NICE National Institute for Health and Care Excellence

Public observer presentation

Esketamine for treatment-resistant depression [ID1414]

Lead team presentation

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7th January 2020

Key issues

Issue 1: Generalisability of evidence
Are TRANSFORM-2 and SUSTAIN-1 generalisable to UK clinical practice?

Issue 2: Time horizon
Are all costs and benefits of ESK captured in a 5-year or 20-year time horizon?
Is TRD chronic or episodic in nature?

Issue 3: Placebo response rate
Should the adjusted or unadjusted estimates of effect be used?

Issue 4: Treatment discontinuation
Would stopping treatment for reasons other than lack of response affect HRQoL?
Should the company's or ERG's estimate of rate of discontinuation be used?

Issue 5: Effect on mortality
Would ESK have an effect on mortality?

Issue 6: Cost of clinic visits
What is a realistic nurse to patient ratio to administer and monitor ESK?
Would non-attendance impact the cost-effectiveness of ESK treatment?

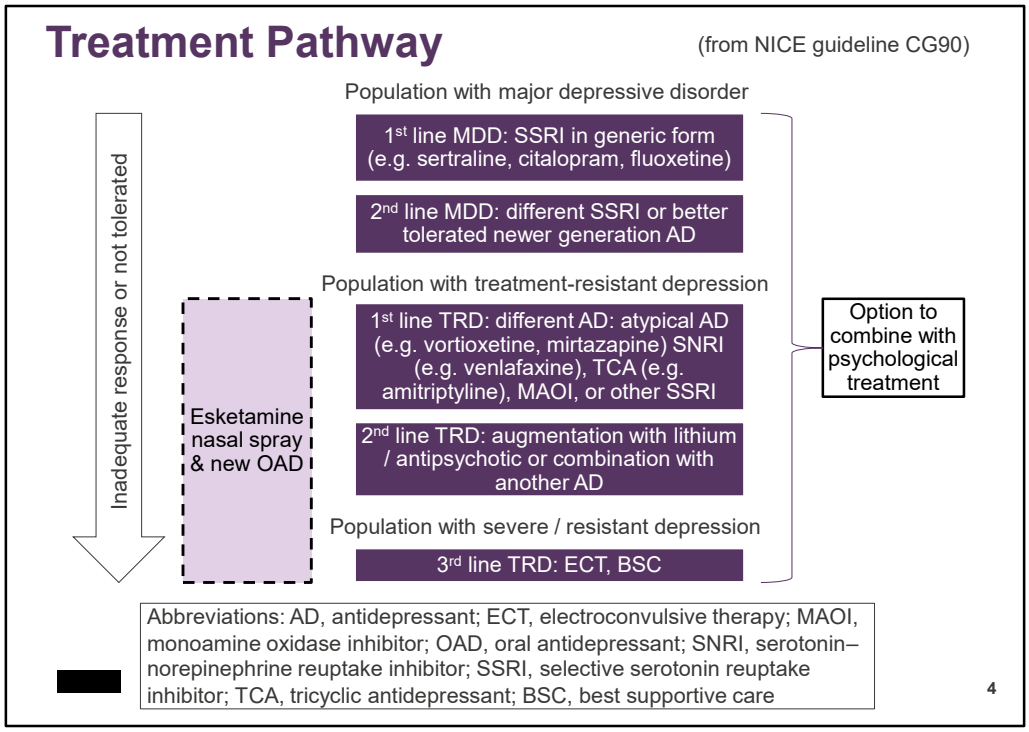
Issue 7: Adoption & Implementation
What type of setting would ESK be used in?
Are there additional infrastructure investments needed to adopt ESK treatment?
What is the likely implementation period required for NHS trusts to adopt ESK?

Issue 8: Uncaptured benefits to carers
Should the company's or ERG's utility gain value be used in the model?

