HIGHLY CONFIDENTIAL

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Esketamine for treatment-resistant depression [ID1414]

Appraisal Committee Meeting – Wednesday 5 August 2020
2nd Committee meeting

The following documents are made available to the Committee:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the ACD from Janssen**
   a. Company response to the ACD
   b. Company additional response to the ACD

3. **Consultee and commentator comments on the ACD from**:
   a. SANE
   b. British Association for Psychopharmacology
   c. Royal College of Psychiatrists

4. **Comments on the ACD from experts:**
   a. Professor Hamish McAllister-Williams – clinical expert, nominated by Janssen
   b. John P Pratt (Peter Pratt) – commissioning expert, nominated by NHS England

5. **Comments on the ACD received through the NICE website**

6. **Evidence Review Group documents prepared by Kleijnen Systematic Reviews (KSR)**
   a. ERG critique of company comments on the ACD
   b. ERG addendum on the additional company response
   c. ERG analysis following the second appraisal committee meeting

Esketamine for treating treatment-resistant depression

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee (professional group)	British Association for Psychopharmacology	"But how much benefit it (esketamine) provides over other oral antidepressants with adjunctive therapy or electroconvulsive therapy is unclear because these treatments have not been compared directly (p3, Summary) "The company did not provide evidence comparing esketamine with all relevant comparators." (Section 3.4, p7) The evidence for adjunctive therapies such as lithium, or oral antipsychotics is not as strong as that reported in the recent trials of esketamine. These studies are highlighted in a recent systematic review and meta-analysis, that used the criteria of failure of depression to respond to two or more antidepressants (Strawbridge et al., 2019). Furthermore, it is noted that comments were made on generalisability of esketamine studies to the UK population of people with Treatment Resistant Depression, these studies excluding people with co-morbid substance misuse and/or suicidal ideation. We note that using this approach, a number of NICE guidelines in mental illness would be obsolete, including recommendations from the 2009 Depression guideline that are cited by the ERG. Furthermore, virtually every recommendation for psychosocial interventions, based on evidence, would be rejected. Regarding suicide, evidence from trials of IV ketamine suggest beneficial effects of the compound on suicidal ideation, highlighted in a recent systematic review (Wilkinson et al., 2018). The ERG stated that results of IV ketamine could not be extrapolated to esketamine. Though mode of administration is different, we consider that, because ketamine is the same broad class of drug, it is reasonable to make inferences about effects, in much the same way one would do for beta-blockers-and thus makes the point regarding generalisability and suicidality difficult to comprehend. The comparison with electroconvulsive therapy is puzzling- these are two entirely different treatments, and many people will not wish to have ECT, for reasons such as stigma, as well as medical or psychiatric co-morbidity. Clinically, people offered ECT for Treatment Resistant Depression are presenting more acutely unwell, have co-morbid psychosis (for which esketamine is contraindicated), and have more medical morbidity, e.g. have stopped eating or drinking. This is a very different cohort to those people entering the esketamine trials.	Comments noted. The committee considered comments on this section. Section 3.4 of the ACD has been updated accordingly. The committee was aware of the issue around using evidence for intravenous ketamine a from the technical report. NICE seeks relevant evidence from several sources. The company submits the principal evidence. The evidence review group (ERG), an external academic organisation independent of NICE, produces a review of the evidence submission (see sections 3.3.8 and 3.3.9 of the NICE TA Process Guide). Consultees provide information and selected clinical experts, NHS commissioning experts and patient experts also give evidence (see section 3.4 of the process guide). The committee was aware of the issue raised about using evidence for intravenous ketamine from the technical report and did not consider it to be a key issue compared with the other issues raised.
2	Consultee (professional group)	British Association for Psychopharmacology	"Also, the available evidence did not include psychological therapies. (p3, Sumary) The effect of psychological therapy in addition to drug treatments is not clear" (Section 3.4, p7)	Comments noted. The committee concluded that psychological therapies are an adjunctive therapy

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			Whilst this is true, the ERG appears to have derived their conclusions about efficacy of psychotherapy in this population from a prior NICE guideline, as opposed to any empirical data. As highlighted in the systematic review above (Strawbridge et al, 2019) there are only two trials of psychotherapy in people with Treatment Resistant Depression, and only one in which a strict definition of failure of response to two antidepressants was used (Hauksson et al., 2017). This CBT trial had a number of methodological limitations, including self-report of the outcome measure, and would not constitute high level of evidence, using any accepted criteria. Therefore, it is puzzling as to why use of psychotherapy should have any bearing here- especially given that this criterion was never placed on the evidence base for adjunctive therapies such as lithium or antipsychotic medication, mentioned above regarding generalisability.	and a relevant part of the treatment pathway, but that its effect would likely be variable depending on the treatment population and severity of depressive symptoms, but it considered the effect of combining psychological therapies with esketamine treatment to be an unresolvable uncertainty with the evidence available (see section 3.4 and 3.6 of the ACD).
3	Consultee (professional group)	British Association for Psychopharmacology	"Esketamine is unlikely to be cost effective for treatment-resistant depression" (p20) The committee's preferred modelling assumptions were reflected in the ERG's base-case analysis: A time horizon of 20 years The ERG had a preference of 20 years for analysis of outcome for the cost-effectiveness analysis, the question being "is TRD episodic or chronic in nature?" This modelling appears instrumental to the overall decision, and both perspectives are difficult to understand. The literature cited by the ERG appears to not be generalisable to this clinical population, or to the esketamine trials, and both the ERG and drug company appear to be unaware of naturalistic studies of people with treatment resistant depression within the NHS. In terms of evidence presented, the ERG cites a meta-analysis of relapse in depression, which showed increased relapse upon discontinuation of antidepressant therapy versus placebo (Geddes et al., 2003). It is questionable as to how generalisable this data is to people with treatment-resistant depression. The longest follow-up meta-analysed is up to three years (the ERG gives a 20-year time horizon), and the comparator in the meta-analysis is placebo, not continued antidepressant therapy, as per the esketamine maintenance trial. There is no citation of literature on treatment resistant depression outcome studies within an NHS setting. A follow-up study of people within a tertiary treatment-resistant depression service within the NHS examined mortality, and found, "Mortality is one of the indicators of unfavourable outcome in depression. Thirteen participants died during follow-up: eight from natural causes (primarily cardiovascular) and five from unnatural causes (suicide, n= 3; accidental deaths, n= 2). There was a significant trend for association between discharge status and mortality (Chi2 = 8.03; p= 0.01). Thus, only two individuals who were discharged in remission died."(Fekadu et al., 2012) Therefore, remission appears to reduce all-cause mortality within the NHS, naturalistically. The prediction of treatment resistant depression outcome is dependent on initial response, though the overall course is difficult to predict. Clinical data from the same tertiary service above indicated that, post-discharge, over a mean of 3 years, 35% of people with TRD had a	Comments noted. The committee noted uncertainty about long-term outcomes (see section 3.17) but concluded that a shorter time horizon may not solve this issue. See section 3.19 of the ACD. The committee considered the generalisability of the evidence submitted (3.14 of the ACD) as part of the appraisal as well as the consultation responses. The committee also considered that the company's economic model did not reflect the course of the disease. For more detailed discussion see 3.17 of the ACD.

