	Spelling mistake.	Typos corrected.
ERG report page 144 "(2 in the CS)"	The proposed amendment is: "(***pg.***2 in the CS)"	Missing word.	Typo corrected.
ERG report page 144 "(170 in the CS)"	The proposed amendment is: "(***pg.***170 in the CS)"	Missing word.	Typo corrected.
ERG report page 145	The proposed amendment is:	Spelling mistake.	Typo corrected.

“With regards to the effectiveness of ***ESK-NW*** +OAD versus OAD”	“With regards to the effectiveness of ***ESK-NS*** +OAD versus OAD”		
ERG report Page 146 “was considerable higher that the company base-case”	The proposed amendment is: “was considerable higher tha***n*** ~~t~~ the company base-case”	Spelling mistake.	Typo corrected.

Technical engagement response form

Esketamine for treatment-resistant depression [ID1414]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **21 November 2019.**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second, fully

redacted, version of your comments (AIC/CIC shown as [redacted]). See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Janssen**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Issue 1: Generalisability of evidence	
Are TRANSFORM-2 and SUSTAIN-1 generalisable to UK clinical practice?	TRANSFORM-2 and SUSTAIN-1 are generalisable to UK clinical practice since the patient characteristics in the studies are similar to those of patients with treatment resistant depression (TRD) treated in NHS clinical practice. Evidence from previous depression studies also suggests that the excluded comorbidities in the trials would not have had an impact on treatment benefit of esketamine nasal spray (ESK-NS); moreover the oral antidepressants (OADs) included in the ESK-NS studies are amongst the top 10 most frequently used by patients with TRD in the UK. In the technical report page 10-11, multiple questions are raised around this topic, and specifically on: 1. Overall generalisability based on patient characteristics 2. The impact of comorbidities, and specifically (alcohol) abuse disorder and suicidality with intent and the proportion of these comorbidities in UK TRD patient population 3. The frequency of use in NHS clinical practice of the OADs included in the ESK-NS Each of these topics are addressed in the sections below as well as the two questions raised during the technical engagement call: 1) the patient characteristics and outcomes of the 12 UK patients included in the SUSTAIN-2 study, and 2) the Polish trial site participating in the SUSTAIN-1 study. **Patient characteristics**

	As indicated in Document B, Section B.3.2.1 of the company submission, treatment resistant major depressive disorder (MDD) was defined as non-response to two or more OADs prescribed in the current moderate to severe episode. This is consistent with the population detailed in the NICE scope, the population included in the TRANSFORM-2 and SUSTAIN-1 trials, and the anticipated European Marketing Authorisation. The majority (61.9%) of the TRANSFORM-2 population were female with an average age of 45.7 years (SD: 11.89), which is very similar to the findings from a retrospective analysis of data of patients with TRD from the South London and Maudsley (SLaM) Trust ([redacted] of which [redacted] was female. Further evidence of generalisability of the patients included in the ESK-NS clinical trial programme to NHS clinical practice is provided from an interim analysis of the patients included in an observational cohort of patients with TRD across Europe. There were 28 patients from the UK included in the interim analysis. The observational study was a prospective, international, multi-center, observational cohort study to document and evaluate the socio-demographic, disease-related and treatment-related characteristics of patients with MDD who fulfilled the most commonly adopted criteria for TRD[1]. Patients enrolled in the observational TRD study and the TRANSFORM-2 study were similar in terms of mean age (50.8 and 45.7 years old, respectively), gender distribution (62.1% and 61.9% were female), time since MDD diagnosis (12.6 and 12.0 years), and pattern of past drug failures. The CGI-S score was reported as "markedly ill" in most patients (49% and 57%) from both studies. The other patient-reported outcomes were similar between the observational TRD study and TRANSFORM-2 and were reported at 22.3 and 24.1 for total mean SDS, 0.41 and 0.42 for mean EQ-5D-5L (UK-based), and 37.3 and 39.7 for mean EQ-VAS, respectively[1]. The similarity in age, gender and race between the trial patient population and patients with TRD included in UK real world evidence (RWE) studies supports generalisability of the ESK-NS studies to UK clinical practice.

	Comorbidities Patients with multiple psychiatric co-morbidities were excluded from the Phase 2 and Phase 3 clinical trials to maximise the homogeneity of the clinical trial population and to minimise the impact of confounding of psychiatric co-morbidities on the assessment of efficacy. Patients with psychiatric diagnoses other than the indication being studied (including current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychosis, bipolar or related disorders (confirmed by the MINI), comorbid obsessive compulsive disorder, intellectual disability (only DSM-5 diagnostic code 319), borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder, or if they have a history of moderate or severe substance or alcohol use disorder according to DSM-5 criteria) were excluded from the Phase 3 clinical trials as these would require separate investigation. The findings from a literature review show that for depressed patients who have a comorbid condition, the relative benefit of an OAD compared with placebo appears to be equal to those effects achieved in depressed patients without comorbidity[2]. Ani and colleagues have conducted a cross-sectional study that used interviewer-administered surveys and medical record reviews[3]. 315 participants were recruited from three public primary care clinics. Depression diagnosis, guideline-concordant treatment, and follow-up care were the primary outcomes assessed in patients with depression with no comorbidities compared with individuals with depression and chronic medical conditions measured using the Charlson Comorbidity Index (CCI). Logistic regression analysis showed no significant difference in the likelihood of depression diagnosis, guideline-concordant treatment, or follow-up care in patients with depression alone compared with those with both depression and chronic medical conditions[3].

	See below for details of available evidence of impact on treatment effect of dual diagnosis of alcohol abuse disorder or suicidal ideation with intent and depression. **Alcohol abuse disorder** In the technical report pages 10 and 11, specific questions were raised on the impact of a dual diagnosis of alcohol abuse disorder. Patients with TRD who had a history (within 6 months) of moderate or severe substance or alcohol use disorder according to DSM-5 criteria were excluded from the ESK-NS trials. A retrospective analysis of SLaM data showed that approximately [redacted] of patients with TRD also had substance abuse disorder as a comorbidity[4]. The proportion of patients with TRD who had a specific alcohol disorder as a comorbidity was not reported but is most likely below [redacted] since it is a sub-diagnosis of substance abuse disorder. The SLaM catchment area is likely to represent a higher proportion of substance abuse disorder than the national average, indicating there is only a relatively small proportion of patients with TRD in the UK are likely to have a dual diagnosis of alcohol abuse disorder. A systematic review and meta-analysis of OAD treatment of depressed patients who have alcohol or substance misuse published by Nunes and Levin[5] is described as “the best attempt to date to examine and interpret the current data”. This review found that the likelihood of finding an antidepressant effect was higher in studies with low placebo response (consistent with findings in OAD trials in subjects without substance abuse) and concluded that OADs can be useful in these patients if used in adequate doses, for an adequate length of time, and in patients whose diagnosis is well established by a thorough history and a structured diagnostic interview. The overall effect size they found was 0.38 (95% confidence interval [CI], 0.18–0.58), which is comparable with the effect size of 0.43 found in a meta-analysis of antidepressant trials in unipolar depression.

	These findings show generalisability of the relative treatment benefit from ESK-NS randomised controlled trials to those patients with a dual diagnosis of (alcohol) abuse disorder in clinical practice. **Suicidal ideation with some intent** It is important to clarify that suicidal ideation is one of the key symptoms of MDD. Patients with (previous) suicidal ideation were included in the ESK-NS studies. Patients with suicidal ideation with current (or within the last 6 months before study entry) intent/plan to act or suicidal behaviour in the 12 months prior to study entry were excluded. Suicidal ideation with some intent/plan to act was assessed by the investigator's clinical judgment and/or based on the Columbia-Suicide Severity Rating Scale (C-SSRS). In general, a psychiatrist assigns a higher level of risk to patients who have higher degrees of suicidal intent or describe more detailed and specific suicide plans, particularly those involving violent and irreversible methods. While the clinical development programme excluded patients of "acute suicide risk", the TRD population studied is representative of population with increased risk of suicidality[6]. Between 15% and 31% of the patients across the Phase 3 studies in TRD had suicidal ideation at baseline (based on last C-SSRS score obtained between screening and Day 1); 25% to 37% of the enrolled patients had a lifetime history of suicidal ideation, and between 14% to 19% of patients had a lifetime history of suicidal behaviour, as assessed using the C-SSRS. The prevalence of suicidal ideation and the lifetime history of suicidal behaviour reported in the studied population is consistent with the data presented in a European population[7]. A retrospective analysis of SLaM data shows that approximately [redacted] of patients with TRD are also at high risk of suicide at any point in time during the 10-year study follow up[4]. The proportion of patients who can be considered at high risk of suicide, i.e. with intent to act, in six months prior to the screening phase are therefore assumed to be [redacted].

	ESK-NS has also been studied in a separate clinical programme in patients with a moderate to severe depressive episode of MDD who have current suicidal ideation with intent. Patients with TRD were not excluded from these trials. The data from one Phase 2 study and two Phase 3 studies show that ESK-NS plus standard of care was similarly effective in reducing depressive symptoms in the population of patients with MDD and suicidal ideation with intent as in the Phase 3 studies in TRD[8,9]. **Failed ECT treatment** Patients who previously demonstrated non-response to an adequate course of treatment with electroconvulsive therapy (ECT) in the current major depressive episode, defined as at least 7 treatments with unilateral/ bilateral ECT, were excluded from the ESK-NS trials to ensure a homogenous population is enrolled in terms of prior antidepressant treatment failures. Given the treatment burden of ECT, including a risk of transient adverse cognitive effects, and repeated exposure to general anaesthesia, ESK-NS may represent a more tolerable intervention to be considered before the last lines of treatment, including ECT. A retrospective analysis of SLaM data showed that ECT is only used by a small proportion ([redacted]) of 18-64-year-old adult patients with TRD and [redacted] in patients with TRD ≥65 years because of the low level of acceptability by patients due to the risks involved[4]. This conclusion is supported by data from the ECT Accreditation Service (ECTAS) from 2016-2017, which shows the limited use of ECT across the country[10]. **OADs included in the ESK-NS spray studies**

	An update of the retrospective longitudinal study on an IQVIA database as referred to in the company submission (CS) Document B section 1.3.7.1 showed that in 3rd line MDD (1st line TRD) the OADs included in the ESK-NS studies are amongst the top 10 most frequently used in the UK TRD patient population: • sertraline is the 2nd most frequently used pharmacological treatment (21.3%) • escitalopram is #10 (2.5%) • venlafaxine is #6 (12.3%) • duloxetine is #7 (7.8%) The study also showed that SSRIs and SNRIs are the most frequently used OAD classes by UK patients with TRD. Evidence suggests that there are few differences in efficacy and tolerability between individual OADs, and therefore not likely to be any treatment difference between OADs used with ESK-NS. As described in CS Document B section 1.3.6.1., based on a network meta-analysis (NMA) conducted by Cipriani et al[11], the Guideline Development Group in NICE CG90 concluded that there was insufficient evidence to indicate a difference in efficacy and tolerability between individual OADs or classes of OADs and therefore no specific OAD treatment recommendations were made. The same conclusion was reached in NICE TA367[12]. The meta-analysis has recently been updated with data from nine additional OADs, which again found few differences between antidepressants when all data were considered[13]. **Conclusion** The TRANSFORM-2 and SUSTAIN-1 study data are generalisable to the UK TRD population. UK RWE studies show that characteristics of patients with TRD in UK clinical practice are similar to those of patients in the trials.

	Evidence from previous depression studies also show that co-morbidities e.g., substance abuse disorder and suicidal ideation with intent, are not expected to affect the treatment effect of antidepressant treatment with ESK-NS. ECT is only used by a very small proportion of patients with TRD in UK, however there is no reason to believe that the efficacy of ESK-NS + OAD would be different when used after failure of ECT. Furthermore, the four OADs included in the ESK-NS trials are amongst the top 10 most frequently used OADs in a UK TRD patient population and SSRIs and SNRIs are the two most frequently used OAD classes. NICE CG90 has also concluded that there is very limited difference in efficacy between the different OADs and OAD classes. There are not likely to be any treatment differences between the OADs used with ESK-NS in clinical practice. <u>References</u> 1. Morrens J, Rive B, Van Dooren G, Umuhire D, Malynn S. Increased use of augmentation therapies illustrates problematic management of treatment resistant depression. ISPOR Poster Copenhagen conference 2019 2. Otte 2008, Incomplete remission in depression: role of psychiatric and somatic comorbidity, Dialogues Clin Neurosci. 2008;10(4):453-60 3. Ani C, Bazargan M, Hindman D, Bell D, Rodriguez M, Baker RS. Comorbid chronic illness and the diagnosis and treatment of depression in safety net primary care settings. J Am Board Fam Med. 2009 Mar-Apr;22(2):123-35. 4. Janssen. Data on File. Esketamine_DoF_12Jun2019_HEMAR_TM_002 5. Nunes EV, Levin FR. Treatment of depression in patients with alcohol or other drug dependence: a meta-analysis. JAMA 2004;291:1887–96 6. Kautzky, A., Dold, M., Bartova, L., Spies, M., Kranz, G., & Souery, D. et al. (2018). Clinical factors predicting treatment resistant depression: affirmative results from the European multicenter study. Acta Psychiatrica Scandinavica, 139(1), 78-88. doi:10.1111/acps.12959 7. Bernal M, e. (2019). Risk factors for suicidality in Europe: results from the ESEMED study. J Affect Disord. 2007 Aug;101(1-3):27-34. Epub 2006 Oct 30.

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Additional questions asked during the technical engagement call

UK patients in SUSTAIN-2

On the technical engagement call, NICE indicated they would like to see the details of the 12 UK patients included in the SUSTAIN-2 study; the supporting, long-term open-label safety study. Eight of the 12 UK patients were male, the average age was 49 years old, and 11 patients were white and one was Asian. Seven patients had suicidal ideation in the six months prior to baseline as measured by the C-SSRS, of which six

patients still had suicidal ideation at baseline. Nine patients can be considered ‘markedly ill’, two patients ‘moderately ill’ and one patient ‘normal/not at all ill’ based on their CGI-S score at baseline.

There was one patient with a family history of alcohol abuse, three patients had a family history of anxiety disorder, one patient with a family history of bipolar disorder, and five patients with a family history of depression. See the table below for more information of the baseline characteristics, including MADRS score.

Analysis Variable : AVAL Analysis Value									
Parameter	**N Obs**	**N**	**Mean**	**Std Dev**	**Minimum**	**Lower Quartile**	**Median**	**Upper Quartile**	**Maximum**
Age when Diagnosed with MDD	[redacted]								
Baseline CGI-S	[redacted]								
Baseline MADRS Total Score	[redacted]								
Baseline PHQ-9 Total Score	[redacted]								
Baseline SDS Total Score	[redacted]								
Duration of Current Episode (wks)	[redacted]								
Previous anti-depressant medications	[redacted]								

Outcome data

[redacted]

[redacted]

Follow up

[redacted]

The data show the potential benefit of treating patients with TRD in the UK to be similar to other countries; however, it is important to note that this is a very small subgroup and no strong conclusions should be drawn.

Polish SUSTAIN-1 clinical trial site

During the technical engagement call, there was a clarification question about a Polish trial site involved in the SUSTAIN-1 study. It is noteworthy that neither the company nor the FDA (after site inspection) found any reason to exclude data from the site in Poland. Nonetheless, a sensitivity analysis was performed excluding this site and using a statistical method appropriate for time to relapse data. Statistical significance is maintained (log-rank test $p<0.05$) and the results remain consistent with the primary efficacy analysis. The prespecified

	primary analysis for this study which formed the basis of type 1 error control was the log-rank test. The SUSTAIN-1 data excluding the Polish site show that ESK-NS + OAD decreased the risk of relapse by [redacted] (hazard ratio [HR]: [redacted]; 95% CI, [redacted]) among patients who achieved stable remission and [redacted] (HR: [redacted]; 95% CI, [redacted]) among those who achieved stable response compared with OAD and PBO-NS treatment.
What proportion of UK population are expected to have had suicidal ideation/intent in the previous 6 months and/or suicidal behaviour in the previous 12 months before treatment?	Patients with suicidal ideation were not excluded from the ESK-NS studies. Patients were excluded only if they had suicidal ideation with some intent to act in 6 months or suicidal behaviour in the 12 months prior to the prospective screening phase. As indicated in the response to the previous question, a retrospective analysis of SLaM data shows that approximately 17% of patients with TRD are also at high risk of suicide at any point in time during the 10-year study follow up[1]. The proportion of patients who can be considered at high risk of suicide, i.e. with intent to act, in six months prior to the screening phase are therefore assumed to be <17%. References 1. Janssen. Data on File. Esketamine_DoF_12Jun2019_HEMAR_TM_002
Is 4 weeks enough time to establish response to treatment with a newly initiated oral antidepressant?	Available clinical guidelines, including NICE CG90 show that 4 weeks is a sufficient period of time to establish response to a newly initiated oral antidepressant. NICE CG90 provide a discussion on when the appropriate time is to change antidepressant treatment when symptoms of depression are not improving (Section 10.15.2). NICE CG90 notes that switching treatment too early could lead to rejection of an effective treatment, which in the long run will be unhelpful when future

	treatment options are considered. In contrast, delaying change in treatment too long could prolong the period of depression if symptoms are not going to respond to current drug/dose, lead to a patient's loss of faith in treatment, and increase depression- related morbidity and even mortality. **NICE CG 90** NICE CG90 recommend the following: • If the person's depression shows no improvement after 2 to 4 weeks with the first antidepressant, check that the drug has been taken regularly and in the prescribed dose. • If response is absent or minimal after 3 to 4 weeks of treatment with a therapeutic dose of an antidepressant, increase the level of support (for example, by weekly face-to-face or telephone contact) and consider: o increasing the dose in line with the SmPC if there are no significant side effects or o switching to another antidepressant if there are side effects or if the person prefers. • If the person's depression shows some improvement by 4 weeks, continue treatment for another 2 to 4 weeks. Consider switching to another antidepressant as described in section 1.8 if: response is still not adequate or there are side effects or the person prefers to change treatment. The time point of four weeks to assess treatment response is additionally supported by the recommendations in the British Association for Psychopharmacology (BAP) evidence-based guidelines for treating depressive disorders. Further evidence which was evaluated in the consideration and cited by NICE CG90 in reaching

	these recommendations are summarised below. As detailed in Section 10.15.2 of NICE CG90, most studies have found that early improvement, as quickly as the first two weeks (20% of greater improvement), is a good predictor of response by the end of the study (1, 2, 3, 4). NICE states that this is consistent with usual clinical practice. Previous work by Szegedi and colleagues (3) suggested that early improvement predicts later stable response with high sensitivity. This was also supported with strong evidence by Szegedi et al (4) in a meta-analysis including 6562 patients. Forty-one clinical trials comparing mirtazapine with active comparators or placebo in inpatients and outpatients with MDD (DSM-III-R or DSM-IV Criteria) were examined for early improvement (>or= 20% score reduction from baseline on the 17-item Hamilton Rating Scale for Depression [HAM-D-17] within 2 weeks of treatment) and its relationship to treatment outcome. The study results indicated that early improvement with antidepressant medication can predict subsequent treatment outcome with high sensitivity in patients with MDD. Data suggests that assessing treatment response and switching treatment at four weeks leads to improved outcomes compared to switching at eight weeks (5). When considering the optimal time to assess treatment response, the outcome of concern is the number of non-improvers at each time point who subsequently respond or remit by the end of a certain time frame because this provides some guide as to when changing treatment is likely to improve outcome. This can be assessed using the negative predictive value (NPV), which is the proportion of non-improvers not going on to achieve response/ remission at the last evaluation. Where this is low, non-improvement at that time point is not a useful predictor of outcome at endpoint.

	A 5-week study found an NPV for 20% improvement on response at five weeks of 48 to 54% at two weeks, 74 to 83% at three weeks and 96 to 99% at four weeks (6). A 6-week study found an NPV defined in the same way as 65 to 72% at two weeks, 77 to 94% at three weeks and 82 to 94% at four weeks (3). Two 8-week studies of fluoxetine (defining improvement as 20% reduction in one and 30% in another) (1, 2) and a pooled analysis of 14 escitalopram studies (20% improvement) (7) found NPVs of 55 to 64% at two weeks, 80 to 82% at four weeks and 90 to 93% at 6 weeks. In contrast, an open 12-week study of fluoxetine (8) using 25% improvement to predict remission (HAMD <8) found an NPV of only 49% at four weeks, 59 to 69% at six weeks and 77% at eight weeks. Finally, a naturalistic study of 795 inpatients (9) with a variable follow-up (discharge, mean= 60 days), using 20% improvement found only a 37% NPV at two weeks for response and 43% at four weeks. NPVs for remission (HAMD <8) were higher at 69% and 72% respectively. From the above evidence, NICE CG90 concludes that a reasonable time to consider a change of treatment in these patients would be at three to four weeks. In NICE CG90 it is acknowledged that in patients who have failed previous trials of treatment, and in more severely ill patients, longer trials of treatment may be warranted before making changes. **Use of 4-week endpoint in ESK-NS clinical trial** The 4-week duration of the induction phase in the ESK-NS studies was chosen to provide sufficient time for the onset of efficacy in the OAD plus placebo nasal spray group. The use of a 4-week timepoint is also aligned to the CHMP guideline for clinical trials in depression and current clinical guidelines for assessment of response after two to four weeks. The 4-week duration of the prospective screening phase as well as the induction phase

	of the esketamine nasal spray studies was consistent with the minimum duration of the range suggested in the CHMP guideline for clinical trials in depression (12)*.* Furthermore, the FDA have conducted a meta-analysis in 2013 to inform the design of future antidepressant studies (10). Based on this, the FDA conducted meta-analysis of data from 24 short-term antidepressant trials submitted to the FDA over a 10-year period. The AD-placebo treatment difference was consistent for trials of four to eight weeks' duration, suggesting that it is plausible to shorten AD trial duration to four weeks (10). The FDA conducted exploratory analyses on aggregated efficacy data from the 24 double-blind short- term randomised placebo-controlled trials (patient level database, 7893 patients with 46 drug treatment arms and 24 placebo arms). Evaluation of response at four, six and eight weeks by use of Mixed-effects model using repeated measures (MMRM) to obtain least squares mean and 95% CI revealed that there was no relative difference between the study arms at these timepoints, so they concluded that the duration of studies can be shortened to four weeks (10, 11). Based on all of the available evidence in the literature, guidelines (NICE CG 90 and BAP), and aligned to regulatory agency recommendations, four weeks is sufficient to establish response to a newly initiated OAD. <u>References</u> 1. Nierenberg, A. A., McLean, N. E., Alpert, J. E., *et al.* (1995) Early nonresponse to fluoxetine as a predictor of poor 8-week outcome*. American Journal of Psychiatry, 152*, 1500–1503. 2. Nierenberg, A. A., Farabaugh, A. H., Alpert, J. E., *et al.* (2000) Timing of onsent of antidepressant response with fluoxetine treatment. American Journal of Psychiatry, 157, 1423–1428 3. Szegedi, A., Muller, M. J., Anghelescu, I., *et al.* (2003) Early improvement under mirtazapine and paroxetine predicts later stable response and remission with high sensitivity in patients with major depression. *Journal of Clinical Psychiatry, 64*, 413–420.

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Issue 2: Time horizon	
Are all differences in costs and effects attributable to esketamine nasal spray plus oral antidepressant (ESK-NS + OAD) likely to be captured in a 5-year time horizon?	An important factor to inform the appropriate time horizon is the natural history of the condition. An episodic modelling approach to model one depressive episode is consistent with the approach used by NICE in this disease area (TA367, Vortioxetine for treating major depressive episodes). In TA 367, the modelling approach was to model one episode of MDD, given the episodic nature of the condition for the majority of patients. The duration of a depressive episode can vary considerably among individuals. A 2-year time horizon was used in TA367, as the majority of MDD episodes last between 6–15 months (1). For patients with TRD, however, episodes are typically three times longer than MDD (2), and therefore a 2-year time horizon is not sufficient. Furthermore, it is clear that a 2-year time horizon is not appropriate, given that at baseline, the mean duration of the current episode was 114.6 weeks in the patients included in TRANSFORM-2. Instead, a 5-year time horizon was chosen in the company model, as being sufficient to capture all the benefits and costs of a single TRD episode, whilst minimising the uncertainty associated with longer time horizons. TRD is an episodic condition and should be modelled as such. An episodic modelling approach also consistent with the label wording, which specifies that ESK-NS is for treatment within the depressive episode: • *esketamine nasal spray, in combination with a SSRI or SNRI, is indicated for adults with treatment-resistant Major Depressive Disorder, who have not responded to at least two different treatments with antidepressants <u>in the current moderate to severe depressive episode</u>*. The Markov trace for the cost-effectiveness model indicates that the majority of differences in costs and effects attributable to ESK-NS + OAD are captured in a 5-year time horizon. The key drivers of differences in costs and

	effects relate to differences in the number of patients in recovery and MDE health states. The recovery health state is associated with lower costs and higher health utilities, whereas the converse is true for the MDE health state. Overall, a 20-year time horizon is not appropriate to use for this modelling approach because: 1. The ESK-NS label indication is only to treat an episode of TRD 2. The model is an episodic model, consistent with the model approach used in TA367 3. The largest proportion of costs and effects attributable to ESK-NS + OAD are captured in 5-year time horizon in the submitted episodic model The level of uncertainty should also be considered when modelling a longer time horizon. Specifically, the absence of evidence to inform the longer time horizon increases the uncertainty in the economic model; hence we have chosen a more appropriate time frame of 5 years that captures all relevant costs and outcomes associated with an episode of TRD without introducing unnecessary uncertainty. <u>References</u> 1. Spijker J, de Graaf R, et al. Duration of major depressive episodes in the general population: results from The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Br J Psychiatry. 2002;181:208-13 2. Kubitz N, Mehra M, et al. Characterization of treatment resistant depression episodes in a cohort of patients from a US commercial claims database. PLoS One. 2013;8(10):e76882
Issue 3: Placebo response rate	

1. How many clinic visits are expected in practice with esketamine treatment and with standard care?	Within the NHS, it would be expected that patients would have two visits in the first four weeks after initiating a new OAD for depression. These visits are to assess the presence of any therapeutic response and adverse events to the new oral treatment. NICE CG90 includes recommendations on what should ideally happen in clinical practice and the NHS Treatment of Clinical Depression website also (see below) outlines what a patient can expect, which recommends two visits for the first four weeks after initiation of an OAD. It is important to note that guidelines from NICE and the NHS provide recommendations based on the ideal number of clinic visits and thus unfortunately do not reflect the reality of patients facing significant waiting times for follow up mental health appointments in the UK. NICE CG90 includes the following recommendations: “For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good.” The NHS website for guidance on the treatment of clinical depression (1) states: “When you start taking antidepressants, you should see your GP or specialist nurse every week or 2 for at least 4 weeks to assess how well they're working. If they're working, you'll need to continue taking them at the same dose for at least 4 to 6 months after your symptoms have eased.” The table that was also included in the company submission Document B section 2.1.4. provides an overview of clinical practice and the number of visits based on UK market research data, feedback from clinical experts,

and a mixed-methods study conducted in the UK. For an OAD, there will be on average four visits in the first 3 months compared to 15 visits when using ESK-NS + OAD (Table 1).

Table 1: Current and future clinical treatment pathway for TRD (2,3,4)

Treatment phase	Existing clinical practice when OAD is prescribed	Future clinical practice for ESK-NS + OAD
Acute treatment phase Aim: complete resolution of TRD symptoms	• Initiation of OAD • First visit on average 3–4 weeks after switching to a new OAD • On average, four visits in the first 3 months after switch to a new OAD • Visit of 20–30 minutes, usually with GP, to assess treatment effect, and consider continuation or change in treatment	• Initiation of ESK-NS + OAD • Eight visits in first 4 weeks • At visit eight (at 4 weeks), there will be time with a prescriber (psychiatrist) to assess treatment response, and consider continuation or change in treatment On average 1 hour and 10 minutes per visit: • 10 minutes self-administration (under supervision of nurse). Blood pressure will be measured before first self-administration • 1-hour observation (by healthcare assistant) where blood pressure is measured 1–3 times
Relapse prevention treatment phase Aim: preventing relapse of MDD episode	• One visit every 4–12 weeks • Visit of 10–30 minutes, usually with GP, to assess treatment effect, and consider continuation or change in treatment	Weeks 5–8: • Weekly visits Weeks 8 onwards: • Fortnightly or weekly visits On average 1 hour and 20 minutes per visit: • 10 minutes self-administration (under supervision of nurse). Blood pressure will

		be measured before first self-administration • 1-hour observation (by healthcare assistant) where blood pressure is measured 1–3 times The need for continued treatment will be evaluated periodically
	After the depressive symptoms resolve, treatment for at least 6 months is recommended for consolidation of the anti-depressive response	After depressive symptoms improve, treatment is recommended for at least 6 months
Recurrence prevention Aim: prevent new episode of MDD	• Prevention of MDD recurrence is with an OAD following entry into a 'recovery' state	• Prevention of MDD recurrence is with an OAD following entry into a 'recovery' state • For patients at high risk of recurrence, ESK-NS treatment may be extended to up to 2 years based on clinical judgement

Abbreviations: GP, general practitioner; MDD, major depressive disorder; OAD, oral antidepressant; TRD, Treatment-resistant depression.

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2. Are the placebo response rates observed in TRANSFORM-2 unusually high?

In many mental health and depression trials historically, a high placebo response rate in many trials of active drugs has led to trials failing to show a statistically significant efficacy outcome compared with placebo. Of the randomised, placebo-controlled studies of OADs, approximately 50% have failed to show statistical superiority over placebo on change from baseline to endpoint (1). This effect is well recognised; NICE CG 90 notes that 'the placebo effect in trials of psychiatric drugs is often so large that specific pharmacological effects can be hard to identify'.

The efficacy results of the active comparator arm in the TRANSFORM-2 trial had an even higher response (with 52% response rates and approximately 31% remission rates) than would be expected, even when taking the well-known placebo effect of antidepressant trials into account. The TRANSFORM-2 response rates can therefore be considered unusually high compared to other trials in this population. This conclusion is supported when comparing to the trials identified in the SLR which contribute to the SSRI/SNRI + placebo treatment node and also report change from baseline MADRs in Table 2 below.

Table 2: Other trials of SSRI/SNRI in a TRD population identified by the systematic literature review

Trial	Randomised treatment regimen	Endpoint, weeks	Change from baseline MADRs score
Corya, 2006	• Switch fluoxetine 25 or 50mg/day	4	-6.92
Shelton, 2005	• Switch fluoxetine 25-50 mg/day	4	-6.84 [0.38]

TRANSFORM-2	• Switch SSRI (escitalopram or sertraline) or SNRI (duloxetine or venlafaxine XR) according to local prescribing guidelines (open label) • Placebo nasal spray twice weekly	4	-16.3 (14.24)

As described in company submission Document B section 2.1.4., the change in MADRS total score from baseline to the end of induction among patients in the OAD + PBO-NS arm of TRANSFORM-2 was more than twice of that observed in equivalent studies in which patients with TRD were treated with a newly initiated OAD (3,4) (Table 2). The SLR of clinical studies in TRD showed there is no other trial conducted with a similarly high number of follow-up visits (eight visits in four weeks) and a placebo nasal spray in the active comparator arm.

One potential explanation is that the active comparator arm included a newly initiated OAD as part of the intervention. In the absence of robust data, the level of remission/response rates in NHS clinical practice of a newly initiated OAD in patients with TRD are expected to be similar to what the STAR*D study has shown. The STAR*D study is the most comprehensive prospective study conducted in the field of MDD/TRD. A comparison to the STAR*D study (2), however, shows that the efficacy of the newly initiated OAD + PBO-NS arm in TRANSFORM-2 remains considerably higher. In STAR*D, patients were followed through up to four lines of OAD treatment for both MDD and TRD. Step 3 refers to patients who have had two OAD treatment failures, (corresponding to first-line TRD). The remission and response rates in the STAR*D study were 16.8% and 13.7% after approximately 14 weeks, respectively, among patients with TRD, some of whom were receiving combination/augmentation therapies. In comparison to STAR*D, the impact of the newly initiated OAD does not provide a full explanation for the high response rates observed in the active comparator arm of TRANSFORM-2.