[redacted]

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


Treatment Pathway
(from NICE guideline CG90)
Population with major depressive disorder
1st line MDD: SSRI in generic form (e.g. sertraline, citalopram, fluoxetine)
2nd line MDD: different SSRI or better tolerated newer generation AD
Population with treatment-resistant depression
1st line TRD: different AD: atypical AD (e.g. vortioxetine, mirtazapine) SNRI (e.g. venlafaxine), TCA (e.g. amitriptyline), MAOI, or other SSRI
2nd line TRD: augmentation with lithium / antipsychotic or combination with another AD
Population with severe / resistant depression
3rd line TRD: ECT, BSC
Inadequate response or not tolerated
Esketamine nasal spray & new OAD
Option to combine with psychological treatment
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; BSC, best supportive care
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Esketamine nasal spray (ESK) (Spravato, Janssen)

Indication	Esketamine, 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 in the current moderate to severe depressive episode
Mechanism	Transient NMDA receptor blockade or modulation
Marketing authorisation	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 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
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)

[redacted]

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 co-administered with a newly initiated oral antidepressant (OAD)	Indication changed to 'ESK 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 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

[redacted]

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

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
Intervention	Flexible dose of ESK plus newly initiated OAD	
Comparator	Placebo nasal spray plus newly initiated OAD	
Study phases	4 week screening phase 4 week double-blind induction phase 24 week post-treatment follow-up	4 week open label induction phase 12 week optimisation phase Double-blind maintenance phase
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

[redacted]

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Key results

TRANSFORM-2

Outcome	ESK + 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

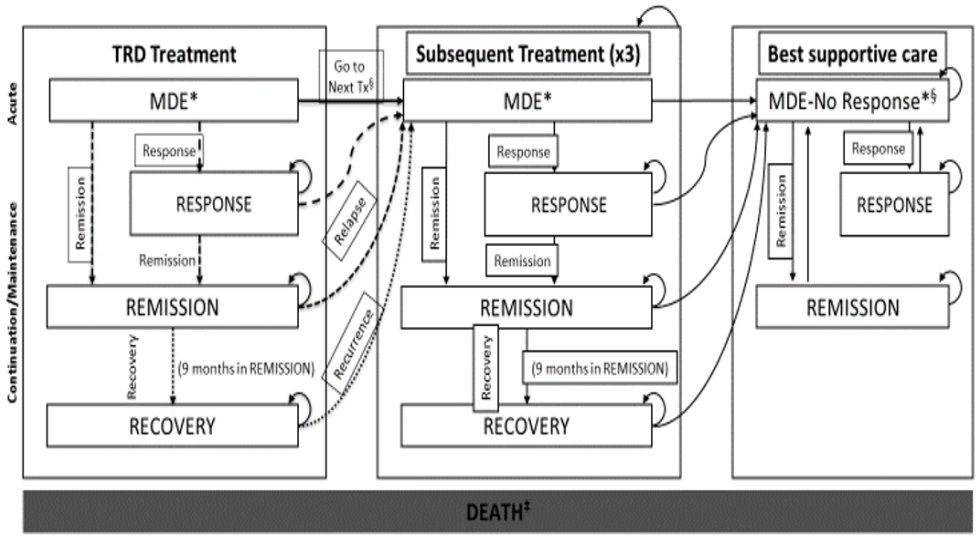
Outcome	ESK + OAD	PBO-NS + OAD
Relapse	Stable remitters: 24/90 (26.7%) Stable responders: 16/62 (25.8%)	Stable remitters: 39/86 (45.3%) Stable responders: 34/59 (57.6%)
HRQoL	Stable remitters: N=88, -0.067 (0.1180) Stable responders: N=61, -0.023 (0.0753)	Stable remitters: N=86, -0.096 (0.1484) Stable responders: N=58, -0.073 (0.1383)

[redacted]

Outcomes used in economic model

Economic model structure

de novo Markov cohort model



Abbreviations: AE, adverse events; MDE, major depressive episode; TRD, treatment-resistant depression

- Time horizon: 5 years
- 5 health states

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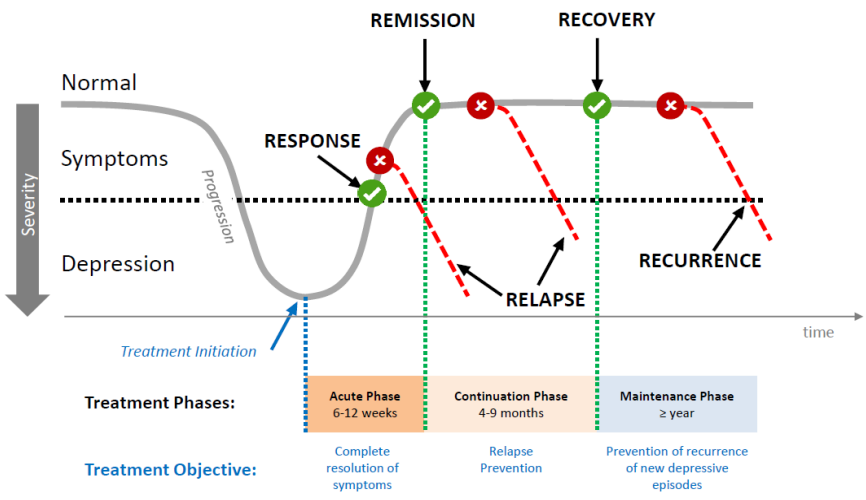
Treatment phases and duration