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			poor outcome, treatment to remission being associated with dichotomised good, versus poor outcome (Fekadu et al., 2011). Further analysis of discontinuation within this patient group found that in long term follow up (1-7 years, median 3 years) patients with TRD generally maintained their improvements seen at the end of acute treatment, and even on average improved further, whilst at the same time 43% of patients were able to reduce the number of medications they were taking compared to the end of acute treatment (35% were taking the same number, 22% more) (Wooderson et al., 2014). Therefore, improvement in treatment resistant depression is often maintained whilst reducing medication. There is no reason to doubt this will occur with esketamine.	
4	Consultee (professional group)	British Association for Psychopharmacology	"no discontinuation by 2 years for reasons other than loss of efficacy…There is no evidence on the effect of stopping esketamine after 2 years for reasons other than lack of efficacy…The committee concluded that, on balance, without data the least biased estimate of cost effectiveness would be to not include discontinuation of esketamine for reasons other than lack of efficacy" The stark reality in clinical practice is that a lot of people do not take psychotropic medication as prescribed. People tend to stop treatment for a variety of reasons other than lack of efficacy. For people with depression these include feeling better, and adverse events (Mitchell, 2006). It is difficult to understand how a cost-effective analysis could be informed by people with treatment resistant depression hypothetically discontinuing medication solely on the basis of lack of efficacy. References Fekadu, A. et al. (2011) 'Long-term impact of residual symptoms in treatment-resistant depression', Canadian Journal of Psychiatry. Revue Canadienne De Psychiatrie, 56(9), pp. 549–557. doi: 10.1177/070674371105600906. Fekadu, A. et al. (2012) 'Prediction of longer-term outcome of treatment-resistant depression in tertiary care', The British Journal of Psychiatry, 201(5), pp. 369–375. doi: 10.1192/bjp.bp.111.102665. Geddes, J. R. et al. (2003) 'Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review', Lancet (London, England), 361(9358), pp. 653–661. doi: 10.1016/S0140-6736(03)12599-8. Hauksson, P. et al. (2017) 'Effectiveness of cognitive behaviour therapy for treatment-resistant depression with psychiatric comorbidity: comparison of individual versus group CBT in an interdisciplinary rehabilitation setting', Nordic Journal of Psychiatry, 71(6), pp. 465–472. doi: 10.1080/08039488.2017.1331263. Mitchell, A. J. (2006) 'Depressed patients and treatment adherence', The Lancet, 367(9528), pp. 2041–2043. doi: 10.1016/S0140-6736(06)68902-2. Strawbridge, R. et al. (2019) 'Augmentation therapies for treatment-resistant depression: systematic review and meta-analysis', The British Journal of Psychiatry, 214(1), pp. 42–51.	Comments noted. The committee noted the comments received at consultation and considered that stopping treatment in clinical practice would be based on people's individual circumstances. This is discussed in section 3.26 of the ACD.

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			doi: 10.1192/bjp.2018.233. Wilkinson, S. T. et al. (2018) 'The Effect of a Single Dose of Intravenous Ketamine on Suicidal Ideation: A Systematic Review and Individual Participant Data Meta-Analysis', The American Journal of Psychiatry, 175(2), pp. 150–158. doi: 10.1176/appi.ajp.2017.17040472. Wooderson, S. C. et al. (2014) 'Long-term symptomatic and functional outcome following an intensive inpatient multidisciplinary intervention for treatment-resistant affective disorders', Journal of Affective Disorders, 166, pp. 334–342. doi: 10.1016/j.jad.2014.05.013.	
	Consultee (company)	Janssen	Janssen welcomes the opportunity to comment on the preliminary recommendation detailed in the appraisal consultation document (ACD). We are disappointed the Appraisal Committee's preliminary decision is that esketamine nasal spray (ESK-NS) is not recommended for patients with treatment resistant depression (TRD) in the NHS; however, we are committed to working with NICE in order to address all the Committee's key concerns outlined in the ACD. ESK-NS is the first new antidepressant in 30 years with a novel mechanism of action, demonstrating additional benefit over the standard of care and providing a much-needed new treatment option for patients with TRD in the NHS. ESK-NS has a substantial evidence base, including five completed phase 3 trials and several additional complementary research projects. The main points outlined in this response to the ACD are as follows: • We wish to address the committee's considerations on the previous approach to economic modelling including retreatment. We have included a retreatment scenario but suggest that this should be considered only a scenario for decision making, given the significant uncertainties associated with the retreatment model and its inconsistency with previous NICE decision making in NICE TA 367 [vortioxetine for treating major depressive disorder] and NICE CG90 (Depression in adults: recognition and management). It is also inconsistent with the advice previously received from NICE PRIMA on the economic model. Regardless, under this scenario, the cost-effectiveness of ESK-NS improves compared to not including retreatment, ranging from being dominant to an ICER of £8,348 (see Table 1 below, Section 1). • We provide a revised company base case which does not include retreatment, and which addresses some of the Committee's other concerns raised in the ACD. • The revised company base case includes the committee's preferred assumptions on excluding treatment adjustment effect, removing excess mortality for the Major Depressive Episode (MDE) health state, and extending the time horizon to 20 years, although available data do not support these assumptions. • The revised company base case maintains ESK-NS treatment discontinuation for	Comments noted. Responses to each main point can be found below.

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			non-efficacy reasons for patients in recovery, based upon market research provided during the technical engagement step. This is the single most important determinant of the cost-effectiveness of ESK-NS. As such, we have further explained how the model currently considers the reduction in health-related quality of life (HRQoL) following discontinuation for non-efficacy reasons, and provided additional scenarios exploring the impact of discontinuing ESK-NS. • The revised base case also continues to include carer disutility for the MDE health state. We note that the Committee acknowledged the impact on carers of people with TRD in the ACD and that the ERG and NICE technical team concluded that the evidence provided was of good quality. The evidence is also significantly stronger than compared to previous appraisals in both mental and physical health conditions where carer utilities have been included. Although we do not agree on the Committee's preferred assumptions for excluding treatment adjustment effect, removing excess mortality for the Major Depressive Episode (MDE) health state, and extending the time horizon to 20 years, we have incorporated these Committee preferred assumptions into our revised base case (see Section 2 for the revised company base case). Based on the previously provided evidence, we suggest that these three assumptions should be considered conservative. The revised base case company ICERs demonstrate that, even with all the Committee's other preferred conservative assumptions, apart from treatment discontinuation in recovery, ESK-NS remains cost effective option for TRD with an ICER range of between £10,790 - £12,26 per QALY. Finally, the Committee have not considered all the evidence regarding comparators, as Janssen previously provided evidence comparing ESK-NS to all relevant comparators in the scope, including combination, augmentation and ECT. ESK-NS was cost-effective compared to all those comparators. Consideration of the combined effect of psychological and pharmacological treatment is also inconsistent with previous NICE decision making and this should not be considered further. A detailed comment for each of these key issues is provided below	
1	Consultee (company)	Janssen	Section 1. Incorporating retreatment and a longer time horizon brings significant uncertainty to the analysis due to the lack of data to inform retreatment assumptions ACD Section 3.11, p14: "The committee would like to see a new model with a longer time horizon that allows for repeat treatment." We acknowledge the Committee had concerns around the time horizon for the model, and specifically the lack of function to include retreatment in the model. We firmly believe, however, that by using a longer time horizon and including assumptions to inform retreatment brings additional uncertainty due to the lack of data to inform the analysis. Including retreatment is also inconsistent with previous NICE decision making in NICE TA 367 [vortioxetine for treating major depressive episodes] and NICE CG 90 [Depression in adults: recognition and management], where it has not been considered. Regardless, as this was explicitly requested by the Committee in the ACD, we have provided scenarios to show the impact of retreatment	Comments noted. The committee acknowledged that there were no data to inform outcomes for people who have repeat treatment. It recognised that the company's preference to model 1 line of esketamine treatment may be the most informative, despite the committee's preference for a longer time horizon. The committee concluded that the company's approach of modelling repeat treatment was not appropriate with

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			on the cost-effectiveness of ESK-NS. The scenarios show that retreatment improves the cost-effectiveness of ESK-NS. Limitations of the retreatment model As noted above, incorporating retreatment increases uncertainty in the analysis, which we believe is insufficient to offset the proposed benefits highlighted by the Committee. The retreatment option is incorporated in the previously submitted Markov model, which comes with a number of restrictions inherent with a Markov model. Further discussion of the limitations are below: • In the retreatment model scenario, retreatment is only for patients treated with ESK-NS + OAD who had previously been in stable remission for at least 9 months, then discontinued ESK-NS, and subsequently experienced a recurrence while in the recovery health state. • The positioning and sequencing of ESK-NS during retreatment of the new episode is uncertain and based on assumptions, since there are many factors that affecting whether a patient will be retreated with ESK-NS in NHS clinical practice, of which access to health care professionals is key. • The data to inform the effectiveness of ESK-NS during retreatment are based on the assumptions taken from initial treatment of the first episode with ESK-NS. • It is assumed similar health states (MDE, remission and recovery (but no response)) also apply to ESK-NS in retreatment of the new episode. • The data to inform relapse and recurrence for ESK-NS are based upon assumptions taken from the initial treatment with ESK-NS. • The dosage and frequency of ESK-NS (and hence treatment costs) are based upon initial ESK-NS treatment. • The safety profile of ESK-NS retreatment is assumed to be consistent with initial treatment with ESK-NS. • The proposed approach assumes that every episode of depression after an episode of TRD will be treatment-resistant and patients will receive ESK-NS retreatment in the absence of data. Overall, the retreatment scenario significantly increases the uncertainty in the cost-effectiveness of ESK-NS, especially when these assumptions are projected over a 20-year time horizon. This was also recognised by NICE PRIMA, who stated the following about extending the time horizon beyond 5 years:  In addition, retreatment has not been considered previously in the other NICE decision making (CG 90 and TA367) in the disease area. We are concerned that the Committee are	the current evidence. See section 3.17 and 3.20 of the ACD.