	Overall, the comparison to other trials of new OADs in the TRD population has shown that the high efficacy observed in the active comparator arm of TRANSFORM-2 is not solely due to the newly initiated OAD. It must, therefore, be attributed to the high levels of patient-healthcare professional contact during the twice-weekly clinic visits as mandated by the TRANSFORM-2 trial, combined with the novelty of a nasal spray treatment for depression and the anticipation of receiving ESK-NS. In particular, the high number of patient visits (8 visits in the first 28 days) is in comparison to just 2-3 clinic visits with patients with TRD in clinical practice. The *post-hoc* adjustment of the treatment effect in the OAD + PBO-NS arm was conducted to adjust for the higher number of clinic visits in TRANSFORM-2, and thus more accurately reflect the treatment effect of an OAD as expected in routine (ie. not ideal) NHS clinical practice. We strongly believe that this adjustment should be applied to the treatment effect to representative a more realistic estimate of effectiveness of OAD in NHS clinical practice. <u>References</u> 1 Khin NA, Chen YF, et al. Exploratory analyses of efficacy data from major depressive disorder trials submitted to the US Food and Drug Administration in support of new drug applications. J Clin Psychiatry. 2011;72(4):464-72. 2 Rush AJ, Trivedi MH, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006;163(11):1905-17 3 Corya SA, Williamson D, et al. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, fluoxetine, and venlafaxine in treatment-resistant depression. Depression and anxiety. 2006;23(6):364-72 4 Shelton RC, Williamson DJ, et al. Olanzapine/fluoxetine combination for treatment-resistant depression: a controlled study of SSRI and nortriptyline resistance. J Clin Psychiatry. 2005;66(10):1289-97

What is the likely effect of an additional clinic visit on key outcomes?	A discussion on the factors of therapeutic contact and patient expectancy as factors which influence treatment response is provided Rutherford & Roose, 2013 (1). As noted by the authors, in an antidepressant clinical trial, patients experiencing social isolation and decreased activity levels as part of their depressive illness enter a behaviourally activating and interpersonally rich new environment. They interact with research coordinators and medical staff, receive lengthy clinical evaluations by highly trained professionals, and are provided with diagnoses and psychoeducation that explain their symptoms. Medical procedures are performed, such as blood tests, ECG, and measurement of vital signs, and clinicians meet with patients to listen to their experiences and facilitate compliance by instilling faith in the effectiveness of treatment. The intensive therapeutic contact used in clinical trials may be contrasted with what patients being treated with OADs receive in UK clinical practice. Assignment to placebo in an antidepressant clinical trial represents an intensive form of clinical management that has therapeutic effects. Overall, it is clear that this is likely to have an impact on key outcomes included in the trial. Considerable empirical evidence supports the therapeutic effectiveness of increased therapeutic contact as a result of the increased number of clinic visits. Optimistic or enthusiastic physician attitudes, as compared with neutral or pessimistic attitudes, are associated with greater clinical improvements in medical conditions as diverse as pain, hypertension, and obesity (2). A therapeutic relationship in which the clinician provides the patient with a clear diagnosis, the patient is given an opportunity to communicate, and the clinician and patient agree on the problem has been shown to produce faster recovery (3). In addition, physical aspects of the treatment, such as the pill dosing regimen, the colour of pills, and the technological sophistication of the treatment procedures, can influence treatment response (4). The frequency of follow up assessments is also acknowledged by Papakostas et al, 2015 (5). The authors note that ‘more frequent measurements may

	unnecessarily expose patients to increased study burden as well as inflate placebo response rates due to increased exposure to nonspecific treatment effects associated with the trial'. Yesaveage et al, 2018 (6) demonstrated the importance of close clinical surveillance, rigorous monitoring of concomitant medication, and regular interaction with clinic staff in bringing about significant improvement in the TRD population. It could be argued that any observed increased responses in placebo arms is due to treatment expectancy, rather than the increased therapeutic contact. Since the ability to generate treatment expectancy requires relatively advanced cognitive capacities, it is puzzling to observe high placebo response in children with depression. Compared with adults, participants in paediatric major depression trials are less cognitively equipped to understand the nature of the study in which they are participating, and they actually receive less information at the time of their enrollment (since their parents provide informed consent). To evaluate the significance of expectancy effects in younger patients, Rutherford analysed antidepressant response between comparator and placebo-controlled studies of OADs for children and adolescents with depressive disorders (7). Unlike the large differences observed between these study types in adults with depression, there was no significant difference in medication response between comparator and placebo-controlled studies enrolling children and adolescents. Rather than patient expectancy, what appeared to influence treatment response was the amount of therapeutic contact patients received: adolescents experienced greater placebo response as the number of study visits increased. This provides evidence of the impact of additional clinic visits on response to antidepressant efficacy. There are limited data on quantifying the effect of an additional clinic visit. Posternak and Zimmerman (2007) (8) provide a point estimate that has been used for the *post-hoc* adjustment of the TRANSFORM-2 OAD +

	PBO-NS treatment effect in the base case included in the company submission. In this study, follow-up visits were shown to account for 40% of the placebo treatment effect[1]. The study showed that each clinic visit was associated with a Hamilton Depression Rating Scale (HAM-D) reduction (improvement) of 0.67–0.86 points, two additional visits were associated with twice the therapeutic effect of one, and the therapeutic impact of visits was cumulative and proportional. This was used as the basis of the *post-hoc* adjustment of the TRANSFORM-2 OAD + PBO-NS treatment effect to approximate the treatment effect of OADs in NHS clinical practice; see company submission Document B section 2.3.7. for more details. NICE CG 90 recognises the impact of additional clinic visits on antidepressant treatment response. In Section 10.15.1, NICE CG 90 notes the rate and degree of antidepressant improvement also appears to be influenced by the frequency of follow up, referencing to the Posternak and Zimmerman (2007) study above. As such, NICE CG 90 recognises the importance of the early stages of treatment in response to antidepressants and highlight the role of frequency of monitoring. Overall, the evidence suggests that there is clearly an impact of additional clinic visits on the key outcomes in depression trials. Furthermore, the conclusion of the impact of additional clinic visits on improved treatment response has been validated by multiple UK clinicians (9,10). As noted in the literature above, this effect is especially prominent in the field of mental health and MDD. <u>References</u> 1. Rutherford, B., & Roose, S. (2013). A Model of Placebo Response in Antidepressant Clinical Trials. American Journal Of Psychiatry, 170(7), 723-733. doi:10.1176/appi.ajp.2012.12040474

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9. Janssen. Data on File. Esketamine_DoF_11Jun2019_HEMAR_TM_001

10. Janssen. Data on File. Esketamine_DoF_28May2019_HEMAR_TM_007

Are there any other likely reasons that placebo response rates may be high?	At two different advisory boards, nine different UK clinical experts have indicated what factors could have resulted in the high response rates of the TRANSFORM-2 OAD + PBO-NS arm as follows: 1. Additional clinic visits (eight clinical visits in four weeks versus maximum of two clinic visits in NHS clinical practice) 2. High expectancy of receiving a highly effective medicine 3. Use of nasal spray with a bitter taste leading to the expectation of receiving something novel 4. The fact that is not a placebo arm, but it includes a newly initiated active drug (SSRI or SNRI) The ERG have also acknowledged that these factors have most probably positively impacted the efficacy of the OAD + PBO-NS (ERG report page 20 and 116). Of these four factors, all factors still remain with ESK-NS in clinical practice, including the eight clinic visits, whilst when switching to a newly initiated OAD in NHS clinical practice, the first three factors would not play a role. Patients receiving ESK-NS will require additional clinic visits, will have a high expectancy effect, the use of the nasal spray will be novel and also there will be an additional OAD administered. This is in comparison to patients receiving a new OAD in NHS clinical practice, who will not have additional clinic visits, will not have a high expectancy effect of receiving a novel medicine or nasal spray, and will only have the expectation of receiving a new OAD medication. As indicated in the CS Document B section B.2.1.4., Janssen have attempted to quantify the impact of the additional clinic visits on the efficacy of the active comparator arm using an evidence-based approach, utilising the best available evidence. Only the Posternak publication (1) provides a point estimate of the impact on effectiveness of an additional clinic visit. In the company submission, Janssen have included sensitivity

	analyses around this point estimate, see Document B section B.3.4.4.1. This also shows that even without adjustment of the treatment effect in the active comparator arm the ICER is below £20,000. There are no data available that would help to quantify the effect of the high expectancy or the placebo nasal spray. This shows that only adjusting for the additional clinic visits might be considered conservative. This is also confirmed by the remission and response rates after adjustment using the data from the Posternak publication (1) (18% remission and 16% response (not remission)) versus the remission and response (not remission) rates from STAR*D, which are lower at 13.7% and 16.8% respectively. Section 3.4.4.1 in the CS document B provides an estimate of the impact on the ICERs if a naïve comparison versus the STAR*D data would be modeled, which is between £1,767 and £3,257 per QALY, which represent ICERs that are lower than the CS base case. References: 1. Posternak MA, Zimmerman M. Therapeutic effect of follow-up assessments on antidepressant and placebo response rates in antidepressant efficacy trials: meta-analysis. Br J Psychiatry. 2007;190:287-92
Issue 4: Treatment discontinuation	
Is the treatment effect of ESK-NS + OAD maintained after stopping treatment?	The treatment effect of ESK-NS + OAD will be maintained after stopping treatment when a patient has reached a full functional recovery. Given the episodic nature of the disease, the timing of discontinuation ESK-NS is a fundamental consideration in determining this. Based on the nature of the disease, the treatment effect of ESK-NS is expected to be maintained after discontinuing treatment, when patients are in a full functional recovery

health state. Furthermore, it is assumed that patients will stay on OAD to help maintain their functional recovery (see Figure 1 below). Full functional recovery is expected to be achieved after 9 months in a remission health state. Please note that this is in contrast to when patients are not in a full functional recovery health state, as was the case at point of re-randomisation in SUSTAIN-1. The SUSTAIN-1 data showed that the treatment effect of ESK-NS is not maintained when discontinuing treatment after *only* 12 weeks in stable remission or stable response and this is explained further below. Consequently, patients who are in the continuation treatment phase are assumed to continue treatment.

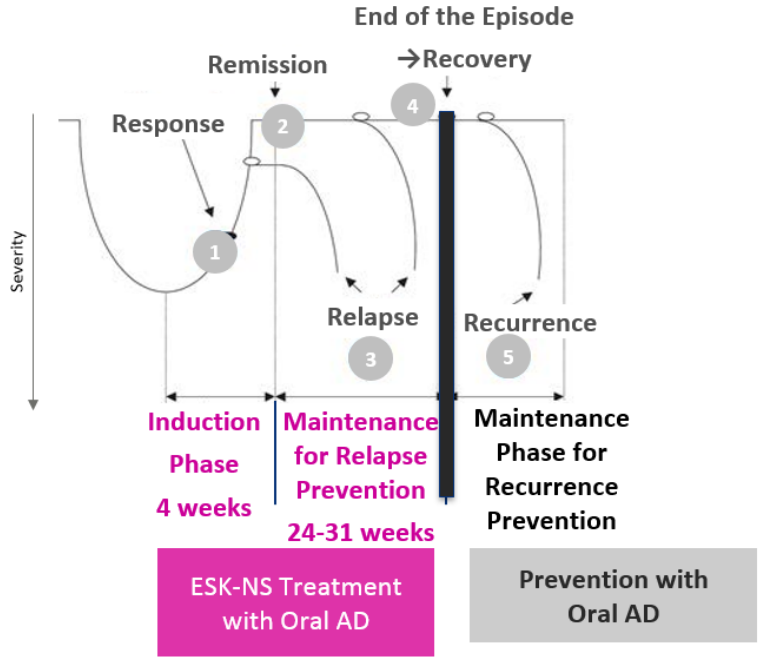


Figure 1: Treatment phases of ESK-NS + OAD treatment

	Timing of discontinuation is fundamental when considering maintenance of treatment effect after discontinuation It is well established that when remission has been achieved and sustained for a sufficient period of time, the risk of relapse falls. The episodic nature of the disease this means that patients have the possibility of exiting the episode and achieving full functional recovery. Clinical guidelines (e.g., NICE CG90, BAP, APA depression guidelines) describe the disease as episodic and this implies that a patient can get out of a depressive episode after a certain time in stable remission (i.e. in recovery). Specifically, NICE CG90 describes the course of an episode as follows: "*Phases of improvement with treatment consist of response (significant improvement) to remission (absence of depressive symptoms) which if stable for 4 to 6 months results in (symptomatic) recovery, meaning that the episode is over*"(1). NICE CG90 also states that after recovery, a further episode of depression is viewed as a recurrence to distinguish it from a relapse of the same episode. When the patient is in full functional recovery, which implies the patient is in full health, clinical guidelines (e.g., NICE CG90) indicate that discontinuing treatment should be considered. NICE CG90 recommends the following: *"Review with the person with depression the need for continued antidepressant treatment beyond 6 months after remission*". The conclusion that there is no impact of discontinuing antidepressant treatment whilst in a recovery health state is similar to findings from studies on OADs. Geddes and colleagues (2003) reviewed all published and unpublished trials available for review up to August 2000, in which continued antidepressant drug therapy was compared with placebo in patients who had responded to acute treatment with antidepressants (2). The authors found no evidence that the risk of relapse after withdrawal from active treatment in the placebo group was due to a direct pharmacological effect (for example, 'withdrawal' or 'rebound') since there was no increase

	of relapses within a month of drug discontinuation. This provides supportive evidence that this conclusion would also apply to discontinuation of ESK-NS treatment. In the economic model, after discontinuing treatment with ESK-NS, the patient will remain on their newly initiated OAD, which will help them to remain in the same recovery health state. It is important to note that patients are still at a continuous risk of recurrence from the recovery health state, which means they can enter back into a MDE health state. Therefore, the treatment effect from ESK-NS + OAD may not be maintained indefinitely, which is reflective of the nature of the disease. **Interpretation of the SUSTAIN-1 data** SUSTAIN-1 provides data to inform the question of discontinuing ESK-NS treatment after 16 weeks of treatment (12 weeks in stable remission or response)**.** As noted above, in the disease of MDD and TRD, the risk of relapse/recurrence is dependent on the timing, and hence the treatment phase, of when the treatment is discontinued. It is clear from the SUSTAIN-1 data that after responding to the 4-week induction treatment and becoming stable remitters or responders after a 12-week optimisation treatment, patients should continue ESK-NS treatment to prevent relapse. The SUSTAIN-1 data show that the treatment effect of ESK-NS is not maintained after completely discontinuing treatment after 16 weeks (12 weeks in remission or response). The maintenance of effect (for any treatment); however, is expected to remain after continuing treatment for 6-9 months, as the depressive episode has ended and the patient has entered a recovery health state. This is based on the understanding of the natural history of the disease. The SUSTAIN-1 data is informative at this time point, as it shows that, after a significant amount of time (6-9 months) is spent in a stable remission state, the risk of relapse/recurrence decreases.

	In the model, patients who are in the response state will continue ESK-NS treatment for the duration of the time that they remain in the response health state. This assumption has been discussed and validated by four UK clinicians as described in CS Document B section 3.2.9.2.3. **Market research** A market research study was conducted to understand the expected real-world treatment duration of ESK-NS to inform and validate the economic modelling of ESK-NS for Health Technology Assessments (HTA), specifically the NICE submission. 25 consultant psychiatrists from the UK were recruited, screened and interviewed via telephone using the blinded ESK-NS product profile and structured questionnaire. The psychiatrists provided insights on the expected treatment duration of ESK-NS and indicated that they expect the largest proportion of patients who have been in a stable remission for 9 months to discontinue ESK-NS treatment. In addition, after two years in stable remission, only a limited proportion (<20%) of patients is expected to need to continue ESK-NS treatment, see response to next sub-questions below for more details. In addition to the feedback on the expected treatment duration of ESK-NS in NHS clinical practice, the psychiatrists also provided insights of what factors play a role in considering to discontinue ESK-NS, and it was clear that they would not decide to discontinue ESK-NS if that would have a negative effect on the patient's health state. As a result, the treatment duration estimates were felt to present a realistic estimation of treatment duration in NS clinical practice. Further details regarding the market research are provided below and in Appendix A. **Additional clarification: Risk of recurrence in CS** The risk of recurrence is the main outcome measure for patients who are in recovery and reflects the nature of the disease and the fact that treatment effect of ESK-NS may not be continued indefinitely after discontinuation

	for those patients in recovery. We have described in CS Document B section 3.4.4.8. that currently for the recurrence rate for ESK-NS + OAD, as well as for OAD + PBO-NS, the pooled rate of both treatment arms from the SUSTAIN-1 study was used. It is important to note that the pooled recurrence rate is already a reduction in risk of recurrence versus the actual recurrence rate from the SUSTAIN-1 ESK-NS + OAD arm, so this could be considered a deterioration of the treatment effect of ESK-NS after patients start actively discontinuing ESK-NS. In the CS base-case model, the ESK + OAD was assumed to discontinue over time in recovery and the recurrence risk was the same for both arms (2.88% per 4-week). If ESK + OAD is only stopped due to loss of efficacy, then it is reasonable to apply the recurrence risks from the SUSTAIN-1 study per arm, namely 2.43% for ESK + OAD and 3.56% for OAD + PBO-NS per 4-week cycle. <u>References</u> 1. Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, Rush AJ, Weissman MM. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. Arch Gen Psychiatry. 1991 Sep;48(9):851-5. 2. Geddes JR, Carney SM, Davies C, Furukawa TA, Kupfer DJ, Frank E, Goodwin GM. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. Lancet. 2003 Feb 22;361(9358):653-61.
Would stopping treatment for reasons other than lack of response have an impact on health-related quality of life?	Available evidence suggests that discontinuing ESK-NS after 9 months in stable remission does not have an impact on health-related quality of life (HRQoL) and no withdrawal symptoms are expected based on the trial data and pharmacokinetic profile. It is important to note that patients are expected to continue treatment with OAD for recurrence prevention after discontinuing ESK-NS.

As noted above, the available evidence shows that the majority of patients with TRD follow an episodic course of their disease, which implies that a patient can get out of a depressive episode after a certain time in stable remission. When the patient is in recovery, which implies the patient will be back in full health, clinical guidelines indicate that discontinuing treatment should be considered. After discontinuing treatment when in recovery, the patients are expected to remain in the same recovery health state, and as long as they stay in the same health state there will be no impact on their HRQoL.

There are no direct data specifically designed for this topic. As such, a *post-hoc* analysis of SUSTAIN-1 data on the impact of discontinuing ESK-NS at the end of the two-week follow-up period was conducted. Only patients randomised to ESK-NS were analysed. The analysis consists of patients who were in a stable remission or stable response state and had at least 24 weeks of ESK-NS treatment (i.e. starting from week 16, at randomisation). The utility scores (after applying Van Hout conversion) at the moment of termination of the study and at the end of the two-week follow-up period were compared to identify if stopping treatment with ESK-NS had an impact on health-related quality of life. A paired T-test (i.e. testing if the difference in utility score before/after was different) was conducted. The results are summarised in Table 3 below.

Table 3: Post hoc analysis of SUSTAIN-1 data

Population	Status at randomisation	N	Mean	SD	P-value
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]						

In summary, the difference in utility scores between moment of termination of the study and discontinuing ESK-NS treatment and end of follow up period were small and not significant, which shows that discontinuing ESK-NS after 9 months- 1.5 years (1.5 years was for the patient with longest DoT in SUSTAIN-1) in stable response or remission does not have an impact on HRQoL. Numerically, utility scores of the combined stable responder and stable remitter group even continued to improve after treatment discontinuation. The data, however, need to be interpreted cautiously as the differences are very small.

As noted above, the market research provided insights from UK psychiatrists on the expected treatment duration of ESK-NS. In addition, they also provided insights of what factors play a role when considering discontinuing ESK-NS, and it was clear that they would not decide to discontinue if that would have a negative effect on the patient's health state (see Appendix A).

Withdrawal symptoms

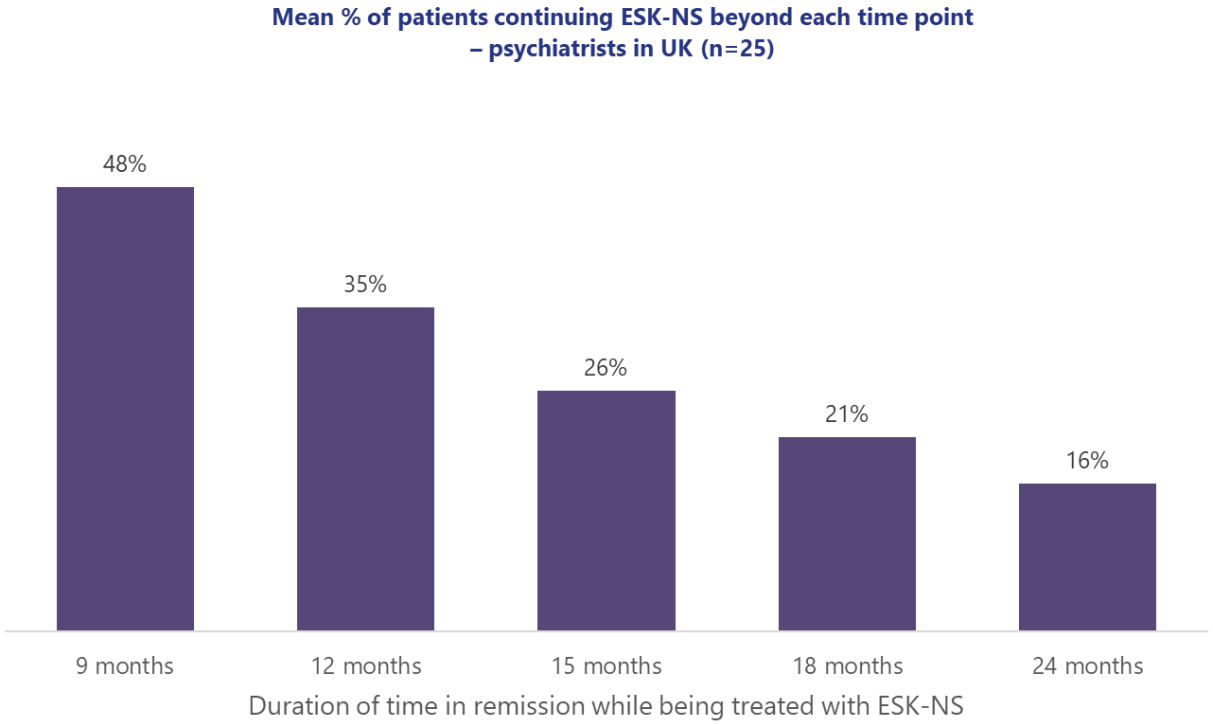
Based on the long-term trial data, there was no evidence suggesting a withdrawal syndrome (set of symptoms occurring in discontinuation or dosage reduction of some types of medications and recreational drugs) after discontinuing ESK-NS in the longer-term studies. The Physicians Withdrawal Checklist - Standardised assessment of 20 symptoms (PWC-20) was developed as a reliable and sensitive instrument to assess benzodiazepine-like discontinuation symptoms[1]. This scale includes some of the symptoms that have been reported with ketamine withdrawal by case reports. In the absence of a more specific scale, all Phase 3 studies

	included the PWC-20 to systematically assess the risk of dependence with short- and long-term use of esketamine nasal spray. Across studies, the changes in withdrawal symptoms assessed by the PWC-20 after cessation of ESK-NS + OAD treatment were consistent with observed changes in symptoms of depression and anxiety. Reported symptoms were primarily mild to moderate in severity. New worsening of depressive symptoms was observed mostly in non-responders to ESK-NS who discontinued treatment due to lack of therapeutic response. Based on the PWC-20 results, there was no evidence suggestive of a distinct withdrawal syndrome in the longer-term studies, i.e., at 1 or 2 weeks after cessation of ESK-NS treatment in SUSTAIN-1 or at 1, 2, or 4 weeks after cessation of ESK-NS treatment in SUSTAIN-2. Furthermore, stopping short-or long-term use of ESK-NS is shown to be highly unlikely to be associated with withdrawal syndrome as assessed by stability, frequency, onset, and severity of PWC-WS (Physicians Withdrawal Checklist- Withdrawal Symptoms- subscale), Serious Adverse Events reported during follow-up phase, low rate of positive urine drug screens and absence of drug-seeking behaviours. PWC-WS were higher in non-responders to ESK-NS; apart from discontinuation of ESK-NS, this may be related to other changes in therapy, i.e. discontinuation of current OAD and/or initiation of new antidepressant during follow up phase[2]. Levels of esketamine in the circulation do not accumulate with twice-weekly or lower dosing frequency. The steady state level for physical dependence is not achieved, therefore a drug withdrawal is not expected, as suggested by the PWC-20 results. Thus, if dosed as proposed in the SmPC, no clear withdrawal syndrome is expected after discontinuation of ESK-NS. The potential for abuse, diversion, and overdose of ESK-NS by the patient is minimised due to the product's design and the administration taking place under the supervision of a

	healthcare professional in the clinic. ESK-NS will be a prescription-only medicine with Schedule 2 controlled drug status, which will have to comply with the existing legal framework in the UK. Overall, the available evidence suggests that there is no impact on HRQoL from stopping treatment with ESK-NS. Data from a *post-hoc* analysis of SUSTAIN-1, market research of UK psychiatrists, and the absence of withdrawal syndrome after discontinuing ESK-NS in the long-term Phase 3 studies provide supportive evidence for this conclusion. <u>References</u> 1. Rickels K.; Garcia-Espana F., et al. Physician Withdrawal Checklist (PWC-20). J Clin Psychopharmacol. 2008;28,447-51 2. Aluisio L.; Wajs E., et al. Withdrawal Symptom Assessment- Intranasal Esketamine: Open-label Safety Study of Esketamine Nasal Spray and An Oral Antidepressant In Treatment-resistant Depression. Presented at ASCP 2019 Meeting, May 28-31, 2019; Scottsdale, Arizona.
What is the expected duration of a course of ESK-NS treatment?	The duration of a course of ESK-NS is expected to be highly variable between patients, due to the heterogenous nature of the disease. Currently, there are a lack of clinical trial data to directly answer this question. In the absence of data, clinical opinion is the most robust source of information. UK as well as international clinical experts expect that the largest proportion of patients who have been in stable remission for 9 months can discontinue. After two years in stable remission, only a limited proportion (<20%) of patients is expected to need to continue ESK-NS treatment. For patients who are in a stable response (not remission) health state, a larger minority (36%) are expected to need to continue treatment beyond two years.

	To answer this question, Janssen have conducted three projects to gain insights from UK and also international clinical experts on the expected treatment duration of ESK-NS in clinical practice: • An advisory board with four UK clinical experts (as included in CS) • The aforementioned market research with 25 UK psychiatrists (new evidence) • A survey amongst four UK clinical experts and investigators in the ESK-NS trials (new evidence) In addition, Janssen has reached out to five UK clinical experts and five international clinical experts to inform the development of discontinuation guidance for ESK-NS. The totality of evidence from all of these interactions means that the assumption that ESK-NS is continued for all patients indefinitely, as included in the ERG base case, is clinically infeasible and not appropriate for NICE decision making. Furthermore, the assumption that antidepressant treatment is continued indefinitely is inconsistent with previous NICE decision making in this disease area. In TA367, the company had assumed that people remain on treatment for 6 months after remission in the maintenance phase. The ERG considered that this was reasonable and consistent with NICE's guideline on depression in adults. It is appropriate to therefore assume that discontinuation of ESK-NS treatment will occur whilst in remission. **Advisory board with four UK clinicians** The CS base case assumptions have been based on feedback from four UK clinical experts as discussed at an advisory board conducted in June 2019. In summary, it was assumed that after nine months in stable remission, patients would be in recovery. A total of 35.4% of patients were assumed to stop ESK-NS immediately upon achieving recovery. This percentage represents patients in SUSTAIN-1 who had ≤2 total

	number of MDD episodes, including the current episode. These patients were estimated to be at low risk of relapse based on available evidence (1-4) and could discontinue ESK-NS at recovery. For the remainder of patients, treatment with ESK-NS + OAD was continued during the maintenance phase and discontinued over time. A 4-week discontinuation risk of 25% for ESK-NS + OAD was used during recovery and validated with the four UK clinical experts. OADs are used to prevent recurrence in the recurrence-prevention phase (5, 6), as per current clinical practice. See CS Document B section 3.2.9.2.3. for more details. For patients who are in the response health state (not remission), it was assumed they would remain on ESK-NS + OAD without active discontinuation, which is a conservative assumption considering the feedback from the clinicians, who state that an estimated 36% of patients who remain in the response (not remission) state will need to continue ESK-NS treatment beyond two years. **UK market research** 25 UK psychiatrists were asked how long patients with TRD who have achieved sustained and stable remission for 36 weeks (nine months) ESK-NS + OAD would be expected to (dis-)continue treatment with ESK-NS at different time points (while continuing treatment with an OAD alone). 52% of patients with TRD are expected to discontinue ESK-NS after 9 months in stable remission, and 16% are expected to continue for ≥2 years. See figure 2 below for more details.



Furthermore, the psychiatrists indicated that on average 52% of patients to be at low risk of relapse and 48% of patients to be at high risk of relapse of those who achieve sustained and stable remission for 36 weeks (nine months) after treatment with ESK-NS. Of the low risk patients in remission after 9 months of treatment, on average, clinicians estimated that after 9 months in stable remission, 65% of the patients will discontinue ESK-NS, and that by 24 months, 10% patients would be likely to remain on treatment with ESK-NS.

	Of the patients at high risk of relapse, clinicians estimated that after 9 months in stable remission, 33% of the patients will discontinue treatment with ESK-NS and that by 24 months, 18% would likely remain on therapy with ESK-NS. The UK psychiatrists indicated that the risk of relapse is associated with the following factors: • Number of previous depressive episodes & duration of depression • Previous history of frequent / severe relapses & treatment resistance • Suicidal attempts / suicidal ideation • Residual symptoms • History of trauma / sexual abuse • Addiction e.g. drugs, alcohol • Co-morbid conditions e.g. diabetes, anxiety • Family history of mental illness • Adverse life events e.g. unemployment, stress • Environmental and psychosocial factors e.g. lifestyle, living alone, poor social support networks, poor coping skills, cognitive impairment • Patient non-compliance For patients who achieve response with ESK-NS + OAD but do not achieve remission (defined as >50% improvement from baseline in the MADRS score but excluding those patients who achieve MADRS ≤12), 36% are expected to continue treatment beyond 2 years in a real-world setting.

The feedback from the market research also indicated that the most important factor influencing the duration of treatment (DoT) of ESK-NS in clinical practice is the NICE guidance on treatment (dis-) continuation for ESK-NS.

An analysis incorporating the above assumptions on duration of treatment (DoT) of ESK-NS of stable remitters in the CS base case as well as the revised based case after inclusion of carer disutility (0.122, see response to Issue 8) results in an ICER of £7,389 per QALY. In this scenario, 52% of the patients who have been in stable remission for 9 months are assumed to discontinue ESK-NS treatment, while 16% of the patients would still be on ESK-NS treatment after 2 years. Patients who remained in the response (not remission) health state are conservatively assumed to remain on ESK-NS + OAD treatment throughout the time horizon.

Company base case ICER	**Revised base case ICER (incorporating carer disutility)**	**Revised base case ICER and MR assumption on DoT of remitters**
£7,699	£6,043	£7,389

ESK-NS clinical trialists survey

A survey was conducted with 4 UK ESK-NS clinical trial investigators to better understand the expected real-world treatment duration of ESK-NS, based on the clinical experience of using ESK-NS in the clinical development program, see Appendix B for more details.

All clinicians surveyed were principal investigators of one of the long-term ESK-NS studies. Three clinicians were consultant psychiatrists and one clinician was a general practitioner with special interest in psychiatry. All four UK clinicians agreed with the assumption that after a total of 9 months of being in a remission health state, the

	patient will enter a recovery health state and they agreed that upon entering the recovery health state, ESK-NS could be discontinued while the OAD is continued for recurrence prevention. UK clinicians estimated there to be 61.25% (mean) of patients discontinued after 9 months in remission. The range of responses (40-75%) indicate that the base case assumption used in the CS of 35.4% should be considered an underestimate of the likely proportion of patients who would be able to stop ESK-NS treatment at 9 months. All respondents clearly agreed with the assumption that patients who are currently in their 1st or 2nd MDD episode will be sufficiently stable to stop ESK-NS treatment upon entering the recovery health state and continue the OAD for re-currence prevention. All respondents agreed that only a small number of very chronic patients would remain on treatment in recovery which is aligned with the approach taken in the base case economic model. The clinicians expect 3%-15% of patients who are in recovery to discontinue ESK-NS every month. Of those patients continuing treatment in recovery, UK clinicians estimated that on average 8% (range: 3-15%) of patients would be expected to discontinue ESK-NS every month (while continuing re-currence prevention with the OAD). An analysis incorporating the above assumptions on DoT of ESK-NS of stable remitters in the CS base case as well as the revised based case after inclusion of carer disutility (0.122, see response to Issue 8) results in an ICER of £7,498 per QALY. In this scenario, 61.25% of the patients who have been in stable remission for 9 months are assumed to discontinue ESK-NS treatment, while 8.33% (range: 3-15%) of patients would be expected to discontinue ESK-NS every month. Patients who remained to be in the response (not remission) health state are conservatively assumed to remain on ESK-NS + OAD treatment throughout the time horizon.

Company base case ICER	Revised base case ICER (incorporating carer disutility)	Revised base case ICER and ESK-NS trialists' assumption on DoT of remitters
£7,699	£6,043	£7,498

Discontinuation guidance

At the NICE technical engagement meeting on 6th November 2019, it was discussed and agreed that guidance on discontinuation of ESK-NS would help to mitigate the uncertainty around the DoT of ESK-NS in NHS clinical practice. Janssen have reached out to 10 clinical experts in the field of TRD, including five UK clinical experts. The discontinuation guidance was built upon the already included recommendations on treatment (dis-) continuation included in the SmPC. See below sub-question on criteria for discontinuing ESK-NS for more details, including the proposed discontinuation guidance.

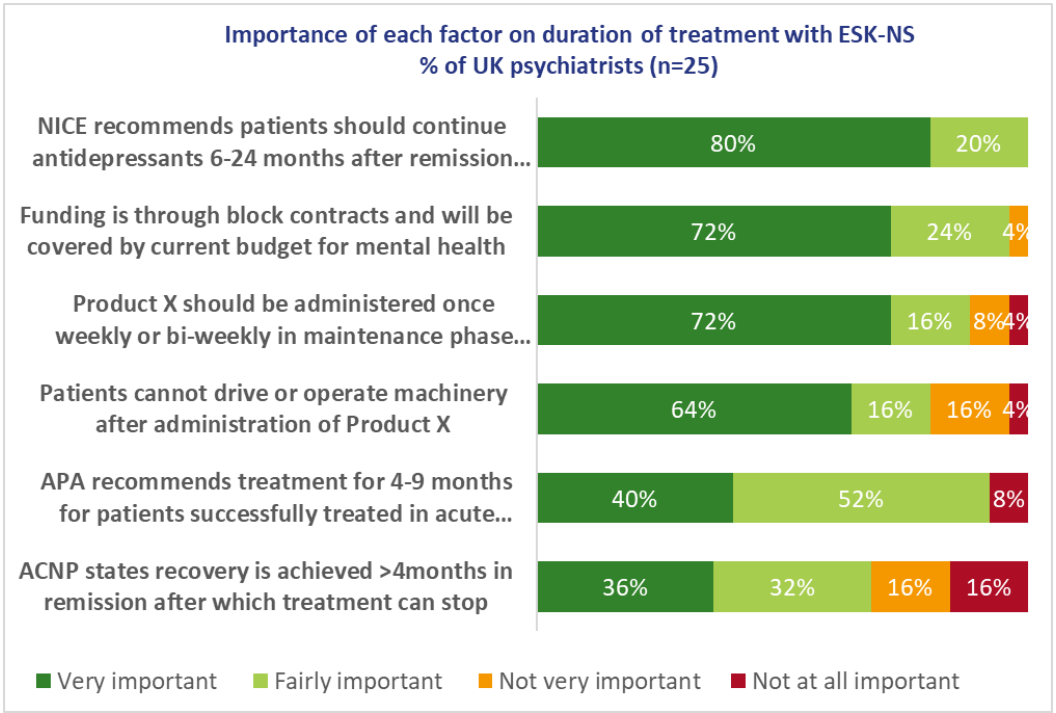
References

1. Keller MB, Shapiro RW. Major depressive disorder. Initial results from a one-year prospective naturalistic follow-up study. J Nerv Ment Dis. 1981;169(12):761-8.
2. Kessing LV, Andersen PK. The effect of episodes on recurrence in affective disorder: a case register study. J Affect Disord. 1999;53(3):225-31.
3. Mueller TI, Leon AC, et al. Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. Am J Psychiatry. 1999;156(7):1000-6.
4. Solomon DA, Keller MB, et al. Multiple recurrences of major depressive disorder. Am J Psychiatry. 2000;157(2):229-33.

	5. National Institute for Health and Care Excellence. Depression in adults: recognition and management (CG90). 2009. 6. Hansen R, Gaynes B, et al. Prevention of major depressive disorder relapse and recurrence with second-generation antidepressants: A systematic review and meta-analysis. Psychiatric services (Washington, DC). 2008;59(10):1121-30.
Are there likely to be some people who remain on ESK-NS treatment for life?	The totality of evidence from all interactions that Janssen has had with clinicians suggests that the proportion of patients that will be treated with ESK-NS for life is very limited and possibly only a few patients. These patients, who are considered a minority group, are thought to follow a chronic course of the disease. The risk of relapse for these patients remains such that the benefit of continuing ESK-NS + OAD treatment outweighs the risk of discontinuing ESK-NS. The 25 UK psychiatrists who participated in the aforementioned market research indicated the following: • A small proportion (estimated to be 16%) of patients who have been in a stable remission for nine months may have a more chronic progression of the disease and may need to continue treatment for ≥2 years. • 10% of the patients who are in stable remission and considered at low risk of relapse are expected to continue ESK-NS treatment for ≥2 years. • Of the stable remitters who are at high risk of relapse, 18% are expected to continue ESK-NS treatment for ≥2 years. For patients who achieve response with ESK-NS + OAD but do not achieve remission, it is expected that 36% will continue treatment beyond 2 years in a real-world setting.

What proportion of patients would stop ESK-NS treatment by 2 years in the recovery state?	Most patients with TRD who have been in stable remission for two years (estimated to be 84%) will discontinue ESK-NS treatment. The largest proportion (52%), however, are expected to discontinue ESK-NS treatment after 9 months in stable remission.
What are the criteria for stopping ESK-NS treatment in the acute, continuation and maintenance phases?	At the NICE technical engagement meeting on 6th November 2019, it was discussed and agreed that guidance on discontinuation of ESK-NS would help to mitigate the uncertainty around the DoT of ESK-NS in NHS clinical practice. Janssen have reached out to 10 clinical experts in the field of treatment resistant depression, including five UK clinical experts (see Appendix C). The discontinuation guidance was built upon the already included recommendations on treatment (dis-) continuation included in the SmPC, which are repeated below: • Evidence of therapeutic benefit should be evaluated at the end of induction phase to determine need for continued treatment • The need for continued treatment should be reexamined periodically • After depressive symptoms improve, treatment is recommended for at least 6 months After consulting with clinical experts, the proposed additional guidance on discontinuing ESK-NS are provided below: • **Assess patients after 4 weeks for response to determine the need for continued treatment** • **The need for continued treatment should be reexamined every 6 months** • **Treat patients who are in stable remission for a total of 9 months after achieving remission and then consider discontinuing esketamine nasal spray while continuing the oral antidepressant for recurrence prevention, based on:**

	○ **the observation of the reduced risk of relapse beyond week 20-26 (= month 9 in stable remission) in SUSTAIN-1 compared to week 1-20** ○ **the observation of convergent Hazard Ratios (HRs) around week 20-26 (= month 9 in stable remission) in SUSTAIN-1** ○ **patients entering the recurrence prevention phase which is managed by an oral antidepressant alone** • **Treat patients who remain in a response health state (not remission) for up to two years based on the higher risk of relapse compared to remitters** ○ **Patients who move from response state to remission, can be treated as per the guidance for patients who are in a stable remission** • **Exceptions will occur based on clinical judgement (e.g., some patients may exceptionally require longer treatment as is seen with ECT)** In summary, in the acute and continuation treatment phase, the criteria for discontinuation will mainly be based on the safety and efficacy of ESK-NS. In the maintenance phase, it will be based on the proposed discontinuation guidance, and clinical judgement of the impact of discontinuing ESK-NS treatment on stability in terms of risk of relapse/recurrence of a patient. In the aforementioned market research, the 25 UK psychiatrists indicated that they that they would decide not to discontinue ESK-NS if that would have a negative effect on the patient's health state. The feedback from the market research also indicated that the most important factor informing the DoT of ESK-NS in clinical practice is the NICE guidance on treatment (dis-) continuation for ESK-NS.