Patient perspectives

Submissions from: SANE (mental health charity), one patient

- Considered the experiences of people affected by depression and an online survey
- 100 UK TRD patients and 90 carers responded to the survey (7% diagnosed with TRD)

Living with the condition

- Both patients and carers are impacted heavily in their personal, social & work lives
- There is a loss of hope for people with TRD
- Experience a wide range of symptoms every day or nearly every day
- 80% of patients report having suicidal thoughts in the previous 12 months

Current treatment in the NHS

- Most significant benefit of antidepressants is elevated mood
- 56% of patients and carers regard their treatment as ineffective
- 35% of TRD patients stopped feeling the benefits of non-drug therapy within a month of the treatment ending
- Unmet needs are for better information, earlier diagnosis and earlier access to non-drug treatments and specialist help

New treatment: Esketamine

- Lifts mood – helps socialise, think more clearly, challenge unhelpful thoughts & sleep better
- Side effects difficult to predict – dissociation, dizzy, sedated, nauseous, blurred vision etc.

[redacted]

Clinician perspectives

Submission from clinical expert

- Aim of current treatment is full remission of symptoms to reduce risk of suicide & relapse
- Unmet need as significant minority fail to respond to current treatments
- Esketamine offers:
  - New therapeutic option with a novel mechanism of action
  - May help with acute management of suicide risk
- Implementation:
  - Use in secondary care with hospital administration and post-dose monitoring
  - Potential investments in training and staff needed to administer
  - May be possible to identify existing infrastructure to administer
  - More burdensome than standard antidepressants, but less than ECT
  - May require a registry to prevent patients accessing ESK from different sources
  - Effects of long-term use are unknown
  - Duration of treatment and number of further courses of treatment are uncertain

Outstanding issues after technical engagement

- Issue 1: Generalisability of evidence – slides 15-16
- Issue 2: Time horizon – slides 17-18
- Issue 3: Placebo response rate – slides 19-20
- Issue 4: Treatment discontinuation – slides 21-23
- Issue 5: Effect on mortality – slides 24-25
- Issue 6: Cost of clinic visits – slides 26-27
- Issue 7: Adoption & Implementation – slides 28-30
- Issue 8: Uncaptured benefits to carers – slides 31-32

Issue 1: Generalisability of evidence (1)

Background

- The company included 2 trials in the economic model (TRANSFORM-2 and SUSTAIN-1).
- The trials excluded patients with moderate/severe alcohol abuse, no response to ECT, multiple psychiatric comorbidities and those who had suicidal ideation with intent in the previous 6 months or suicidal behaviour in the previous 12 months.
- The trials did not enrol any patients from the UK.

Judgement in draft technical report

- It is unclear if the results of the trials are generalisable to UK clinical practice because of the exclusions and lack of UK patients.
- Also unclear if 4 weeks is enough to determine treatment response and whether the OADs used in the trials reflect clinical practice.

Company response

- Referred to observational evidence to show that:
  - Trials are representative of a UK patient population
  - [redacted] people with TRD have a dual diagnosis of alcohol abuse disorder
  - [redacted] of patients with TRD are at high risk of suicide
  - OADs included in the trials are amongst the top 10 in the UK
- Cipriani et al. study suggests there are not likely to be any efficacy differences between types of OAD used in the trials
- NICE guideline CG90 suggests 4 weeks is sufficient to determine treatment response

[redacted]

Issue 1: Generalisability of evidence (2)

Company response cont…

- Studies (Otte 2008, Ani 2009) indicate people with a comorbid condition equally benefit from OAD treatment compared to depressed patients without comorbidities
- Fu 2019 & Ionescu 2019 found ESK + standard care was similarly effective in patients with MDD and high risk of suicide compared with the studies in TRD

Guideline expert response

Trial data may not represent a TRD population in England. Adult Psychiatric Morbidity Survey* indicates 7% lifetime prevalence of suicide attempts in general population, may be higher in TRD.