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<tr><td></td><td></td><td></td><td>considering retreatment in the context of this appraisal only, as existing NICE guidance and guidelines have not made specific recommendation on the topic previously. This leads to inconsistency with the NICE guidance and guidelines where there are no recommendations given for retreatment for any other intervention. The above limitations show that the retreatment model should not be considered more than a scenario and should be interpreted with caution.

New scenarios incorporating retreatment improves the cost effectiveness of ESK-NS

Given the Committee’s explicit request and despite our reservations highlighted above, we have developed a model which attempts to incorporate retreatment, presented below. It is important to note that based upon clinical opinion, retreatment will only be used in clinical practice if the active treatment was successful before, and the patient is no longer on that treatment, i.e. patients who have been in stable remission for at least 9 months and have discontinued ESK-NS will be eligible for ESK-NS retreatment. This is aligned to the modelling approach that we have taken in this exploratory scenario. These scenarios show that including repeat courses of ESK-NS treatment for patients who discontinue in recovery but subsequently have a recurrence improves the cost-effectiveness of ESK-NS. Even if assuming all the preferred NICE assumptions (excluding treatment discontinuation assumptions since patients have to discontinue before being eligible for retreatment), retreatment ranges in results from ESK-NS dominance, to ICERs of £8,348.
<table>
<tr><th></th><th>Revised company base case post ACD (see Section 2)*</th><th>Scenario with NICE preferred assumptions (excluding treatment discontinuation using market research data, see Section 4.2)</th></tr>
<tr><td>Original base case model (see Table 2), no retreatment</td><td>£10,790 - £12,264</td><td>£13,821 – £17,326</td></tr>
<tr><td>Retreatment model (using TRANSFORM-2 remission data)</td><td>£ 4,348 - £ 5,518</td><td>£ 5,568 - £ 8,348</td></tr>
<tr><td>Retreatment model (assuming 100% retreatment efficacy)</td><td>-£1,087 (Dominant) to £-174 (Dominant)</td><td>-£ 1,392 (Dominant) - £778</td></tr>
</table>
*range from 1:6 to 1:2 nurse: patient ratio

The analysis shows that including retreatment improves the cost effectiveness of ESK-NS. This is because recurrence (transition from recovery to the active MDE health state), increases the proportion of patients subsequently entering remission compared to the original model. In the original model, patients who had a recurrence moved to a subsequent treatment rather</td><td></td></tr>
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			than being re-treated with ESK-NS. The increased proportion of patients entering remission reflects the additional clinical benefit of ESK-NS retreatment compared to the subsequent therapies, as well as best supportive care treatment efficacy. Keeping more patients in the remission health state significantly reduces the disease management costs, which offsets the additional drug and administration costs of ESK-NS re-treatment. Full assumptions used for the scenarios including retreatment are provided in Appendix A. **Conclusion**: Given the uncertainty associated with the retreatment model, the existing company model is the most robust to base decision making on for ESK-NS Due to the complex nature of depression, the frequency of recurrence, how these recurrent episodes manifest and are subsequently treated, and consistency with previous decision making used by NICE, Janssen propose that the scenarios including retreatment should be considered only as a scenario. The high level of uncertainty in the scenarios including retreatment should be considered when used to inform decision making. The rest of the response is therefore presented on the basis of the current economic model originally considered by the Committee, with a revised base case presented below.	
2	Consultee (company)	Janssen	Section 2. Janssen wish to present a revised company base case, which includes some of the Committee's preferred assumptions and should be considered a conservative estimate of ESK-NS cost-effectiveness We have noted the Committee's preference for retreatment in Section 1 above. Given the Committee's other considerations in the ACD, Janssen wish to provide the below revised base case (Table 2). We do not agree with the Committee's judgement based on all the evidence provided, as we believe in some instances the Committee have been overly conservative given the evidence available. There are several topics which we have now included in the revised base case, based upon the Committee's preferred assumptions. This includes: • Excluding the treatment adjustment effect on the TRANSFORM-2 OAD results based on the Posternak et al method • Exclusion of additional mortality for the MDE health state, and • Extending the time horizon of the economic model to 20 years. If the unadjusted efficacy data are taken directly from the clinical trials, the cost-effectiveness analysis should be considered conservative for the reasons outlined previously (see p683-691 of Committee Papers). As noted in NICE CG90, it is widely accepted that social support plays an important part in a person's propensity to develop depression and his or her ability to recover from it. This was additionally recognised by the patient expert and patient advocacy group in their stakeholder responses to NICE (p454 and p433 of Committee Papers). Similarly, if no excess mortality for MDE is included, the analysis should be considered	Comments noted. The committee considered the company's revised base case. It considered that further analysis with its preferred modelling assumptions were also required: • the ERG's scenario for subsequent treatments (see section 3.18) • no carer disutility and sensitivity analysis with the ERG's method of applying carer disutility (see section 3.24) • the company scenario for stopping treatment that included an increased rate of stopping after 9 months on treatment (referred to as scenario C by the company, see section 3.25) • costs associated with a ratio of 1 to 2 nurses to patients during the monitoring phase of treatment (see section 3.29) • equalising the costs of resource

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<tr><td></td><td></td><td></td><td>conservative. We note that the Committee considered that it is plausible that ESK-NS could affect mortality. Although the guideline expert stated that “people with treatment resistant depression are likely to have an increased risk of suicide” (ACD section 3.7, P9). The committee have not included this assumption in the base case. The revised company base case assumes no excess mortality for MDE.
Even with these conservative assumptions and considering a nurse to patient: ratio of 1:2 – 1:6 for the post-administration observation, the ICER ranges between £10,790 - £12,264. This shows ESK-NS is a very cost-effective new treatment option for TRD to the NHS.

Table 2: Revised company base case
<table>
<tr><th>Parameter</th><th>Input</th><th>ICER</th></tr>
<tr><td>Treatment discontinuation</td><td>Data from market research from 25 UK psychiatrists*</td><td rowspan="4">£ 10,790- £ £12,264</td></tr>
<tr><td>Carer disutility</td><td>Applying a disutility to the MDE health state of [redacted] to represent carer disutility*</td></tr>
<tr><td>Administration costs</td><td>1:2* - 1:6 nurse to patient ratio</td></tr>
<tr><td>Other modelling topics</td><td>• No adjustment for clinic visits
• No additional mortality in MDE health state
• Time horizon extended to 20 years</td></tr>
</table>
*Note: assumptions are different from NICE preferred model assumptions

There remains, however, a number of Committee assumptions which are not implemented in the revised company base case. These include:

• Considering that no patients will discontinue ESK-NS for reasons other than lack of efficacy
• Excluding carer disutility
• Including a 1:1 ratio of nurse to patients for the post self-administration monitoring

The rationale and evidence for why we do not agree with these topics are provided below. In summary, we believe the Committee has insufficiently understood the episodic and/or chronic recurrent nature of the disease, not fully considered all previously submitted evidence, and displayed inconsistency with previous NICE decision making, when using these assumptions. In particular, the key issue of treatment discontinuation for patients in recovery is further discussed below in Sections 3 and 4, as this is pivotal to the exploration of the cost-effectiveness of ESK-NS.</td><td>use between esketamine with oral antidepressants and placebo with oral antidepressants (see section 3.28). see section 3.32 of the ACD). The committee had further concerns (detailed in 3.32 of the ACD) and concluded that the most plausible ICER was substantially higher than what NICE considers a cost-effective use of NHS resources (see NICE’s guide to the methods of technology appraisal).</td></tr>
</table>