Could the requirement for attendance at clinics and the need for monitoring influence compliance with treatment?	In the acute and continuation treatment phases, the requirement for attendance at clinics may improve compliance with treatment. The 25 UK psychiatrists who participated in the market research indicated that attendance at clinics and the need for monitoring would be one of the factors impacting the DoT of ESK-NS in NHS clinical practice, however it is not considered to be the most important factor. The most important factor is the NICE guidance on treatment (dis-)continuation. Funding through block contracts and subsequently the administration plus monitoring requirements are also considered to be important factors, but not by all psychiatrists. The important of each factor cited by the psychiatrists are presented below, in Figure 3:  Figure 3: Importance of each factor on duration of treatment with ESK-NS

Is there any evidence that ESK-NS is a disease modifying treatment?	There is no direct evidence that shows that ESK-NS modifies the disease. ESK-NS + OAD has shown to enable patients to reach response, remission and improved functioning earlier and at greater rates compared to an OAD plus PBO-NS. The impact of getting more patients with TRD into response, remission and improved functioning earlier on the further progress of the disease, could be considered disease modifying. Typically, the severity of the MDD episode increases with each recurrence, rendering effective treatment an increasing challenge[1]. ESK-NS is intended to address the significant unmet medical need for new treatment options for TRD due to its novel mechanism of action and evidence of rapid, robust, and sustained efficacy[2,3]. Efficacy data are provided in CS document B section 2.6 from the global clinical ESK-NS development program in TRD. The studies involve >1,700 adults exposed to ESK-NS. Results from the clinical studies show that ESK-NS works quickly (within hours to days) to relieve symptoms of depression, achieving high rates of response and remission within the first 4 weeks of starting ESK-NS + OAD treatment[2]. Furthermore, in a relapse prevention study using a randomised withdrawal design, continued treatment with ESK-NS provided a statistically significantly longer time to relapse relative to discontinuation of ESK-NS (in the context of continued OAD therapy) in patients who were in stable remission or stable response after 16 weeks of therapy with ESK-NS + OAD[3]. In the TRANSFORM-2 study, after just 2 doses of ESK-NS, 16 to 19% of adults showed at least a 50% improvement in clinician-rated depression symptoms as measured by the MADRS (approximately twice as many as in the OAD + PBO-NS group). At the end of induction treatment, 69% and 53% of patients treated with ESK-NS + OAD in these studies achieved this level of clinical response and remission (MADRS total score ≤12) respectively, compared to 52% and 31% of patients treated with OAD + PBO-NS which is much higher

	than expected from a newly initiated OAD in clinical practice (see Issue 3). The Number Needed to Treat (NNT) with ESK-NS + OAD for response was 6, and the NNT for remission was 5. Improvements in functional impairment and associated disability, as assessed by SDS, favoured the ESK-NS + OAD arm over OAD + PBO-NS (nominal 1-sided p≤0.003). Greater improvements in SDS translates into reduced impact of depressive symptoms on work, social, and family functioning. Because more patients get into remission and improved functioning when using ESK-NS + OAD, the overall course of the disease can be modified. Greater remission rates as well as improved functioning are claimed to be key to achieve the ultimate outcome: full functional recovery. Habert et al conducted a literature review and identified 30 antidepressant studies reporting predictor criteria and outcome measures[5]. Shorter duration of the current depressive episode and duration of untreated depression are associated with better symptomatic and functional outcomes in MDD. Early improvement of depressive symptoms predicts positive response and remission, and early functional improvement predicts an increased likelihood of functional remission. This may accelerate recovery and lower the risk of residual functional deficits[5]. ESK-NS has the potential to address the critical unmet medical need for patients with TRD due to its novel mechanism of action. ESK-NS is a NMDA receptor blocker hypothesised to modulate glutamate in the brain to restore synaptic function in key brain regions involved in mood. Unlike currently available OADs, which primarily target the monoamine system, esketamine targets the glutamate system to directly address the pathophysiology of depression, providing an additional treatment option for patients who have not responded to treatment that targeted the monoamine system. <u>References</u>

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Issue 5	
Is severity of TRD a proxy for risk of excess mortality due to suicide?	Available evidence shows that it is appropriate to add excess mortality risk to the depressive health state in the model. MDD is the leading cause of disability worldwide according to the WHO[1] and is associated with a reduction in life expectancy by 10 years[2]. TRD is a life-threatening disorder, given the high suicide risk and increased likelihood to experience co-morbid physical conditions. The risk of suicide in patients with TRD is well characterised. Approximately 30% of patients with TRD attempt suicide at least once in their life time[3,4,5]. This is >16 times higher compared with the 1.8% in the general European population[6,7]. This is recognised in the NICE guideline on depression in adults (CG90), which notes that increased feelings of hopelessness and

	helplessness lead to an increase in risk of suicide. NICE CG90 also state that having depression leads to over a four-times higher risk of suicide compared with the general population, which rises to nearly 20 times in the most severely ill[8]. In addition to the increased risk of suicide, patients with TRD experience a more severe and protracted course of illness and are more likely to experience co-morbid physical conditions than patients with MDD who do not develop treatment resistance. These patients are also more likely to have co-morbid mental health problems and have significant short- and long-term social impairment[9], which ultimately contribute to the increased risk of excess mortality. The increased mortality associated with TRD is well characterised within the literature. There are no studies available that specifically shows a direct link between the depressive health state and mortality. Multiple studies; however, provide supportive evidence for the increased excess mortality risk in the TRD population. Studies have shown there is a higher all-cause mortality in patients with TRD compared with non-TRD MDD patients[10]. In a cohort study using a US claims database identifying 355,942 MDD patients and 34,176 patients with TRD, TRD was associated with a significantly higher mortality compared with non-TRD MDD (adjusted HR: 1.29; 95% CI 1.22–1.38; $p < 0.0001$). Survival time was significantly shorter in the TRD cohort compared with the non-TRD MDD cohort ($p < 0.0001$). In a Swedish study, Reutfors et al. reported that patients with TRD had a 35% higher all-cause mortality than non-TRD MDD patients (adjusted HR: 1.35; 95% CI: 1.21-1.50). The study reported a 5-year relative survival of 0.97 for patients with TRD compared with the general population[11]. Bergfeld and colleagues[12] conducted a meta-analysis that included 30 studies to evaluate the suicide rate among TRD patients undergoing various types of treatment. In this study, the overall incidence of completed

	and attempted suicides was 0.47 and 4.66 per 100 patient-years (PY), respectively. Taken together, these studies provide evidence of the increased risk of mortality of TRD compared to MDD. Studies also suggest that the severity of depressive symptoms is associated with the risk of suicide. This finding is to be expected, given that suicidality is a core symptom of MDD. Melhelm et al[13] conducted a longitudinal study in the US with more than 12 years of follow up, which showed that the severity and variability of depression symptoms may be the only indicator of suicide attempt above and beyond clinical characteristics. The trajectory of depressions symptoms with the highest mean scores and variability over time was the only trajectory to predict suicide attempt (odds ratio [OR], 4.72; 95% CI, 1.47-15.21; P = .01). This finding is also suggested by Dold et al[14], who observed the higher degree of suicidality was in a cohort of 1410 MDD patients, the higher degree of the depressive symptom severity. Further, Dold et al suggest that the failure of achieving treatment response leads to suicidality, or that, at least, the relationship can be regarded as bidirectional (see figure 4 below).

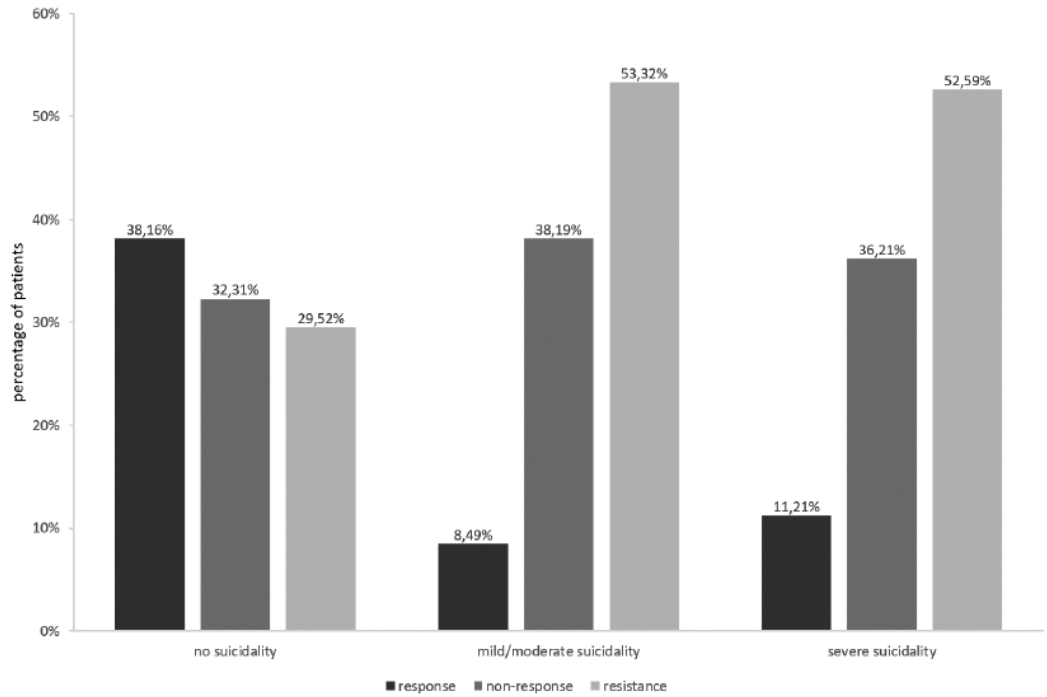

Figure 4: Treatment response, nonresponse and resistance rates in the no, mild/ moderate and severe suicidality patient groups (14)

Other studies provide supportive evidence of the relationship between depressive symptoms and mortality risk. A 5-year, prospective, open-label observational study including 795 patients with TRD suggests that reducing the symptoms of depression is associated with a reduction in all-cause mortality[15]. The study showed that all-cause mortality was markedly lower in the VNS (Vagus Nerve Stimulation) arm (3.53 per 1,000 person-years [95% CI=1.41, 7.27]) than in the treatment-as usual arm (8.63 per 1,000 person-years [95% CI=3.72, 17.01]).

	This reduction in all-cause mortality is correlated with the clinical response rate between the VNS arm and the treatment-as-usual arm through the 5-year follow-up period (cumulative response rates, 67.6% [95% CI=63.4, 71.7] and 40.9% [95% CI=35.4, 47.1], respectively; p<0.001). It is possible that the intervention, VNS, directly reduced the mortality rate, however, it is more likely that the reduction in all-cause mortality was due to the reduction in depressive symptoms. The increased risk of all-cause mortality, however, is not associated solely with suicide. Co-morbidities contribute to the increased rate of all-cause mortality. NICE CG90 also state that depression can exacerbate the pain, distress and disability associated with physical health problems as well as adversely affecting outcomes. Depression combined with chronic physical health problems incrementally worsens health compared with physical disease alone or even combinations of physical diseases[16]. In addition, for a range of physical health problems, findings suggest an increased risk of death when comorbid depression is present[17]. In coronary heart disease, for example, depressive disorders are associated with an 80% increased risk, both of its development and of subsequent mortality in established disease, at least partly through common contributory factors[18]. Based on a review of clinical studies, Carney et al.[19] concluded that TRD is associated with a higher cardiovascular mortality as compared with treatment responders. In heart failure, depression is related to increased all-cause mortality risk[20]. There is a high rate of comorbidities in patients with TRD, at around 13% at 4 to 8 years, or 32% at 7 years of co-morbidity duration, with variations observed between studies[21]. Additionally, the incidence of co-morbidities is significantly higher in patients with TRD compared with patients with non-treatment resistant forms of MDD[22]. The conclusions reached by these studies and NICE CG90 are also aligned to the views expressed to the NICE technical team and by the clinical expert, who stated that ‘more generally successful treatment of depression leads to a reduction in all-cause mortality.’

	The association between TRD and mortality is complex, as several risk factors for TRD, as well as several detrimental outcomes from TRD, may themselves be associated with increased mortality. Among these are social and functional impairment, comorbidities such as substance use disorders (SUD), anxiety disorders, and personality disorders, frequent and recurrent episodes of depression, and frequent hospitalisations [21, 23, 24]. Given the evidence within the literature, however, it is clear that patients who do not achieve clinical response and remain in a MDE health state have an increased mortality risk. Considering all of the available evidence, it can be concluded that the assumptions of an increased risk of mortality in the MDE and response health state are reasonable to be included in the economic model. **Additional clarification: Clarifying applied methodology** The draft NICE Technical Report includes a background/ description of the issue in Issue 5 (mortality). Currently, the draft Technical Report states the following sentence: 'The company estimated the number of suicide attempts for patients in each health state and then estimated the proportion of these suicide attempts that were fatal, giving the total of patients who died from suicide.' As acknowledged in the factual inaccuracy check of the ERG report, it is not correct that the model used in the NICE submission included this methodology of incorporating mortality. As such, Janssen request that this statement is removed from the NICE Technical Report given that it is not implemented in the economic model. It is important to note that the ERG is incorrect in their conclusion that 'The ERG was concerned with the company's assumption that the risk of excess mortality will decrease when treated with ESK-NS'. This is a factual inaccuracy, as the risk of excess mortality is linked to the MDE health state and not to ESK-NS treatment (see response below).

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Would ESK-NS treatment effect the risk of mortality?	It is important to note that no intervention is directly linked with a risk of mortality in the economic model. Aligned with the available evidence (see above), excess mortality is assigned to patients who remain in the MDE health state and the response health state, independent of treatment arm. In the draft NICE Technical report, the Technical team states that 'It also considers that it has not seen sufficient evidence to support the assumption that treatment with ESK-NS + OAD reduces risk of excess mortality.' Janssen wish to clarify that the assumption stated above has not been made in the CS. This was also noted by Janssen in the factual inaccuracy check on the ERG report (Issue 7: the data to inform the effect on mortality) which has been previously submitted to NICE. While having MDD or TRD may increase a person's risk for suicide, ESK-NS is not assumed to be linked to reducing or preventing suicidality. Currently, there are a lack of data to show a direct treatment effect of ESK-NS on the risk of mortality. The available data have insufficient follow-up in the TRD patient population to show a direct effect of ESK-NS on mortality. As noted in the factual inaccuracy response to the draft ERG report (Issue 7: the data to inform the effect on mortality), the ESK-NS clinical development programs were not designed to provide comparative evidence on mortality (including completed suicide) between ESK-NS + OAD and OAD + PBO-NS. As noted above in the response to Issue 1, suicidality is a core symptom of MDD and TRD in this vulnerable patient population. As noted previously in the factual inaccuracy response to the draft ERG report, the completed suicides in the ESK-NS clinical development programme were recorded as safety endpoints. The three completed suicides are from the trials 2003, SUSTAIN-2 and SUSTAIN-3. The completed suicide in 2003 occurred three weeks after the last dose of ESK-NS during the post treatment follow-up phase. SUSTAIN-2 and SUSTAIN-3 are

	single-arm, open label studies. The suicides occurred in the clinical studies in patients with TRD as of the clinical cut-off date of 4 March 2018 (1,861 unique patients treated with ESK-NS + OAD; 1045 patient-years of exposure and 486 unique patients treated with OAD + PBO-NS; 100 patient-years of exposure). Based on the severity of patients' underlying illness, and the lack of a consistent pattern, the suicides were considered unrelated to ESK-NS treatment. All cases of completed suicide occurred in completed and ongoing open-label studies/study phases with no control group. It is important to put into perspective the rate of completed suicides in the ESK-NS study arms in comparison to a control arm in this vulnerable patient population. A recent meta-analysis of 30 studies that evaluated treatment of patients with TRD with ECT, deep brain stimulation, or vagus nerve stimulation found that completed suicide incidents were 0.47 per 100 patient-years, respectively.[0] As an indirect comparison to the published background data in patients with TRD, the completed suicide rate of 0.29 per 100 patient-years of treatment observed in the Phase 2/3 TRD studies is lower than the completed suicide rate of 0.47 per 100 patient-years of treatment reported in this meta-analysis of 30 TRD studies that included over 15,000 patients with TRD.[0] As the trials in the ESK-NS clinical development programme do not provide comparative efficacy on completed suicide between ESK+AD and PBO+AD, there is no direct link between ESK-NS and mortality. Aligned to the available evidence, it was assumed that additional mortality from completed suicide is per health state and not by treatment arms (see answer to sub question for Issue 5 above for additional details). <u>References</u> Bergfeld IO, Mantione M, Figee M, Schuurman PR, Lok A, Denys D. Treatment-resistant depression and suicidality. J Affect Disord. 2018;235:362–367

Are the interventions in the meta-regression representative of standard care in the UK?	In the Bergfeld et al (1) publication, the interventions included were deep brain stimulation (DBS, n=9), VNS (n=9), ECT (n=5), treatment-as-usual (n = 3), capsulotomy (n = 2), cognitive behavioural therapy (n = 2), ketamine (n = 1), and epidural cortical stimulation (n = 1). These interventions included in the meta-regression are not widely available in the UK and therefore considered not representative of standard of care in the UK for patients with TRD. Out of these treatments, ECT is the most commonly used. From data generated from the SLaM CRIS database, ECT is only used by a very small proportion (1.7%) of patients aged 18-64 with TRD (2). As noted in the response to the previous question, no intervention is directly linked with a risk of mortality in the economic model. Aligned with the available evidence (see above), excess mortality is assigned to patients who remain in the MDE health state and response health state, independent of treatment arm. <u>References</u> 1. Bergfeld IO, Mantione M, Figee M, et al. Treatment-resistant depression and suicidality. J Affect Disord. 2018;235:362-367 2. Janssen data on file. Esketamine_DoF_12Jun2019_HEMAR_TM_002
Issue 6: Cost of clinic visits	
In clinical practice, how many patients could 1 nurse concurrently supervise and monitor following administration of ESK-NS?	Janssen acknowledges that there may be a range of clinic staffing models to deliver the administration of ESK-NS per locality, once adopted in NHS clinical practice. It is clear, however, throughout all interactions with UK healthcare professionals on this topic, that a ratio of 1:1 of nurse-patient is not clinically realistic. It is important to note that a 1:1 ratio, which is used in the ERG base case, is even more ambitious than the aspirational ratio (1:2) recommended for Intensive Care Units (ICU) by the Royal College of Nursing (1). Unlike patients typically presenting in ICU, during the self-administration of ESK-NS, patients with TRD are not

	critically acutely ill patients. Furthermore, the expected label wording does not stipulate “continuous monitoring” (unlike the stipulation for surgery, or ICU). Under the heading ‘Post Administration Observation’ the SmPC states ‘After dosing with Spravato, blood pressure should be reassessed at approximately 40 minutes and subsequently as clinically warranted (see section 4.4). In addition it states: ‘Because of the possibility of sedation, dissociation and elevated blood pressure, patients must be monitored by a healthcare professional until the patient is considered clinically stable and ready to leave the healthcare setting’ Given the nature of the non-acute condition of the patients, and the transient and mild nature of the most common AEs, a 1:1 ratio is not plausible in NHS reality. Clinical trialists and nurses involved in the ESK-NS trials indicated that patients mainly preferred to be left alone, in silence and in darkness during the post-administration observation phase. The available evidence shows that one nurse would be able to supervise several patients concurrently. Feedback from multiple UK clinical experts on their understanding of the safety profile, and how ESK-NS will be implemented in the NHS, is that two nurses would be able to monitor up to between 10-20 patients at the same time. This feedback is aligned to the feedback received from the clinical expert, who stated that there is no ‘reason why one nurse could not monitor multiple patients at the same time’, given the minor tasks required during the observation time period. As noted in Section B.3.2.11.2 of the NICE submission, following discussions with UK HCPs, it was assumed that the self-administration of ESK-NS would be managed in a clinic environment. Based on trial investigators’ experience, the supervision of self-administration of a group of six patients in a clinic could be managed by one

or two nurses. It was conservatively assumed that two nurses were needed for the consecutive supervision of the self-administration of ESK-NS for six patients.

Subsequently, Janssen has conducted market research with 59 UK psychiatrists from across the UK to estimate the number of patients that a nurse could concurrently observe during and after the administration of ESK-NS (2).

	Psychiatrists
England North	12
England Midlands	11
England South	11
Greater London	11
Wales	4
Scotland	10
Total	**59**

On average, clinicians estimated that one nurse would be able to monitor 4-6 patients concurrently. Clinicians indicated that in order to account for the costs of administration, it is appropriate to model multiple patients flowing through the system sequentially for self-administration (e.g., 6 or 12 patients) and in parallel for the post-self-administration observation time period. As noted above, it was conservatively assumed that two nurses were needed for the supervision of the consecutive self-administration of ESK-NS for six patients and one nurse per four to six patients for the subsequent monitoring. This results in an estimated cost per administration of £30.08-£35.29.

Ratio of nurses: patients for post-self-administration monitoring	Cost per patient per administration	Revised base case ICER	Revised base case ICER (including carer disutility of 0.122, see Issue 8 below)
1:6 (base case)	£30.08	£7,699	£6,043
1:5	£32.17	£7,856	£6,165
1:4	£35.29	£8,089	£6,349

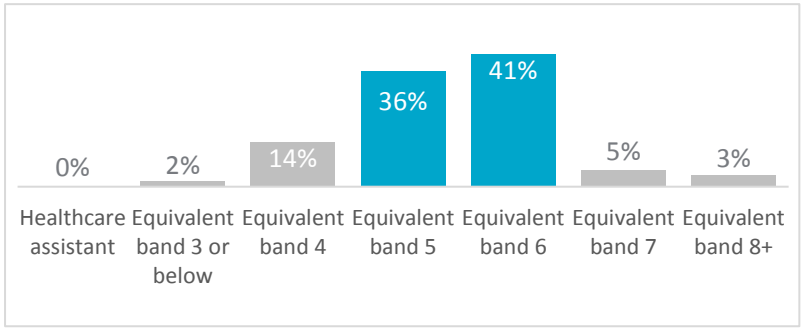
It is expected that, after increased experience with ESK-NS (after 1-2 years), it is reasonable that the efficiency of clinics would improve, and cost of administration per patient would subsequently further decrease. As such, the assumptions used for the cost of administration of ESK-NS above can be considered conservative when estimating the cost-effectiveness of ESK-NS to the NHS.

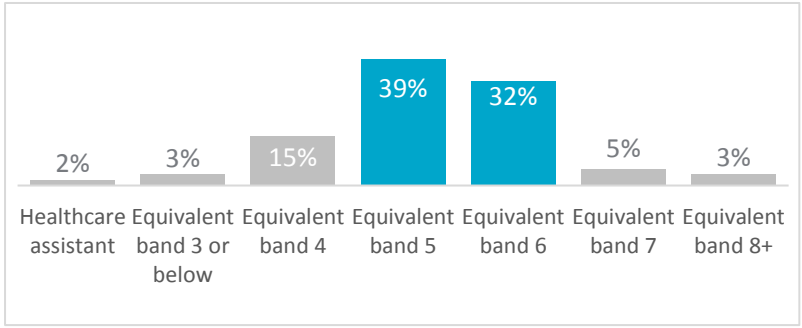
Additional clarification: Cost per health state

Janssen understand the technical team would also like to see evidence of how the health state costs were derived from the retrospective chart analysis. A full report, including the derivation of the cost per health state, was previously sent to the NICE Technical team in August 2019. This report details the objectives, methodology and full results of the retrospective chart analysis. Further information can be found in Appendix D.

References:

1. Royal College of Nursing, 2011. Guidance on safe nurse staffing levels in the UK.
2. Janssen, 2019. Data on File [Available on request]

What band would the nurse(s) be?	In the above-mentioned market research, psychiatrists were additionally asked their opinion for the band of nurse suitable to supervise the self-administration of ESK-NS and observe patients after the administration, based on their understanding of the safety profile. The results of the band of nurse suitable to supervise the self-administration and observe patients after administration are provided below: <u>Band of Nurse Suitable to Supervise Patients' Self-Administration of ESK-NS (n=59)</u>  The majority of psychiatrists (combined 77%) thought that a band 5 or band 6 nurse would be suitable to supervise the self-administration, with a minority supporting a band 4 (14%). The majority of psychiatrists also thought that a band 5 or band 6 (combined 71%) would be most suitable to observe patients' post-administration, with 15% suggesting an equivalent band 4 would be suitable.

	Band of Nurse Suitable to Monitor Patients Post-Administration of ESK-NS (n=59)  The use of a Band 5 nurse in the CS is based on feedback from 10 UK clinical experts at two different advisory boards. The only difference between a band 5 and band 6 nurse is that band 6 is trained and certified to undertake management activities. Given this is not required for monitoring patients after administration of esketamine nasal spray, a Band 5 nurse is used in the analyses.
Would non-attendance at clinic appointments affect the cost-effectiveness of ESK-NS treatment?	Janssen acknowledge there is some uncertainty regarding the issue of non-attendance at clinic appointments which cannot be resolved until the adoption of ESK-NS in real world NHS practice. The final draft SmPC provides guidance on missed treatment sessions to help mitigate the risks of treatment failure. The final draft SmPC states: *Missed treatment session(s)* In case one or two treatment sessions are missed, the next session should be scheduled when the next session was scheduled to occur based on current treatment frequency. If more than 2 treatment sessions have been missed, per clinical judgment, adjustment of the dose or frequency of Spravato may be clinically appropriate.

	Furthermore, data from the clinical trials show the incidence of non-attendance as minimal. For continued non-attendance at clinic appointments, which translates into treatment discontinuation, the impact is dependent on the timing and treatment phase that the patient is in. This is related to the above Issue 4 on the risk of relapse in the continuation phase compared to the maintenance phase.
Issue 7: Adoption	
Are there any infrastructure investments associated with the adoption of ESK-NS + OAD that need to be accounted for in the model?	Infrastructure cost should not be accounted for in the model, as feedback indicates that there is existing infrastructure within the NHS that can be used. As noted by the NHS commissioning expert, adoption of the use of ESK-NS will require adjustments in the service delivery for patients with TRD. These adjustments to existing service delivery are primarily due to the requirement for clinic visits for the administration of ESK-NS and post-administration observation, which is to manage any transient adverse events, such as sedation and dissociation. Regarding these costs to account for the adjustment of services for the administration for ESK-NS, these are already accounted for in the economic model. According the NICE Methods Guide (Section 5.5.8), 'if the introduction of the technology requires changes in infrastructure, costs or savings should be included in the analysis'. Across the country, Janssen has received consistent feedback from local NHS healthcare professionals and clinical experts showing that additional infrastructure investments are not required for the adoption of ESK-NS + OAD. Feedback collected from 71 Pharmacists (including CCG pharmacists, Chief Pharmacists, and Mental Health Pharmacists), 16 Medical and Clinical Directors, 31 Service Leads, CCG Leads and Medicines Management,

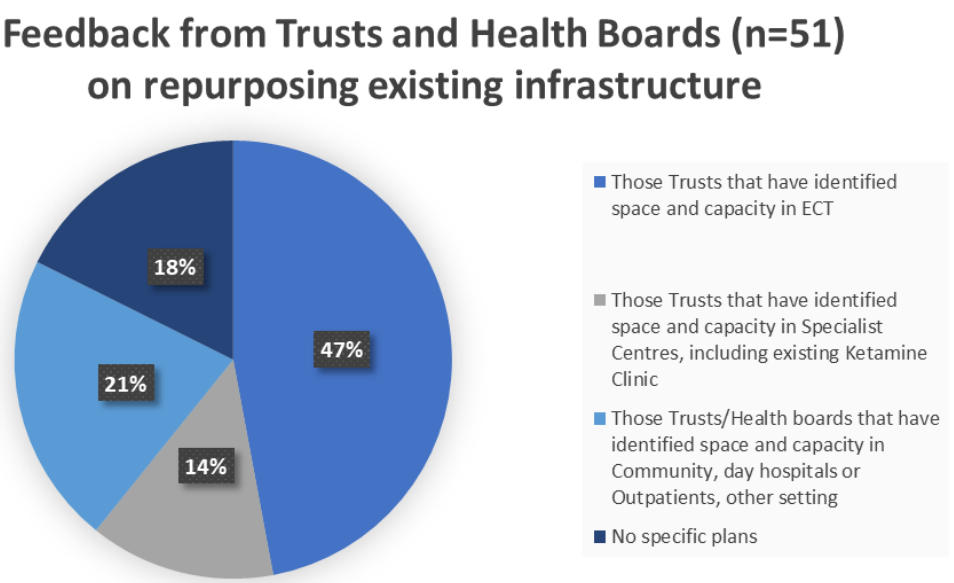
10 ECT managers and leads across the NHS all indicate that existing infrastructure is to be used for ESK-NS.

A geographic breakdown of the healthcare professionals can be found below:

NHS healthcare professionals	Region that HCPs are from
3 Service Leads 4 Chief Pharmacists 1 AHSN Mental Health programme lead 3 ECT managers	[redacted]
5 Mental Health Pharmacists 1 Associate Medical Director 1CSU Medicine Management 13 CCG Medicine Management 1 private hospital club director	[redacted]
12 MH pharmacists 5 ECT/CMHT managers 4 Clinical Directors 3 D&T Chairs.	[redacted]
3 Chief Pharmacists 5 MH Lead Pharmacists (NI Trusts) 3 Medical Directors 2 Clinical Directors 1 H&SC Board Meds Management 1 CSU Meds Mgmt lead	[redacted]
2 chief pharmacists 3 MH Lead Pharmacists 2 Service Leads 1 Medical Director	[redacted]
5 Chief pharmacists 1 Medical director 2 Service leads 2 CCG Primary Care Network GP MH leads 1 Private Hospital MH Pharmacist	[redacted]

2 Private hospital service leads	
9 Chief Pharmacists 1 CCG pharmacist 3 Clinic leads	[redacted]
6 Chief pharmacists, 1 Medical Director 1 CCG/ STP MH lead	[redacted]
2 Medical Directors 6 Chief Pharmacists 2 ECT leads	[redacted]
10 Lead MH Pharmacists	[redacted]

From the feedback received from Trusts and Health Boards, 82% of the sites said that they will repurpose existing premises for the adoption of ESK-NS into the NHS and 18% had no specific plans yet. 47% of the Trusts indicated that they intent to repurpose space and capacity of existing ECT suites, 21% said they will repurpose the space and capacity of outpatient clinics, 14% have identified space and capacity within specialist centres (incl. ketamine clinics) for ESK-NS adoption and 18% was not sure (yet), see Figure below.



The table below includes the various Trusts and Health boards per category.

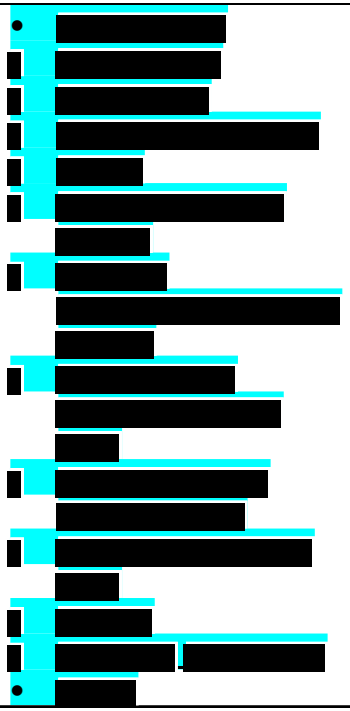
Those Trusts that have identified space and capacity in ECT	Those Trusts that have identified space and capacity in Specialist Centres, including existing Ketamine Clinic	Those Trusts/Health boards that have identified space and capacity in Community, day hospitals or Outpatients, other setting	No specific plans
24	7	11	9

Existing pharmacy services will cover the storage, transportation, disposal and monitoring facilities, and adequate medical equipment will be repurposed from ECT suits or outpatient resuscitation equipment. This is

	aligned with the view of the clinical expert input, who stated that it may be possible that existing infrastructure could be used as treatment locations (e.g., ECT clinics, wards, day hospitals, outpatient clinics etc). As such, no additional infrastructure investment costs should be included in the model. Furthermore, no extensive additional training investment is required from discussions with NHS healthcare professionals and from the clinical trial sites. Janssen aims to provide the required medical training to healthcare providers. As such, no additional infrastructure investment costs should be included in the model. Furthermore, no extensive additional training investment is required from discussions with NHS healthcare professionals and from the clinical trial sites. Janssen aims to provide the required medical training to healthcare providers. **Additional clarification: feasibility of adoption within 90 days** During the technical engagement call, NICE and the NHS representative were asking the question if it would be feasible for the NHS to adopt the new technology within 90 days, as is standard for most other new pharmacological interventions. Janssen begun advance notifying for the launch of ESK-NS in TRD and the related expected budget implications in August 2018 to resource managers, lead pharmacists, service managers and commissioners across the NHS. In addition, a service advance notification was developed and communicated to the same local NHS stakeholders on the service needs to administer ESK-NS, which begun in July 2019. During the discussion after sharing one of the advanced notifications, Janssen have received feedback from 33 trusts on the following questions:

- Have we had any feedback on how the NHS will adopt ESK-NS within the 90-day period after TAG (do they think they can do this)?
- Would you consider the 90-day period sufficient post TAG for ESK-NS implementation?

The feedback on these questions shows that most Trusts (n=16) feel that 90 days is sufficient for implementation, 13 are not sure and four Trusts do not think that 90 days is sufficient. Please see below table for more details.

Yes- 90 days is sufficient	**Not Sure**	**No- 90 days isn't sufficient**
16	13	4
		

	• [redacted]		
Issue 8: Uncaptured benefits to carers			
Are there any additional benefits and costs to carers of people with TRD receiving ESK-NS?	The impact of TRD is not confined to the patient; a substantial burden is also commonly experienced by family members or friends who are acting as carers, reducing the ability of carers to support themselves, and increasing their need for healthcare. As noted previously, the NICE guideline on depression (CG90) acknowledges the additional significant impacts on the carers of people with depression. Carers are impacted heavily in most areas of their lives. Qualitatively, there can be a sense of helplessness/hopelessness from carers around people with TRD as it can be difficult for them to know how to help and there can be a sense of uncertainty. There can be expectations from healthcare professionals as to how carers should be coping or acting with this difficult condition. Carers reported feeling drained or exhausted and that their relationships, mental health, work performance and financial lives were negatively affected when looking after someone with TRD. As well as additional burden to carers, TRD has additional costs to carers. As noted in Section B.3.4.4.7 of the Company Submission, a UK specific study[1] has shown there is a significant societal economic burden associated with TRD due to lost productivity and carer burden. The study found the mean total societal cost per patient with TRD to be £22,124, and 80% of which was due to lost work and care required of families. A scenario analysis (Table 75 of the company submission) showed the potential impact of including wider societal		

<table>
<tr><td></td><td>costs. Given the substantial economic burden of TRD, the true cost-effectiveness of ESK-NS is underestimated in all scenarios currently being considered by NICE and the ERG.

<u>References:</u>
1. McCrone P, Rost F, et al. The economic cost of treatment-resistant depression in patients referred to a specialist service. J Ment Health. 2018;27(6):567-73</td></tr>
<tr><td>If so, are all the additional benefits and costs to carers captured within the model?</td><td>Given the substantial societal burden of TRD noted above, the benefits of treatment with ESK-NS extend directly to carers, as well as directly by the patient with TRD. In all previous scenarios considered by the ERG and NICE, the impact of these benefits for carers is not accounted for in the model. Janssen propose to include data from a recently conducted, unpublished cross-sectional UK health related quality of life (HRQoL) study in the economic model. This cross-sectional study was conducted to assess the HRQoL of carers of patients with symptomatic TRD as well as patients with TRD in remission. For further information regarding the study, a full study report can be found in Appendix E. A summary of the main results from the study can be found below in Table 4:

Table 4: Summary of carer quality of life for carers of patients with symptomatic TRD and carers of patients with TRD in remission
<table><tr><th></th><th colspan="2">Carer Groups</th></tr><tr><th>Results</th><th>Symptomatic TRD</th><th>TRD in remission</th></tr><tr><td>No. of participants</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Gender (n, % female)</td><td>[redacted]</td><td>[redacted]</td></tr></table></td></tr>
</table>

	EQ-5D-5L (mapped to 3L) index value (mean, 95% CI)**	[redacted]	[redacted]

* Score range 0-27 (higher scores indicate more severe depression), scores of 5, 10, 15 and 20 represent thresholds for mild, moderate, moderately-severe and severe depression, respectively; ** EQ-5D utility values were calculated by mapping the 5L descriptive system data onto the 3L valuation set using the mapping function developed by van Hout et al (2012)4 (also known as the Crosswalk Link Function).