EPAR highlights greater risk of ESK abuse by people with a history of drug abuse

ERG comments

- There is a lack of evidence as to how this intervention would work in an NHS setting
- The exclusion criteria of the trials increases uncertainty in generalisability
- The exclusion of patients with "acute suicide risk" remains of concern to the ERG
- Do not agree that there are no differences between OAD effectiveness
- 4 weeks to determine treatment response seems reasonable

Final technical report judgement

The technical team consider that uncertainty remains regarding the exclusion criteria and the population in the trials may not represent a UK TRD population

Are TRANSFORM-2 and SUSTAIN-1 generalisable to UK clinical practice?

[redacted]

*Adult Psychiatric Morbidity Survey: Survey of Mental Health and Wellbeing, England, 2014

Issue 2: Time horizon (1)

Background
- Company modelled a 5-year time horizon to capture the costs and benefits of ESK.
- 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.

Judgement in draft technical report

A 20-year time horizon is preferable to ensure all important differences in cost or QALYs between technologies are captured in the model.

Company response
- TRD is modelled as an episodic condition in line with the label wording
- A 5-year time horizon is sufficient to capture majority of benefits and costs of single TRD episode & minimises the uncertainty associated with longer time horizons
- 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

[redacted]

Issue 2: Time horizon (2)

NHS commissioning expert response
Given the possibility of long-term or repeated courses of ESK treatment, a 5-year time horizon would not be adequate to assess the impact on NHS services

ERG comments
- A lifetime time horizon is in line with the NICE Reference Case
- The company state that 5 years is designed to capture only 1 major depressive episode but model allows for recurrence suggesting a chronic condition for some patients
- Company estimates of subsequent treatment efficacy are low compared to the values in the data source (STAR*D trial)
- The ERG provide a scenario where efficacy of subsequent treatment uses the same method of adjusting the values from STAR*D as applied in TA367

Final technical report judgement
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.

Are all costs and benefits of ESK captured in a 5-year or 20-year time horizon?

Is TRD chronic or episodic in nature?

[redacted]

Issue 3: Placebo response rate (1)

Background

- The company stated that the efficacy estimates for the placebo arm of the TRANSFORM-2 trial were high potentially because of the number of clinic visits.
- In clinical practice, people on ESK + OAD would be offered 8 clinic visits and people switching to a newly initiated OAD would be offered 2 clinic visits.
- Company made post-hoc adjustment to estimate the effect of reducing visits for placebo.
- The ERG was concerned that this would overestimate the treatment effect of ESK.

Judgement in draft technical report

The technical team recognise that the OAD arm of the trials had more clinic visits than in clinical practice. However, not enough evidence to conclude with certainty that the values observed in the placebo arm had been overestimated. The technical team preferred the ERG's approach of using the unadjusted values.

Outcome	ESK + OAD	PBO-NS + OAD
Response (≥50% reduction in MADRS total score)	69.3%	52.0% (unadjusted) 34.0% (adjusted)
Remission (MADRS total score of ≤12)	52.5%	31.0% (unadjusted) 18.0% (adjusted)

Guideline expert response

Response rates are unusually high but concerns over the approach taken to adjust for this

[redacted]

Issue 3: Placebo response rate (2)

Company response

- UK market research data, feedback from clinical experts and data from other TRD trials suggest that the placebo response rate is high in TRANSFORM-2.
- Evidence suggests the high placebo response rate is due to increased clinic visits rather than treatment expectancy
- It is possible that other factors are reasons for the high response rate: (high expectation, use of a nasal spray, an active drug is used)
- Experts indicated that it is due to an active drug being used in the comparator arm as new OAD treatment would not include the other factors

ERG comments

- It is possible that patients on ESK in clinical practice would also get less clinical contact than recommended
- The placebo response is just as likely to apply to the intervention arm
- It cannot be assumed that the placebo response is due solely or even in large part due to the amount of clinical contact
- Other factors could include treatment expectation

Final technical report judgement

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.

Should the adjusted or unadjusted estimates of effect be used?

[redacted]

Issue 4: Treatment discontinuation (1)

Background

- 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 + OAD treatment varied by treatment phase. Stopping treatment was assumed to stop incurring the cost of ESK but have no effect on QALYs.
- The ERG noted that SUSTAIN-1 found a significantly greater relapse rate in those patients who discontinued ESK than those who remained on ESK.
- There is a lack of evidence on the effect of discontinuation of ESK and the ERG preferred to assume that no one stops treatment unless they have a lack of response.