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3			Section 3. Treatment discontinuation: Data submitted shows that patients who achieve recovery are likely to stop ESK-NS over time for reasons other than efficacy and are at continuous risk of recurrence, which captures the risk of a worsening of symptoms and HRQoL that the Committee believe is not captured in the model. We welcome the Committee's statement that they believe people would stop ESK-NS for reasons other than lack of efficacy over a 2-year period (ACD section 3.12 p15). This is consistent with available evidence. We note, however, that the Committee decided to conservatively conclude that no patients in recovery would stop ESK-NS for reasons other than efficacy. We understand the main reason for the Committee's conclusion is the uncertainty regarding the impact of discontinuing ESK-NS on patient's symptoms or quality of life. We wish to highlight that even if patients discontinue treatment after achieving recovery from the depressive episode, in the model, they remain at risk of recurrence and associated worsening of their depressive symptoms and quality of life. NICE ACD Section 3.12, p15: "The company assumed that people would not stop taking oral antidepressants for any reason other than lack of response. But it assumed that people would stop esketamine treatment for other reasons, in line with the criteria in the SPC and additional discontinuation guidance provided by the company. In the company model, rates of discontinuation (for reasons other than lack of response) for esketamine varied by treatment phase. Based on advice from clinicians, the company modelled that 52% of people stopped treatment after 9 months in stable remission, with 16% expected to continue treatment for more than 2 years. Stopping treatment was assumed to stop incurring the cost of esketamine but have no effect on QALYs. The clinical experts suggested that a proportion of responders who were not in stable remission would discontinue. The committee were aware that in SUSTAIN-1 the rate of relapse increased when esketamine was stopped. The ERG highlighted that no evidence was submitted to determine the effect of discontinuation on symptoms or quality of life. The clinical expert explained that the decision to stop treatment would be done after a full discussion of all the circumstances associated with the individual patient. The patient expert noted that people would be concerned and worried about relapse. The committee recognised that people would be fully involved in the decisions around continuing treatment, and that decisions about how long treatment lasts and reasons for stopping it vary based on individual circumstances. Also circumstances are very different in people with comorbidities compared with those without. The committee considered that assuming an indefinite improvement in quality of life after stopping esketamine treatment was implausible. It recognised that people may have changes in MADRS score below the threshold for 'relapse' but that still affect quality of life. The clinical experts supported this view and explained that the MADRS is a non-linear scale, meaning that increases in score at the lower end of the scale represent a larger change in symptoms than at higher points of the scale. The ERG and clinical experts also highlighted that there were no data to accurately determine discontinuation rates. Because of this, the ERG preferred to assume no discontinuation for reasons other than lack of efficacy at 2 years. The committee	Comments noted. The committee considered the company's scenarios on treatment discontinuation. It concluded that the scenario with a faster stopping rate after 9 months was the most clinically plausible, given the expected population. But estimating when people would stop treatment is highly uncertain without any data (see section 3.25 of the ACD). In section 3.26 of the ACD, the committee recognised that, in practice, people may have repeat courses of esketamine, but it increased uncertainty when this was included in the model (see section 3.20 of the ACD). The committee considered the additional stopping criteria introduced by the company. But it concluded that because of people's individual circumstances and preferences, stopping treatment would rarely be guided by these criteria. This would particularly be the case for the expected population in NHS clinical practice (see section 3.4 of the ACD)

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			considered that it's likely that people would stop esketamine for other reasons over a 2-year period, but that it's unclear how many. The committee recognised that, in practice, people who were 'responders' or 'stable remitters' and stopped treatment for reasons other than lack of efficacy could have repeat courses of esketamine, but that this was not accommodated in the model (see section 3.11). The committee concluded that, on balance, without data the least biased estimate of cost effectiveness would be to not include discontinuation of esketamine for reasons other than lack of efficacy." Overview The following provides clarification of how treatment is discontinued in the current model. In the acute treatment phase, the model assumes that patients who do not achieve response or remission to the active treatment discontinue, and then receive the next subsequent treatment. Patients can discontinue treatment due to two reasons in the continuation and maintenance treatment phases: loss of efficacy, and non-efficacy reasons. In the continuation phase, patients who relapse (transition from remission to MDE) or lose response (transition from response to MDE) discontinue treatment and move to the subsequent treatment. Furthermore, patients can discontinue for reasons other than efficacy, based on the observed data from SUSTAIN-1. Similarly in the maintenance phase, whilst patients are in recovery, patients can discontinue due to efficacy reasons and reasons other than efficacy. We address the Committee's concerns on the impact of discontinuing ESK-NS on symptoms or patient's quality of life below. Based on the Committee's consideration in the ACD, we believe that the discontinuation due to other reasons than efficacy of most concern in the recovery phase, as prior to that in the model reasons to discontinue is based on trial data. We refer the Committee to the previously provided data from a post-hoc analysis of SUSTAIN-1 (p697-698 of Committee papers) and now provide an additional post-hoc analysis of SUSTAIN-2 (see Section 3.2). Both of these data sources show there is a limited impact on risk of recurrence from discontinuing ESK-NS in recovery. Recurrence is a simplifying assumption to capture the reduction in quality of life from returning to the MDE health state. The Committee have concluded that there may be sub-threshold reductions in quality of life where the person in recovery may not fully have a recurrence of the disease but may experience some worsening of the disease again. To try and account for this artefact, we have provided scenarios where the recurrence risk after discontinuation of ESK-NS is increased in recovery to take account of people experiencing a worsening of the disease again. This is likely to be a conservative assumption, as it assumes that people are not just having a slight worsening of the disease, i.e. a sub-threshold change in the disease, but they are having a full recurrence of the disease and have returned to the MDE health state. The scenario below shows that even with this conservative assumption, ESK-NS remains a cost-effective option for TRD to the NHS. Overall, Janssen respectfully request the Committee to re-consider the totality of evidence and change their assumption that patients will not discontinue for reasons other than efficacy. The current model accurately captures the impact of discontinuing ESK-NS and resulting change in	

<table>
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<tr><td></td><td></td><td></td><td>HRQoL. Considering all model parameters, ESK-NS is cost-effective once this conclusion is reached.
The points below provide further explanation.

3.1 Patients who achieve recovery are assumed to be at a continuous risk of recurrence, which accounts for a significant worsening of the disease in patients who discontinue for reasons other than efficacy

We understand from the ACD that the Committee are concerned about how many patients would be discontinuing treatment for other reasons than efficacy in the first two years. In order to provide context for our rationale below, it is important to clarify the company model transitions in each health state. There are three different treatment phases and associated treatment objectives upon which the cost-effectiveness model is built:

<table>
<tr><th>Treatment phase</th><th>Treatment objective</th></tr>
<tr><td>The induction phase (first 4 weeks after initiating ESK-NS treatment)</td><td>To achieve response/ remission of depressive symptoms.</td></tr>
<tr><td>The continuation phase (9 months for continuous stable remitters)</td><td>To prevent loss of response and relapse into the MDE health state.
Note that patients who relapse initiate a subsequent treatment. Patients have a continuous risk of relapse.</td></tr>
<tr><td>The maintenance phase (from 9 months in stable remission onwards)</td><td>To prevent recurrence of a new episode of depression.
Note that recurrence is the risk of returning to the MDE health state and experience the associated reduction in HRQoL. Patients have a continuous risk of recurrence.</td></tr>
</table>

As noted above in the overview, the relevant issue of discussion is the assumptions of treatment discontinuation in the maintenance treatment phase (when patients are in recovery). Currently when patients are in recovery, a continuous risk of recurrence (2.88% per 4 weeks) is assumed in the model for both the ESK-NS and the OAD treatment arm, which is applied whether the person is on treatment or off treatment. This is based on the pooled SUSTAIN-1 data from both study arms. This was pooled in the model despite the ESK-NS arm showing a lower risk of recurrence than the OAD treatment arm in SUSTAIN-1 (see below).</td><td></td></tr>
</table>

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Experiencing recurrence signifies a significant reduction in quality of life through returning to an active disease state. The inclusion of the recurrence risk means that patients in recovery have a constant risk of transitioning to the MDE health state and losing their quality of life. The utility score of patients in recovery is 0.866 and for patients in the MDE health state is 0.417 (Committee papers p184), which show the considerable impact on HRQoL when a patient has a recurrence. We believe that this more than accounts for the Committee's concern that there is no reduction or even an improvement in QALYs following discontinuation of ESK-NS in recovery.