Janssen propose to include a disutility in the model to estimate the wider impact, by deducting the difference in utility scores of between the two groups of carers. The study shows there is a difference in utility of [redacted] between carers of patients with symptomatic TRD and carers of patients with TRD in remission. The disutility of [redacted] is applied once per patient in the MDE health state, representing the impact on one carer per patient. Given that multiple people (parents, partners, children, and friends) will be directly affected by TRD, including the disutility in the model for only one carer per patient is conservative.

An analysis incorporating the above disutility ([redacted]) into the revised company base case model (previous base case ICER=£7,699) results in incremental QALY gain of 0.366 compared to 0.287 in the previous base case. This results in an ICER of £6,043 per QALY.

Company base case ICER	Revised base case ICER (incorporating carer disutility)
£7,699	£6,043

Appendices to Technical Engagement Response Form

Esketamine for treatment-resistant depression [ID1414]

About you

Your name	
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Janssen**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

A – UK market research on expected treatment duration of esketamine nasal spray
B – Survey report on ESK-NS treatment duration
C – Report on ESK-NS treatment discontinuation guidance development and validation
D - Additional information for calculation of health state costs from retrospective chart review
E – TRD QoL study report

Appendix A

Market research amongst UK psychiatrists: expected treatment duration of esketamine nasal spray in real world clinical practice

November 2019

Aim

A market research study was conducted to understand the expected real-world treatment duration of esketamine nasal spray (ESK-NS) to inform and validate the economic modelling of ESK-NS for Health Technology Assessments (HTA), specifically the NICE submission.

Study Objective

The study objective was to understand the likely duration of treatment with esketamine nasal spray, taking into account:

- The doctor's decision to discontinue treatment with ESK-NS (taking account of both their clinical judgement about the need for continued treatment for patients in remission / recovery and resourcing issues associated with the use of ESK-NS) and,
- The potential desire of patients in remission / recovery to stop treatment with ESK-NS (e.g. if they feel they no longer require this treatment and /or the impact of attending clinic sessions to receive treatment is no longer regarded as worthwhile by the patient, in the context of not being able to drive to clinic appointments).

Methodology

A blinded product profile and subsequent questionnaire were developed for use in a telephone survey. 25 consultant psychiatrists from the UK, including 20 in England and 5 in Scotland, were recruited, screened and interviewed via telephone using the product profile and questionnaire. Each interview lasted 30-40 minutes. These psychiatrists were required to fulfil the below criteria:

1. Seeing 10+ adult patients in the last month with moderate to severe depression excluding patients with bipolar disorder, schizophrenia or other psychotic illnesses:
2. Seeing 5+ patients/month with unsatisfactory response to two or more different antidepressants of an adequate dose and duration in their current depressive episode

Respondents were provided details of ESK-NS as product X and invited to comment on duration of use in a real-world setting. An independent market research agency (Synergy), commissioned by Janssen, undertook the telephone interviews with the psychiatrists; all interviews were conducted in October 2019.

The results below are from the full sample of UK consultant psychiatrists.

Sample Overview

The geographic location of the consultant psychiatrists are found below in Table 1.

Table 1: Geographic location of respondents

Region	Number of respondents per region (n=25)
London	8
South England	5
Midlands / East England	2
North England	5
Scotland	5

Summary and Interpretation of Results

The below section presents the key questions and results from the survey, which are used in a scenario analysis for the NICE submission for ESK-NS. The full results can be found in the *Full Results* section below.

Q4: Factors which influence real world treatment duration of Product X (ESK-NS)

Overall, clinicians recognised a number of factors which influence real world treatment duration of ESK-NS, including patient's circumstances, geographic location, level of social support to access services, homelessness, patient compliance, existence of co-morbid conditions, side effects and funding (how long the budget may cover the costs of ESK-NS).

Q10: Proportion of high risk and low risk patients

On average, clinicians estimated 52% of patients to be at low risk of relapse and 48% of patients to be at high risk of relapse of those who achieve sustained and stable remission for 36 weeks (nine months) after treatment with Product X (ESK-NS).

Q11a: Proportion of low risk patients in remission remaining on therapy

Of the low risk patients in remission after 9 months of treatment, on average, clinicians estimated that by 24 months, 10% patients would be likely to remain on treatment with ESK-NS.

Low risk patients in remission continuing therapy beyond each time point	UK psychiatrists Mean response (n=25)
9 months/36 weeks	**35%**
12 months	**22%**
15 months	**16%**
18 months	**12%**
24 months	**10%**

Q12 a: Proportion of high risk patients in remission remaining on therapy

On average, clinicians estimated that by 24 months, 18% of high-risk patients in remission would likely remain on therapy with ESK-NS.

High risk patients in remission continuing therapy beyond each time point	UK psychiatrists Mean response (n=25)
9 months/ 36 weeks	**67%**
12 months	**53%**
15 months	**44%**
18 months	**37%**
24 months	**18%**

Q13: Clinical approach to treatment discontinuation

100% of psychiatrists (25/25) agreed with the statement that:

'**I would expect to continue product X if I was concerned that the patient would be likely to relapse or experience a recurrence as a consequence of discontinuation'**

88% of psychiatrists agreed with the following statement (12% neither disagreed or agreed):

'I would only discontinue product X if I felt confident that the patient would be unlikely to relapse or experience a recurrence as a consequence of this. 1/5 psychiatrists did neither disagree or agree with the statement.'

Full Results

The sections below present the questions and mean results from the UK consultant psychiatrists.

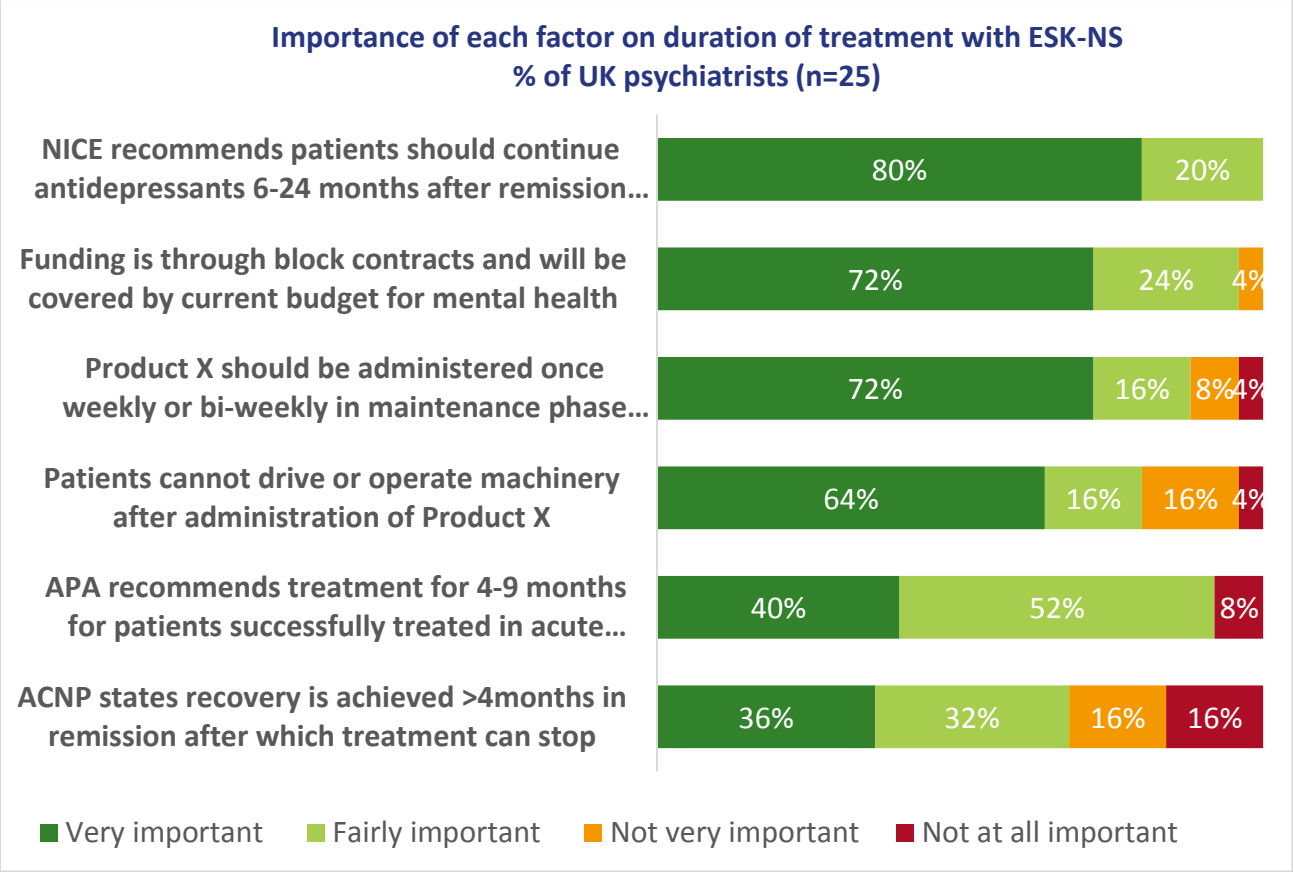
Q1a. What % of your patients who achieve and maintain stable remission remain on one antidepressant therapy for >2years?

Q1b. What % of your patients who achieve and maintain stable remission after treatment with two antidepressant treatments in combination remain on both antidepressants for >2 years?

% patients - mean response	UK consultant psychiatrists (n=25)
% patients in remission continuing to be treated with one antidepressant for >2 years	45%
% patients in remission on two antidepressants continuing to be treated with two antidepressants for >2 years	36%

Note: the results shown above contrast very strongly with data from the literature. In a study of five primary care practices in England, only 41% of patients were treated with OADs reported continuing with treatment over six months of therapy (1).

Q3. Please can you confirm how important each of the following factors would be in terms of influencing how long patients will be treated with product X, on a scale of very important, fairly important, not very important and not at all important



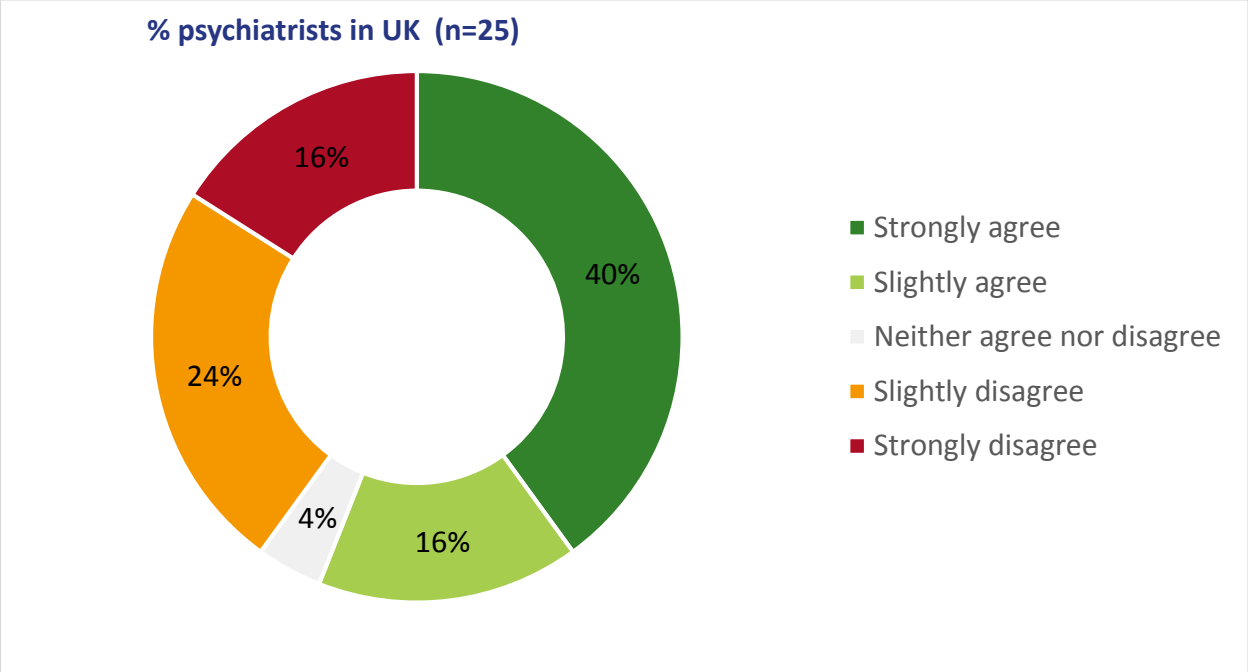
Q4 What other factors, if any, will influence how long patients will remain on treatment with product X in a real-world setting?

- Efficacy and tolerability of treatment
- History of relapse / Duration and intensity of previous episodes
- Patient's circumstances including both environmental & social factors
    - Geographic location - rural areas may present logistical difficulties; patients may not drive
    - Level of social support to access services
    - Patients moving home
    - Homelessness
- Patient compliance / concordance
    - Patients may choose to discontinue treatment once they feel their depression has improved
    - Support from the carer will impact on patient concordance
- Existence of physical co-morbidities affecting ability to attend clinic
- Adverse life events e.g. problem with relationships, losing a job may encourage longer continuation
- Funding: How long the budget covers the costs of treatment

Q5. I'd firstly like to ask you to consider **patients who achieve response** with product X nasal spray **but do not achieve remission** (defined as >50% improvement from baseline in the MADRS score, but excluding those patients who achieve MADRS ≤12). What proportion of these patients, if any, would you expect to receive treatment with product X for >2 years in a **real-world setting**?

	Total UK psychiatrists mean response
% of patients who achieve response but not remission expected to continue treatment >2 years in a real-world setting	**36%**

Q6. I'd now like to focus only on those patients who **achieve remission** (**IF NECESSARY, SAY:** defined as MADRS score of 12 or less) as a result of treatment with product X in combination with an oral antidepressant. To what extent would you agree or disagree with the suggestion that for patients who achieve remission on treatment with product X nasal spray + an oral antidepressant and have remained in sustained remission for 36 weeks (nine months), product X nasal spray could be stopped, with the oral antidepressant continued for recurrence prevention?



Q7a Please consider a scenario where 100 patients under your care who have failed two prior antidepressants, have achieved sustained and stable remission for 36 weeks (nine months) on product X + an oral antidepressant. How many of these 100 patients would you expect to discontinue treatment with product X at this point (continuing treatment with an oral antidepressant alone) and how many would you expect to continue on product X +oral antidepressant despite having been in sustained and stable remission for 36 weeks (nine months)

Patients in remission continuing Product X beyond each time point	Total sample of UK psychiatrists (n=25) Mean response
9 months (36 weeks)	40% (10/25)
12 months	16% (4/25)
15 months	4% (1/25)
18 months	24% (6/25)

24 months	16% (4/25)

Q8 We've been discussing the potential duration of the use of product X in **patients achieving sustained and stable remission**. Thinking about this groups of patients, which patient characteristics would you associated with high risk vs low risk of relapse despite achieving sustained remission?

Higher risk of relapse associated with:

- Number of previous depressive episodes & duration of depression
- Previous history of frequent / severe relapses & treatment resistance
- Suicidal attempts / suicidal ideation
- Residual symptoms
- History of trauma / sexual abuse
- Addiction e.g. drugs, alcohol
- Co-morbid conditions e.g. diabetes, anxiety
- Family history of mental illness
- Adverse life events e.g. unemployment, stress
- Environmental and psychosocial factors e.g. lifestyle, living alone, poor social support networks, poor coping skills, cognitive impairment
- Patient non-compliance – e.g. due to weight gain / sexual dysfunction with oral antidepressant; limited engagement with psychological treatments
- Varying perceptions of patient age and gender impacting on risk of relapse; some regard young adults, older males, menopausal women at higher risk

Q9 To what extent would you regard each of the following patients with MDD at a high or low risk of relapse despite achieving sustained remission?

Patient history of depressive episodes	Total UK psychiatrists (n=24*) mean response
Patients in remission with residual symptoms	• 42% (10/25)
Patients being treated for their first depressive episode	• 8% (2/25)
Patients with 1 or 2 prior depressive episodes	• 50% (12/25)
Patients with 3 or more prior depressive episodes	• 92% (22/25)

*1 psychiatrist did not answer due to a lack of time

Q14 To what extent would you agree or disagree with the following statements: I would expect most of the patients treated with product X and an oral antidepressant who have remained in stable remission for 36 weeks (nine months) to remain in remission/recovery after this point for another 36 weeks if they were to discontinue treatment with Product X while continuing to receive an oral antidepressant to prevent recurrence

1) Agree: 40%
2) Neither agree nor disagree: 32%
3) Disagree: 28%

References:

1. Hunot VM, Horne R, et al. A cohort study of adherence to antidepressants in primary care: the influence of antidepressant concerns and treatment preferences. Prim Care Companion J Clin Psychiatry. 2007;9(2):91-9.

Appendix B: Survey report on ESK-NS treatment duration

Survey of UK clinicians: expected treatment duration of esketamine nasal spray in real world clinical practice

Aim

A survey was conducted to better understand the expected real-world treatment duration of esketamine nasal spray, based on a mixture of clinical experience of using esketamine nasal spray in the clinical development programme and clinical expert opinion after reviewing the clinical data for esketamine nasal spray.

Methodology

The Janssen medical team approached a number of leading specialists in psychiatry. All clinicians surveyed were principal investigators of one of the long-term esketamine nasal spray studies. Clinical experts were individually approached by the Janssen medical team and asked four key questions:

Question 1: From your experience of treating patients and the results of the SUSTAIN 1 trial, do you agree with the assumption that after 40 weeks of being in a remission health state on esketamine nasal spray plus oral antidepressant (OAD), the patient enters a recovery health state, and esketamine nasal spray could be stopped, and the OAD continued for recurrence prevention?
If you do not agree, at what time point should this be? Why?

Question 2: At the time point answered above, what % of patients with treatment-resistant depression (TRD) (as defined above) would be able to stop esketamine nasal spray treatment, while continuing OAD treatment for recurrence prevention?

Question 3: Do you agree with the assumption that the patients who are currently in their 1st or 2nd MDD episode will be sufficiently stable to stop esketamine nasal spray treatment upon entering the recovery health state and continue the OAD for re-currence prevention?

Question 4: After continuing esketamine nasal spray plus OAD into recovery, what % of patients would you expect to discontinue esketamine nasal spray every month (while continuing re-currence prevention with the OAD)?

Each clinical expert was also asked whether they would consent to being acknowledged as contributing to the survey, provided the individual responses remain anonymised.

As each clinical expert was approached individually, each response reflects that individual's practice at their own institution, without bias or influence from other respondents.

Sample Overview

Three clinicians were consultant psychiatrists and one clinician was a general practitioner with special interest in psychiatry.

Clinician 1	Consultant Liaison Psychiatrist
Clinician 2	Consultant Psychiatrist In-Patient Services
Clinician 3	General Practitioner with special interest in psychiatry
Clinician 4	Consultant Psychiatrist

Results

A tabulated summary of all four responses is provided in Table 1.

Table 1: Clinical expert responses to questions relating to their expected esketamine real world treatment duration

Respondent	Question 1	Question 2	Question 3	Question 4
1	Yes	70%	Yes	60-70% (at 9 months) thereafter the cessation rate would be less than 5% because very chronic dependant group of patients
2	Yes	60%	Yes	Can only answer with data - cannot speculate. If patients were restarted on esketamine nasal spray in trial this will give us the answer. They should continue to be monitored whilst reducing to the dose to monthly for 2-3 months. And then stop depending on observed stability.
3	Yes	75%	Yes	15% of the remaining group would cease every subsequent month past the 36 weeks and a small proportion 10% would remain on it continuously.
4	Yes	40%	Yes	3-5%

Summary and Interpretation of Results

Question 1: From your experience of treating patients and the results of the SUSTAIN 1 trial, do you agree with the assumption that after 40 weeks (9 months) of being in a remission health state on esketamine nasal spray plus oral antidepressant (OAD), the patient enters a recovery health state, and esketamine nasal spray could be stopped, and the OAD continued for recurrence prevention?

If you do not agree, at what time point should this be? Why?

All respondents clearly agreed with the assumption that after a total of 9 months of being in a remission health state, the patient will enter a recovery health state. All respondents agreed that upon entering the recovery health state, esketamine nasal spray could be discontinued while the OAD is continued for recurrence prevention.

Question 2: At the time point answered above, what % of patients with TRD(as defined above) would be able to stop esketamine nasal spray treatment, while continuing OAD treatment for recurrence prevention?

The range of responses (40-75%) indicated that the base case assumption used in the submission of 35.4% should be considered an underestimate of the likely proportion of patients who would be able to stop esketamine nasal spray treatment at 9 months. UK clinicians estimated there to be 61.25% (mean, calculated by taking sum of 70% + 60% + 75% + 40% (= 245%) and divide this by 4) of patients discontinued after 9 months in remission.

Question 3: Do you agree with the assumption that the patients who are currently in their 1st or 2nd MDD episode will be sufficiently stable to stop esketamine treatment upon entering the recovery health state and continue the OAD for re-currence prevention?

All respondents clearly agreed with the assumption that patients who are currently in their 1st or 2nd MDD episode will be sufficiently stable to stop esketamine nasal spray treatment upon entering the recovery health state and continue the OAD for re-currence prevention.

Question 4: After continuing esketamine nasal spray plus OAD into recovery, what % of patients would you expect to discontinue esketamine nasal spray every month (while continuing re-currence prevention with the OAD)?

All respondents agreed that only a small number of very chronic patients would remain on treatment in recovery which is aligned with the approach taken in the base case economic model. The clinicians expect 3%-15% of patients who are in recovery to discontinue ESK-NS every month. Of those patients continuing treatment in recovery, on average, UK clinicians estimated that 8% (mean, calculated by taking sum of 15% + 4% + 5% (= 24%) and divide this by 3) of patients would be expected to discontinue esketamine nasal spray every month (while continuing re-currence prevention with the OAD).

A factor to consider when interpreting the responses to this last question is that respondents assumed that a smaller proportion (25-60%) of the total cohort would continue treatment in recovery state compared to the 64.6% as assumed in the company base case model.

Another factor which should be considered when interpreting these data is that respondents may be considering the overall cohort of patients, which includes those patients who only remain in the response health state after 9 months of esketamine nasal spray treatment. In the model it is assumed that all patients in the response health state continue to receive esketamine nasal spray treatment until they lose response or die. The answer from Respondent 3 indicate that this perhaps was the consideration when clinicians were asked this question.

Appendix C: Report on ESK-NS treatment discontinuation guidance development and validation

NICE Technical Engagement Report: Esketamine nasal spray (ESK-NS) Discontinuation guidance

Background and objective:

A series of 1:1 calls with psychiatrists from across the UK (n= 5) and globally (n= 5) were conducted in November 2019, with the purpose to:

1. better understand the expected and effective "real-life" treatment duration of ESK-NS based on the respondents' experience as an expert in the ESK-NS clinical development program and/or in the field of depression and their own clinical judgement.
2. Develop and inform discontinuation guidance for the use of ESK-NS in clinical practice based on the clinical experts' insights.

Specifically, the clinicians were asked their feedback on the proposed discontinuation guidance for ESK-NS (see below). It was asked when it would be appropriate to discontinue ESK-NS, based on patients' health outcomes, (achieving response, remission or recovery), health state and treatment phase while keeping in mind that patients would remain on an oral antidepressant (OAD) after they would discontinue ESK-NS. A breakdown of the country of origin of the clinicians is provided below:

	Country of origin/ practice
Clinician 1	UK
Clinician 2	UK
Clinician 3	UK
Clinician 4	UK
Clinician 5	UK
Clinician 6	USA
Clinician 7	USA
Clinician 8	Italy
Clinician 9	Poland
Clinician 10	Sweden

Draft guidance for discontinuation of ESK-NS

Discontinuation recommendations are already included in the SmPC. Clinicians were asked their opinion of the wording of the discontinuation guidance included in the SmPC, as well as the proposed additional guidance on discontinuing ESK-NS below:

Already included recommendations on treatment (dis-) continuation included in the SmPC

- 'Evidence of therapeutic benefit should be evaluated at the end of induction phase to determine need for continued treatment'

- 'The need for continued treatment should be reexamined periodically'
- 'After depressive symptoms improve, treatment is recommended for at least 6 months'

Proposed additional guidance on discontinuing ESK-NS

In addition to the above discontinuation recommendations in the SmPC, the below additional guidance was proposed to clinicians:

- 'Assess patients after 4 weeks for response (~30% can stop per our experience)='
- 'Treat remitters for a total of 9 months based on:
    - the observation of convergent HR around week 20-26 (= month 9 in stable remission) in SUSTAIN-1
    - patients entering recurrence prevention phase which is managed by oral antidepressant alone'
- 'Treat responders (not remitters) for a total of two years based on the higher risk of relapse compared to remitters and the NICE CG90 recommendations for the high-risk patients to continue treatment with an oral antidepressant for at least two years'
- 'Exceptions will occur based on clinical judgement (e.g., some patients may exceptionally require longer treatment as is seen with ECT)'

A summary of the high-level feedback received from all of the clinicians is provided below.

- Overall, 9/10 clinicians agreed with the proposed wording of the discontinuation guidance, of which most had some additional suggestions to refine the wording
- 1 UK clinician did not agree/disagree as there was too much uncertainty to be able to create discontinuation guidance

<u>Submitted Guidance for discontinuation of ESK-NS</u>

After consulting with all of these clinical experts, the proposed additional guidance on discontinuing ESK-NS was amended, and is provided below:

- Assess patients after 4 weeks for response to determine the need for continued treatment
- The need for continued treatment should be re-examined every 6 months
- Treat patients who are in stable remission for a total of 9 months after achieving remission and then consider discontinuing esketamine nasal spray while continuing the oral antidepressant for recurrence prevention, based on:
    - the observation of the reduced risk of relapse beyond week 20-26 (= month 9 in stable remission) in both treatment arms included in SUSTAIN-1 compared to week 1-20
    - the observation of convergent Hazard Ratios (HRs) of both treatment arms around week 20-26 (= month 9 in stable remission) in SUSTAIN-1
- Treat patients who remain in a response health state (not remission) for up to two years based on the higher risk of relapse compared to remitters and then consider discontinuing esketamine nasal spray

- Patients who move from response state to remission, can be treated as per the guidance for patients who are in a stable remission

- Exceptions will occur based on clinical judgement (e.g., some patients may exceptionally require longer treatment as is seen with ECT)

Appendix D: Additional information for calculation of health state costs from retrospective chart review

The appendix below presents additional clarification for the calculation of the health state costs from the retrospective chart review. Please see the full report, submitted to NICE previously for further information.

How was the study designed?

This study was designed to capture all healthcare resource used over a period, spanning from 1st January 2016 to the 31st May 2018. To be eligible patients must have been classified as TRD in the index window of 1st January 2016 to the 31st May 2016. By using an index window it was ensured that each patient had a minimum of 2 years follow up data but it should be noted patients who died within the follow up period were still eligible.

How was data collected?

The case report form (CRF) for this study was designed to collect individual uses of resources related to the treatment and management of TRD. This included the following:

- Consultations in primary and secondary care (e.g. GPs and psychiatrists)
- Use of Crisis Resolution Home Treatment (CHRTT)
- Use of non-drug treatments such as counselling or psychotherapy
- Use of drug treatments
- Any hospitalisations, including time spent in ICU or on a psychiatric ward

For each resource a patient used, their heath state at time of use was determined to allow us to categorise patients as being in a state of:

1. MDE (whether initial MDE or a relapse following remission)
2. Remission
3. Recovery

The definitions of these health states were determined via physician interviews and can be found in the study report.

How were data pooled for the health states?

The patient journey throughout TRD can see patients experiencing several health states prior to recovery, including several of the same health state (e.g. multiple states of relapse or remission can occur). This was observed in the data we collected but for analysis purposes data for each health state was pooled for any single definition. Therefore, it should be noted that patients may be counted more than once for each health state if they had experienced that health state more than once.
Data was pooled by taking each patient's calculated values (counts, counts per 28 days, costs, and costs per 28 days) during each health state, and reshaping the data to be at health state level. Therefore, all counts or costs associated with any period of that health state are grouped together, and the reported values represent all occurrences during any period of that health state.

How were the unit costs of each resource determined?

All resources collected in the CRF were assigned a unit cost derived from either the British National Formulary (BNF) or the Personal Social Service Research Unit (PSSRU 2017). The costs applied to each resource are displayed in Table 4 of the report.

How did were the overall counts and costs of each resource calculated?

Overall Counts

Unit costs were applied to each resource. For primary and secondary care consultations, hospitalisations and visit based therapies, a price per visit was applied. For drug costs a price per day was calculated from the per packet cost and applied using the dosing information provided in the chart abstraction. The counts of each resource use per patient was multiplied by the costs derived to produce a value for each resource use per patient. For each instance of resource use per patient the clinical state was determined (as per data abstracted in the eCRF) and collective costs applied from all patients in said clinical state. The resulting figure provided an overall cost per clinical state for each resource.
The data provided in this section was collected throughout the total duration of the follow-up period for all patients. The follow-up period, therefore, within each clinical state is not standardised and varies for all patients. Therefore, the data for overall counts, and indeed overall costs, should not be compared directly across health states. Follow up periods also vary between patients within the same health state. Care should be taken when interpreting the unstandardised counts.

Counts per 28 days

Data in the report has also been standardised to a 28-day period to allow for a uniform follow-up period for all patients included in the analysis. The 28 days refers to 28 days of health state time; it is unrelated to length of resource utilisation. So, for a whole 28 day period of each health state, the data presented is the mean amount of times the resource is used (and the n=number of patients who we have data for that specific resource, even if it is 0), and the mean cost. For example, if a patient had 1 primary care consultation in a 12 month period, we would calculate their average use per 28 days as:

$$\frac{1\ (consultation)}{13\ months^{*}\ of\ follow\ up\ \left(defined\ as\ \frac{365\ days}{28\ days}\right)} = 0.08\ consultations\ per\ 28\ days$$

* here 1 month is defined as 28 days

If a resource was utilised by a patient across health states the cost of the resource relative to each health state was calculated on a pro rate basis.

Overall costs

The data provided in this section was collected throughout the total duration of the follow-up period for all patients. As a result, the follow-up period within each clinical state is not standardised and varies across patients.
Within each table, the resource is reported for all patients with data for that specific resource (i.e. patients with missing data for each resource are not included). As such, the sample size within each table does vary and therefore the total HCRU cost for patients cannot be derived by totalling the cost of individual resources. The total costs described in section 8.5 are calculated by totalling the total HCRU cost associated with each individual patient. As in the overall counts, durations are not standardised. Care should be taken when interpreting these results.

Costs per 28 days

As with the counts, data in this section has been standardised to a 28-day period to allow for a uniform follow-up period for all patients included in the analysis. The figures were converted from overall costs in the same manner as the counts per 28 days were calculated from overall counts.

Appendix E: Carer QoL Report

Study Title: A research study to understand the impact of depression on the lives of people with depression and on the family and friends who support them

Confidential

Date: October 2019

Study Sponsor: Janssen-Cilag Limited

Report Authors: OPEN VIE Ltd

EXECUTIVE SUMMARY

Study aim: To expand existing understanding of the impact of MDD and TRD on health-related quality of life (HRQoL) of patients and carers.

- **Primary objective:** To quantify HRQoL (assessed as health utility using the EQ-5D-5L questionnaire) of: patients with symptomatic major depressive disorder (MDD), patients with symptomatic treatment-resistant depression (TRD) and patients with TRD in remission.
- **Secondary objective:** To quantify HRQoL (assessed as health utility using the EQ-5D-5L questionnaire) of: carers of patients with symptomatic TRD and carers of patients with TRD in remission.

Study design and methodology: This UK cross-sectional, observational research study collected quantitative HRQoL data. Patients completed the EQ-5D-5L questionnaire (a generic, preference-based measure of HRQoL) and the Patient Health Questionnaire-9 (PHQ-9; a brief patient-reported measure of depression severity). The PHQ-9 was used to define if patients' level of symptoms were moderately-severe or severe. Carers completed the EQ-5D-5L. The study was conducted across ten National Health Service (NHS) sites in the UK, including a mix of both primary care and secondary care sites. Participants were recruited between April and September 2019. All patient participants were recruited via the participating NHS sites. Carer participants were recruited mainly via NHS sites (through patient participants) but also by a specialist market research recruitment agency, posters placed in primary and secondary care sites, online adverts and social media posts.

Participants: The study sample comprised five mutually exclusive groups:

1) **Patients with symptomatic MDD:** individuals with diagnosed MDD who were on their first oral antidepressant medication for a maximum of eight weeks within the current major depressive episode, without clinically meaningful response (still having symptoms of moderately severe to severe level). For this report, the focus is on a pre-specified subgroup-analysis of patients with a PHQ-9 score ≥17.8, which indicates moderately-severe to severe depression and is equivalent to a Montgomery-Åsberg Depression rating Scale (MADRS) score of ≥28 (similar to the inclusion criteria in the short-term esketamine nasal spray trials [TRANSFORM-1 and TRANSFORM-2][1,2]), using the Hawley et al. 2013 PHQ-9 to MADRS conversion equation[3].
2) **Patients with symptomatic TRD:** individuals with TRD (on their second or subsequent oral antidepressant within the current major depressive episode) without clinically meaningful response to their current antidepressant medication (still having symptoms of moderately severe to severe level). For this report, the focus was on a pre-specified subgroup-analysis of patients with a PHQ-9 score of ≥17.8 (see above for patients with symptomatic MDD).
3) **Patients in remission from TRD:** individuals who were on their third or subsequent oral antidepressant medication within the current major depressive episode, and had been in remission from depressive symptoms, according to clinical opinion for at least four weeks, having previously met the criteria for TRD. For this report, the focus was on a pre-specified subgroup analysis of patients with confirmed remission based on PHQ-9 score (≤ 9.4), which is equivalent to a MADRS score of 12 (the threshold for remission in the short-term esketamine nasal spray trials[1,2]), using the Hawley et al. 2013 PHQ-9 to MADRS conversion equation[3].

4) **Carers of patients with symptomatic TRD:** identified by a patient participant as defined in Group 2 or self-identified as a carer of a patient with symptomatic TRD (eligibility confirmed by telephone screening).
5) **Carers of patients in remission from TRD:** identified by a patient participant as defined in Group 3 or self-identified as a carer of a patient with TRD in remission (eligibility confirmed by telephone screening).

Summary of main results:

	Patient Groups			Carer Groups	
Results	**Symptomatic MDD (PHQ-9 ≥17.8)**	**Symptomatic TRD (PHQ-9 ≥17.8)**	**TRD in remission (PHQ-9 ≤9.4)**	**Symptomatic TRD**	**TRD in remission**
No. of participants (unless specified)					
Gender (n, % female)					
Age, years (mean, SD)					
PHQ-9 score (mean, SD)*					
EQ-5D-5L (mapped to 3L) index value (mean, 95% CI)**					

** Score range 0-27 (higher scores indicate more severe depression), scores of 5, 10, 15 and 20 represent thresholds for mild, moderate, moderately-severe and severe depression, respectively; ** EQ-5D utility values were calculated by mapping the 5L descriptive system data onto the 3L valuation set using the mapping function developed by van Hout et al (2012)[4] (also known as the Crosswalk Link Function).*

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LIST OF ABBREVIATIONS

Abbreviation	Definition
95% CI	95% confidence interval
CFR	Code of Federal Regulations
DSM-IV	Diagnostic and Statistical Manual-IV
eCRF	Electronic case report form
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EQ-5D-3L	EuroQol-5 Dimensions questionnaire, three level version
EQ-5D-5L	EuroQol-5 Dimensions questionnaire, five level version
FDA	Food and Drug Administration
GP	General practitioner
HCP	Healthcare professional
HRQoL	Health-related quality of life
ICD-10	International Classification of Diseases – Version 10
IQR	Interquartile range
ISPE	International Society for Pharmacoepidemiology
MADRS	Montgomery-Åsberg Depression Rating Scale
MAOI	Monoamine oxidase inhibitor
MDD	Major depressive disorder (can also be called 'depression' or 'major depression' in the UK)
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PHQ-9	Patient Health Questionnaire-9
PIS	Participant information sheet
PRO	Patient-reported outcome
R&D	Research and Development
REC	Research Ethics Committee
SAP	Statistical analysis plan
SD	Standard deviation
SNRI	Serotonin and norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
TeCA	Tetracyclic antidepressant
TRD	Treatment resistant depression
VAS	Visual Analogue Scale
YLD	Years of life lost due to disability

1 INTRODUCTION

1.1 Background and rationale

Major depressive disorder (MDD) is a serious, recurrent and highly prevalent condition, estimated to affect 2.3% of the global population[5] and 3.3% of people in England[6]. Depression is one of the leading causes of years of life lost due to disability (YLD) globally[7].