Judgement in draft technical report

It is unclear whether the treatment effect is maintained or if there is an effect on quality of life if ESK was stopped for any reason. Further evidence is needed on the duration of a course of ESK treatment.

Company response

- Treatment effect of ESK is expected to be maintained after discontinuing treatment when patients are in a full functional recovery health state (after 9 months in remission)
- Episodic nature of TRD → patients exit depressive episode after time in remission
- Evidence from Geddes et al. = no pharmacological impact of stopping treatment when in recovery

[redacted]

Issue 4: Treatment discontinuation (2)

Company response cont…

- Model includes risk of recurrence from recovery (taken from SUSTAIN-1)
- Market research & experts suggest:
  - 52% patients in stable remission for 9 months expected to discontinue ESK
  - After two years, <20% patients in stable remission and 36% patients in stable response expected to continue
  - Few patients would be treated with ESK for life
- Stopping criteria for ESK is in SmPC and clinicians would use their judgement
- Clinicians would not discontinue ESK if would affect on the patient's health state
- Post-hoc analysis of SUSTAIN-1 indicates minimal difference in utility scores between end of study and end of 2-week follow-up
- Withdrawal symptoms across studies were mild to moderate
- Company revised base-case to include 61.25% discontinuation at 9 months and 8.33% per month thereafter.

Guideline expert response

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

NHS commissioning expert response

Agree with ERG to use no discontinuation for reasons other than lack of efficacy

[redacted]

Issue 4: Treatment discontinuation (3)

ERG comments

- 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
- Evidence suggests some of the effect of ESK is due to the placebo effect (clinic visits & administration method) → would not be maintained after stop treatment
- Experts suggest that 36% in stable response continue ESK treatment at 2 years
  - Implies 64% discontinue when not in the recovery phase
  - Would these patients experience negative effects of discontinuation
- Consider there is sufficient evidence to include an estimate for rate of discontinuation due to reasons other than lack of efficacy
- Additional analysis included estimate of 64% discontinue treatment by 2 years
- ERG chose not to accelerate the rate of discontinuation early after 9 months remission in the way that the company assumed 61.25% would discontinue immediately

Final technical report judgement

There remains uncertainty in the approach to incorporate a rate of discontinuation of ESK. There is a lack of clinical data on treatment duration which increases uncertainty.

Would stopping treatment for reasons other than lack of response affect HRQoL?

Should the company's or ERG's estimate of rate of discontinuation be used?

[redacted]

Issue 5: Effect on mortality (1)

Background

- 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.
- The ERG was concerned with the company's assumption that the risk of excess mortality will decrease when treated with ESK. No mortality effect was included in NICE's previous appraisal of vortioxetine (TA367). Therefore, the ERG assumed no effect on mortality of ESK + OAD in its base-case.

Judgement in draft technical report

No sufficient evidence to support the assumption that treatment with ESK + OAD reduces risk of excess mortality. Without this evidence, the technical team prefers the ERG's assumption of no effect on mortality of ESK + OAD.

Company response

- 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.
- ESK is not assumed to be directly linked to reducing or preventing suicidality.
- ESK reduces mortality through reduced time spent in MDE state.

[redacted]

Issue 5: Effect on mortality (2)

Guideline expert response
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.

ERG comments
- There were 3 suicides in patients treated with ESK in the trials
- It is unlikely that the reduction in mortality when treated with ESK would be observed in clinical practice

EPAR special warnings & precautions for use
- Depression is associated with increased risk of suicide/suicidal thoughts
- Risk of suicide may increase in early stages of recovery
- Patients with history of suicide-related events or suicidal ideation at increased risk
- Monitoring and supervision of high risk patients should accompany treatment especially in early treatment and following dose changes

Final technical report judgement
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 + OAD

Would ESK-NS have an effect on mortality?

[redacted]

Issue 6: Cost of clinic visits (1)

Background

- ESK is self-administered but needs to be monitored by a healthcare professional.
- Company model assumed that one band 5 nurse could monitor a group of 6 patients.
- The ERG did not consider the 1:6 ratio to be realistic.
- The ERG believes that the most plausible patient to nurse ratio would be 1:1 and modelled this in the ERG base-case.

Judgement in draft technical report

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.

Company response

- Not realistic to have 1:1 for the administration and monitoring of ESK. However, a range of models could be used in NHS practice.
- Based on clinical expert input, assume 1 or 2 nurses to manage 6 patients and that costs would decrease over time with increased clinic experience of administering ESK.
- The company's analysis used band 5 nurse in their model.
- Uncertainty about effect of non-attendance to appointments cannot be resolved until the adoption of ESK in real world NHS.