The pooled recurrence risk of 2.88% per 4 weeks from both SUSTAIN-1 study arms is used for both ESK-NS + OAD as well as the OAD when patients are in recovery. This is an increase in recurrence risk versus the data from the SUSTAIN-1 ESK-NS + OAD arm, which was 2.43% per 4 weeks. The recurrence risk is 3.56% per 4 weeks from the OAD + PBO-NS arm of the SUSTAIN-1 trial shown in Table 3.

Table 3: Recurrence risk used in the model and from SUSTAIN-1
<table>
<tr><th>Recurrence risk used in base case model (pooled SUSTAIN-1 data)</th><th>Recurrence risk from SUSTAIN-1 ESK-NS+OAD arm</th><th>Recurrence risk from SUSTAIN-1 OAD+PBO-NS arm</th></tr>
<tr><td>2.88% per 4 weeks</td><td>2.43%</td><td>3.56%</td></tr>
</table>

Over the course of the model, this recurrence risk is cumulative and means that a significant number of patients are at risk of recurrence of the disease and a worsening of their depressive symptoms and quality of life (Figure 1). Over time, a large proportion of patients in recovery will have a recurrence, and hence start a new depressive episode with a significant worsening of quality of life. At the end of 2 years, approximately 40-50% of patients will have had a recurrence of the disease.

A visual graphic displaying the difference over time that this transition probability represents is displayed below.

Figure 1: Impact of recurrence risk over time
</td><td></td></tr>
</table>

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			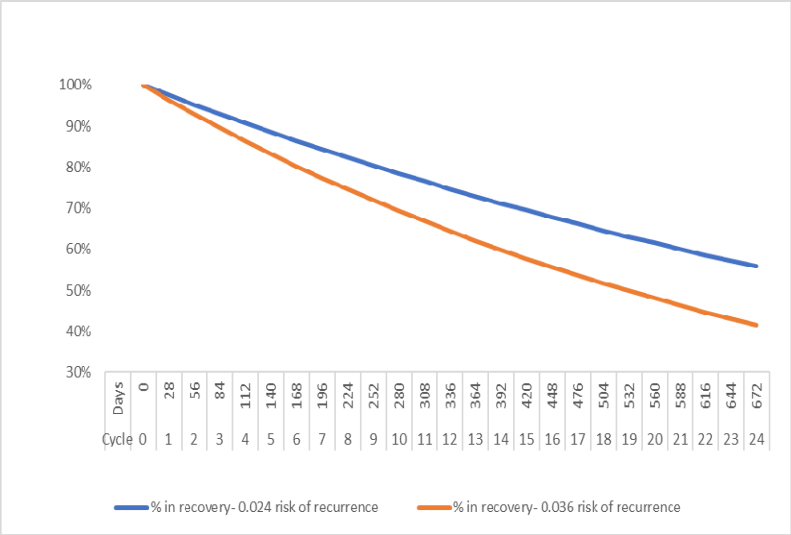 Taken cumulatively over the time frame of the model, the recurrence risk sufficiently accounts for the worsening of depressive symptoms and quality of life that may occur once ESK-NS treatment is stopped. **3.2 For patients who achieve recovery, previously submitted (SUSTAIN-1 post hoc) data show there is no impact of discontinuing ESK-NS** In the Response to the Draft Technical Engagement report, a *post-hoc* analysis of SUSTAIN-1 data was submitted showing there was no impact in the 2 weeks after discontinuing ESK-NS in patients who have been in remission for at least 9 months (range from 9 months- 1.5 years) (NICE ACD papers page 696-698). Longer follow-up is not available from the trial. **3.3 For patients who achieve recovery, additional evidence (SUSTAIN-2 *post hoc*) show the risk of recurrence does not increase after discontinuation of ESK-NS** We believe that the recurrence risk included in the model addresses the Committee's concern that there is no reduction in QALYs when patients discontinue treatment due to reasons other than lack of efficacy. In addition, an additional *post-hoc* analysis of SUSTAIN-2, the long-term safety study, has been conducted and presented here. These data support the conclusion that there is a very limited increase in risk of recurrence after discontinuation of ESK-NS after 9 months in stable remission. The additional evidence shows the proportion of relapse in patients who have been	See response above. See response above.

<table>
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<tr><td></td><td></td><td></td><td>in remission for at least 9 months [redacted] at week 4 after discontinuing ESK-NS. This is similar to the recurrence risk included in the company model (the pooled risk of 2.88% from both study arms of SUSTAIN-1) of when patients are on treatment. This demonstrates that, for patients who achieve recovery, the risk of recurrence/relapse does not increase substantially after discontinuing treatment. Together, these available data suggest patients are able to discontinue ESK-NS once reaching a recovery health state without increasing recurrence risk.

3.4 It is incorrect to use SUSTAIN-1 data to infer that the impact of discontinuing ESK-NS in terms of increased risk of relapse/recurrence during the continuation phase is equivalent to the impact of discontinuing ESK-NS in recovery the phase

We ask the committee to reconsider their comment in Section 3.12 of the ACD (p15) where the Committee appear to be applying the SUSTAIN-1 trial data, which was conducted during the continuation phase of treatment to the recovery phase in the model:
“Based on advice from clinicians, the company modelled that 52% of people stopped treatment after 9 months in stable remission, with 16% expected to continue treatment for more than 2 years. Stopping treatment was assumed to stop incurring the cost of esketamine but have no effect on QALYs. The clinical experts suggested that a proportion of responders who were not in stable remission would discontinue. The committee were aware that in SUSTAIN-1 the rate of relapse increased when esketamine was stopped.”
In the treatment of depression, after discontinuation of an active treatment, the risk of relapse/recurrence is highest in the first 4 weeks. The relapse risk has been demonstrated to decrease over time, whether on or off ESK-NS (see SUSTAIN-1 KM curve, p122 of Committee Papers). Together, these show that the [redacted]% recurrence risk after 9 months in stable remission is higher than what is expected in the following 4-week periods.
The 2.7% recurrence risk is contrasted to the SUSTAIN-1 primary outcome analysis for patients who have been in stable remission for 12 weeks, where the proportion of patients who relapsed at 4 weeks after ESK-NS treatment discontinuation was [redacted]Clearly, discontinuing ESK-NS after 9 months (after recovery), with a [redacted]% risk of recurrence after 4 weeks of follow-up compared to 12 weeks in SUSTAIN-1 with [redacted]% relapse after 4 weeks of follow up is very different (Table 4).

Table 4: Comparison of impact of discontinuation of ESK-NS
<table>
<tr><th>SUSTAIN-2 post hoc: Proportion of patients who relapse after discontinuation of ESK-NS after 9 months of treatment</th><th>SUSTAIN-1 primary analysis: Proportion of patients who relapse after discontinuation of ESK-NS after 12 weeks of treatment</th></tr>
<tr><td>[redacted]</td><td>[redacted]</td></tr>
</table>

The evidence from the trial clearly shows that the risk of relapse/recurrence of patients with TRD is dependent upon the health state, the timing and hence the treatment phase of when the treatment is discontinued. This is consistent with other trials and studies. Furthermore, it confirms the episodic nature of the disease. We therefore ask that the Committee consider that</td><td>Comments noted. See section 3.25 of the ACD</td></tr>
</table>

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when a patient is in recovery, the impact of discontinuing ESK-NS is much lower than when a patient would be in remission and during the continuation treatment phase as seen in the SUSTAIN-1 trial.

3.5 New scenario: Increased risk of recurrence after discontinuation of ESK-NS

We believe the model adequately captures the worsening of quality of life using the recurrence risk from discontinuing ESK-NS treatment in recovery, but we recognise the Committee considered this a key topic of uncertainty and thus we have further tried to address the Committee’s concerns regarding sub-threshold changes in quality of life.

To allow for this, the recurrence risk after discontinuation of ESK-NS can be varied. The recovery health state has a utility of 0.866 and the MDE health state has a utility of 0.417. Increasing the recurrence risk after discontinuation of ESK-NS results in a loss in quality of life due to the change in health state from recovery to MDE. This can be considered conservative as these patients transition fully from the recovery health state to the MDE health state, whereas in clinical reality, as the Committee has noted, some patients may not worsen to the threshold of recurrence.