MDD is associated with decreased patient well-being[8], a significant burden on health care costs, and productivity losses[9]. More than 50% of the patients who seek treatment for depression experience recurrent depressive episodes, at a mean of 16 weeks in duration[10]. Further, a substantial proportion (estimates range from 10.6% up to 30%) of patients are resistant to two or more currently marketed conventional oral antidepressant medications[11,12], which is often referred to as 'treatment resistant depression' (TRD). Currently, no established clinical criteria exist for diagnosing TRD and a consistently used definition is lacking. One of the most common definitions, provided by the European Medicines Agency (EMA), is 'a lack of clinically meaningful improvement despite the use of at least two different antidepressant agents (of the same or a different class), prescribed in adequate dosages for adequate duration and with adequate affirmation of treatment adherence within a single major depressive episode'[11], but there is variation in definitions used in both research and clinical practice settings. Patients with TRD are more likely than patients with treatment-responsive MDD to experience relapse and recurrence and have lower remission rates[12]. TRD is also associated with higher rates of suicidal ideation and suicide attempts[13]. Currently, there is no EMA-approved treatment for TRD and although treatments approved for MDD are being prescribed in patients with TRD, these have shown to be of limited effect[12]. There is a significant unmet need for new treatment options for patients with TRD.

With the advent of new treatments that have the potential to improve response and remission rates, it is important to gain a better understanding of the current experiences of patients living with MDD and TRD and their carers, and the impact of the condition on health-related quality of life (HRQoL).

A number of previous studies using quantitative patient-reported outcome (PRO) measures, have shown the development of MDD to have a substantial impact on HRQoL[14–16]. In TRD, a recent systematic review of the HRQoL literature suggested that HRQoL status decreases with

increasing levels of TRD/non-response within an MDD episode[17]. However, clear interpretation and comparison across studies was limited by inconsistent definitions of TRD. Furthermore, none of the studies evaluating HRQoL burden in patients with TRD that were included in the systematic review reported HRQoL data obtained from UK patients, highlighting a particular need for more UK-specific data on HRQoL in patients with TRD [17]. No studies have been identified that assessed the impact of TRD on carers of patients with TRD.

This study has addressed these evidence gaps by collecting UK-specific quantitative data directly from patients with symptomatic MDD, patients with symptomatic TRD, patients in remission from TRD and carers of people with TRD and TRD in remission, to expand existing understanding of the impact of MDD and TRD on HRQoL.

2 STUDY AIMS & OBJECTIVES

2.1 Aim

The overall aim of this study was to expand existing understanding of the impact of MDD and TRD on HRQoL of patients and carers.

2.2 Objectives

Primary objective:

- To quantify HRQoL (assessed as health utility using the EQ-5D-5L questionnaire) of:
    - patients with symptomatic MDD
    - patients with symptomatic TRD
    - patients with TRD in remission.

Secondary objective:

- To quantify HRQoL (assessed as health utility using the EQ-5D-5L questionnaire) of:
    - carers of patients with symptomatic TRD
    - carers of patients with TRD in remission.

3 STUDY DEFINITIONS

MDD: a mood disorder characterised by persistent low mood and/or a loss of interest and energy in activities for at least two weeks, along with five or more of the following symptoms: weight

loss/weight gain, insomnia/hypersomnia, psychomotor agitation/retardation, fatigue/loss of energy, feelings of worthlessness, diminished ability to think or concentrate and recurrent thoughts of death[1]. MDD can also be called 'depression' or 'major depression' in the UK.

TRD (formal study definition): depression that has been treated with at least two different oral antidepressant agents (of the same or different classes) prescribed in adequate dosages for adequate duration and with adequate affirmation of treatment adherence and showed lack of clinically meaningful improvement within a single major depressive episode[2,3].

TRD (definition used in patient-facing materials, agreed in collaboration with the Rethink

Mental Illness patient association): depression that has not improved with two or more oral antidepressant therapies.

Still symptomatic: patient continues to experience significant symptoms of MDD suggesting that antidepressants have not yet achieved adequate therapeutic effect (if within eight weeks of starting treatment) or have failed to achieve adequate therapeutic effect (if treated with adequate dose, duration and compliance for a minimum of eight weeks).

TRD in remission: A remission of depressive symptoms, according to clinical opinion, for at least four weeks after an episode of depression that met the criteria for TRD.

Carers of TRD/TRD in remission: individuals who have a personal relationship with and/or provide unpaid support or care to someone with TRD or TRD in remission. For example, this may be a spouse/ partner, son/ daughter, other relative, neighbour or friend.

4 METHODOLOGY

4.1 Design

This UK non-interventional research study collected quantitative data on HRQoL in an observational setting through the completion of patient and carer questionnaires at a single point in time. In addition to the completion of questionnaires by patients and carers, data on patients' demographic characteristics and treatment history were collected retrospectively from

medical records. The study was conducted across ten National Health Service (NHS) clinical sites in the UK, including a mix of both primary care and secondary care sites (full details in Section 4.3.1,

Table 2).

The study sample included five mutually exclusive groups (as defined in Section 4.2):

1) patients with symptomatic MDD

2) patients with symptomatic TRD

3) patients in remission from TRD

4) carers of patients with symptomatic TRD

5) carers of patients in remission from TRD.

The study was designed and conducted according to the requirements of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP; http://www.encepp.eu/index.shtml) and International Society for Pharmacoepidemiology (ISPE; https://www.pharmacoepi.org/resources/guidelines_08027.cfm) guidance, as appropriate.

Approval was obtained from the Health Research Authority (HRA) and North West – Liverpool Research Ethics Committee (REC; reference 19/NW/0146). There was no change to the management of patients for the purposes of any part of this study.

4.2 Participant eligibility

4.2.1 Inclusion criteria for the five study groups

1) Patients with symptomatic MDD: individuals with diagnosed MDD (as defined in Section 3) who were on their first oral antidepressant medication for a maximum of eight weeks within the current major depressive episode, without clinically meaningful response (still symptomatic, as defined in Section 3). Must have completed the questionnaires within two weeks of being screened as eligible (or have been re-screened prior to questionnaire completion

to confirm they were still eligible, specifically that they were still symptomatic [if more than two weeks had elapsed since screening]) AND within eight weeks since starting their first oral antidepressant medication.

Note: patients who switched to a different antidepressant medication due to intolerance were included in the study if the total duration of both treatments was no longer than eight weeks.
For this report, the focus was on a pre-specified subgroup analysis of patients with symptomatic MDD with a PHQ-9 score of ≥17.8, which indicates moderately-severe to severe depression, and is equivalent to a Montgomery-Åsberg Depression rating Scale (MADRS) score of ≥28 (similar to the inclusion criteria in the short-term esketamine nasal spray trials [TRANSFORM-1 and TRANSFORM-2][1,2]), using the using the Hawley et al. 2013 PHQ-9 to MADRS conversion equation[3].

2) Patients with symptomatic TRD: individuals with TRD (as defined in Section 3) without clinically meaningful response to their current antidepressant medication, either;

a) Patients who had been on their second line of oral antidepressant within a single major depressive episode at adequate dose, duration and adherence who had not responded (i.e. minimum eight weeks of adequate treatment with no further changes to treatment on this line of treatment and were still symptomatic). Must have completed the questionnaires within two weeks of being screened as eligible (or have been re-screened prior to questionnaire completion to confirm they were still eligible (still symptomatic) [if more than two weeks had elapsed since screening]).

b) Patients who had been on their third or later oral antidepressant medication within a single major depressive episode, without clinically meaningful response. Must have completed the questionnaires within two weeks of being screened as eligible (or have been re-screened prior to questionnaire completion to confirm they were still eligible (still symptomatic) [if more than two weeks had elapsed since screening]).

For this report, the focus was on a pre-specified subgroup analysis of patients with symptomatic TRD with a PHQ-9 score of ≥17.8 (see above for patients with symptomatic MDD).

3) Patients in remission from TRD: individuals who were on their third or subsequent oral antidepressant medication within the current major depressive episode, and had been in remission from depressive symptoms, according to clinical opinion, for at least four weeks, having previously met the criteria for TRD (as defined in Section 3). Must have completed the questionnaires within two weeks of being screened as eligible (or have been re-screened prior to questionnaire completion to confirm they were still eligible [in remission from depressive symptoms] if more than two weeks had elapsed since screening).

For this report, the focus was on a pre-specified subgroup-analysis of patients in remission from TRD with a confirmed remission based on PHQ-9 score (≤9.4), which is equal to a MADRS score of ≤12 (the threshold for remission in the short-term esketamine nasal spray trials)[1,2], using the Hawley et al. 2013 PHQ-9 to MADRS conversion equation[3].

4) Carers of patients with symptomatic TRD: identified by a patient participant as defined in Group 2 or self-identified as a carer of a patient with symptomatic TRD (eligibility confirmed by telephone screening). Carers recruited via patient participants must have completed the questionnaires within three weeks of the date of patient screening/re-screening (i.e. confirmation of patient eligibility). Carers recruited via other methods must have completed the questionnaires within two weeks of the date of carer screening.

5) Carers of patients with TRD in remission: identified by a patient participant as defined in Group 3 or self-identified as a carer of a patient with TRD in remission (eligibility confirmed by telephone screening). Carers recruited via patient participants must have completed the questionnaires within three weeks of the date of patient screening/re-screening (i.e. confirmation of patient eligibility). Carers recruited via other methods must have completed the questionnaires within two weeks of the date of carer screening.

All patient and carer Groups (1-5):

- Aged 18 years or over at the time of consent to participate in the research.
- Resident in the UK.

It was not a requirement that patients who took part in this study (Groups 1-3) had a carer. Nor was it a requirement that carers who took part in the study (Groups 4-5) also had the person

they provide care or support for take part in the study (although the preferred carer recruitment method was via study patients with symptomatic TRD or TRD in remission – Groups 2 and 3).

4.2.2 Exclusion criteria for the five study groups

All patient Groups (1-3 [see section 4.2.1]):

- Patients who were unwilling or unable to complete the study questionnaires.
- Patients who did not consent for their general practitioner (GP; or mental health care professional, as appropriate) to be contacted if, at any time during the study, they reported an active safety risk (of harm to themselves or others).
- Patients with a current or prior documented International Classification of Diseases – version 10 (ICD-10) diagnosis of bipolar or related disorders, intellectual disability, autism spectrum disorder, borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder.
- Patients with a current documented ICD-10 diagnosis of a psychotic disorder or MDD with psychotic features, or obsessive-compulsive disorder.
- Patients with a documented history of moderate or severe substance or alcohol use disorder according to ICD-10 criteria.
- Patients who had a neurodegenerative disorder (e.g. Alzheimer's disease or Parkinson's disease), or evidence of cognitive impairment.
- Patients enrolled in any interventional clinical trial or a non-interventional trial (requiring active follow-up) at the time of screening.

Carer Groups (4-5 [see section 4.2.1]):

- Carers who were unwilling or unable to complete the questionnaires.
- Carers who had contact with the person with symptomatic TRD or TRD in remission less than once per week.

4.3 Participant identification, sampling and recruitment

Patient and carer participants for the study were recruited between April and September 2019. All participants provided written informed consent to take part and were offered a £15 shopping voucher to thank them for taking the time to complete the study questionnaires.

4.3.1 Patient recruitment

All patient participants (Groups 1-3 [see section 4.2.1]) were recruited via ten participating NHS sites, which comprised six primary care sites and four specialist mental health secondary care centres (see

Table 2). Potentially eligible patients were identified by healthcare professionals (HCPs) who were members of their care team (or trained research staff at the NHS site, where permissible locally) either (a) during a routine (clinic, telephone or home) visit within the designated recruitment period, or (b) by identifying potentially eligible patients from the participating site's clinical database. Patients were approached about the study and provided with a participant information sheet (PIS). For those patients who were interested in taking part, eligibility was confirmed using a screening checklist and written consent obtained. Following this, a suitable time was arranged for the patient to complete the questionnaires whilst an HCP or member of trained research staff was available. Patients were re-screened to ensure they remained eligible (i.e. still symptomatic for Groups 1 and 2; in remission for Group 3), if the questionnaire was not completed within two weeks of initial screening.

Table 2: Participating NHS sites

Centre name	Centre type
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

4.3.2 Carer recruitment

The main recruitment method for carers of patients with symptomatic TRD or TRD in remission was via the participating NHS sites. This was the preferred approach as it ensured that definitive confirmation of the patient's TRD diagnosis could be obtained. Carers recruited via the NHS sites were identified and approached in one of two ways, either a) HCPs or research staff at the site provided carer information packs to patients with symptomatic TRD or TRD in remission who were already participating in the study, to pass on to up to three of their carers; or b) HCPs or research staff at the site provided study information directly to carers, where they were present when the study was being discussed with patients. Carers who were interested in taking part in the study were asked to complete the consent form and questionnaires.

Although recruitment of carers via the study patients from the NHS sites was the preferred method of recruitment, additional methods were needed in order to increase the sample size for both groups of carers; these included recruitment using posters placed in primary and secondary care study sites, online adverts and social media posts. Additionally, via a specialist healthcare market research recruitment agency, who approached the carers of people with depression from their database of individuals interested in participating in research. All carers who responded to these alternative (non-NHS) approaches were screened for eligibility over the telephone by OPEN VIE or the recruitment agency and asked to complete the study questionnaires once consent had been obtained.

4.4 Data source and collection

4.4.1 Patient and carer-reported outcomes

Patients (Groups 1-3) and carers (Groups 4-5) completed a single set of paper-based questionnaires at the time of enrolment to the study (or shortly afterwards, within the timeframes outlined in Section 4.2). Questionnaires were completed between April and September 2019. Details of the questionnaires completed are provided in Section 4.4.2.

Patient questionnaires were completed either during a routine follow-up appointment, or a separate (clinic, telephone or home) appointment arranged specifically for the study.

Carers recruited via NHS sites filled out the questionnaires either during the clinic visit of the patient with TRD or at home, returning the consent form and completed questionnaires to the NHS site by post. Carers recruited via other methods filled out questionnaires at home, initially returning the consent form and subsequently the completed questionnaires to OPEN VIE or the recruitment agency by post.

4.4.2 Study questionnaires

The questionnaires listed below were used to evaluate HRQoL and severity of depression. The questionnaires were selected based on evidence of validation for use in the population of interest, their ease of use and short time required for completion in order to minimise the burden on participants.

Patient and carer questionnaire:

EQ-5D-5L: The EQ-5D-5L questionnaire is a generic, preference-based measure of HRQoL in adults, designed to yield health state utilities that may be used in cost utility modeling[21]. The EQ-5D-5L consists of two parts; the EQ-5D-5L descriptive system and the EQ Visual Analogue scale (VAS).

In the descriptive system, respondents rate their degree of impairment in five different health dimensions (mobility, self-care, usual activities, pain/discomfort, and depression/anxiety) using five response levels: no problems, slight problems, moderate problems, severe problems and extreme problems. EQ-5D-5L health states, defined by the EQ-5D-5L descriptive system, can then be converted into a single index value ranging from less than 0 (where 0 is a health state equivalent to death; negative values are valued as worse than death) to 1 (perfect health). The VAS assesses the respondent's overall self-rated health status. Respondents rate their current health from 0 (worst health you can imagine) to 100 (best health you can imagine)[22] by placing a mark on the VAS. They are also asked to write this number in a separate box. The number reported in the box is recorded as the response. The recall period is one day (today).

Patient only questionnaire:

Patient Health Questionnaire (PHQ-9): The PHQ-9 is a brief patient-reported measure of depression severity that is increasingly used in UK clinical practice[23]. The measure has also been widely used in clinical trials, including those for the Sponsor's new antidepressant

treatment[1]. The items cover the nine Diagnostic and Statistical Manual- IV (DSM-IV) criteria for depression assessed on a four levels scale (not at all, several days, more than half the days, nearly every day)[24]. The recall period is two weeks. Scores range from 0-27, with higher scores indicating more severe depression. Scores of 5, 10, 15 and 20 represent thresholds for mild, moderate, moderately-severe and severe depression, respectively[25].

4.4.3 Retrospective data collection from medical records

Patients' demographic and clinical data (including treatment history) were collected retrospectively from medical records by members of the NHS care team, research staff at the NHS site or external researchers (where locally permitted). Data were collected in anonymised-coded format, using a specifically-designed electronic case report form (eCRF).

4.5 Safeguarding procedures

The patients taking part in this study represented a vulnerable population, potentially at risk of suicide. A safeguarding procedure, detailed below, was developed in collaboration with the Sponsor and Chief Investigator, to assist in the identification of risk and the appropriate process to follow:

- To help prevent the recruitment of patient participants who may be adversely affected by taking part in the study, the patient's HCP or clinical carer was required to confirm (based on recent clinic visit[s]), prior to providing study information to potential patients, that they did not have any concerns with regards to recruiting each patient to the study from a safeguarding perspective. If any such concerns were identified, the patient was excluded from the study.
- All participants received an information sheet in advance of enrolment. This contained the contact details of organisations that can provide help and support if the participant is distressed (such as Rethink, Mind, and Samaritans).
- All patient participants were recruited from NHS services/sites and questionnaires were completed by the patient whilst an HCP or member of trained NHS research staff was available.
- In case of any clinical and/or welfare risk to the patient, detected during and/or as a result of the completion of questionnaires with NHS staff, the staff were required to adhere to the safeguarding procedures/policies specific to the NHS service/site for each patient.

Following questionnaire completion, NHS study staff reviewed the patient's responses to the questionnaires, to check for any safeguarding issues (whether responses are indicative of potential risk of harm to self or others) and discussed these with the patients / carers whilst they were at the clinic/ GP practice / patient's home (or over the telephone) and with their clinical team should risk be identified.

- Carers were provided with the contact details of either the lead NHS contact from the recruitment site (if recruited via a site) or the lead contact at OPEN VIE (if recruited via other methods). This information was provided with the questionnaires so that they could contact someone if they needed to, if completing questionnaires away from the clinic / GP practice.

4.6 Data management and quality control

NHS care team members, research staff and external researchers collecting data for the study were provided with data collection guidelines to facilitate consistent completion of the eCRF and received training in the requirements of the study protocol and correct completion of the eCRF prior to commencement of data collection.

Patient demographic data submitted in the eCRF were checked for completeness and accuracy by the OPEN VIE data management team using agreed manual and programmed validation checks, as documented in the data management plan. Queries were raised with each site by the data management team, and resolutions documented.

No queries with sites, patients or carers were raised on data collected from questionnaires. However, the accuracy and quality of questionnaire data entry was monitored by OPEN VIE. A check of the accuracy and quality of questionnaire data entered into the database was performed on a random sample of 10% of patients from each group and 10% of carers.
Data management for eCRFs was carried out using MACRO™, a data management system which has a secure web-based data entry interface and is fully validated and compliant with Food and Drug Administration (FDA) Information Governance standard 21 Code of Federal Regulations (CFR) Part 11.

4.7 Data analysis

Analysis assumptions

The following assumptions were applied for analysis:

- When a treatment was started before the start of the current depressive episode, the start date of the depressive episode was used as the start date of treatment.
- When a patient was on two different classes of antidepressant medication concurrently as their most recent treatment, the therapy combination (e.g. SSRI and TeCA) is reported.
- To calculate the duration of most recent treatment for concurrently prescribed therapies, the start date of the most recently initiated medication was used as the start date of the treatment (i.e. the first date that both therapies were prescribed concurrently). When the stop date was not available (or treatment was recorded as ongoing), the date of electronic signature on the eCRF OR the date of questionnaire completion (whichever was earliest) was used instead.
- The time since diagnosis of the current or most recent depressive episode at the date of data collection was calculated as the difference between the diagnosis date of the current or most recent depressive episode and the date of electronic signature on the eCRF OR the date of questionnaire completion (whichever was earliest).

4.7.1 Data analysis

Data from all participating sites were pooled for analysis. Data were analysed separately for each study group (see Section 4.1). Analyses were carried out by OPEN VIE according to a pre-defined statistical analysis plan (SAP) using R statistical software, Stata™ (StataCorp LLC) version 14 and Microsoft Excel™ as appropriate.

Analysis for validated instruments adhered to the licensed scoring guidelines from the associated questionnaire manuals[26,27].

Patient PHQ-9 scores were calculated by summing the scores (not at all = 0, several days = 1, more than half the days = 2 and nearly every day = 3) associated with each of the nine questions to give a score out of 27. Responses are presented as distributions and percentages according to the following categories, to indicate the level of depression severity: none, score 0-4; mild, score 5-9; moderate, score 10-14; moderately-severe, score 15-19; severe, score 20-27) and as

means (standard deviation [SD]), medians (interquartile range [IQR]) and ranges. To enable comparisons between PHQ-9 scores and MADRS (an in-depth clinician-rated measure of depression severity which is commonly used in clinical trials to screen patients for eligibility and assess response to treatment), MADRS score boundaries were converted into corresponding PHQ-9 scores using published formulae[3]. The PHQ-9 scores were used to identify the patients with symptomatic MDD or TRD with equivalent severity of depressive symptoms (moderately-severe to severe) to those included in the short-term esketamine nasal spray trials (TRANSFORM-1 and TRANSFORM-2[1,2]) and the patients in remission from TRD equivalent to the score threshold for remission used in the same trials.

For the EQ-5D-5L descriptive system data, the proportion of participants reporting each level of problem on each dimension is presented. EQ VAS scores are reported as means (SD) with 95% confidence intervals (95% CI), medians (IQR) and ranges.

Calculating EQ-5D index values: NICE currently recommend that utility values in reference-case analyses should be calculated by mapping the EQ-5D-5L descriptive system data onto the EQ-5D-3L valuation set[28]. For consistency with the current guide to the methods of technology appraisal[29], the EQ-5D-5L health states (defined by the EQ-5D-5L descriptive system) were converted into a single index value using the mapping function developed by van Hout et al (2012)[4] (also known as the Crosswalk Link Function) which is incorporated into the 'EQ-5D-5L Crosswalk Index Value Calculator' provided by the EuroQoL group)[3]. Index values are presented as means (SD) with 95% CI, medians (IQR) and ranges.

Participant demographics were analysed descriptively as distributions with percentages, mean (SD), median (IQR) and range, as appropriate.

All percentages have been reported to the nearest whole number; therefore, in reporting study results in tables, figures and associated text, percentages may not add up to 100% due to rounding.

4.7.2 Handling of missing data

Missing questionnaire data was handled in accordance with the user guidelines. For the PHQ-9[26], if one or two values were missing from the score, they were substituted with the average

score of the non-missing items. Questionnaires were not included in the analysis when more than two values were missing.

For the EQ-5D-5L, the number of participants with missing data is reported for the VAS. All participants who completed the EQ-5D-5L had complete descriptive system data and therefore there are no missing index values.

Where dates in the eCRF (for example, dates of treatment initiation or discontinuation) were ambiguous because of missing day and/or month, standard imputation was applied: where day was missing the approximate mid-point of the month (15th) was assumed. When day and month were missing the approximate mid-point of the year (1st of July) was assumed.

For other missing data, the affected analyses was conducted using only the results of those patients with data available and the number included in each analysis is stated. No other data imputation was carried out.

5 RESULTS

This report focuses on pre-specified subgroup analyses for the following patient groups:

- [redacted]
- [redacted]
- [redacted]

[redacted]

5.1 Study sample

[redacted]

Table 3: Participant recruitment

Recruitment method	Patients with symptomatic MDD (PHQ-9 ≥17.8)	Patients with symptomatic TRD (PHQ-9 ≥17.8)	Patients with TRD in remission (PHQ-9 ≤9.4)	Carers of patients with symptomatic TRD	Carers of patients with TRD in remission	Total participants
Primary care NHS sites						
Secondary care NHS sites						
Recruitment Agency						
Alternative (non-NHS) methods of carer recruitment*						
Total						

* Alternative methods of carer recruitment used for the study were: posters placed in participating primary and secondary care sites, online adverts and social media posts.

5.2 Patient demographic and clinical characteristics

Patient demographic characteristics are shown in Table 4. [redacted]

[redacted]

Table 4: Patient demographic characteristics

	Symptomatic MDD (PHQ-9 ≥17.8)	Symptomatic TRD (PHQ-9 ≥17.8)	TRD in remission (PHQ-9 ≤9.4)
n (unless specified)			
Gender (n, %)			
Male			
Female			
Age (years) - overall			
Mean (SD)			
Median (IQR)			
Range			
Age (years) - male patients			
Mean (SD)			
Median (IQR)			
Range			
Age (years) - female patients			
Mean (SD)			
Median (IQR)			
Range			
Employment status (n, %)			
Employed, full-time			
Employed, part-time			
Looking after family/ home			
Retired			
Student			
Unemployed			
Other*			

Not recorded	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Patient clinical characteristics are summarised in Table 5. [redacted]

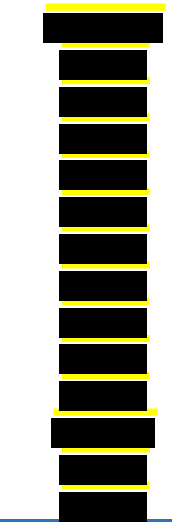
[redacted]

[redacted]

[redacted]

Table 5: Patient clinical characteristics

	Symptomatic MDD (PHQ-9 ≥17.8)	Symptomatic TRD (PHQ-9 ≥17.8)	TRD in remission (PHQ-9 ≤9.4)
n (unless specified)			
Time (years) from MDD diagnosis to data collection Mean (SD) Median (IQR) Range Not available			
Time since diagnosis of current (or most recent) depressive episode Mean (SD) Median (IQR) Range			
Severity of depressive symptoms according to PHQ-9 score (n, %) None (0-4) Mild (5-9) Moderate (10-14) Moderately-severe (15-19) Severe (20-27) Mean (SD) Median (IQR) Range			
Number of antidepressant medications prescribed since diagnosis of current (or most recent) depressive episode Mean (SD) Median (IQR) Range			

Current (or most recent) antidepressant medication class (n, %) SSRI SNRI SNRI and TCA SNRI and TeCA SSRI and SNRI SSRI and TCA SSRI and TeCA SSRI, TeCA and Other TCA TCA and Other TCA and TeCA TeCA TeCA and Other Other			
Time (years) on current (or most recent) antidepressant medication Mean (SD) Median (IQR) Range			

5.3 Carer demographics

Carer demographic characteristics are summarised in Table 6. [redacted]

Table 6: Carer demographics

	Carers of patients with symptomatic TRD	Carers of patients with TRD in remission
n (unless specified)		
Gender (n, %)		
Male		
Female		
Age (years) at questionnaire completion (n, %)		
< 20		
20 < 30		
30 < 40		
40 < 50		
50 < 60		
60 < 70		
70 < 80		
Missing		
Relationship to family member or friend with depression (n, %)		
Brother or Sister		
Friend or neighbour		
Son or Daughter		
Spouse or Partner		
Other*		
Employment status (n, %)		
Employed, full-time		
Employed, part-time		
Homemaker/ Looking after family		
Retired		
Student		
Unemployed		
Other**		
Ongoing health conditions requiring frequent medical care (n, %)		
Ongoing health condition		
No ongoing health condition		
Frequency of contact with family member or friend with depression (n, %)		
Lives with family member or friend		
Every day/ most days		
Every other day		
Once or twice a week	2	
Has carer ever accompanied the family member or friend with depression to see their doctor? (n, %)		
Yes		
No		

Frequency with which carer accompanies family member or friend to see their doctor (n, %)		
Always	[redacted]	[redacted]
Hardly ever	[redacted]	[redacted]
Now and then	[redacted]	[redacted]
Often	[redacted]	[redacted]
Not available	[redacted]	[redacted]

[redacted]

5.4 Primary outcome: patient EQ-5D scores

[redacted]

[redacted]

Table 7: Patient EQ-5D-5L (mapped to 3L) index values and EQ VAS scores

	Symptomatic MDD (PHQ-9 ≥17.8)		Symptomatic TRD (PHQ-9 ≥17.8)		TRD in remission (PHQ-9 ≤9.4)	
EQ-5D score						
Mean						
SD						
Median						
IQR						
Range						
95% CI						
Missing						

Figure 1: Patient EQ-5D-5L (mapped to 3L) index values

Figure 2: EQ-5D-5L dimension scores for patients with symptomatic MDD (PHQ-9 score ≥17.8)

Figure 3: EQ-5D-5L dimension scores for patients with symptomatic TRD (PHQ-9 score ≥17.8)

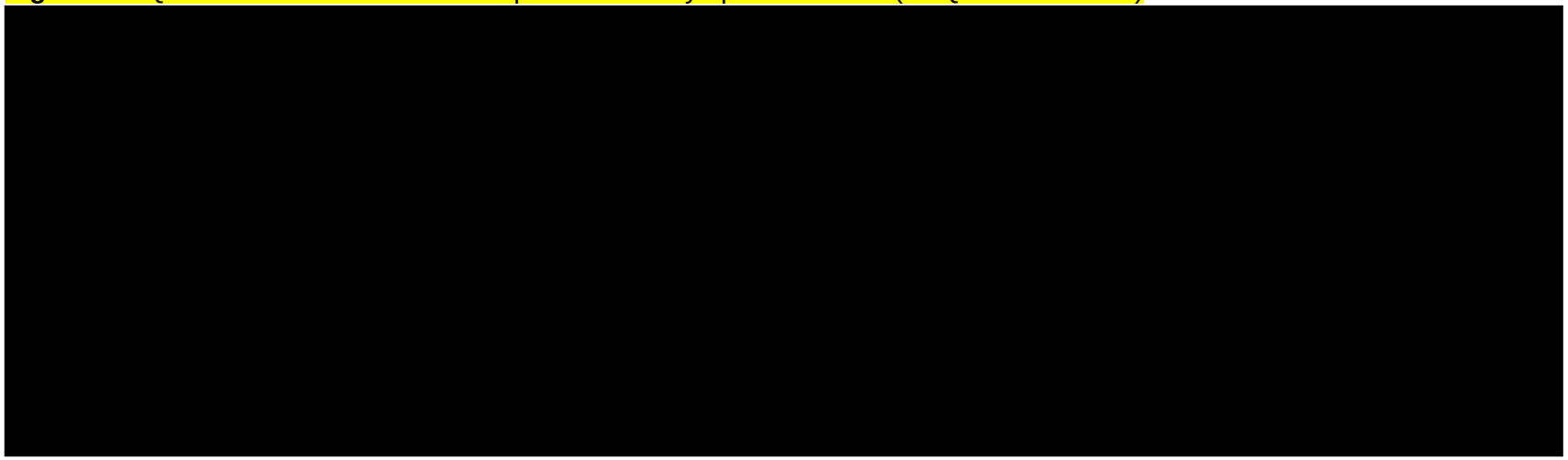


Figure 4: EQ-5D-5L dimension scores for patients with TRD in remission (PHQ-9 score ≤9.4)

5.5 Secondary outcome: carer EQ-5D scores

Carer EQ-5D-5L (mapped to 3L) utility and EQ VAS scores are shown in Table 8 and Figure 5. [redacted]

Table 8: Carer EQ-5D-5L (mapped to 3L) index values and EQ VAS scores

Carer EQ-5D score	Carers of patients with symptomatic TRD		Carers of patients with TRD in remission	
	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Not available*	[redacted]	[redacted]	[redacted]	[redacted]

* One carer in each group did not complete the EQ-5D-5L questionnaire

Figure 5: Carer EQ-5D-5L (mapped to 3L) index values

Figure 6: EQ-5D-5L dimension scores for carers of patients with symptomatic TRD

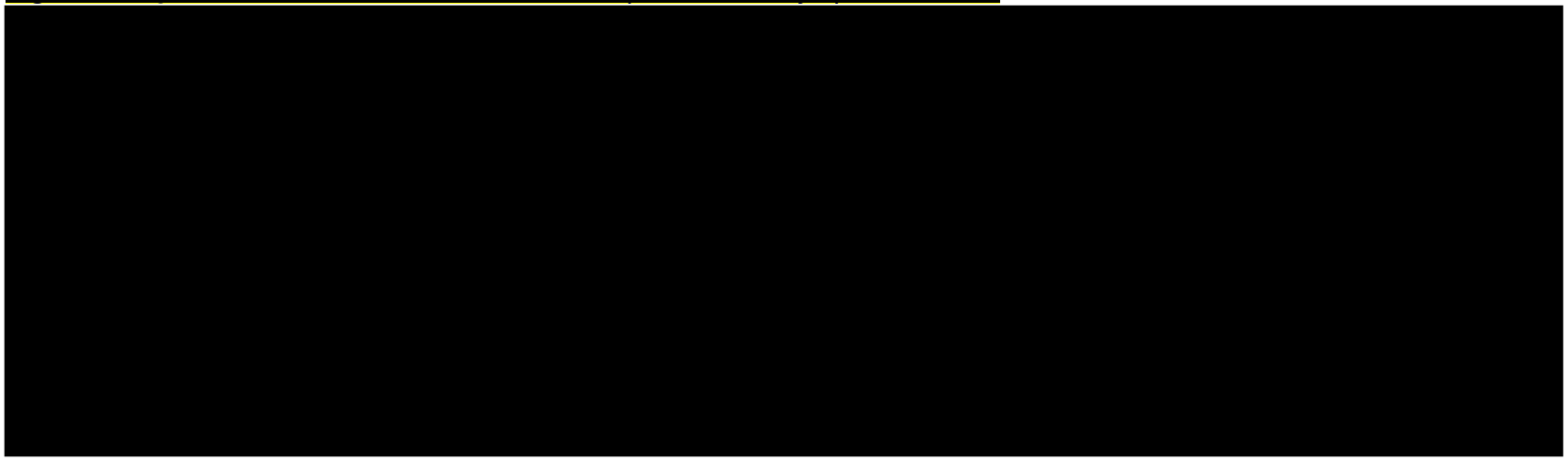


Figure 7: EQ-5D-5L dimension scores for carers of patients with TRD in remission

6 DISCUSSION

6.1 Main findings

6.1.1 Patient groups

The inclusion criteria for the patient study groups were chosen to reflect real world clinical practice definitions of MDD, TRD and TRD in remission and were based on clinician-assessment of the presence or absence of symptoms, rather than using a validated depression rating scale. The patients completed a self-reported measure of depression severity, the PHQ-9, at the time of study enrolment. Given the lack of widely accepted definitions of MDD and TRD, this assessment was intended to describe the level of depressive symptoms across the three groups and facilitate comparison with other studies in order to contextualise the results. Although all of the patients were considered by their clinician to have symptomatic MDD, symptomatic TRD or TRD in remission, a minority had PHQ-9 scores that were inconsistent with their group assignment. This might be caused by the time between screening and completing the questionnaires, although this was kept as brief as possible and limited to two weeks. [redacted] For this reason and to align with the inclusion criteria in the short-term esketamine nasal spray trials [TRANSFORM-1 and TRANSFORM-2][1,2], a subgroup analysis was undertaken including only patients with symptomatic MDD and symptomatic TRD who had moderately-severe or severe depression according to their PHQ-9 score (i.e. ≥17.8, equivalent to MADRS ≥28) and patients with TRD confirmed to be in remission (i.e. PHQ-9 ≤9.4). The results of these subgroup analyses were the focus of this report.

[redacted]

[redacted]

6.1.2 Carer groups

[redacted]

[redacted]

6.2 Strengths and limitations

This study helps to improve existing understanding of the impact of MDD and TRD on HRQoL by providing UK-specific EQ-5D-5L data obtained directly from patients with MDD or TRD and their carers. All patient participants and most carer participants were recruited via NHS sites. This approach was taken primarily for safeguarding purposes, to allow the patients (who were vulnerable and potentially at risk of suicide) to complete the questionnaires in the presence of an HCP, but also ensured that clinician-confirmation of the MDD or TRD diagnosis and treatment history could be obtained. This would not have been possible with alternative (e.g. direct-to-patient) methods of recruitment and helps to increase the validity of the results. Although recruitment via NHS sites was the preferred method of carer recruitment, recruiting the target number of carers proved to be challenging and therefore a range of alternative (non-NHS) approaches were employed to increase the sample size for both carer groups. Although it was not possible in these cases to clinically verify the diagnosis of the person with depression for whom the carer provided support, screening questionnaires were developed and used to confirm carer eligibility, which increased the likelihood of carers being assigned to the correct study group.

Identification and recruitment of patients with TRD in remission was challenging for a variety of reasons, primarily because patients with TRD in remission typically require fewer healthcare visits than those who remain symptomatic and therefore are less likely to have been approached and invited to participate in the study. Furthermore, the remission rate for patients receiving second and subsequent lines of oral antidepressant treatment is known to be below 15%[12] and therefore the overall source population is likely to be smaller than for the other groups. Although the study definition of remission was based on clinical opinion, only three patients were recruited in this group with PHQ-9 scores equivalent to the threshold for remission used in the esketamine nasal spray trials and as such, no definitive conclusions can be drawn from the results.