[redacted]

Issue 6: Cost of clinic visits (2)

ERG comments

- The ratio proposed by the company is theoretically possible but it may not be feasible to establish a service to safely supervise that amount of TRD patients at any given time.
- Uncertainty about safety of supervising multiple patients at the same time, as symptoms for which they need to be supervised might arise in more than one patient at a time.
- The ERG agree that the issue of non-attendance cannot be resolved until adoption of esketamine in real world NHS practice.
- This raises a question regarding the feasibility of coordinating multiple patient clinics, which would have an impact on cost.

Final technical report judgement

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.

What is a realistic nurse to patient ratio to administer and monitor ESK?

Would non-attendance impact the cost-effectiveness of ESK treatment?

[redacted]

Issue 7: Adoption & Implementation (1)

Background

- Reference case = if introduction of the technology requires changes in infrastructure, costs or savings should be included in the analysis.
- 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 will require adjustments in the configuration of services for people with TRD.
- Clinical expert stated that ESK will need to be administered in a hospital setting. Significant investment in training and staff is required to administer the treatment. It may be possible that existing infrastructure could be used as treatment locations.

Judgement in draft technical report

Any additional infrastructure investments associated with the adoption of ESK + OAD should be accounted for in the economic model.

Company response

- Infrastructure cost should not be accounted for in the model, as existing infrastructure within the NHS that can be used.
- Costs to account for the adjustment of services are already included in the model.
- 82% of Trusts indicated existing premises could be used and 18% had no adoption plans.
- Of 33 Trusts – 16 feel 90 days is enough for implementation, 13 are not sure, and 4 do not think 90 days is sufficient.

[redacted]

Issue 7: Adoption & Implementation (2)

NHS commissioning expert response
In communication with NICE, highlighted that given the changes required to services, at least 6 months is required for implementation if use is restricted to in-patient services.
12 months would be required if ESK is approved for use outside of in-patient facilities.

The original commissioning expert's statement mentions concerns about the budget impact for mental health trusts:

- 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)

The NICE methods guide 6.2.14: 'The potential budget impact of the adoption of a new technology does not determine the Appraisal Committee's decision. The Committee does take account of how its advice may enable the more efficient use of available healthcare resources. In general, the Committee will want to be increasingly certain of the cost effectiveness of a technology as the impact of the adoption of the technology on NHS resources increases.'

Guideline expert response
Notes complexity of use, population, treatment pathway, resource use, and indication drift.

[redacted]

Issue 7: Adoption & Implementation (3)

ERG comments

- The company suggestion that no additional infrastructure investment is needed does not fit with the comments from NHS and guideline experts.
- There may be opportunity costs if another service is impinged if facilities have to be located for the supervision of multiple patients concurrently.

Final technical report judgement

The technical team maintain that any additional infrastructure investments associated with the adoption of ESK + 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 would have on the NHS.

What type of setting would ESK be used in?

Are there additional infrastructure investments needed to adopt ESK treatment?

What is the likely implementation period required for NHS trusts to adopt ESK?

[redacted]

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Issue 8: Uncaptured benefits to carers (1)

Background

- The company included carer health-related quality of life (HRQoL) as an additional outcome.
- NICE guideline on depression (CG90) states that there are additional significant impacts on the carers of people with depression.
- The company conducted a scenario analysis where the impact on family and/or carers was considered.

Judgement in draft technical report

The technical team would like to see further evidence of any potential costs and benefits to carers associated with ESK, including any costs involved in administrating ESK.

Company response

- There is additional burden and costs to carers not accounted for in the model.
- Data from a cross-sectional HRQoL study suggests a utility difference of [redacted] between carers of patients with symptomatic TRD and carers of patients with TRD in remission.
- Company revised base-case to include this difference to the MDE state as a carer disutility.

[redacted]

Issue 8: Uncaptured benefits to carers (2)

Patient expert comments
- Carers can have a sense of helplessness/hopelessness.
- Can be uncertain how to help but have expectations.
- After esketamine treatment, need someone to help take you home.

Patient organisation comments
- Carers negatively impacted heavily in most areas of their lives.
- It is also likely that carers would need to be involved during administration.