The submitted model includes a new option to include a different risk of recurrence for patients in recovery when on or off ESK-NS treatment. Two new scenarios have been considered. The scenarios below include all the Committee’s preferred assumptions apart from having no treatment discontinuation for reasons other than loss of efficacy. The first scenario uses a risk of recurrence after ESK-NS discontinuation taken from SUSTAIN-2. The constant recurrence risk used in this scenario ([redacted]) should be considered conservative given this is derived from the first 4 weeks after ESK-NS discontinuation in SUSTAIN-2, whilst in the following 4-week periods it is expected to be lower. A second scenario is using a recurrence risk of 3.6% per 4-weeks after discontinuation of ESK-NS is also presented taken from the SUSTAIN-1 OAD+PBO-NS arm. The scenario shows that ESK-NS remains cost-effective even when patients in the recovery state have a 50% relative increase in recurrence risk after discontinuation of ESK-NS. This scenario should be considered highly conservative give the constant risk of recurrence which is assumed over time.

Scenario 3.5: Increase risk of recurrence after discontinuation of ESK-NS
<table>
<tr><th>Key Parameters</th><th>Revised base case assumptions</th><th>Inputs using SUSTAIN-2 post hoc</th><th>Inputs using OAD+PBO SUSTAIN-1 recurrence risk</th></tr>
<tr><td>Treatment discontinuation</td><td>Data from market research from 25 UK psychiatrists</td><td>Data from market research from 25 UK psychiatrists</td><td>Data from market research from 25 UK psychiatrists</td></tr>
<tr><td>Recurrence risk</td><td>0.028 (pooled SUSTAIN-1 arms)</td><td>0.024 (SUSTAIN-1 ESK-NS arm)</td><td>0.024 (SUSTAIN-1 ESK-NS arm)</td></tr>
</table>
</td><td>Comments noted. The committee considered the company’s scenarios. See section 3.25 of the ACD.</td></tr>
</table>

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ESK-NS + OAD			
Recurrence risk OAD + PBO-NS	0.028 (pooled SUSTAIN-1 arms)	0.036 (SUSTAIN-1 OAD+PBO-NS arm)	0.036 (SUSTAIN-1 OAD+PBO-NS arm)
Recurrence risk after ESK-NS discontinuation	0.028	[redacted] (SUSTAIN-2 post hoc recurrence rate)	0.036 (SUSTAIN-1 OAD+PBO-NS arm)
Administration cost	1:6 – 1:2	1:6- 1:1	1:6- 1:1
Other key assumptions	• No adjustment for clinic visits • Including carer disutility • No excess mortality for MDE health state • 20-year time horizon	• No adjustment for clinic visits • No carer disutility • No excess mortality for MDE health state • 20-year time horizon	• No adjustment for clinic visits • No carer disutility • No excess mortality for MDE health state • 20-year time horizon
Retreatment	No	No	No
ICER	£ 10,790 - £12,264	£ 8,007 - £11,015	£ 18,484 - £22,386

Further details on this scenario are provided in Appendix B.

3.6 Conclusion

Overall, Janssen request the Committee to re-consider the totality of evidence provided, which demonstrate that patients in recovery (who have no depressive symptoms for at least 9 months) will be clinically justified to discontinue ESK-NS treatment for reasons other than lack of efficacy. Previously submitted and additional evidence (see Section 3.2 and Section 3.3) have shown there is only a very limited impact of discontinuing ESK once in recovery and that the impact on HRQoL of discontinuing ESK-NS is adequately capture in the model through the recurrence risks. Scenarios have shown that even conservatively increasing the recurrence risk results in ESK-NS remaining cost-effective (Section 3.5) to take account of sub-threshold changes in HRQoL.

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4	Consultee (company)	Janssen	**Section 4. Previous submitted data on the rate of discontinuation consistently shows a similar proportion of patients discontinuing ESK-NS over time and if applied in the economic model shows ESK-NS to be cost-effective.** **Overview** We welcome the Committee's original conclusion that it is likely patients will discontinue for reasons other than efficacy, as noted in Section 3.15 of the ACD (p15): *"The committee considered that it's likely that people would stop esketamine for other reasons over a 2-year period."* We note that this is aligned to previous NICE decision-making in NICE TA267 and NICE CG90 and consistent with the three sources of data that Janssen has previously submitted. We believe that the additional evidence and clarification provided above in Section 3, regarding the impact on quality of life that results from discontinuing ESK-NS, is sufficient to consider the discontinuation of ESK-NS in the recovery period. If this is the case, we would like to remind the Committee of the consistency in the data regarding discontinuation rates for patients of ESK-NS in recovery. When using the various sources of data in the economic model, ESK-NS remains a cost-effective option for treating TRD. **4.1 The Committee's initial conclusion, that it is likely that patients will discontinue for reasons other than efficacy, is consistent with the judgement of the ERG and NICE Technical Team, and previous NICE decision making in NICE TA367 and NICE CG90.** We note and thank the Committee for acknowledging the previously submitted evidence on ESK-NS discontinuation based on market research from 25 UK psychiatrists. The use of this evidence was agreed with the NICE technical team during the technical engagement call on the 6th November 2019. We believe this is the best evidence to inform the discontinuation of ESK-NS for those people who are in recovery. We note that after the Technical Engagement Step, the ERG also considered this market research data to be sufficiently robust to develop a model scenario in their response to the technical engagement (p825 of Committee papers). Based on the market research data input for the expected treatment duration of combination OADs (p826 of Committee papers), the ICER for the ERG scenario changed to £25,827. We also note that after receiving the data, the NICE technical team decided to incorporate treatment discontinuation into the model (p856 of Committee Papers). NICE have previously accepted similar assumptions used in the model for TA367. These assumed that patients discontinued treatment after 6-22 months. Furthermore, the economic model used in NICE CG90 assumed that: *"patients who responded to treatment and did not relapse during follow up, it was assumed that no further additional treatment or mental health and social care resources beyond the 6-month maintenance period were required' (p407 of NICE CG90)."* The model assumptions used in NICE CG90 and TA367 are therefore inconsistent with the current <u>final</u> conclusion by the Committee that patients in recovery continue ESK-NS treatment	Comments noted. The committee considered consultation comments on this point. See sections 3.25 and 3.26 of the ACD. Comments noted. The committee considered consultation comments on stopping treatment. See sections 3.25 and 3.26 of the ACD.

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in recovery until loss of efficacy. If the concerns of the Committee are addressed in Section 3, we request the market research data previously submitted on the numbers of patients in recovery discontinuing ESK-NS treatment over time can be used as part of the Committee's decision making. As NICE note, in the absence of clinical data, clinical expert opinion should subsequently be considered, as indicated by the NICE Process Guide:
"Evidence is obtained from a range of sources, including randomised controlled trials, observational studies and <u>expert opinion (of clinical professionals and/or patients/carers)" (1)</u>

4.2 Multiple sources provide clear estimates on how many patients will discontinue due to other reasons than efficacy and if any of these sources are included in the model, ESK-NS is cost-effective

The market research data are included in the revised base case which generate robust estimates of the ESK-NS rate of discontinuation for patients who have been in stable remission for 9 months (p702-705 and 742-748 of Committee papers). The market research data are aligned to the feedback on the survey with four UK clinical trialists (p705-707 and 749-751 of Committee papers), and the feedback of four UK clinical experts involved in an advisory board who have validated the assumptions on ESK-NS treatment duration in the initial base case (p178, 701 and 702 of Committee papers).
The clinical expert opinions from all methods consistently suggest that the initial conclusion by the Committee, that patients are likely to discontinue ESK-NS for reasons other than efficacy, are appropriate. The opinions are <u>not</u> aligned to the final conclusion from the Committee that <u>no</u> patients in recovery would discontinue ESK-NS for other reasons than efficacy.
A summary of the data and the impact on the ICER with varying model assumptions are presented in Table 5 below.