The ten participating NHS centres were spread geographically across England and comprised a mix of both primary and secondary care sites. As such, the overall results should be generalisable to wider UK clinical practice.

A window of up to two-weeks (three weeks for carers) was allowed between confirmation of eligibility (screening) and completion of the study questionnaires. This was needed to allow sufficient time for follow-up appointments to be arranged for patients or carers to complete the study questionnaires, if they were unable to complete them at the screening visit. The time window was agreed in collaboration with the clinician investigators who considered it unlikely that any significant changes in the severity of patients' depressive symptoms (which might result in a change in group allocation) would occur during this time, although this cannot be excluded completely. This has been addressed by the subgroup analysis based on PHQ-9 scores converted from MADRS thresholds, which forms the focus of this report.

The requirement for consent for this study may have introduced selection bias and resulted in a study sample that may not be representative of the wider patient population of interest. For example, the patients who agreed to take part in the study may be in better physical and/or mental health and more able to engage with the research study than other individuals. Alternatively, those patients and carers in worse health may be more willing to take part in the research in order to share their experience. It was not possible to assess selection bias statistically in this study as this approach would have required information on the subset of the population for which data could not be collected.

The interpretation of any data collected retrospectively is dependent on the completeness and quality of the source medical records and the reliability of the abstraction of data from the medical records. The risk of missing data impacting the results in this study was low as the primary outcome was based on patient-reported data and only demographic characteristics and treatment history, which should be well-recorded, were collected from medical records.

7 CONCLUSION

This study provides UK-specific data to quantify the HRQoL impact in patients with MDD or TRD and their carers. [redacted]

[redacted]

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9 APPENDIX 1: Results for overall patient groups

Table 9: Patient demographic characteristics (overall group)

	Symptomatic MDD (overall group)	Symptomatic TRD (overall group)	TRD in remission (overall group)
n (unless specified)			
Gender (n, %)			
Male			
Female			
Age (years) - overall			
Mean (SD)			
Median (IQR)			
Range			
Age (years) - male patients			
Mean (SD)			
Median (IQR)			
Range			
Age (years) - female patients			
Mean (SD)			
Median (IQR)			
Range			
Employment status (n, %)			
Employed, full-time			
Employed, part-time			
Looking after family/ home			
Retired			
Student			
Unemployed			
Other*			
Not recorded			

Table 10: Patient clinical characteristics (overall group)

	Symptomatic MDD (overall group)	Symptomatic TRD (overall group)	TRD in remission (overall group)
n (unless specified)			
Time (years) from MDD diagnosis to data collection			
Mean (SD)			
Median (IQR)			
Range			
Time since diagnosis of current (or most recent) depressive episode			
Mean (SD)			
Median (IQR)			
Range			
Severity of depressive symptoms according to PHQ-9 score (n, %)			
None (0-4)			
Mild (5-9)			
Moderate (10-14)			
Moderately-severe (15-19)			
Severe (20-27)			
Mean (SD)			
Median (IQR)			
Range			
Number of antidepressant medications prescribed since diagnosis of current (or most recent) depressive episode			
Mean (SD)			
Median (IQR)			
Range			

Current (or most recent) antidepressant medication class (n, %)			
SSRI			
SNRI			
SNRI and TCA			
SNRI and TeCA			
SSRI and SNRI			
SSRI and TCA			
SSRI and TeCA			
SSRI, TeCA and Other			
TCA			
TCA and Other			
TCA and TeCA			
TeCA			
TeCA and Other			
Other			
Time (years) on current (or most recent) antidepressant medication			
Mean (SD)			
Median (IQR)			
Range			

Table 11: Patient EQ-5D-5L (mapped to 3L) index values and EQ VAS scores (overall group)

	Symptomatic MDD (overall group)		Symptomatic TRD (overall group)		TRD in remission (overall group)	
EQ-5D score	[redacted]		[redacted]		[redacted]	
Mean	[redacted]		[redacted]		[redacted]	
SD	[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]	
IQR	[redacted]		[redacted]		[redacted]	
Range	[redacted]		[redacted]		[redacted]	
95% CI	[redacted]		[redacted]		[redacted]	
Missing	[redacted]		[redacted]		[redacted]	

NICE National Institute for Health and Care Excellence

Technical engagement response form

Esketamine for treatment-resistant depression [ID1414]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **21 November 2019.**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second, fully

redacted, version of your comments (AIC/CIC shown as [redacted]). See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Peter Pratt**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**NHSE (specialised commissioning)**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**none**

Questions for engagement

Issue 1: Generalisability of evidence	
Are TRANSFORM-2 and SUSTAIN-1 generalisable to UK clinical practice?	
What proportion of UK population are expected to have had suicidal ideation/intent in the previous 6 months and/or suicidal behaviour in the previous 12 months before treatment?	
Is 4 weeks enough time to establish response to treatment with a newly initiated oral antidepressant?	
Issue 2: Time horizon	
Are all differences in costs and effects attributable to esketamine nasal spray plus oral antidepressant (ESK-NS + OAD) likely to be captured in a 5-year time horizon?	**Given the possibility of long term/ repeated "courses" of treatment I do not think that a 5 year time horizon would be adequate to assess the impact on NHS services**
Issue 3: Placebo response rate	
How many clinic visits are expected in practice with esketamine treatment and with standard care?	
Are the placebo response rates observed in TRANSFORM-2 unusually high?	
What is the likely effect of an additional clinic visit on key outcomes?	

Are there any other likely reasons that placebo response rates may be high?	
Issue 4: Treatment discontinuation	
Is the treatment effect of ESK-NS + OAD maintained after stopping treatment?	
Would stopping treatment for reasons other than lack of response have an impact on health-related quality of life?	
What is the expected duration of a course of ESK-NS treatment?	
Are there likely to be some people who remain on ESK-NS treatment for life?	Unless the SPC for this product states otherwise – The long term/very long term use of this product has to be considered as a possibility,
What proportion of patients would stop ESK-NS treatment by 2 years in the recovery state?	
What are the criteria for stopping ESK-NS treatment in the acute, continuation and maintenance phases?	
Could the requirement for attendance at clinics and the need for monitoring influence compliance with treatment?	
Is there any evidence that ESK-NS is a disease modifying treatment?	
Issue 5: Effect on mortality	
Is severity of TRD a proxy for risk of excess mortality due to suicide?	

Would ESK-NS treatment effect the risk of mortality?	
Are the interventions in the meta-regression representative of standard care in the UK?	
Issue 6: Cost of clinic visits	
In clinical practice, how many patients could 1 nurse concurrently supervise and monitor following administration of ESK-NS?	
What band would the nurse(s) be?	
Would non-attendance at clinic appointments affect the cost-effectiveness of ESK-NS treatment?	
Issue 7: Adoption	
Are there any infrastructure investments associated with the adoption of ESK-NS + OAD that need to be accounted for in the model?	Given the likely change to current service models and associated cost/ service infrastructure implications I do not think that the NHS would be in a position to implement this technology in a safe manner within the usual NHS timeframe of 3 months. If the TA received a positive opinion from NICE I suspect that the majority of NHS services would require at least 6 months (or longer) in order to ensure that they put in place the necessary systems and processes to adopt the technology.
Issue 8: Uncaptured benefits to carers	
Are there any additional benefits and costs to carers of people with TRD receiving ESK-NS?	

If so, are all the additional benefits and costs to carers captured within the model?	

NICE National Institute for Health and Care Excellence

Technical engagement response form

Esketamine for treatment-resistant depression [ID1414]

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We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

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- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second, fully

redacted, version of your comments (AIC/CIC shown as [redacted]). See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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About you

Your name	**Professor Nav Kapur**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**NGA – chair of NICE Depression GC.**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Generalisability of evidence	
Are TRANSFORM-2 and SUSTAIN-1 generalisable to UK clinical practice?	Some concerns about generalisability. Exclusion of people who had suicidal thoughts in the last six months or suicidal behaviours in the last 12. There are some useful general population data from the Adult Psychiatric Morbidity Survey. (Lifetime prevalence of suicidal thoughts around 20%, and suicide attempts 7%, prevalence of suicidal thoughts in the last year around 5%). Of course these proportions are likely to be considerably higher in people who have treatment resistant depression. Depression content experts may be able to advise. This is a concern from the point of view of representativeness of the trials and of particular concern given that one of the main therapeutic targets for the drug appears to be reduction of suicidality. No data on over 65's Also be aware how NICE guideline (draft consultation version 2018) deals with TRD (under the 'Limited response and treatment resistant depression' heading with most of the recommendations focussing on limited or no treatment response to first line pharmacological or psychological treatment). The rationale for this is on page 503 of the draft full guideline "Other considerations When reviewing the evidence for further line treatment the GC had originally decided to separately examine the evidence base for treatment resistant depression (usually defined as no or limited response to two adequate courses of an antidepressant) from no or limited response to treatment. However, after carefully reviewing the trial populations and the

	variation in the criteria used to identify both no or limited response and treatment resistance the GC came to the view that there were considerable similarities and overlaps between the two populations and therefore decided to use the same data sets for both questions to inform the development of recommendations for no or limited response".
What proportion of UK population are expected to have had suicidal ideation/intent in the previous 6 months and/or suicidal behaviour in the previous 12 months before treatment?	
Is 4 weeks enough time to establish response to treatment with a newly initiated oral antidepressant?	
Issue 2: Time horizon	
Are all differences in costs and effects attributable to esketamine nasal spray plus oral antidepressant (ESK-NS + OAD) likely to be captured in a 5-year time horizon?	
Issue 3: Placebo response rate	
How many clinic visits are expected in practice with esketamine treatment and with standard care?	
Are the placebo response rates observed in TRANSFORM-2 unusually high?	Yes they are. I have concerns over the approach taken to deal with this though. Adjustment – the response in the comparator arm was greater than in TRD trials to date. The company hypothesised that this was due to increased clinical contact. This would not be seen in usual clinical practice so they factored it out of the comparator arm but not the intervention arm.

	This doesn't seem correct to me. Surely at this stage we want to know the additional benefits conferred by the drug itself rather than the additional benefit of increased clinical contact.
What is the likely effect of an additional clinic visit on key outcomes?	
Are there any other likely reasons that placebo response rates may be high?	
Issue 4: Treatment discontinuation	
Is the treatment effect of ESK-NS + OAD maintained after stopping treatment?	I am unable to say. We need more information. How long do people stay on the treatment and what happens when people stop the drug?
Would stopping treatment for reasons other than lack of response have an impact on health-related quality of life?	
What is the expected duration of a course of ESK-NS treatment?	
Are there likely to be some people who remain on ESK-NS treatment for life?	
What proportion of patients would stop ESK-NS treatment by 2 years in the recovery state?	
What are the criteria for stopping ESK-NS treatment in the acute, continuation and maintenance phases?	
Could the requirement for attendance at clinics and the need for monitoring influence compliance with treatment?	
Is there any evidence that ESK-NS is a disease modifying treatment?	

Issue 5: Effect on mortality	
Is severity of TRD a proxy for risk of excess mortality due to suicide?	
Would ESK-NS treatment effect the risk of mortality?	Economic models presented seem to assume effect on suicide mortality but no direct evidence to support this
Are the interventions in the meta-regression representative of standard care in the UK?	
Issue 6: Cost of clinic visits	
In clinical practice, how many patients could 1 nurse concurrently supervise and monitor following administration of ESK-NS?	
What band would the nurse(s) be?	
Would non-attendance at clinic appointments affect the cost-effectiveness of ESK-NS treatment?	
Issue 7: Adoption	
Are there any infrastructure investments associated with the adoption of ESK-NS + OAD that need to be accounted for in the model?	Existing comments in reports should be noted particularly those around: complexity of use (specialist administration, post dose monitoring); who exactly it is for and where it fits within current treatment options; significant resource and wider infrastructure considerations; the danger of indication drift [redacted]
Issue 8: Uncaptured benefits to carers	
Are there any additional benefits and costs to carers of people with TRD receiving ESK-NS?	

If so, are all the additional benefits and costs to carers captured within the model?	

Response from Peter Pratt (NHS Commissioning Expert)
Issue 2: Time Horizon (page 3 of 6)
Agree with response which supports a time horizon longer than 5 years, e.g. the ERG base case of 20 years.
Issue 4: Treatment discontinuation (page 4 of 6)
Agree with response which supports ERG base case of no discontinuation for reasons other than lack of efficacy.
Issue 7: Adoption (page 5 of 6)
The ERG base case might be conservative because it has under-estimated infrastructure costs/timings, although it is difficult to estimate the size of the effect of such changes.
Response from Navneet Kapur (National Guidelines Alliance)
Issue 1: Generalisability of evidence (page 3 of 7)
Agree with concern regarding generalisability given relatively high rate of lifetime suicide attempts (7%), which might be higher in TRD as well as the observation in the trials that suicide only observed in those treated with esketamine.
Issue 3: Placebo response rates (page 4 of 7)
Agree that *"… we want to know the additional benefits conferred by the drug itself rather than the additional benefit of increased clinical contact"*.
Issue 4: Treatment discontinuation (page 5 of 7)
Agree that no evidence has been provided as to the rate of discontinuation for reasons other than lack of efficacy or for the consequences of such discontinuation.
Issue 5: Effect on mortality (page 6)
Agree that no direct evidence to support reduction in risk of suicide and actually evidence, albeit weak, to perhaps support an increased risk of suicide.
Issue 7: Adoption (page 6 of 7)
ERG base case might be conservative because it has under-estimated infrastructure costs/timings. The ERG cannot comment on the "…danger of indication drift…"
Response from Janssen
Issue 1: Generalisability of evidence
Patient characteristics (page 3 of 149)
Although the company has provided evidence on the similarity of patients in the esketamine trials and those seen in UK practice, it is important to note that there is still a lack of evidence as to how this intervention might work in a UK NHS setting. This issue links with the issue of adoption of the intervention and necessary infrastructure highlighted by the clinical experts (see comments on issue 7).
Comorbidities (page 5 of 149)
According to the company, *"patients with psychiatric diagnoses other than the indication being studied (including current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychosis, bipolar or related disorders (confirmed by the MINI), comorbid obsessive compulsive disorder, intellectual disability (only DSM-5 diagnostic code 319), borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder, or if they have a history of moderate or severe substance or alcohol use disorder according to DSM-5 criteria) were excluded from the Phase 3 clinical trials as these would require separate investigation"* and *"to maximise the homogeneity of the clinical trial population"*. It should be noted that this affects the generalisability of the study results to the aforementioned patients.
Alcohol abuse disorder (page 6 of 149)
As stated before, patients with TRD who had a history (within 6 months) of moderate or severe substance or alcohol use disorder according to DSM-5 criteria were excluded from the ESK-NS trials. The company cited data from a systematic review (published in 2004) of patients with depression who also had alcohol or substance misuse and compared it to a meta-analysis of patients with unipolar depression (reference not provided). The company stated that *"these findings show generalisability of the relative treatment benefit from ESK-NS randomised controlled trials to those patients with a dual diagnosis of (alcohol) abuse disorder in clinical*

practice". However, the studies did not specifically compare esketamine which the company stated has a *"novel mechanism of action"*. Furthermore, esketamine has the potential for addiction.
Suicidal ideation with some intent (page 7 of 149)
Patients with (previous) but not current (within 6 months) suicidal ideation / intent were included in the esketamine trials. Patients with suicide behaviour in the 12 months prior to the study were excluded. The company stated that *"the TRD population studied is representative of a population with increased risk of suicidality"*. However, the exclusion of patients with *"acute suicide risk"* remains of concern to the ERG. The company have conducted a separate clinical programme in patients with a moderate to severe depressive episode of MDD who have current suicidal ideation with intent. Patients with TRD were not excluded from these trials. The results of these trials, when published in full, may be informative in relation to patients with TRD and at *"acute suicide risk"*.
Failed ECT treatment (page 8 of 149)
Similarly to patients with certain comorbidities (see above), *"patients who previously demonstrated non-response to an adequate course of treatment with electroconvulsive therapy (ECT) in the current major depressive episode, defined as at least 7 treatments with unilateral/ bilateral ECT, were excluded from the ESK-NS trials to ensure a homogenous population is enrolled in terms of prior antidepressant treatment failures"*, i.e. that study results are not generalisable to this group.
OADs included in the ESK-NS studies (page 8 of 149)
While *"the OADs included in the ESK-NS studies are amongst the top 10 most frequently used in the UK TRD patient population"*, these only account for less than half the OADs used in the UK TRD population. Furthermore, the ERG does not agree with the statement that *"evidence suggests that there are few differences in efficacy and tolerability between individual OADs, and therefore not likely to be any treatment difference between OADs used with ESK-NS"*. As detailed in the ERG report, *"there are differences between the type of OAD for remission rates after 28 days, e.g. within the SSRI group: sertraline (odds ratio (OR) 1.38, 95% CI 0.26 to 7.22) vs. escitalopram (OR 4.71, 95% CI 1.08 to 20.63)"*.
Is 4 weeks enough time to establish response to treatment with a newly initiated oral antidepressant? (page 14 of 149)
Four weeks to determine response does seem reasonable and is in accordance with CG90.
Issue 2: Time horizon (page 20 of 149)
A lifetime time horizon is recommended as part of the NICE Reference Case. The company argue that longer than 5 years is inappropriate because the model was designed to capture only one MDE. However, this appears not to be the case given that recurrence can occur for which subsequent therapy is administered. What this highlights is the low company estimates of the efficacy of subsequent therapy since over a 5 year time horizon only 0.737 years are spent in the recovery (at least 9 months remission) state. Indeed at 5 years over 75% of the cohort, having received esketamine, are in the MDE state, which seems to be high if patients can switch treatment on relapse. The ERG report provided a scenario where the efficacy of subsequent therapy was raised in line with the method of estimation used in TA367. This scenario results in under 50% being in the MDE state at 5 years with 44.4% at 20 years.
Issue 3: Placebo response rates
How many clinic visits are expected in practice with esketamine treatment and with standard care? (page 22 of 149)
The company argued that it cannot be assumed that patients would receive more clinical contact with standard care partly because patients currently receive less than the recommended amount of clinical contact. However, if there is such a discrepancy between the recommended and actual clinical practice, the ERG wonders how it can be assumed that it will not also apply to participants receiving esketamine, i.e. the receipt of less than the ideal amount of clinical contact.
Are the placebo response rates observed in TRANSFORM-2 unusually high? (page 25 of 149)
Regardless of whether the placebo response is higher in the esketamine trials or not, two facts remain:

1.) the placebo response is just as likely to apply to the intervention arm as the comparator arm. Indeed, the company have implicitly assumed this by stating that it is largely attributed to the large amount of clinical contact that occurred in the trial and in both arms.
2.) It cannot be assumed that the placebo response is due solely or even in large part due to the amount of clinical contact. As the company also identifies, other factors could include the anticipation of receiving a new and possibly more effective treatment. As the ERG have pointed out, if the amount of clinical contact plays a large part in increasing the chance of response and remission then the logical action would be to increase the amount of clinical contact, which might imply a different scope.

Issue 4: Treatment discontinuation

Is the treatment effect of ESK-NS + OAD maintained after stopping treatment? (page 33 of 149)
Would stopping treatment for reasons other than lack of response have an impact on health-related quality of life? (page 38 of 149)

As already stated by the ERG, the company have provided no direct data that discontinuing esketamine for reasons other than lack of efficacy will not have a not deleterious effect.
The company argue that the evidence from SUSTAIN-1 that there is an advantage to maintaining treatment with esketamine does not inform the effect of discontinuing esketamine in the recovery phase. However, one cannot be confident that this is the case given no evidence for the so-called recovery phase. The company cited a study of OADs by Geddes et al. 2003, which showed no effect of withdrawal. However, the company have argued that one of the main reasons for the efficacy of esketamine is the placebo effect, whether it be due to the novel method of delivery or the extra clinical contact time, both of which would be curtailed on discontinuation and neither of which were studied by Geddes et al. 2003.
The company did provide a post hoc analysis of SUSTAIN-1, the results of which were reported in Table 3 of the response to technical engagement. This seemed to show that there was no decrease in utility between the *"…moment of termination of the study and at the end of the two-week follow-up period…"*. However, it is unclear whether the patients included in this analysis were still on esketamine.
The company also argue that withdrawal symptoms observed in the esketamine trials were *"…primarily mild to moderate in severity"*. How significant this is would require further evidence, at least in the form of some clinical expert opinion. What is a concern to the ERG is that the company stated in the section on withdrawal symptoms that *"new worsening of depressive symptoms was observed mostly in non-responders to ESK-NS who discontinued treatment due to lack of therapeutic response"*. This implies a comparison with those who discontinued treatment for reasons other than lack of therapeutic response.
In summary, the company have provided no data as to the quality of life or rate of relapse post-discontinuation for reasons other than lack of efficacy. During the technical engagement phone conference, the company indeed stated that no such data exist.

What is the expected duration of a course of ESK-NS treatment? (page 42 of 149)
Are there likely to be some people who remain on ESK-NS treatment for life? (page 50 of 149)
What proportion of patients would stop ESK-NS treatment by 2 years in the recovery state? (page 51 of 149)

In the absence of data, the company elicited opinion from 25 UK psychiatrists, presented in Appendix A of the response to technical engagement. This indicated that most would not discontinue treatment if they believed the patient was likely to relapse or experience a recurrence. The ERG would argue that this is not the same as saying that no deleterious effect would actually occur. Responses to other questions suggested that most patients would be expected to have discontinued treatment by two years. For example, the percentage of patients in remission on two antidepressants continuing to be treated with two antidepressants for >2 years was 36%. This would imply that 64% had discontinued. However, doubt as to the validity of this figure is raised because this was also the figure for those who had achieved response, but not remission. If recovery, i.e. *"sustained and stable remission"* is required to be able to discontinue esketamine then it is difficult to see how patients be expected to discontinue (with no ill effect) after only experiencing response, but not remission.
Doubt as to the meaning of the responses in general is also raised by potential inconsistencies between responses. In particular, when considering the percentage who would remain on therapy after being in remission

for 9 months by risk, the highest, which is for the high-risk group, was only 18%. It is difficult to reconcile the idea that 36% of patients continue therapy in total for > 2 years and only 18% of those who have been in remission for 9 months at high risk (low risk was only 10%). Also, the percentage in remission continuing *"product X"* in combination with an OAD at two years was estimated to be only 16%. This might be considered roughly consistent with the estimates by risk. However, the figure of 16% at two years is given in a table with a lack of internal consistency with 16% being the figure for 12 months as well and that for 15 months being considerably lower at 4%. These figures are made more confusing by each of them being accompanied with a fraction out of 25, which is the number of psychiatrists in the sample, thus casting doubt as to what these percentages actually mean. The ERG would suggest that some of the inconsistency might be due to the figures having been reported as means as opposed to per respondent.

The company also conducted a survey of four UK esketamine clinical trial investigators, reported in Appendix B. The main purpose of this survey seemed to be to elicit the percentage of patients who would discontinue esketamine (and continue only on the OAD) at 9 months, as opposed to up to 2 years, as in the survey of 25 psychiatrists reported in Appendix A. These results were also reported per respondent as opposed to as a mean. The results of this appeared to be to some degree also inconsistent with those from the survey reported in Appendix A. They do support they assertion by the company that a large proportion of patients might discontinue esketamine as early as 9 months after initiation and with 3 respondents indicating that the percentage might be considerably higher than assumed in the company base case (60% to 75% vs. 35.4%).

The pychiatrists were also asked to estimate the discontinuation rate per month thereafter, which elicited a response of between 3-5% and 15%, although one respondent refused to respond and the one who stated 15% also stated that 10% would remain on esketamine *"continuously"*. The company then produced a revised base case ICER of £7,498, which they stated was based on a mean of 61.25% discontinuation at 9 months and 8.33% per month thereafter, also incorporating a carer disutility decrement of [redacted] for the MDE state (see discussion of issue 8 below). The ERG have confirmed the effect of the carer disutility to be an ICER of £6,043, vs. £7,699 in previous company base case. The ERG were also able to reproduce the ICER of £7,498, although only by setting the input cell for 4-week risk to 8.00%.

The company argue that only a very small number of patients would be on treatment for life and that this is an assumption of the ERG base case. However, in the ERG base case no patients are on treatment for life and the average time on treatment is only 1.2 years.

<u>New ERG scenarios</u>

On the basis of the company response to the technical report, the ERG have conducted some additional analyses. The ERG considered that there was sufficient evidence from expert opinion to warrant the inclusion of an estimate for the rate of discontinuation of esketamine (remaining on OAD only) for reasons other than lack of efficacy. The ERG considers that the evidence from the survey of 25 UK psychiatrists is probably more reliable than that from the 4 trialists due to greater sample size and greater likelihood of independence. On this basis and to provide a plausible alternative to both the ERG and company base cases, the ERG have chosen to employ the estimate of 36% patients in remission on two antidepressants continuing to be treated with two antidepressants for >2 years. The 36% has been input into the model as a figure of 100-36=64% for the percentage of patients who discontinued treatment in recovery by 2 years (cell E71, Clinical Inputs tab). This rate of discontinuation might be too high given that the 36% should be applied to a larger proportion of the cohort, i.e. those in stable remission as opposed to those in recovery. However, it is still lower than the company base case: it implies a 4-week risk of discontinuation of 6.15% (as opposed to 8.33% per month in the new company base case). The ERG also chose not to accelerate the rate of discontinuation early after 9 months remission in the way that the company did by assuming that 61.25% would discontinue immediately. Also, the ERG chose to incorporate carer disutilities according to the ERG estimates in the section about Issue 8 in the following way: -0.036 for MDE, +0.084 for remission and zero adjustment to response and recovery states. No other changes were made to the ERG base case, i.e. time horizon still 20 years, no adjustment for placebo effect, no reduction

in mortality and nurse to patient ratio 1:1. The resulting ICER is £25,827. A summary of this scenarios plus two others, consistent with the ERG report Section 7.3, is provided in an appendix to this document.
What are the criteria for stopping ESK-NS treatment in the acute, continuation and maintenance phases? (page 51 of 149)
The company consulted ten clinical experts, with five being from the UK, to elicit guidance on rules to determine discontinuation, i.e. stopping rules, as reported in Appendix C of the response to technical engagement. In terms of discontinuation for reasons other than lack of efficacy, the additional guidance includes, for those *"…who are in stable remission for a total of 9 months after achieving remission…consider discontinuing esketamine nasal spray while continuing the oral antidepressant…"*. They do also state that *"exceptions will occur based on clinical judgement…"*. The ERG have no comment on these rules as these are a matter of clinical judgement.
Could the requirement for attendance at clinics and the need for monitoring influence compliance with treatment? (page 53 of 149)
The company refers to the market research involving the 25 UK psychiatrists (Appendix A of the response to technical engagement), which reveals that 80% of the psychiatrists stated that patients' inability to drive or operate machinery after administration of a drug would be important in determining the duration of treatment with such a drug. This supports the concern expressed by the ERG that, if patients discontinue treatment for reasons other than loss of efficacy, then they might incur some harm expressed as loss of quality of life and/or risk relapse.
Is there any evidence that ESK-NS is a disease modifying treatment? (page 54 of 149)
The company stated that there is no direct evidence that esketamine modifies the disease, i.e. depression. The ERG are unsure as to what the test might be by which one determines disease modification, particularly given that depression is defined according to the presentation of symptoms (see NICE CG 90).
Issue 5: Effect on mortality
Would ESK-NS treatment affect the risk of mortality? (page 63 of 149)
The company argues that esketamine reduces mortality through reduced time spent in the MDE state, given that depression is associated with increased risk of mortality. This is plausible, but the ERG remains skeptical that this reduction in mortality would be observed in clinical practice, given that it is contrary to evidence of three suicides in the esketamine trials, all of which, whilst considered unrelated to ESK-NS treatment, occurred in patients treated with esketamine. The company asserted that there is a factual inaccuracy in the Technical Report, where mortality was estimated as a function of suicide attempt. The ERG would agree with the company, as stated in the ERG report (Section 5.2.6.7): although this is how it was reported in the company submission (CS), an examination of the model reveals that the method described in the CS is not the way that excess mortality was incorporated. In fact, excess mortality was more correctly estimated by treating the 0.47% from Bergfeld et al. 2018 as a hazard ratio such that the excess was independent of risk of suicide.
Issue 6: Cost of clinic visits
In clinical practice, how many patients could 1 nurse concurrently supervise and monitor following administration of ESK-NS? (page 66 of 149)
The company stated that they had elicited opinion from 59 UK psychiatrists as to the number of patients that a nurse could observe concurrently. Although no further details were provided, they stated that on average, the ratio of one nurse to 4-6 patients was found to be appropriate. They further stated that a ratio of 1:1, as in the ERG base case, is infeasible. This is on the basis of a comparison with the ratio of staffing in intensive care being 1:2 and that patients presenting for administration of esketamine are not acutely ill. The main flaw with this argument is that the ratio for ICU is required for a lot longer than the hour likely for esketamine. The ERG does not dispute that the ratio propose by the company is theoretically possible. However, the ERG would argue that it also of questionable feasibility to be able to establish a service that enables a number of TRD patients to attend

at the same time in order to be supervised and, given than that the symptoms for which they need to be supervised might arise in more than one patients at a time, for all of those patients to be safely supervised.

Would non-attendance at clinic appointments affect the cost-effectiveness of ESK-NS treatment?

The company state that the uncertainty regarding the issue of non-attendance cannot be resolved until adoption of esketamine in real world NHS practice. The ERG concur, although, as stated above, this does raise a question regarding the feasibility of coordinating multiple patient clinics, which would have an impact on cost. It also relates to issue 4, i.e. the effect of discontinuation.

Issue 7: Adoption

Are there any infrastructure investments associated with the adoption of ESK-NS + OAD that need to be accounted for in the model? (page 72 of 149)

The company provided feedback from a variety of health care professionals that indicates that all of their have identified space and capacity for the adoption of esketamine provision. On this basis, the company claims that no additional infrastructure investment costs should be included in the model. The ERG notes that this seems to be at odds with comments from Peter Pratt and Navneet Kapur. It is also not clear that this does not mean that there might be an opportunity cost, i.e. some existing service might be impinged, especially if facilities have to be located for the supervision of multiple patients concurrently.

Issue 8: Uncaptured benefits to carers

Are there any additional benefits and costs to carers of people with TRD receiving ESK-NS? (page 79 of 149)
If so, are all the additional benefits and costs to carers captured within the model? (page 80 of 149)

The company included data from a recently conducted, unpublished cross-sectional UK health-related quality of life (HRQoL) study in the economic model, the study report for which was reported in Appendix E of the response to technical engagement. The ERG consider that this seems to have been a well conducted study to inform the utility of carers, in terms of the following characteristics:

1) Includes a sample of carers of those with TRD
2) EQ-5D-5L elicited and EQ-5D-3L calculated appropriately

However, the ERG would question the way that the effect of carer disutility was incorporated in the model. This was done by applying a disutility to the MDE state as the difference in utility between carers of patients with symptomatic TRD and carers of patients with TRD in remission, equal to [redacted]. This would imply that carers of all patients in the MDE state would otherwise experience the utility associated with being in remission. However, it might be argued that a methodologically better way to estimate disutility associated with a given state is to subtract the utility of that state from the utility associated with full health, in this case not caring for someone with MDE. Therefore, the ERG calculated the average utility for the sample by weighting the age-based utilities from a large (n=79,522) catalogue of UK values (Web Table 1 of Sullivan et al. 2011) by the proportions in each of the same age groups reported in Table 5 of Appendix E (Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. Med Decis Making 2011;31(6):800-4.). This produced a value of 0.835, which is higher than the [redacted]. This would suggest that the carer disutility associated with MDE might be lower than [redacted]. Of course, the fact that the utility for TRD in remission was found to be [redacted] higher, as reported in Appendix E, does suggest that remission is associated with an improvement. Therefore, the ERG repeated the exercise of calculating a weighted average for the carers of those in remission. This resulted in an average of 0.837, which is very similar to that for the other carers and is lower than the [redacted]. This would suggest a carer utility gain, which the ERG agrees with the company might be plausible, at least temporarily.

Abbreviations: CG = clinical guidance; CI = confidence interval; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ECT = electroconvulsive therapy; ERG = Evidence Review Group; ESK NS = esketamine nasal spray; HRQoL = health-related quality of life; ICER = incremental cost effectiveness ratio; ICU = intensive care unit; MDD = major depressive disorder; MDE = major depressive episode; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; OAD = oral antidepressant; OR = odds ratio; SSRI = selective serotonin reuptake inhibitor; TA = technology appraisal; TRD = treatment-resistant depression; UK = United Kingdom

Appendix: new ERG scenarios

Scenario 1:

1) Time horizon 20 years
2) No adjustment for placebo effect to OAD acute response or remission transition probabilities
3) Discontinuation for reasons other than lack of efficacy set to 64% by 2 years
4) No effect on mortality of esketamine nasal spray (ESK-NS) + OAD
5) Cost of clinic visit for ESK-NS + OAD based on patient to nurse ratio of 1:1
6) Carer disutilities incorporated

Scenario 2:

Assumptions (1) to (6) plus:

7) No difference between ESK-NS + OAD and OAD in the loss of response and relapse transition probabilities

Scenario 3:

Assumptions (1) to (6) plus:

8) A decrease in response and remission was applied at each line of subsequent therapy (including best supportive care (BSC)) by multiplying the values for OAD by a factor equal to the ratio of values in step 3 versus step 4 in STAR*D.[1] These ratios are: 13.7/13.0 and 16.8/16.3 for remission and response respectively. The ERG used the same method of adjusting by line for loss of response and relapse in this ERG scenario. This was achieved by using the company estimated values, for loss of response, of 22.2% for first-line treatment-resistant depression (TRD) and 22.8% for second-line TRD and, for relapse, of 6.8% for first-line TRD and 12.8% for second-line TRD.[2]

Table 0.1: New ERG scenario analyses

Scenario		ICER £/QALY
1	Assumptions (1) to (6)	£25,827
2	Assumptions (1) to (7)	£73,554
3	Assumptions (1) to (6) plus (8)	£46,258

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life years

[1] Rush AJ, Kraemer HC, Sackeim HA, Fava M, Trivedi MH, Frank E, et al. Report by the ACNP Task Force on response and remission in major depressive disorder. Neuropsychopharmacology 2006;31(9):1841-53.
[2] Janssen. Esketamine for treatment-resistant depression [ID1414]. Document B: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Janssen, 2019 [accessed 11.7.19]. 237p.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Esketamine for treating treatment-resistant depression

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

After technical engagement the technical team has collated the comments received and, if relevant, updated the scientific judgement by the technical team and rationale.

Issue date: January 2020

Scientific judgements that have been updated after engagement are highlighted in **bold** in section 2 below.