ERG comments
- The HRQoL study seems well conducted
- ERG's alternative approach estimated the disutility associated with a given state by subtracting the utility of that state from the utility associated with full health
- Calculated average utility by weighting the age-based utilities from UK values (Sullivan et al.) by the proportions in each of the same age groups reported by the company
- Suggests a plausible carer utility gain of [redacted] which is lower than the company's [redacted]

Final technical report judgement
There is some agreement between the company and ERG for a carer utility gain. The technical team prefer the ERG's method for calculating and incorporating carer disutility.

Should the company's or ERG's utility gain value be used in the model?

[redacted]

Additional areas of uncertainty

Issue	Cause of uncertainty
Population age	• The maximum age in the trials (TRANSFORM-2 and SUSTAIN-1) used to inform the economic analysis is 64 years • A supporting trial (TRANSFORM-3) does include patients over 64 years but used different doses • The ERG and the company base-case used combined data in the model
Dose distribution	• Unclear distribution of the 56 mg and 84 mg doses in trials • ERG model used an estimated dose between 56mg and 84mg • Cost of 84 mg dose is higher than 56 mg dose • Unclear whether there is a dose-response relationship
Network meta-analysis	• Company used an NMA for the acute phase of treatment • ERG concerned about differences between studies
Transition probabilities	• Dosing differences between studies make it difficult to know how applicable to clinical practice the transition probabilities would be
Adverse events	• More adverse events for ESK in induction, maintenance and follow-up phases in TRANSFORM-2 • Potential adverse events, especially psychiatric disorders (47.8% vs. 19.3%) in TRANSFORM-2
Subsequent treatment	• STAR*D study used for transition probabilities of subsequent treatment • Company's methods for estimating transition are unclear • Resulting values found to be lower than those in STAR*D • Full effectiveness of the subsequent therapies may be underestimated

Other issues for information

Issue	Cause of uncertainty
Trial data	• Data from supporting trials not to be pooled due to different doses
Outliers in data	• Results from one trial site show 100% relapses in placebo arm • Unclear if this outlier site affects results
Intravenous ketamine	• There is available real world evidence for IV ketamine • However, classed as different drugs and not listed as a comparator
Utility values	• 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
Implementation	• ESK 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
Administration	• The patient organisation & patient expert considered it an advantage that ESK would be administered in a clinic because of the contact with healthcare practitioners
Innovation	• The company considers the drug to be innovative • However, QALY captured all relevant benefits associated with innovation

[redacted]

Equalities

- 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.
- The technical team also noted that the main trials only include people aged 18 – 64.

[redacted]

Assumptions in updated models

Company assumptions	ERG assumptions
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 + OAD	No effect on mortality of ESK + OAD
Cost of clinic visit for ESK + OAD based on patient to nurse ratio of 6:1	Cost of clinic visit for ESK + OAD based on patient to nurse ratio of 1:1
Carer disutility applied	No carer disutility applied

Base-case	Δ QALYS	Δ Costs	ICER
Company	0.366	£2,701	£7,389
ERG	0.246	£15,298	£62,078

[redacted]

Cost effectiveness results

Technical team preferred assumptions and impact on the cost-effectiveness estimate

Alteration	Technical team rationale	Cumulative ICER	Cumulative change
Company updated 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 lack of efficacy by 2 years	Issue 4	£53,254	+£40,511
4. No effect on mortality	Issue 5	£55,478	+£2,224
5. Cost of clinic visit for ESK + 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		**£49,097 to £55,388**	**+£41,708 to +£47,999**

[redacted]

Cost effectiveness results

ERG base-case assumptions and impact on the cost-effectiveness estimate

Alteration	Technical team rationale	Cumulative ICER	Cumulative change
Company updated 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 lack of efficacy by 2 years	Issue 4	£53,254	+£40,511
4. No effect on mortality	Issue 5	£55,478	+£2,224
5. Cost of clinic visit for ESK + OAD based on patient to nurse ratio of 1:1	Issue 6	£62,078	+£6,600
6. No carer disutility incorporated	Issue 8	£62,078	+/-£0
ERG's base-case	Cumulative	**£62,078**	**+£54,689**

[redacted]