Table 5: Scenarios using different sources of discontinuation data
<table>
<tr><th>Data source</th><th>Proportion of stable remitters <u>dis-continuing</u> at 9 months</th><th>Proportion of stable remitters <u>continuing</u> beyond 24 months#</th><th>4-weekly discon-tinuation rate after 9 months in stable remission</th><th>ICER using company revised base case assump-tions* (£/QALY)</th><th>ICER using ERG/NICE base case assump-tions** (£/QALY)</th></tr>
<tr><td>Market research - 25 UK psychiatrists</td><td>52.0%</td><td>16.0%</td><td>10.7%</td><td>£ 10,790-£12,264</td><td>£13,821 – £17,326</td></tr>
<tr><td>Survey - four UK clinical experts involved in</td><td>61.3%</td><td>26.0%</td><td>8.0%</td><td>£10,904-£12,383</td><td>£13,967-£17,484</td></tr>
</table>
</td><td>Comments noted. The committee considered consultation comments on this point. See sections 3.25 and 3.26 of the ACD.</td></tr>
</table>

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ESK-NS trials						
Advisory board - 4 UK clinical experts and 2 HE experts	35.4%	1%	25.0%	£9,246-£10,649	£11,815–£15,146
NICE Committee preferred assumptions	0%	100%	0%	N/A	£55,027-£62,078

*ICERs using company revised base case assumptions, range from 1:6 to 1:2 nurse patient ratio. **ICERs using NICE/ERG base case assumptions and 1:6 to 1:1 nurse: patient ratio, NICE ACD page 20. # for proportion of patients that do not get a relapse or recurrence

Using any of the three data sources for ESK-NS treatment duration of patients who have been in stable remission for at least 9 months, even when assuming all of the other NICE preferred model assumptions, results in ICERs consistently below £20,000 per QALY.

4.3 The previously submitted discontinuation guidance provides additional certainty for the Committee that patients will discontinue treatment in recovery for reasons other than lack of efficacy if included in the recommendation by NICE

The previously submitted discontinuation guidance is a key item of consideration for the Committee. We propose for NICE to include the ESK-NS discontinuation guidance explicitly in the NICE ESK-NS recommendation to the NHS.
At the NICE technical engagement meeting on 6th November 2019, the NICE team stated that guidance on discontinuation of ESK-NS would help to mitigate the uncertainty around the treatment duration of ESK-NS in NHS clinical practice. Subsequently, Janssen reached out to 10 clinical experts in the field of treatment resistant depression, including five UK clinical experts.
The 25 UK clinicians who participated in the market research also indicated that discontinuation guidance for ESK-NS as recommended by NICE in any guidance would be the most important factor for informing the duration of treatment of ESK-NS in NHS clinical practice.
Together with the clinical community, and based on the available evidence, Janssen submitted practical and clinically relevant discontinuation guidance for ESK-NS to NICE in the response to the Draft Technical Report.
The proposed clinical guidance on discontinuing ESK-NS was developed and is presented below:

Comments noted. The committee considered consultation comments on this point. See sections 3.25 and 3.26 of the ACD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			ESK-NS treatment discontinuation guidance • **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** • **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** • **Exceptions will occur based on clinical judgement (e.g., some patients may exceptionally require longer treatment as is seen with Electroconvulsive Therapy (ECT)** Janssen propose that NICE include the discontinuation guidance in their recommendation of ESK-NS to the NHS. The full rationale for each of the discontinuation guidance recommendations are found on pages 709-710 of the Committee papers. The discontinuation guidance is in addition to the current recommendations on treatment (dis-) continuation in the SmPC. Note that the discontinuation guidance is not modelled in the company base case economic model. The discontinuation guidance provides additional certainty that the discontinuation rates implemented in the model will occur in NHS clinical practice. NICE have precedent to consider similar discontinuation guidance in several other TAs. Some examples include: o TA342: Vedolizumab for treating moderately to severely active ulcerative colitis o TA260: Botulinum toxin type A for the prevention of headaches in adults with chronic migraine We therefore ask the Committee to consider the discontinuation guidance in their decision making for ESK-NS. In addition, Janssen have planned to collect real world evidence on ESK-NS, and specifically the discontinuation rate and impact of discontinuing of patients who have been at least 9 months in stable remission treated within NHS clinical practice. This will help to inform any future re-assessment of ESK-NS. **4.4 Conclusion** The Committee recognised that it is likely some patients will discontinue for reasons other than efficacy. This is aligned to the conclusions of extensive and representative clinical expert	Comments noted. The committee considered consultation comments

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			consultation. In addition, the previously submitted discontinuation guidance is a key item of consideration for the Committee to reduce the uncertainty. We propose for NICE to include the ESK-NS discontinuation guidance explicitly in the NICE ESK-NS recommendation to the NHS. Overall, Janssen request the Committee to reconsider their conclusion that no patients will discontinue due to reasons other than efficacy and consider the evidence submitted on the discontinuation guidance provided for ESK-NS.	on this point. See sections 3.25 and 3.26 of the ACD.
5	Consultee (company)	Janssen	**Section 5. Carer disutility: The Committee decision to exclude carer disutility is inconsistent with previous appraisals and the determination of the ERG and NICE, who concluded that there was evidence and that it was of good quality.** **Overview** We are concerned that the Committee have acknowledged the impact on people with TRD, families and their carers in the ACD, but have then concluded that there is insufficient data to include carer disutility. This is not consistent with previous appraisals and the level of evidence accepted by previous Committees. It is also in contrast to the view from the ERG: "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" (p866 Committee Papers) and NICE technical team: "The technical team prefer the method used by the ERG for calculating and incorporating carer disutility" (p866 Committee Papers). Both the ERG and NICE technical team concluded there are sufficient data and the evidence provided is of good quality and applicable to the decision problem. Janssen have therefore included a disutility for the MDE health state to represent carer disutility in the revised base case. We note in the NICE ACD Section 3.14, p16 regarding the Committee conclusion on carer disutilities: *"However, the committee considered that there was uncertainty about the appropriateness of including a carer disutility because of the lack of data on the direct effect on carers of people with treatment-resistant depression. It is also noted the lack of evidence on any direct benefit to carers after treatment with esketamine. The committee also noted that adjusting for carer disutility was not part of any other NICE technology appraisals in mental health and may lead to inequities across disease areas."* In this technology appraisal, it is appropriate for the Committee to consider inclusion of carer disutility. In response to each of the reasons included in the ACD for not considering carer disutility in the base case, Janssen would like to highlight the following points in the sections below.	Comments noted. The committee considered consultation comments on carer disutility. It concluded that it was appropriate to consider scenarios with both the ERG carer disutility scenario and no carer disutility because the effect was uncertain. See section 3.24 of the ACD.

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			5.1 Contrary to the statement in the ACD, there are several previous NICE TAs where carer HRQoL was included. By not including carer HRQoL, NICE are being inconsistent with previous decision making. The ACD states that a reason for not including carer disutility is to avoid inequalities across disease areas. We would like to point the Committee to the NICE DSU report published in April 2019 (2), which undertook a review of carer disutility across TAs. Of 422 appraisals, the DSU found 12 TAs and four HSTs where carer QALYs had been included in the economic evaluation, either by the submitting company or the Evidence Review Group (ERG)/Assessment Group (AG), either in the base case or scenario analyses. The NICE DSU states that *"In the appraisals where quantitative analysis including carer QALYs were presented, the committee felt that they should be included in decision-making in most cases".* In these appraisals, we note that carer disutility were included when a person caring for a patient with more severe disease may have to spend more time performing caring tasks or worry more about the patient, and so the HRQL impact would be higher. Treatment resistant depression has a similar significant impact on the patient and carer, as was explained by the patient expert and clinical expert at the Appraisal Committee meeting: ACD, section 3.1, p5: "*The patient expert explained that treatment resistant depression is associated with a significant burden on all aspects of life, with a range of symptoms. The patient expert emphasised that people living with treatment resistant depression often have feelings of hopelessness, fear and despair. This can affect the person's family and carers. The clinical expert noted that there is also an impact on the lives of children of people with treatment resistant depression. The committee concluded that the condition has a negative effect on people, their families and their carers.*" The approach of including carer QALYs but modelling a disutility by patient's disease severity for ESK-NS is also aligned to the approach taken in TA493 (Cladribine tablets for treating relapsing–remitting multiple sclerosis) and TA527 (Beta interferons and glatiramer acetate for treating multiple sclerosis). The evidence provided for ESK-NS is of a similar and arguably higher quality. We would ask the Committee to consider the previous appraisals in the field of neuroscience, TA127, TA254, TA312, TA303, TA320, TA533 (all Multiple Sclerosis), and TA217 (Alzheimer's), which all modelled carer disutility by disease severity. It is important to note that the ERG method of incorporating carer disutility assumes a carer utility once patients achieve remission. This is not aligned to previous approaches, as it is appropriate to apply the full disutility based on the severity of the MDE health state. Since the NICE DSU was published in April 2019, a number of other appraisals have included carer disutility in their decision making, such as TA614 (Cannabidiol with clobazam for treating seizures associated with Dravet syndrome). Janssen were aware of the precedence from	Comments noted. The committee considered consultation comments on carer disutility. It concluded that it was appropriate to consider scenarios with both the ERG carer disutility scenario and no carer disutility because the effect was uncertain. See section 3.24 of the ACD.