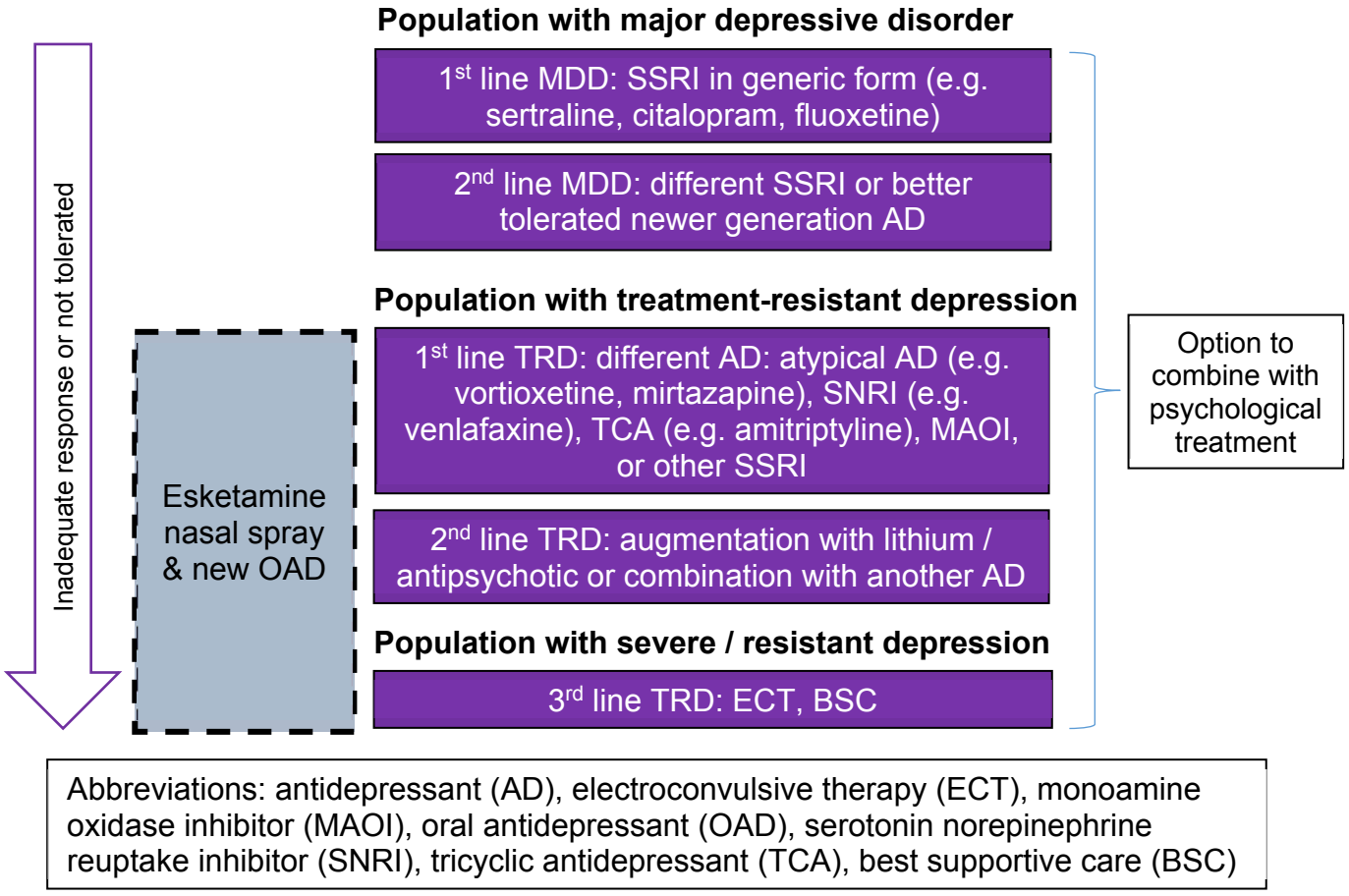
Issue date: January 2020

1. Topic background

1.1 Disease background

- Treatment-resistant depression (TRD) is defined as major depressive disorder (MDD) that has not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode
- MDD affects about 2 million people at any given time in the UK
- TRD affects more than 130,000 people in England
- Symptoms include psychological, physical and social effects
- At least 30% of people with TRD attempt suicide at least once
- Additional impact on carers and family

1.2 Treatment pathway and positioning of esketamine



Abbreviations: antidepressant (AD), electroconvulsive therapy (ECT), monoamine oxidase inhibitor (MAOI), oral antidepressant (OAD), serotonin norepinephrine reuptake inhibitor (SNRI), tricyclic antidepressant (TCA), best supportive care (BSC)

Issue date: January 2020

1.3 Information on the technology

Esketamine nasal spray (ESK-NS) (Spravato, Janssen)	
Marketing authorisation indication	Esketamine in combination with an SSRI or SNRI, is indicated for adults with treatment-resistant major depressive disorder, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode.
Mechanism	Transient NMDA receptor blockade or modulation
Regulatory timelines	CHMP positive opinion received in October 2019 with marketing authorisation granted by the European Commission in December 2019
Administration	Single-use device that delivers a total of 28 mg of esketamine in two sprays (one 14 mg spray per nostril) Self-administered under supervision of healthcare professional
Dose	Induction phase weeks 1-4: 56mg (<65yr) or 28mg (≥65yr) on day 1, subsequent doses are 56mg or 84mg twice a week. Maintenance phase weeks 5-8: 56mg or 84mg once weekly, and From week 9: 56mg or 84mg every 2 weeks or once weekly Dose adjustments are based on efficacy and tolerability
List price	£163 per 28 mg device (£10,554.25 average course of therapy) 56 mg dose (2 x 28 mg devices, £326) 84 mg dose (3 x 28 mg devices, £489)

1.4 Decision problem

	Decision problem addressed in the company submission	Rationale if different from scope
Population	Adults with treatment resistant MDD who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode	In line with scope
Intervention	ESK-NS co-administered with a newly initiated oral antidepressant (OAD)	Indication changed to 'ESK-NS in combination with an SSRI or SNRI'

Comparators	As per the scope, plus the tetracyclic antidepressant (OAD) mirtazapine	Mirtazapine included as a comparator as it is amongst the 5 most frequently prescribed treatments for TRD
Outcomes	As per the scope, with the addition of the impact of ESK-NS on indirect costs and carer health related quality of life (HRQoL) Clinician reported Montgomery-Asberg Depression Rating Scale (MADRS) used to measure severity of depression	TRD-associated disability has been associated with substantial indirect costs

1.5 Clinical evidence used in the model

	TRANSFORM-2	SUSTAIN-1
Study design	Randomised, double-blind, parallel-group, active-controlled, phase 3	Single-arm, long-term, follow-up study
Population	Adults 18-64 years	Adults 18-64 years with stable remission or stable response after treatment with ESK-NS
Intervention	Flexible dose of ESK-NS plus newly initiated OAD	
Comparator	Placebo nasal spray plus newly initiated OAD	
Study phases	4-week screening 4-week double-blind induction 24-week post-treatment follow-up	4-week open label induction 12-week optimisation Double-blind maintenance
Primary outcomes	Response (MADRS) Remission (MADRS) Adverse effects HRQoL (EQ-5D)	Relapse (MADRS) Adverse effects HRQoL

Studies used as supporting evidence in company submission

TRANSFORM-1	TRANSFORM-3	SUSTAIN-2	SUSTAIN-3
Used fixed dose not in line with licence	Used 28mg – below minimum effective dose	Non-comparative & minimal efficacy data	Ongoing study & minimal efficacy data

1.6 **Key trial results (data in red box used in model)**

TRANSFORM-2

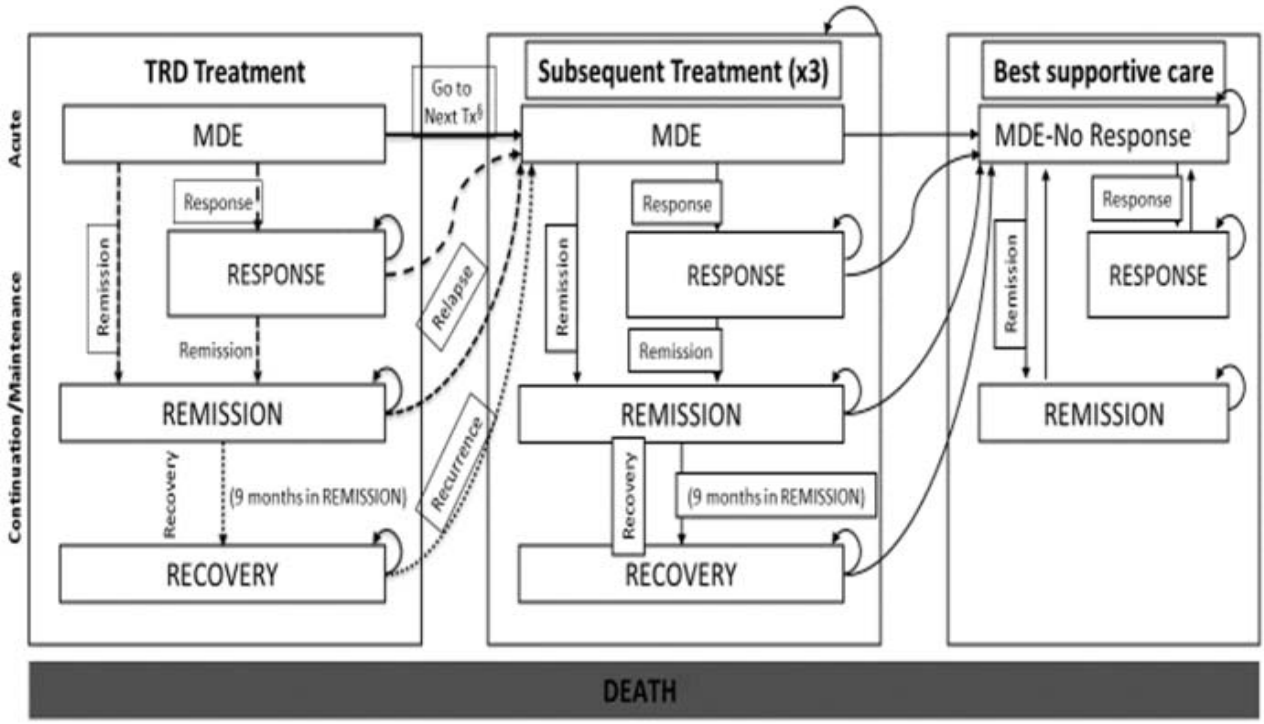
Outcome	ESK-NS + OAD	PBO-NS + OAD	
MADRS	N=101, -21.4 (12.32)	N=100, -17.0 (13.88)	-4.0 (1.69, -7.31 to -0.64)
Response	69.3%	52.0% (unadjusted) 34.0% (adjusted)	
Remission	52.5%	31.0% (unadjusted) 18.0% (adjusted)	
HRQoL	N=104, 0.310 (0.2191)	N=100, 0.235 (0.2525)	Not reported

SUSTAIN-1

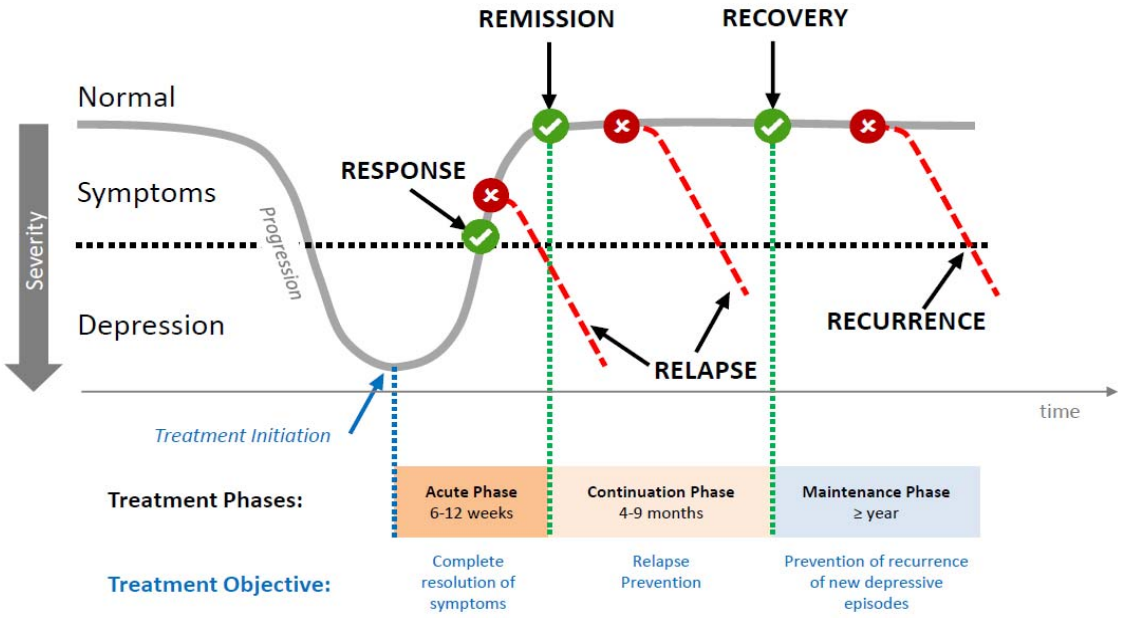
Outcome	ESK-NS + OAD	PBO-NS + OAD
Relapse		
Stable remitters	24/90 (26.7%)	39/86 (45.3%)
Stable responders	16/62 (25.8%)	34/59 (57.6%)
HRQoL		
Stable remitters	N=88, -0.067 (0.1180)	N=86, -0.096 (0.1484)
Stable responders	N=61, -0.023 (0.0753)	N=58, -0.073 (0.1383)

TRANSFORM-2 outcomes reported from baseline to day 28
SUSTAIN-1 outcomes reported after 16 weeks of ESK-NS + OAD treatment

1.7 Model structure (de novo Markov cohort model)



1.8 Treatment phases and duration



1.9 Key terminology definitions

- Severity of depressive symptoms assessed using the Montgomery-Asberg Depression Rating Scale (MADRS) score
- **Response:** ≥50% reduction from baseline in the MADRS total score
- **Remission:** a MADRS total score of ≤12 (symptom-free or only minimal symptoms)
- **Recovery:** stable in remission (absence of symptoms) for 9 months
- **Stable response:** ≥50% reduction in the MADRS total score from baseline in each of the last two weeks of the optimisation phase without meeting the criteria for stable remission
- **Stable remission:** MADRS total score of ≤12 for at least three of the last four weeks of the optimisation phase. The MADRS total score at Weeks 15 and 16 was required to be ≤12
- **Relapse:** MADRS total score of ≥22 for two consecutive assessments separated by 5–15 days and/or hospitalisation for worsening

depression or any other clinically relevant event determined per clinical judgment to be suggestive of a relapse of depressive illness such as suicide attempt, completed suicide, or hospitalisation for suicide prevention

- **Recurrence**: transition from the recovery health state to the MDE health state

1.10 **Key model assumptions**

Company	ERG
Time horizon 5 years	Time horizon 20 years
Adjustment for placebo effect to the acute response or remission transition probabilities only for the comparator	No adjustment for placebo effect to OAD acute response or remission transition probabilities
Discontinuation for reasons other than loss of efficacy	No discontinuation for reasons other than loss of efficacy by 2 years
Effect on mortality of ESK-NS + OAD	No effect on mortality of ESK-NS + OAD
Cost of clinic visit for ESK-NS + OAD based on nurse to patient ratio of 1:6	Cost of clinic visit for ESK-NS + OAD based on nurse to patient ratio of 1:1
Carer disutility applied	No carer disutility applied

2. Summary of the draft technical report

2.1 In summary, the technical team considered the following:

Issue 1 Some evidence to support the generalisability of patients in the trials have been provided. **However, there is still uncertainty about the generalisability as the company highlighted**

further exclusions from the trials with co-morbid psychiatric illness being excluded. The extent of the impact of excluding patients with suicidal ideation also remains unclear.

Issue 2 **The episodic nature of the condition is yet to be determined or defined**; as such, a lifetime horizon or the ERG's 20-year time horizon is preferred.

Issue 3 There remains uncertainty about whether the values observed in the placebo arm have been overestimated relative to those in the intervention arm. The technical team prefer the ERG's approach of using the unadjusted values.

Issue 4 There is still some uncertainty about whether treatment effect is maintained following discontinuation of esketamine or if there is an effect on quality of life.

Issue 5 The technical team consider that there remains insufficient evidence to determine effect on mortality and continues to prefer the ERG's assumption of no effect on mortality of ESK-NS + OAD.

Issue 6 It is unclear what the patient to nurse ratio would be in clinical practice, **so a range of possible ratios from 1:1 to 6:1 is considered**. The technical team continue to consider both the company and ERG ratios as equally valid.

Issue 7 The technical team maintain that any additional infrastructure investments associated with the adoption of ESK-NS + OAD should be accounted for in the economic model.

Issue 8 **There is some agreement between the company and ERG of a carer utility gain. The technical team prefer the method used by the ERG for calculating and incorporating carer disutility.**

2.2 The technical team recognised that uncertainties would remain in the analyses and could not be resolved (see Table 2).

2.3 Taking these aspects into account, the technical team's preferred assumptions result in an incremental cost-effectiveness ratio (ICER) range from £49,097 to £55,388 per QALY gained (see Table 1).

2.4 The company considered the drug to be innovative. However, the technical team considered that the QALY captured all relevant benefits associated with innovation.

2.5 The company, patient organisation and the ERG highlighted that because esketamine nasal spray requires attendance and monitoring at a clinic, geographic access may be an equalities consideration. The commissioning expert raised considerations about equity of access for people in the criminal justice system. The patient expert raised considerations about people with additional physical health conditions who may need additional support when accessing treatment. The patient organisation noted that some groups of people may have difficulties self-administering treatment or attending a clinic. The patient organisation raised that there may be cultural or religious objections to treatment with ESK-NS. The technical team also noted that the main trials only include people aged 18 – 64 (see Table 3).

2.6 The NICE Guide to the methods of technology appraisal (section 5.5.8) states that if introduction of the technology requires changes in infrastructure, costs or savings should be included in the analysis. The technical team considers that any additional infrastructure investments associated with the adoption of ESK-NS + OAD should be accounted for in the economic model, however, it is unclear what elements remain unaccounted. The technical team believes that the time in which the NHS has to comply with the recommendation may need to be extended beyond the usual 3 months in England, and 2 months in Wales.

3. Key issues for consideration

Issue 1 – Generalisability of evidence

Questions for engagement	1. Are TRANSFORM-2 and SUSTAIN-1 generalisable to UK clinical practice? 2. What proportion of UK population are expected to have had suicidal ideation/intent in the previous 6 months and/or suicidal behaviour in the previous 12 months before treatment? 3. Is 4 weeks enough time to establish response to treatment with a newly initiated oral antidepressant?
Background/description of issue	The company included 2 trials in the economic model (TRANSFORM-2 and SUSTAIN-1) which were randomised, double-blind controlled trials involving adults aged 18-64 years. Both trials compared ESK-NS plus a newly initiated OAD to a newly initiated OAD plus placebo and both involved flexible dosing of 56mg / 84mg of ESK-NS. In TRANSFORM-2, ESK-NS was given for 4 weeks and patients followed-up for 24 weeks or joined SUSTAIN-1. SUSTAIN-1 also enrolled patients directly who had not taken part in TRANSFORM-2. In SUSTAIN-1, ESK-NS was given until relapse or trial termination. TRANSFORM-2 and SUSTAIN-1 did not enrol any patients in the UK. One UK patient was enrolled in the supporting trial, TRANSFORM-3, and 12 UK patients were enrolled in the long-term safety study, SUSTAIN-2. The trials excluded: • patients with moderate/severe alcohol abuse according to DSM-5 criteria • patients who had not responded to an adequate course of treatment with ECT in the current major depressive episode • patients who had suicidal ideation with intent in the previous 6 months or suicidal behaviour in the previous 12 months. **The ERG** considered that the lack of UK patients in the main trials is a limitation, particularly given the mode of delivery of this intervention. It considered that there is a lack of evidence about how well ESK-NS might work in the NHS setting as it is a nasal spray that requires monitoring both of which are not part of standard care currently in the NHS. The ERG also considered that it is unclear whether the OADs prescribed across the trials reflect those prescribed at this stage of the pathway

	in an NHS setting. The ERG questioned whether there are any differences in the effectiveness of different OADs that impacts the overall effectiveness of ESK-NS. **The patient organisation** noted that in a survey of 100 patients and 90 carers, 80% of patients report having had suicidal thoughts in the previous 12 months. The patient organisation suggested that people with suicidal ideation might benefit more from ESK-NS than others. They also noted that people for whom ECT was not appropriate may also benefit more from ESK-NS. **The technical team** noted that the TRANSFORM-2 trial included a 4-week trial of an oral antidepressant during the screening phase to determine response to treatment. This was followed by a 4-week double-blind induction phase. The technical team were unclear whether 4 weeks is long enough to determine response to treatment with a new oral antidepressant. The technical team noted that there might have been challenges maintaining adequate blinding in the trial due to the dissociative effects of esketamine. It was also noted that TRANSFORM-2 and SUSTAIN-1 are trials of the additive benefit or harm of esketamine and not a direct comparison of esketamine to an oral antidepressant. **The clinical expert** noted that in the trials the treatment was given earlier in the pathway than would be likely in current UK clinical practice and that generally it is not standard practice to change 2 treatments at the same time as occurred in the trials. Response rates are likely to be lower in patients who have failed more treatments before receiving ESK-NS.
Why this issue is important	Patients with a dual diagnosis of mental health and drug or alcohol misuse problems, those with previous ECT treatment, and people experiencing suicidal ideation or behaviours were excluded from the trials. The patient organisation statement suggests that these groups would represent a high proportion of the UK eligible population. The trial exclusion criteria could mean that the trial cohort is not representative of the TRD population in clinical practice. This increases the uncertainty in the cost-effectiveness estimates.
Technical team preliminary judgement and rationale before engagement	The effect of limitations of generalisability are unknown but increase the uncertainty in cost-effectiveness results. The technical team are concerned that a proportion of the TRD population with a dual diagnosis, previous treatment with ECT, or those with suicidal ideation/behaviours are excluded from the trials and would like to see evidence supporting transferability of results. The technical team would like to see further information on the reasons for excluding patients from the trials.

	It is also possible that the 4-week screening phase of TRANSFORM-2 limits the generalisability of the trial to clinical practice. The technical team would like to see evidence on whether 4 weeks is enough time to consider response to treatment, and how blinding was ensured in the trial. The technical team would also like to see evidence of whether the OADs prescribed across the trials reflect clinical practice, and whether there are any differences in the effectiveness of different OADs that impacts the overall effectiveness of ESK-NS.
Summary of comments	Comments from company TRANSFORM-2 and SUSTAIN-1 are generalisable to UK clinical practice because: • Data from an observational study of patients with TRD across Europe (which included 28 UK patients) were similar to TRANSFORM-2 in terms of mean age, gender distribution, time since diagnosis, pattern of past drug failures, and some patient-reported outcome scores. • Patients with multiple psychiatric comorbidities were excluded from the clinical trials to maximise the homogeneity of the clinical trial population. • A literature review (Otte 2008) and a cross-sectional study (Ani 2009) have indicated that people with a comorbid condition equally benefit from OAD treatment compared to depressed patients without comorbidities. • A retrospective analysis of data from an NHS trust indicated that only a relatively small proportion of patients [redacted] with TRD have a dual diagnosis of alcohol abuse disorder. • A systematic review and meta-analysis (Nunes et al. 2004) found OAD treatment effect sizes for depressed patients with alcohol or substance misuse to be comparable with effect sizes for unipolar depression. • Whilst people with high suicide risk were excluded from the trials, patients with suicidal ideation (without intent) were included meaning the trial population is representative of a population with increased risk of suicidality. A retrospective analysis of data from an NHS trust suggests [redacted] of patients with TRD are at high risk of suicide. • A separate clinical programme of two phase 3 studies (Fu 2019, Ionescu 2019) found that ESK-NS plus standard care was similarly effective in patients with MDD and high risk of suicide compared with the studies in TRD.

	• Patients with non-response to ECT treatment were excluded from the trials to ensure a homogenous population in terms of prior antidepressant treatment failures. • ECT is only used by a small proportion of patients because of the low level of acceptability of the risks involved. • The OADs included in the ESK-NS studies are amongst the top 10 most frequently used in the UK for TRD. • There are not likely to be any treatment efficacy or tolerability differences between individual or classes of OADs used with ESK-NS. • The NICE guideline on depression (CG90) and recommendations in the British Association for Psychopharmacology guideline suggest that 4 weeks is sufficient to establish response to a newly initiated OAD The company provided patient characteristics of the 12 UK patients from the SUSTAIN-2 study along with a subgroup analysis. <u>Comments from guideline expert</u> The exclusion of suicidal ideation and intent from the trial means trial data may not represent the population with TRD. The Adult Psychiatric Morbidity Survey indicates a 7% lifetime prevalence of suicide attempts in the general population, and this may be higher in people with TRD. There is also no data on the population aged over 65 in the included trials. The draft NICE guideline on depression developed recommendations using the same data sets for no or limited response to first-line treatment and TRD because there were considerable similarities and overlaps between the two populations. <u>ERG critique of engagement responses</u> Although the company has provided evidence on the similarity of patients in the esketamine trials and those seen in UK practice, there is still a lack of evidence as to how this intervention might work in a UK NHS setting (see comments on Issue 7). The exclusion of psychiatric co-morbidities affects the generalisability of the study results.

	The company cited data from a systematic review (published in 2004) of patients with depression who also had alcohol or substance misuse and compared it to a meta-analysis of patients with unipolar depression (reference not provided). However, the studies did not specifically compare esketamine which the company stated has a "novel mechanism of action" and has the potential for addiction. The ERG were still concerned about the exclusion of patients with "acute suicide risk" from the trials. The ERG agreed with the guideline expert's comment about generalisability given relatively high rate of lifetime suicide attempts (7%) in the general population, which might be higher in the TRD population. The ERG also noted that in the trials, suicide was only observed in those treated with esketamine. The company have conducted a separate clinical programme of two phase 3 studies (Fu 2019, Ionescu 2019) in patients with a moderate to severe depressive episode of MDD who have current suicidal ideation with intent. Patients with TRD were not excluded from these trials. The results of these trials may be informative in relation to patients with TRD and at "acute suicide risk". Patients who previously demonstrated non-response to an adequate course of treatment with ECT in the current major depressive episode (MDE) were excluded from the trials; study results may not be generalisable to this group. While "the OADs included in the ESK-NS studies are amongst the top 10 most frequently used in the UK TRD patient population", these account for less than half the OADs used in the UK TRD population. The ERG does not agree with the company's statement that "evidence suggests that there are few differences in efficacy and tolerability between individual OADs, and therefore not likely to be any treatment difference between OADs used with ESK-NS". As detailed in the ERG report, there are differences between the type of OAD for remission rates after 28 days. The ERG considers that 4 weeks to determine response does seem reasonable and is in accordance with NICE guideline on depression CG90.
Technical team judgement after engagement	Some evidence to support the generalisability of patients in the trials have been provided. However, there is still uncertainty about the generalisability as the company highlighted further exclusions from the trials with co-morbid psychiatric illness being excluded. The extent of the impact of excluding patients with suicidal ideation also remains unclear. Evidence was provided on 4 weeks being sufficient to determine response to treatment but the concerns about blinding in the trials (due to the dissociative effects of esketamine) were not addressed.

	The technical team is satisfied that the OADs prescribed across the trials are used in clinical practice but it is still unclear if different OADs impact the overall effectiveness of ESK-NS.

Issue 2 – Time horizon

Questions for engagement	4. Are all differences in costs and effects attributable to esketamine nasal spray plus oral antidepressant (ESK-NS + OAD) likely to be captured in a 5-year time horizon?
Background/description of issue	The NICE reference case states that the time horizon should be long enough to reflect all important differences in costs or outcomes between the technologies being compared. **The company** outlined in its submission that 5 years is necessary to capture the expected costs and benefits of esketamine as episodes of depression in people with treatment-resistant depression (TRD) are typically 3 times longer than in people with major depressive disorder (MDD). NICE's previous appraisal of vortioxetine for treating major depressive episodes (TA367) used a time horizon of 2 years. **The ERG** questioned whether a 5-year time horizon was long enough to capture the chronic nature of the condition. The ERG's sensitivity analysis showed that by 20 years the proportions of patients in the response, remission or recovery health states were equal between treatment arms. The ERG concluded that there would be no difference in cost or QALYs beyond this point, and so used a 20-year time horizon in its base-case.
Why this issue is important	The duration of the time horizon has an impact on the cost-effectiveness results as differences in costs and outcomes continue beyond 5 years. The ERG base-case when using a 20-year time horizon reduces the ICER to £4,774 from the company's base-case of £7,699.
Technical team preliminary judgement and rationale before engagement	A 20-year time horizon is preferable to ensure all important differences in cost or QALYs between technologies are captured in the model.
Summary of comments	Comments from company TRD was modelled as an episodic condition in the company submission in line with the label wording. Modelling one episode is consistent with the model used in TA367 but a 2-year time horizon, as used in TA367 for MDD, is not sufficient for patients with TRD where episodes are

	typically 3 times longer. A 5-year time horizon is sufficient to capture the majority of benefits and costs of a single TRD episode, and minimises the uncertainty associated with longer time horizons. Comments from NHS commissioning expert Given the possibility of long-term or repeated courses of ESK-NS treatment, a 5-year time horizon would not be adequate to assess the impact on NHS services. ERG critique of engagement responses The ERG interpret a lifetime time horizon to be in line with the NICE Reference Case. The company argued that a horizon of longer than 5 years is inappropriate because the model was designed to capture only one major depressive episode (MDE). However, the model allows for recurrence to occur, for which subsequent therapy is administered. The company estimates of the efficacy of subsequent therapy are low; over a 5-year time horizon only 0.737 years are spent in the recovery state. At 5 years, over 75% of the cohort that received esketamine are in the MDE state. The ERG report provided a scenario where the efficacy of subsequent therapy was raised in line with the method of estimation used in TA367. This scenario results in under 50% being in the MDE state at 5 years with 44.4% at 20 years.
Technical team judgement after engagement	The episodic nature of the condition is yet to be determined or defined; as such, a lifetime horizon or the ERG's 20-year time horizon is preferred.

Issue 3 – Placebo response rate

Questions for engagement	5. How many clinic visits are expected in practice with esketamine treatment and with standard care? 6. Are the placebo response rates observed in TRANSFORM-2 unusually high? 7. What is the likely effect of an additional clinic visit on key outcomes? 8. Are there any other likely reasons that placebo response rates may be high?

Background/description of issue	The main trials compared esketamine nasal spray plus oral antidepressant (ESK-NS + OAD) with placebo nasal spray plus oral antidepressant (PBO-NS + OAD). Administration involved 8 clinic visits during the 4-week acute treatment phase for both treatment arms. In clinical practice, it is expected that people with TRD would get 2 clinic visits in the first 4 weeks after switching to a newly initiated OAD. **The company** stated that the efficacy estimates (response and remission) for the placebo arm of the TRANSFORM-2 trial were high compared with other TRD studies, potentially because of the number of clinic visits in this group. The company believes that in clinical practice, people on ESK-NS + OAD would be offered 8 clinic visits during the acute treatment phase and people switching to a newly initiated OAD would be offered 2 clinic visits. The company stated that the positive effect in outcome increases with the number of clinic visits. However, this positive effect would only be observed in clinical practice for ESK-NS and not for standard care. To account for this, the company used a post-hoc adjustment of the TRANSFORM-2 PBO-NS + OAD to model treatment effect. This adjustment estimated the effect of reducing the number of clinic visits from 8 down to 2 on the rates of response and remission in the PBO-NS + OAD arm.

Treatment	Remission, % (SE)[a]	Response (but not remission), % (SE)[b]	Response[c]
ESK-NS + OAD	52.48% (4.97)	16.83% (3.72)	69.31%
PBO-NS + OAD (unadjusted)	31.00% (4.26)	21.00% (4.07)	52.00%
PBO-NS + OAD (adjusted for six visits[d])	18.00% (3.84)	16.00% (3.67)	34.00%

	Based on Table 45 of the CS [a] MADRS ≤12; [b] ≥50% reduction in MADRS from baseline but MADRS score >12; [c] ≥50% reduction in MADRS from baseline; [d] Base-case CS = company submission; ESK-NS = esketamine nasal spray; MADRS = Montgomery-Åsberg Depression Rating Scale OAD = oral antidepressant; PBO-NS = placebo nasal spray; SE = standard error **The ERG** was concerned that removing the placebo effect associated with clinic visits for PBO-NS + OAD while not removing it for ESK-NS + OAD may overestimate the treatment benefit of esketamine. It argued that a randomised controlled trial is designed to isolate the relative treatment effect of the intervention and that any placebo effect would apply to the intervention as well as the control arm. Removing the effect of clinic visits from only the comparator arm would bias the estimate of relative treatment effect. The ERG considered that the evidence for the presence and size of the effect of additional clinic visits is weak as the trial does not identify the number of clinic visits to be the basis of a placebo effect. The company supported its assumption with evidence from a paper by Posternak and Zimmerman (2007). However, the ERG questioned the applicability of the study due to differences in outcome measures and lack of information reported. The ERG also considered that there may be other plausible reasons for a placebo effect such as the use of a nasal spray or high patient expectations. The company provided unadjusted estimates of response for PBO-NS + OAD in a scenario analysis and the ERG used these unadjusted values in its base-case.
Why this issue is important	If the treatment effect estimates are adjusted and reduced in only the placebo arm, then the clinical benefit of ESK-NS + OAD may be overestimated. Using the unadjusted treatment effect estimates increases the company's base-case ICER by £7,969.
Technical team preliminary judgement and rationale before engagement	The technical team recognise that the OAD arm of the trials had more clinic visits than usually attended in clinical practice. However, it has not seen enough evidence to conclude with certainty that the values observed in the placebo arm to have been overestimated relative to those in the intervention arm. Because of this, the technical team prefer the ERG's approach of using the unadjusted values to estimate the relative treatment effect of ESK-NS + OAD.
Summary of comments	Comments from company

	Patients in the NHS would have 2 clinic visits in the first 4 weeks after initiating a new OAD for depression. According to UK market research data, feedback from clinical experts, and a mixed-methods study from the UK, patients would on average have 4 clinic visits in the first 3 months for an OAD and 15 visits when using ESK-NS. There is a high placebo response rate in many mental health and depression trials as recognised by the NICE guideline on depression. The active comparator arm in the TRANSFORM-2 trial had higher response rates than would be expected compared to other trials in a TRD population (such as the STAR*D study). The systematic literature review in the company's submission did not find any other trials with similarly high number of follow-up visits and a placebo nasal spray. Data from other trials in TRD indicate that the high response rate in the comparator arm of TRANSFORM-2 is not solely due to the newly initiated OAD. The company attributes the high placebo response rates to the number of clinic visits, the novelty of a nasal spray treatment and anticipation of receiving ESK-NS. The company provided evidence from the Rutherford & Roose (2013) study to show that therapeutic contact and patient expectancy influence treatment response in antidepressant clinical trials. The company also suggests that younger patients would be less cognitively equipped to develop treatment expectancy, meaning that high placebo response rates are more likely to be caused by additional clinic visits as opposed to patient expectations. The company clarified that their post-hoc adjustment for the placebo effect was based on a point estimate provided in the Posternak & Zimmerman (2007) study. The company acknowledged that there is limited data on quantifying the effect of an additional clinic visit but highlight that NICE guideline on depression CG90 recognises the impact of additional clinic visits on key outcomes. The company provided evidence from advisory boards to indicate 4 reasons for high response rates in the placebo arm. All 4 factors would be present in ESK-NS treatment in clinical practice but treatment with a newly initiated OAD would not include 3 of these (additional clinic visits, high expectation, and use of a nasal spray). Only the fourth factor would remain which is that an active drug is used. <u>Comments from guideline expert</u> The guideline expert agrees that the placebo response rates observed in TRANSFORM-2 are unusually high. However, there are concerns over the adjustment approach taken to deal with this;

	the appraisal is considering the additional benefits conferred by the drug itself rather than the additional benefit of increased clinical contact. ERG critique of engagement responses The company argued that in clinical practice patients on standard care currently receive less than the recommended amount of clinical contact. The ERG questions whether any discrepancy between the recommended and actual clinical practice would also apply to people receiving esketamine. The ERG considers that a placebo response is just as likely to apply to the intervention arm as the comparator arm. The company have implicitly assumed this by stating that it is largely attributed to the large amount of clinical contact that occurred in the trial and in both arms. It cannot be assumed that the placebo response is due solely or even in large part due to the amount of clinical contact. As the company also identifies, other factors could include the anticipation of receiving a new and possibly more effective treatment.
Technical team judgement after engagement	The technical team prefers the ERG's approach of using the unadjusted values because there remains uncertainty about whether the values observed in the placebo arm have been overestimated relative to those in the intervention arm.

Issue 4 – Treatment discontinuation

Questions for engagement	9. Is the treatment effect of ESK-NS + OAD maintained after stopping treatment? 10. Would stopping treatment for reasons other than lack of response have an impact on health-related quality of life? 11. What is the expected duration of a course of ESK-NS treatment? 12. Are there likely to be some people who remain on ESK-NS treatment for life? 13. What proportion of patients would stop ESK-NS treatment by 2 years in the recovery state? 14. What are the criteria for stopping ESK-NS treatment in the acute, continuation and maintenance phases? 15. Could the requirement for attendance at clinics and the need for monitoring influence compliance with treatment?