ERG scenario 1 results

ERG amended assumptions and impact on the cost-effectiveness estimate

Alteration	Technical team rationale	Cumulative ICER	Cumulative change
Company updated base case		**£7,389**	-
1. Time horizon 20 years	Issue 2	£4,627	-£2,762
2. No adjustment for placebo effect to OAD acute response or remission transition probabilities	Issue 3	£12,557	+£7,930
3. Discontinuation for reasons other than lack of efficacy set to 64% by 2 years and 6.15% per month thereafter	**Issue 4**	£24,052	+£11,495
4. No effect on mortality	Issue 5	£24,521	+£469
5. Cost of clinic visit for ESK + OAD based on patient to nurse ratio of 1:1	Issue 6	£28,946	+£4,425
6. Carer disutility incorporated	**Issue 8**	£25,827	-£3,119
ERG's scenario 1 ICER (with changes to assumptions 3 & 6)		**£25,827**	**+£18,438**

[redacted]

ERG scenario 2 & 3 results

Extensions to ERG scenario 1

ERG scenario 2:

Alteration	Cumulative ICER
ERG scenario 1	£25,827
7. No difference between ESK + OAD and OAD in the loss of response and relapse transition probabilities	**£73,554**

ERG scenario 3:

Alteration	Cumulative ICER
ERG scenario 1	£25,827
8. Decrease in response and remission transition probabilities applied at each line of subsequent therapy in line with company approach*: Loss of response = 22.2% for 1L TRD & 22.8% for 2L TRD Relapse = 6.8% for 1L TRD & 12.8% for 2L TRD	**£46,258**

[redacted]

* Values in ERG base-case applied by multiplying the values for OAD by the ratio of values in step 3 vs step 4 in STAR*D (13.7/13.0 and 16.8/16.3 for remission and response respectively)

ERG scenario exploring effect of changing patient to nurse ratio

Alteration	ERG base-case	ERG scenario 1	ERG scenario 2	ERG scenario 3
1:1	£62,078	£25,827	£73,554	£46,258
4:1	£55,977	£ 22,411	£66,904	£41,531
5:1	£55,408	£ 22,092	£66,283	£41,090
6:1	£55,027	£ 21,879	£65,868	£40,795
ICER range	**From £55,027 to £62,078**	**From £21,879 to £25,827**	**From £65,868 to £73,554**	**From £40,795 to £46,258**

[redacted]

ERG scenario exploring effect of changing discontinuation rate

Immediate discontinuation and 4-week risk of discontinuation for reasons other than lack of response in maintenance phase

4-week risk for remaining patients	ERG base-case	ERG scenario 1	ERG scenario 2	ERG scenario 3
0%[a]	£62,078	£55,388	£131,105	£87,163
3%	£37,844	£33,766	£89,011	£57,244
6.15%[b]	£28,950	£25,827	£73,554	£46,258
8.33%[c]	£25,617	£22,856	£67,771	£42,147
15%	£20,351	£18,158	£58,624	£35,646
ICER range	**From £20,351 to £62,078**	**From £18,158 to £55,388**	**From £58,624 to £131,105**	**From £35,646 to £87,163**

a: ERG base-case, b: ERG scenarios, c: company base-case

All scenarios modelled assume 0% patients stop treatment immediately after entering maintenance phase

ERG scenario varying dose, frequency of dosing and treatment duration during maintenance

Scenario			Average cost of treatment	ICER under ERG base-case
Dose	Frequency	Average duration		
56mg	Weekly	1.2 years	£1,304	£73,568
84mg	Fortnightly	1.2 years	£978	£48,286
56mg	Fortnightly	1 year (1% 4-week risk of discontinuation)	£652	£23,413

Key issues

Issue 1: Generalisability of evidence
Are TRANSFORM-2 and SUSTAIN-1 generalisable to UK clinical practice?

Issue 2: Time horizon
Are all costs and benefits of ESK captured in a 5-year or 20-year time horizon?
Is TRD chronic or episodic in nature?

Issue 3: Placebo response rate
Should the adjusted or unadjusted estimates of effect be used?

Issue 4: Treatment discontinuation
Would stopping treatment for reasons other than lack of response affect HRQoL?
Should the company's or ERG's estimate of rate of discontinuation be used?

Issue 5: Effect on mortality
Would ESK have an effect on mortality?

Issue 6: Cost of clinic visits
What is a realistic nurse to patient ratio to administer and monitor ESK?
Would non-attendance impact the cost-effectiveness of ESK treatment?

Issue 7: Adoption & Implementation
What type of setting would ESK be used in?
Are there additional infrastructure investments needed to adopt ESK treatment?
What is the likely implementation period required for NHS trusts to adopt ESK?

Issue 8: Uncaptured benefits to carers
Should the company's or ERG's utility gain value be used in the model?

[redacted]