<table>
<tr><td></td><td>16. Is there any evidence that ESK-NS is a disease modifying treatment?</td></tr>
<tr><td>Background/description of issue</td><td>
The company assumed that patients would not discontinue OAD in any phase for any reason other than lack of response. Assumptions about discontinuation from ESK-NS + OAD treatment varied by treatment phase – the model included an acute phase of 6-12 weeks to initiate treatment, a continuation phase following treatment success in the acute phase of up to 9 months to prevent relapse, and finally a maintenance phase for up to 2 years to prevent recurrence. Stopping treatment was assumed to stop incurring the cost of esketamine but have no effect on QALYs. The risk of discontinuation for any reason other than lack of response was presented for the acute, continuation and maintenance phases.
<table>
<tr><th></th><th colspan="6">Risk of discontinuation for any reason other than lack of response</th></tr>
<tr><th rowspan="2"></th><th colspan="2">Acute phase</th><th colspan="2">Continuation phase</th><th colspan="2">Maintenance phase</th></tr>
<tr><th>Risk</th><th>SE</th><th>Risk</th><th>SE</th><th>Risk</th><th>SE</th></tr>
<tr><td>ESK-NS + OAD</td><td>0.00%</td><td>0.00%</td><td>1.69%</td><td>0.42%</td><td>24.89%</td><td>6.22%</td></tr>
</table>

The company assumed patients would not stop ESK-NS + OAD treatment in the acute phase unless they had a lack of response. The company derived the risk of discontinuation from ESK-NS + OAD in the continuation phase from the extrapolation of data observed in SUSTAIN-1. The percentage of discontinuation in the maintenance phase (35.4%) was assumed to be equivalent to the number of patients in SUSTAIN-1 who recovered and had a low risk of relapse (≤2 total number of MDD episodes). These patients were assumed to stop ESK-NS immediately upon achieving recovery. A 4-week discontinuation risk of 25% for ESK-NS was assumed for those patients who did not discontinue immediately.
The ERG considered the assumptions about the discontinuation rates for the acute and continuation phases to be reasonable as they are estimated from the trial data. However, they considered the maintenance phase discontinuation rates to be based on assumptions and not observed data. The ERG suggested an alternative approach is to extrapolate data from SUSTAIN-1. The ERG did not consider it to be reasonable to assume that stopping esketamine has no impact on treatment effect. They referred to the company submission (page 51), which noted that SUSTAIN-1 found a significantly greater relapse rate in those patients who discontinued ESK-NS than those who
</td></tr>
</table>

	remained on ESK-NS. The ERG also did not consider it to be reasonable to assume that discontinuation of esketamine does not result in a decrease in QALYs. The company did not present evidence relating to the rate of relapse in the continuation phase and the rate of recurrence in the maintenance phase of those who discontinue. This lack of evidence made it unclear as to whether there might be a decrease in utility and a loss of QALY even if relapse or recurrence do not occur in people who stop treatment. Given the lack of evidence on the effect of discontinuation of ESK-NS, the ERG preferred to assume that no one stops treatment unless they have a lack of response. **The commissioning expert** stated that there is uncertainty about the duration of a course of ESK-NS treatment and the number of repeated courses over time. **The clinical expert** also highlighted that there is uncertainty about repeated courses of treatment. In the ERG's base-case model, the expected treatment duration of esketamine is 1.2 years and in the company's base-case it is 0.45 years. The models also do not include repeated courses of ESK-NS and assume that once it has been stopped there is no possibility of taking it again.
Why this issue is important	In the company's model, the impact of discontinuation of ESK-NS for reasons other than lack of response was to stop incurring the cost of ESK-NS and only incur the cost of OAD whilst having no effect on QALYs (because patients were assumed to remain in the remission state until loss of response, relapse or recurrence). Removing discontinuation for reasons other than loss of efficacy has a large effect on the ICER, adding £40,511 to the company's base-case.
Technical team preliminary judgement and rationale before engagement	The technical team have not seen evidence that the treatment effect is maintained following discontinuation of esketamine and continuing OAD. There is some evidence from the greater relapse rates in SUSTAIN-1 to suggest that the treatment effect of ESK-NS is not maintained when discontinued. The evidence on the effect of discontinuation on relapse, recurrence or utility is unclear. It is also unclear whether there is an effect on quality of life if ESK-NS was stopped for any reason. Therefore, the technical team would like to see further evidence of treatment effect after discontinuation and on the effect of discontinuation on quality of life. The technical team did not see any evidence on the expected duration of a course of ESK-NS treatment. The technical team note that treatment with ESK-NS would involve regular clinic visits, and that the time and travel associated with visit might affect adherence to treatment. It is unclear if there are likely to be some people who remain on ESK-NS treatment for life. The technical team would like to see evidence and exploratory analyses of the average time on treatment for ESK-NS.

Summary of comments	Comments from company The treatment effect of ESK-NS is expected to be maintained after discontinuing treatment when patients are in a full functional recovery health state. Full functional recovery is expected to be achieved after 9 months in a remission health state and patients are assumed to stay on OAD to help maintain functional recovery. The episodic nature of TRD implies that patients can get out of a depressive episode after a certain time in stable remission (i.e. in recovery). Evidence from Geddes et al. (2003) suggests that there is no pharmacological impact of stopping antidepressant treatment whilst in a recovery health state. In the economic model, patients have a continuous risk of recurrence from the recovery health state, meaning the treatment effect from ESK-NS + OAD may not be maintained indefinitely. The company clarified that the risk of recurrence rate for ESK-NS + OAD, as well as for OAD + PBO-NS, was the pooled rate of both treatment arms from the SUSTAIN-1 study. The risk of relapse/recurrence is dependent on when ESK-NS treatment is discontinued. Data from SUSTAIN-1 indicates that ESK-NS treatment should be continued for 6-9 months to maintain treatment effect at discontinuation. The company acknowledged that there is a lack of clinical data to determine the expected duration of a course of ESK-NS treatment. Data from market research and clinical experts indicated that 52% of patients who have been in a stable remission for 9 months are expected to discontinue ESK-NS treatment. Experts estimated that after two years, <20% patients in stable remission and 36% patients in stable response would be expected to continue ESK-NS treatment. Experts suggested that only a few patients would be treated with ESK-NS for life and that these are thought to follow a chronic course of the disease. The company clarified that the criteria for stopping ESK-NS treatment is included in the SmPC which recommends that evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine need for continued treatment, the need for continued treatment should be re-examined periodically, and after depressive symptoms improve treatment is recommended for at least 6 months. Consultation with clinical experts suggested that in the acute and continuation treatment phase, the criteria for discontinuation will mainly be based on the safety and efficacy of ESK-NS. In the maintenance phase, it will be based on the proposed discontinuation guidance, and clinical judgement of the impact of discontinuing ESK-NS treatment on stability in terms of risk of relapse/recurrence of a patient. The company's market research indicated that attendance at clinics and the need for monitoring would be one of the factors impacting the duration of ESK-NS treatment

	in NHS clinical practice but it was not considered to be the most important factor. The psychiatrists who took part in the market research also indicated that they would not decide to discontinue ESK-NS if that would have a negative effect on the patient's health state. The company conducted a post-hoc analysis of SUSTAIN-1 data on the impact of discontinuing ESK-NS and effect on health-related quality of life. The analysis found that the difference in utility scores between the end of the study and the end of the 2-week follow-up period were small and not significant. The company also notes that changes in withdrawal symptoms observed across studies were primarily mild to moderate and were consistent with observed changes in symptoms of depression and anxiety. Worsening of depressive symptoms was observed mostly in non-responders to ESK-NS who discontinued treatment due to lack of therapeutic response. The company highlight that in TA367, the ERG supported the assumption that people remain on treatment for 6 months after remission in the maintenance phase. The company acknowledged that there is no direct evidence that shows that ESK-NS modifies the disease but highlight that it does have a novel mechanism of action unlike currently available OADs. <u>Comments from NHS commissioning expert</u> Agree with ERG's pre-engagement preferred assumption of no discontinuation for reasons other than lack of efficacy. <u>Comments from guideline expert</u> Agree that no evidence has been provided as to the rate of discontinuation for reasons other than lack of efficacy or for the consequences of such discontinuation. <u>ERG critique of engagement responses</u>

	The company have provided no data about quality of life or rate of relapse post-discontinuation for reasons other than lack of efficacy. SUSTAIN-1 suggests that there is an advantage to maintaining treatment with esketamine. However, the company argues that this does not reflect the effect of discontinuing esketamine in the recovery phase. The ERG considers that there is no direct evidence for the company's position. The company have argued that one of the main reasons for the efficacy of esketamine is the placebo effect, whether it be due to the novel method of delivery or the extra clinical contact time. However, these would not be maintained after stopping treatment. It is unclear whether the patients included in the post-hoc analysis of SUSTAIN-1 were still on esketamine. Clinical expert opinion is needed to assess whether the "primarily mild to moderate" withdrawal symptoms observed in the esketamine trials are significant. The claim that "new worsening of depressive symptoms was observed mostly in non-responders to ESK-NS who discontinued treatment due to lack of therapeutic response" implies a comparison with those who discontinued treatment for reasons other than lack of therapeutic response. The ERG considers that the evidence that most psychiatrists would not discontinue treatment if they believed the patient was likely to relapse or experience a recurrence is not the same as saying that no negative effect would actually occur. The experts' suggestion that 36% patients in stable response would continue ESK-NS treatment at 2 years, implying that 64% would have discontinued at this point. If recovery, i.e. "sustained and stable remission" is required to be able to discontinue esketamine, the ERG question how patients can be expected to discontinue with no negative effect after only experiencing response, but not remission. The ERG also notes evidence in Appendix A of the company response to engagement which suggests that 36% of patients in remission would continue to be treated with two antidepressants for more than 2 years. The company conducted a survey of four UK esketamine clinical trial investigators to elicit the percentage of patients who would discontinue esketamine at 9 months. These results support they assertion by the company that a large proportion of patients might discontinue esketamine as early as 9 months after initiation and with 3 respondents indicating that the percentage might be considerably higher than assumed in the company base case.

	The company argue that only a very small number of patients would be on treatment for life and that this is an assumption of the ERG base case. However, in the ERG base case no patients are on treatment for life and the average time on treatment is only 1.2 years. On the basis of the company response to the technical report, the ERG considered that there was sufficient evidence to warrant the inclusion of an estimate for the rate of discontinuation of esketamine for reasons other than lack of efficacy. The ERG considers that the evidence from the survey of 25 UK psychiatrists is probably more reliable than that from the 4 trialists due to greater sample size and greater likelihood of independence. On this basis, the ERG conducted a scenario analysis with a model that has 36% patients in remission continuing to be treated for more than 2 years. This rate of discontinuation might be too high given that the 36% should be applied to a larger proportion of the cohort, i.e. those in stable remission as opposed to those in recovery. However, it is still lower than the company base case: it implies a 4-week risk of discontinuation of 6.15% (as opposed to 8.33% per month in the new company base case). The ERG also chose not to accelerate the rate of discontinuation early after 9 months remission in the way that the company did by assuming that 61.25% would discontinue immediately. The ERG have no comment on the stopping rules as these are a matter of clinical judgement. The technical team note that potential retreatment with ESK-NS is not captured in the model.
Technical team judgement after engagement	There is still uncertainty about whether treatment effect is maintained following discontinuation of esketamine or if there is an effect on quality of life. Although the technical team prefer the ERG's approach to incorporate a rate of discontinuation of ESK-NS, it recognised that the discontinuation rate due to reasons other than lack of efficacy was highly uncertain. Additional scenarios should be considered to explore the effect of changing the 4-week risk of discontinuation rate with a range between 0% to 15%. The technical team consider that there is a lack of clinical data on treatment duration, and therefore cannot conclude whether the duration modelled by the company or ERG are realistic. This increases the uncertainty associated with the cost-effectiveness of ESK-NS.

Issue 5 – Effect on mortality

Questions for engagement	17. Is severity of TRD a proxy for risk of excess mortality due to suicide? 18. Would ESK-NS treatment effect the risk of mortality? 19. Are the interventions in the meta-regression representative of standard care in the UK?
Background/description of issue	In its economic model, **the company** assumed there were 2 different sources for risk of death: all-cause mortality risk (specific to age and gender) and an excess annual mortality for TRD associated with suicide. A weighted mortality risk for each age was modelled according to the proportion of males and females in the cohort and the baseline age. This was informed by results of a published meta-regression based on 28 small interventional studies of different interventions. The company assumed an excess annual mortality of 0.47% linked to the major depressive episode (MDE) health state and that half the excess mortality risk associated with suicide would still be present in the response state. All excess mortality was assumed to be removed when moving to the remission state. For both sources of risk of death, the risk was applied to the number of patients alive at the beginning of the cycle in each health state.[1] The NICE guideline on depression in adults (CG90) highlights a possible increase in risk of suicide when starting treatment with OADs but that this risk generally declines during treatment. It also notes that increased feelings of hopelessness and helplessness lead to an increase in risk of suicide. **The ERG** considered the use of gender and age-specific mortality tables to be appropriate but had concerns that trial-based data were ignored in favour of the results of a published meta-regression (Bergfeld et al. 2018). The ERG considered that it had not seen evidence that the distribution of interventions is representative of standard care in the UK, and that the company had not justified using results from the meta-regression over trial-based evidence. The ERG noted that none of the treatments listed in Bergfeld et al. were explicitly stated to be OADs and many were more invasive (capsulotomy, deep brain stimulation, ECT, vagal nerve stimulation).

[1] The draft technical report has been updated to remove "The company estimated the number of suicide attempts for patients in each health state and then estimated the proportion of these suicide attempts that were fatal, giving the total of patients who died from suicide".

	The ERG was concerned with the company's assumption that the risk of excess mortality will decrease when treated with ESK-NS. The ERG noted that the trials excluded people who had suicidal ideation/intent in the previous 6 months or suicidal behaviour in the previous 12 months. However, the company submission stated that there were 3 completed suicides across the trials in people who had ESK-NS + OAD. The ERG highlighted that no mortality effect was included in NICE's previous appraisal of vortioxetine for treating major depressive episodes (TA367). Therefore, the ERG assumed no effect on mortality of ESK-NS + OAD in its base-case. **The clinical expert** stated that ESK-NS has a specific anti-suicidal effect in addition to its anti-depressant effect and that more generally successful treatment of depression leads to a reduction in all-cause mortality.
Why this issue is important	Mortality effects were accounted for in the company's economic model. The ERG base-case when assuming no effect on mortality of ESK-NS + OAD increases the company's base-case ICER by £2,224.
Technical team preliminary judgement and rationale before engagement	The technical team would like to see more evidence exploring whether the interventions in the meta-regression studies are representative of standard care in the UK, together with further clarification on the rationale for using the results of the meta-regression over the trial based evidence. The technical team notes that the key trial excluded patients who had suicidal ideation/intent in the previous 6 months or suicidal behaviour in the previous 12 months (see Issue 1). The technical team considers that it has not seen evidence of the relationship between TRD and risk of suicide and would like to see evidence of any link. It also considers that it has not seen sufficient evidence to support the assumption that treatment with ESK-NS + OAD reduces risk of excess mortality. Without this evidence, the technical team prefers the ERG's assumption of no effect on mortality of ESK-NS + OAD.
Summary of comments	Comments from company It is appropriate to add excess mortality risk to the depressive health state in the model as approximately 30% of patients with TRD attempt suicide at least once in their lifetime. Additionally, patients with TRD experience a more severe and protracted course of illness and are more likely to experience co morbid physical conditions than patients with MDD who do not develop treatment resistance. These patients are also more likely to have co-morbid mental health problems and social impairment which contribute to the increased risk of excess mortality. There are studies (Dunner

	2006, Hantouche 2010, & Nelsen 1995) that show an increased excess mortality risk in the TRD population and that the severity of depressive symptoms is associated with the risk of suicide. The company clarified that having MDD or TRD may increase a person's risk for suicide, but ESK-NS is not assumed to be linked to reducing or preventing suicidality. There is a lack of data to show a direct treatment effect of ESK-NS on the risk of mortality. In the economic model, additional mortality from completed suicide is per health state and not by treatment arms. The suicides in the ESK-NS studies were considered unrelated to the ESK-NS treatment. The company recognised that the interventions included in the meta-regression are not widely available in the UK and therefore considered not representative of standard of care in the UK for patients with TRD. <u>Comments from guideline expert</u> There is no direct evidence to support reduction in risk of suicide; weak evidence perhaps supports an increased risk of suicide. <u>ERG critique of engagement responses</u> The company argues that esketamine reduces mortality through reduced time spent in the MDE state, given that depression is associated with increased risk of mortality. This is plausible, but the ERG remains sceptical that this reduction in mortality would be observed in clinical practice, given that it is contrary to evidence of three suicides in the esketamine trials, all of which, whilst considered unrelated to ESK-NS treatment, occurred in patients treated with esketamine.
Technical team judgement after engagement	The technical team consider that there remains insufficient evidence to determine effect on mortality and continues to prefer the ERG's assumption of no effect on mortality of ESK-NS + OAD.

Issue 6 – Cost of clinic visits

Questions for engagement	20. In clinical practice, how many patients could 1 nurse concurrently supervise and monitor following administration of ESK-NS?

	21. What band would the nurse(s) be? 22. Would non-attendance at clinic appointments affect the cost-effectiveness of ESK-NS treatment?
Background/description of issue	**The company** conducted a systematic literature review (SLR) to determine UK based costs and healthcare resource use associated with MDD and TRD. Although 19 studies were identified, none were determined to meet the requirements to inform the analysis. A retrospective chart review was conducted specifically for the company submission to identify cost and resource use data. Although ESK-NS is self-administered, this needs to be performed under the supervision of a healthcare professional to monitor for sedation and dissociation and to monitor blood pressure. The company model assumed that patients would be observed for 60 minutes on average after administration. The model also assumed that 2 nurses (one band 5 and one band 4) could supervise administration and monitor a group of 6 patients in a clinic, with one band 5 nurse monitoring patients post-administration. These assumptions were based on the experiences of trial investigators and resulted in an average cost per patient, per administration of £30.08. **The patient expert** stated that if a patient had difficult or distressing dissociative experiences following administration then they may need extra support from the nurse. **The ERG** was unclear how the monthly costs for each health state were calculated from the retrospective chart review because it only contained information about the source of the costs. The ERG did not consider the assumption in the company model that 6 patients can be concurrently supervised to be realistic. The company conducted additional sensitivity analysis to assess the impact on the average administration cost per session per patient by varying the number of patients seen in a clinic at any one time. The ERG believes that the most plausible patient to nurse ratio would be 1:1 and modelled this in the ERG base-case.
Why this issue is important	The company's sensitivity analysis included a range from 20 patients down to 1 patient per nurse. The sensitivity analysis resulted in the ICER of £6,420 when patient to nurse ratio was set to 20:1 and the ICER was £9,252, when patient to nurse ratio was set to 1:1. The company used a ratio of 6:1 in their base-case giving an ICER of £7,699. The ERG's preference to use a 1:1 ratio increased the company base-case by £7,088. Lowering the ratio to 1:1 of healthcare professionals to patients has a large impact on the ICER as this increases the cost of clinic visits associated with ESK-NS treatment.

Technical team preliminary judgement and rationale before engagement	Further evidence is needed to determine the most realistic number of patients that any one nurse could adequately supervise and monitor in clinical practice. The technical team would like to see ICERs for a range of scenarios that consider nurse to patient ratios between 1 and 6 and evidence supporting the likely implementation of these. In the absence of this, the technical team consider both the company and ERG ratios as equally valid. The technical team would also like to see evidence of how the health state costs were derived from the retrospective chart analysis.
Summary of comments	Comments from company The company recognises that there may be a range of models that could be used in NHS clinical practice but considers that a ratio of 1 nurse to 1 patient to administer ESK-NS is not clinically realistic. Monitoring is not continuous as TRD patients are not acutely ill. Feedback from clinical experts indicates that 1 nurse could monitor several patients concurrently and that self-administration would be managed in a clinic environment. The company maintains that 1 or 2 nurses could manage a group of 6 patients and that costs would decrease over time with increased clinic experience of administering ESK-NS. The company's market research suggests that band 5 or band 6 nurses would be suitable to supervise and monitor the use of ESK-NS. The company's analysis used band 5 nurse in their model. The company acknowledged that there is some uncertainty regarding the issue of non-attendance at clinic appointments which cannot be resolved until the adoption of ESK-NS in real world NHS practice. Data from the clinical trials show the incidence of non-attendance as minimal. Continued non-attendance at clinic appointments would be considered as treatment discontinuation and the impact is dependent on the timing and treatment phase that the patient is in. ERG critique of engagement responses The ERG considers that the comparison with staffing in an ICU is flawed because the ratio for ICU is required for a lot longer than the hour likely for esketamine. The ERG question whether patients can be safely supervised in a service that enables a number of TRD patients to attend at the same time, given that the symptoms for which they need to be supervised might arise in more than one patients at a time.

	The ERG agrees that the uncertainty regarding the issue of non-attendance cannot be resolved until adoption of esketamine in real world NHS practice.
Technical team judgement after engagement	The technical team were presented with ICERs for a range of scenarios that consider nurse to patient ratios between 1 and 6. The technical team continue to consider both the company and ERG ratios as equally valid.

Issue 7 – Adoption and implementation

Questions for engagement	23. Are there any infrastructure investments associated with the adoption of ESK-NS + OAD that need to be accounted for in the model?
Background/description of issue	The NICE Guide to the methods of technology appraisal (section 5.5.8) states that if introduction of the technology requires changes in infrastructure, costs or savings should be included in the analysis. **The commissioning expert** stated that most mental health services are not well established to offer esketamine administration and post-dose monitoring. Adoption of the use of ESK-NS will require adjustments in the configuration of services for people with TRD. The expert also stated that the following investments are needed to introduce the technology: • Suitable premises and adequate staffing for administration and post-dose monitoring • Adequate storage, transportation, disposal and monitoring facilities in relation to the controlled drug status of this drug • Adequate "medical" equipment to deal with the immediate management of any post-dose medical complications **The clinical expert** stated that ESK-NS will need to be administered in a hospital setting and that facilities and staff would be required to administer and monitor treatment. Significant investment in training and staff is required to administer the treatment, however, it may be possible that existing infrastructure could be used as treatment locations.
Why this issue is important	If there are additional costs associated with the introduction of ESK-NS into UK clinical practice, these costs would likely impact the cost-effectiveness.

Technical team preliminary judgement and rationale before engagement	Any additional infrastructure investments associated with the adoption of ESK-NS + OAD should be accounted for in the economic model. The technical team would like to see further information about the likely impact that adoption of ESK-NS would have on the NHS.
Summary of comments	Comments from company Infrastructure costs should not be accounted for in the model, as feedback indicates that there is existing infrastructure within the NHS that can be used. Regarding the costs to account for the adjustment of services for the administration for ESK-NS, these are already accounted for in the economic model. Feedback from local NHS healthcare professionals and clinical experts show that additional infrastructure investments are not required for the adoption of ESK-NS + OAD. From the feedback received from Trusts and Health Boards, 82% of the sites said that they will repurpose existing premises for the adoption of ESK-NS into the NHS and 18% had no specific plans yet. The company aims to provide the required medical training to healthcare providers. The company clarified if it would be feasible for the NHS to adopt the new technology within 90 days. Feedback from 33 Trusts indicated that 16 feel that 90 days is sufficient for implementation, 13 are not sure and 4 Trusts do not think that 90 days is sufficient. Comments from NHS commissioning expert Given the likely change to current service models and associated cost/ service infrastructure implications, the NHS would not be in a position to implement this technology in a safe manner within the usual NHS timeframe of 3 months. If a positive recommendation from NICE is given, the majority of NHS services would require at least 6 months (or longer) in order to ensure that they put in place the necessary systems and processes to adopt the technology. Comments from guideline expert Issues around complexity of use (specialist administration, post dose monitoring), population, position in treatment pathway, significant resource and wider infrastructure implications, and the indication drift should all be considered. ERG critique of engagement responses

	The company's claim that no additional infrastructure investment costs should be included in the model seems to be at odds with comments from the NHS and guideline experts. The feedback from NHS trusts does not provide information about potential opportunity cost, i.e. some existing service might be impinged, especially if facilities have to be located for the supervision of multiple patients concurrently.
Technical team judgement after engagement	The technical team considers that any additional infrastructure investments associated with the adoption of ESK-NS + OAD should be accounted for in the economic model, however it is unclear what elements remain unaccounted. The technical team believes that the time in which the NHS has to comply with the recommendation may need to be extended beyond the usual 3 months in England, and 2 months in Wales.

Issue 8 – Uncaptured benefits to carers

Questions for engagement	24. Are there any additional benefits and costs to carers of people with TRD receiving ESK-NS? 25. If so, are all the additional benefits and costs to carers captured within the model?
Background/description of issue	**The company** included carer health-related quality of life (HRQoL) as an additional outcome in its submission. They stated that 80% of the total UK society burden of TRD was due to lost productivity and carer burden. The NICE guideline on depression (CG90) states that there are additional significant impacts on the carers of people with depression and market research of 90 carers in the UK conducted by the company found that carers reported an impact on their own quality of life when looking after someone with TRD. The company conducted a scenario analysis where the impact on family and/or carers was considered. **The patient expert** stated that there can be a sense of helplessness/hopelessness from those around people with TRD as it can be difficult for them to know how to help and there can be a sense of uncertainty for carers. There can be expectations from professionals as to how carers should be coping or acting with this difficult condition. The patient expert also stated that after the treatment, you are unable to drive therefore need someone to collect you. **The patient organisation** highlighted that carers are impacted heavily in most areas of their lives. They noted the results from the company's market research indicating that carers reported feeling drained or exhausted and that their relationships, mental health, work performance and financial lives were negatively affected when looking after someone with TRD. It is also likely that carers would need to be involved during administration.
Why this issue is important	The potential benefits of treatment with ESK-NS may extend beyond those experienced directly by the person with TRD and these may not be captured within the model.
Technical team preliminary judgement and rationale before engagement	The technical team considered the potential additional benefits to carers' quality of life which are not directly included within the economic model. The technical team would like to see further evidence of any potential costs and benefits to carers associated with ESK-NS, including any costs involved in the administration of ESK-NS.
Summary of comments	Comments from company The company suggest that there is an additional burden along with additional costs to carers of people with TRD and that this is not accounted for in the model. The company propose to include

	data from a recently conducted, unpublished cross-sectional UK health related quality of life (HRQoL) study in the economic model. The data suggests a difference in utility of [redacted] between carers of patients with symptomatic TRD and carers of patients with TRD in remission. ERG critique of engagement responses The ERG considered that the HRQoL study seems to have been a well conducted study to inform the utility of carers as it includes a sample of carers of those with TRD. EQ-5D-5L/3L values were elicited and calculated appropriately However, the ERG questioned the way that the effect of carer disutility was incorporated in the company model. This was done by applying a [redacted] disutility to the MDE state as the difference in utility between carers of patients with symptomatic TRD and carers of patients with TRD in remission. This would imply that carers of all patients in the MDE state would otherwise experience the utility associated with being in remission. The ERG preferred to estimate the disutility associated with a given state by subtracting the utility of that state from the utility associated with full health. The ERG calculated the average utility for the sample by weighting the age-based utilities from a large catalogue of UK values (Sullivan et al. 2011) by the proportions in each of the same age groups reported by the company. The ERG calculated the weighted average for the carers of those in remission to be [redacted], which is very similar to that for the other carers and is lower than the [redacted] in the company model. The ERG preferred approach for incorporating carer disutility was included in its scenario analysis.
Technical team judgement after engagement	There is some agreement between the company and ERG for a carer utility gain. The technical team prefer the method used by the ERG for calculating and incorporating carer disutility as it includes utilities associated with full health and uses weighted averages derived from a large catalogue of UK values.

4. Issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1: Technical team preferred assumptions and impact on the cost-effectiveness estimate

Alteration	Technical team rationale	Cumulative ICER	Cumulative change
Company revised base case	**–**	**£7,389**	**–**
1. Time horizon 20 years	Issue 2	£4,774	-£2,615
2. No adjustment for placebo effect to OAD Acute response or remission transition probabilities	Issue 3	£12,743	+£7,969
3. No discontinuation for reasons other than loss of efficacy by 2 years	Issue 4	£53,254	+£40,511
4. No effect on mortality of ESK-NS + OAD	Issue 5	£55,478	+£2,224
5. Cost of clinic visit for ESK-NS + OAD based on patient to nurse ratio of: 6:1 1:1	Issue 6	 £55,027 £62,078	 -£451 +£6,600
6. Carer disutility incorporated (with range including patient to nurse ratio of 6:1 to 1:1)	Issue 8	£49,097 £55,388	-£5,930 -£6,690
Technical team preferred ICER range	**Issues 2 – 6 & 8**	**£49,097 to £55,388**	**+£41,708 to +£47,999**

Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Population age	The maximum age in the trials (TRANSFORM-2 and SUSTAIN-1) used to inform the economic analysis is 64 years. TRANSFORM-3 does include patients over 64 years but used different doses. The results in 65 – 74 year old patients were similar in magnitude to those in the younger adult population. The company considered the lower treatment effect results from the 75+ age group to be an artefact of the small sample size (n=22). The ERG questioned the applicability of TRANSFORM-2 to the age 65 years+ age group. It also questioned the applicability of SUSTAIN-1 to the 65 years+ age group. SUSTAIN-2 included older patients but relapse was not measured and no separate subgroup analysis was provided. Therefore, given that the NICE scope has no upper age limit, in the clarification letter the ERG requested that the main cost effectiveness analysis, i.e. for age <65 years, informed by TRANSFORM-2 and SUSTAIN-1 be combined with that for age 65 years+, using TRANSFORM-3 as well as SUSTAIN-2.	At clarification the company submitted a new version of the base-case model to include acute response and remission transition probabilities and utilities for MDE, response and remission/recovery states from both TRANSFORM 2 and TRANSFORM 3, weighted by % in each age group such that if set to 0% for age >65 years one gets the same result as in the original base-case. This forms the starting point for the ERG base-case. The ERG and the company base-case used this combined data within the model.
Dosing distribution	The trials (TRANSFORM-2 and SUSTAIN-1) used a flexible dose of either 56 mg or 84 mg of ESK-NS. It is not known how many of the	Unknown. Uncertainty in the dosing distribution increases the uncertainty in the cost-effectiveness results.

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
	two different doses were given to patients in the trials. The cost of the 84 mg dose is higher than the 56 mg dose. As the distribution of the different doses is unknown, there is uncertainty in the cost of a course of treatment. Without knowing the distribution of the doses or a separate analysis, it is unclear whether there is a dose-response relationship.	
Network meta-analysis	The company conducted a network meta-analysis (NMA) comparing ESK-NS with SSRI, SNRI, MAOI, tricyclic antidepressants, vortioxetine, mirtazapine, augmentation with antipsychotics, combination with lithium, and ECT. The company's feasibility assessment identified that the NMA could only be conducted for the acute phase of treatment. However, it did not include the comparisons in its base-case analysis because it did not consider the NMA of acute treatment comparisons to be robust. The ERG had concerns about the NMA results due to the clinical and methodological differences between the studies included in each network. The company included studies where patients received multiple OADs which the ERG considered was outside the scope and should not be included in the network. They also noted heterogeneity in overall	There are considerable uncertainties in the NMA scenario and the results should be interpreted cautiously.

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
	study design, inclusion criteria and patient population. The ERG was convinced that the limitations of the NMA are sufficient to exclude those included comparators except in a scenario analysis.	
Transition probabilities	The ERG considered that the reporting of dosing in TRANSFORM-2 and TRANSFORM-3 trials plus the complex dose changes in SUSTAIN-1 and SUSTAIN-2, make it difficult to know how applicable to clinical practice the transition probabilities estimated from the trials would be. The ERG also considered that it was unclear whether data informing transition probabilities is derived from patients that were directly entered into the trials or were transferred from the TRANSFORM trials.	Unknown. Uncertainty in the calculation of the transition probabilities increased the uncertainty in the cost-effectiveness results.
Adverse events	In the induction phase of TRANSFORM-2, more adverse events were observed in patients treated with ESK-NS + OAD compared to those receiving PBO-NS + OAD (85.2% vs. 60.6%, see Tables 37 and 38 of the CS). No comparative data was provided for the induction phase and the optimisation phase of SUSTAIN-1. However, in line with results from TRANSFORM-2, more adverse events were seen in the maintenance phase (82.2% vs. 45.5%) and the follow-up phase	Unknown.

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
	(11.0% vs. 7.8%). Potential adverse events, especially psychiatric disorders (47.8% vs. 19.3% in TRANSFORM-2), need to be considered before considering ESK-NS as a treatment option for patients with TRD.	
Subsequent treatment	The company estimated the transition probabilities for each of three further lines of subsequent treatment based on evidence from STAR*D. This was an open-label trial and is the largest study to examine the durability of OAD response in MDD and TRD. This was also the source for the transition probabilities for best supportive care treatment (for patients whose disease has failed all previous treatments; fifth-line TRD and onwards). Subsequent treatments in the STAR*D trial could range from switching to another OAD, augmenting the current therapy, or initiating ECT and this varied from patient to patient. The ERG found the company's methods for estimating transition to subsequent therapy unclear, and found that the resulting values were much lower than those in STAR*D. Given that the values from STAR*D were stated to have been adjusted to a four-weekly risk and that the model did not allow transition from MDE to response or remission over more than one cycle, the ERG	Unknown.

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
	concluded that the full effectiveness of the subsequent therapies must have been underestimated.	
Treatment duration	The technical team consider that there is a lack of clinical data on treatment duration, and therefore cannot conclude whether the duration modelled by the company or ERG are realistic (see Issue 4).	This increases the uncertainty associated with the cost-effectiveness of ESK-NS

Table 3: Other issues for information

Issue	Comments
Trial data	TRANSFORM-1 and TRANSFORM-2 are both randomised controlled trials with similar populations of 18-64 year olds. However, TRANSFORM-1 was only a supporting trial in the company submission as, with the exception of the first dose (56mg for all patients), ESK-NS was administered at fixed doses of either 56mg or 84mg which is not reflective of the anticipated esketamine licence. The ERG considered that data from TRANSFORM-1 and TRANSFORM-2 should not be pooled as TRANSFORM-1 might not represent clinical practice because of the fixed doses. It would not be possible to pool the esketamine arms without making further assumptions as TRANSFORM -2 is esketamine vs placebo but TRANSFORM -1 is randomised to the 2 different esketamine doses. To do a meta-analysis, it would require either having to choose one dose or pool the 2 esketamine arms.
Outliers in the data	The SUSTAIN-1 study included data from a number of different trial sites. The results from one site in Poland show a 100% rate of relapses in the placebo arm. In the company's response to technical engagement, they performed a sensitivity analysis to exclude this site. The primary analysis used was the log-rank test. Results showed that statistical significance was maintained for the decrease in risk of relapse amongst patients in stable remission or stable response for ESK-NS+OAD compared with PBO-NS+OAD. However, a published sensitivity analysis (Turner 2019) using Fisher's exact test found that removing the outlier site changes the relapse rate results from significant to non-significant.
Intravenous ketamine	The clinical expert raised the possibility of using available real-world evidence for IV ketamine. However, the ERG considered esketamine nasal spray and ketamine IV to be different drugs. According to the CS, "esketamine is the S-enantiomer and more potent form of ketamine". It is also delivered via a different pathway (nasal vs. IV). Furthermore, ketamine IV was not listed as a relevant comparator and therefore not considered in the ERG report.
Utility values	EQ-5D-5L was used to measure the quality of life of patients in the TRANSFORM-2 trial from which utility values could be derived and data were retrospectively mapped to EQ-5D-3L based on the UK valuation set.

	The ERG considered that the use of HRQoL and utility data reported directly from patients and mapping of this data to be in line with the NICE reference case. The ERG noted that the company originally intended to use data from several trials not just TRANSFORM-2 to generate utility values. It also noted that EQ-5D-5L data from SUSTAIN-1 could be converted and used in the economic model. However, the ERG did not consider that there is a better source for utility values and so did not change base-line utility in the ERG base-case.
Implementation	The commissioning expert stated that ESK-NS is a schedule 2 controlled drug with a need for administration in a health care setting and is not appropriate for use in primary care. They also highlighted that: • Acquisition plus associated costs of administration and monitoring would fall on the secondary care mental health service • The 'tariff' system does not apply as TRD services are not commissioned nationally as part of specialised commissioning arrangements
Administration	The patient organisation considered it an advantage that ESK-NS would be administered in a clinic because of the structured setting and the contact with healthcare practitioners. The patient expert stated that they found regular contact with the clinic to be helpful as the staff monitor mood, get to know them and offer support whilst taking the medication.
Innovation	The company considers the drug to be innovative. However, the technical team considered that the QALY captured all relevant benefits associated with innovation.
Equality considerations	The company, patient organisation and the ERG highlighted that because esketamine nasal spray requires attendance and monitoring at a clinic, geographic access may be an equalities consideration. The commissioning expert raised considerations about equity of access for people in the criminal justice system. The patient expert raised considerations about people with additional physical health conditions who may need additional support when accessing treatment. They may require additional support to attend and return from clinic appointments. Some physical health conditions may also restrict mobility and prevent self-administration of ESK-NS. The patient organisation noted that some groups of people may have difficulties self-administering treatment or attending a clinic. The patient organisation raised that there may be cultural or religious objections to treatment with ESK-NS. The technical team also noted that the main trials only include people aged 18 – 64.

	The technical team would like to see additional information about any groups of patients who may find it difficult to access ESK-NS treatment or attend clinics for treatment.

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