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			NICE in including carer disutility in other TAs. As such, in the Scoping workshop conducted in September 2018, Janssen explicitly asked NICE if carer quality of life should be added to the Decision Problem, to which the NICE Committee co-chair agreed, given the impact that TRD has on patients and their carers. The above shows that the Committee's decision is inconsistent with previous NICE precedent from other therapeutic areas. **5.2 Carer disutility was previously included by NICE technical team and ERG during Technical Engagement and at all stages prior to Appraisal Committee meeting** By excluding carer disutility from the base case, the Committee are being inconsistent with the approach taken by the ERG and NICE technical team at previous stages of the appraisal. It has been recognised by the patient expert, the company, ERG, NICE Technical Team and the Committee at all previous stages of the NICE process that TRD has a substantial impact on wider society. The patient expert emphasised that TRD can affect the person's family and carers (ACD Section 3.1, p5). This was also evidenced in the survey results from the submission from SANE, which included 100 patients and 90 carers with TRD from the UK. As previously noted in the company submission, NICE CG90 recognises the additional significant impact on carers of people with depression. The ERG also included the carer disutility in a scenario (p866 of Committee Papers), which was also incorporated by the NICE Technical team (p866 of Committee Papers). The Committee themselves '*acknowledged that there is an impact on the families and carers of people with treatment-resistant depression'* (ACD Section 3.1, p5). It is therefore not clear why the Committee has now decided to exclude carer disutility when the submitted evidence, as the NICE technical team, ERG, NICE CG90 have shown it to be relevant. **5.3 Direct robust evidence was provided previously in the TRD carer HRQoL study which demonstrates impact on carers of patients with TRD (p758-808 of Committee papers)** ACD Section 3.14, p16: "*The committee considered that there was uncertainty about the appropriateness of including a carer disutility because of the lack of data on the direct effect on carers of people with treatment-resistant depression"* It is unclear where the uncertainty regarding the carer disutility has come from for the Committee, as we note that the ERG have judged the TRD HRQoL study to be well conducted and provides robust evidence on the effect on carers of people with TRD. *"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*" (p866 of Committee papers). This is in contrast to the evidence that was previously used by NICE to incorporate carer QALYs in previous appraisals, which had severe limitations. For example, in seven of the MS TAs, the carer disutility was not even taken from carers of patients who had MS, but from a	Comments noted. The committee considered consultation comments on carer disutility. It concluded that it was appropriate to consider scenarios with both the ERG carer disutility scenario and no carer disutility because the effect was uncertain. See section 3.24 of the ACD. Comments noted. The committee considered consultation comments on carer disutility. It concluded that it was appropriate to consider scenarios with both the ERG carer disutility scenario and no carer disutility because the effect was uncertain. See section 3.24 of the ACD.

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			study conducted in patients with Alzheimer's (NICE TA217: Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease). Carer utility in NICE TA217 (MS) was based on an unpublished Short-Form 36 data, and a non-comparative study measuring the quality of life of carers of Alzheimer's patients using the Health Utilities Index. For TA254, TA312, TA303, TA320 and TA533 (all MS), these all subsequently used the same caregiver disutilities and approach as TA127 in the base case analyse. The ERGs for these five TAs did not challenge the inclusion of, or data source for, caregiver disutilities. In two of the MS appraisals, the use of the Alzheimer's data were included in the final decision making (TA320 and TA303). The robust data provided by the TRD HRQoL study (p758-808 of Committee Papers) show there is a difference in utility of [redacted] between carers of patients with symptomatic TRD and carers of patients with TRD in remission. The evidence from the TRD HRQoL study is more robust than that used in previous NICE appraisals. The TRD HRQoL study provides direct evidence of carers of patients with TRD in the UK to show there is a disutility associated with caring for a patient with TRD who is symptomatic. **5.4 Conclusion** Overall, we ask the Committee to reconsider their conclusions on the topic of carer disutility for the following reasons: • It is appropriate and consistent with Committee decisions in other TAs to include carer disutility in the base case analysis. • Carer disutility was previously included by the NICE technical team and ERG during Technical Engagement and at all stages prior to the Appraisal Committee meeting. • Direct evidence was provided previously from the TRD HRQoL study, which the ERG have judged to be robust and is of a higher quality than previous appraisals. • TRD has a substantial impact on society including carers. The current approach is conservative given that it is likely that multiple family members will be impacted by one patient with TRD.	Comments noted. The committee considered consultation comments on carer disutility. It concluded that it was appropriate to consider scenarios with both the ERG carer disutility scenario and no carer disutility because the effect was uncertain. See section 3.24 of the ACD.
6	Consultee (company)	Janssen	**Section 6. The Committee have not considered all the evidence regarding comparators, as Janssen previously provided evidence comparing ESK-NS to all relevant comparators in the NICE Final Scope. Consideration of the combined effect of psychological and pharmacological treatment is inconsistent with previous NICE decision making.** **Overview** The Committee have not considered all evidence submitted by Janssen on the comparators included in the NICE scope ahead of the first Appraisal Committee meeting. In the ACD Section 3.4, (p7), the Appraisal Committee have incorrectly concluded that Janssen did not submit evidence comparing ESK-NS with all relevant comparators :	Comments noted. The ACD has been updated to acknowledge the comparisons provided in the company submission (see section 3.5 of the ACD). The committee concluded that the results comparing esketamine with some of the relevant comparators listed in the scope, such as combination or augmentation therapy and ECT, were highly uncertain. So, it considered only the results from the trials. These compared esketamine

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			"The company submission included oral antidepressants as comparators, stating that these were the most common oral treatments for the condition. The clinical expert highlighted that other oral antidepressants as included in the esketamine appraisal scope, sometimes combined, are also used in clinical practice. The committee acknowledged that different treatments are used at different points in the pathway (see section 3.3). The committee heard from other clinical experts who noted that ECT should also be a comparator because the processes involved in administering esketamine are similar to those for ECT. The committee noted that oral antidepressants augmented with lithium or antipsychotic medicines were also included as a comparator in the esketamine appraisal scope, and included in the NICE guideline on depression. The committee acknowledged the company did not provide evidence comparing esketamine with all the relevant comparators listed in the scope, such as combination or augmentation treatments and ECT, were not included as comparators in the company's model." The data comparing ESK-NS to all relevant comparators was reported in both the company submission (p127 of Committee Papers) and the ERG report (p601 of Committee Papers). The data shows that ESK-NS was compared to all relevant comparators in the scope, including combination, augmentation and ECT, and that ESK-NS is a cost-effective option for TRD. Please note that psychological treatments were not a comparator in the NICE Scope, and psychological treatments have an additive effect that could be applied to all pharmacological treatments, including ESK-NS. The Committee's conclusions are also inconsistent with the Committee's considerations in TA367, as they did not consider psychological therapies as comparator, and did not consider the combined effect of CBT plus pharmacological treatment. **6.1 The Committee have not considered all the evidence regarding comparators, as Janssen previously provided evidence comparing ESK-NS to all relevant comparators in the scope, including combination, augmentation and ECT, which showed ESK-NS is cost effective.** Janssen have previously submitted a network meta-analysis (NMA) which compared to augmentation/ combination treatments and ECT. The clinical systematic literature review (SLR) and NMA conducted for ESK-NS demonstrate that there is only limited evidence available for the treatments used for TRD. This shows the unmet need and lack of evidence-based treatments for this patient population. Nevertheless, the original results of the indirect comparison to augmentation/ combination treatments and ECT can be found in: • Page 127 of committee papers (B2.9) of company submission NMA scenario, with the results of indirect comparison presented in Section B.2.9.2 (p130 of Committee papers). The following comparisons were conducted: o ESK-NS vs ECT: indirect comparative efficacy data presented for response at 4–6 weeks and 4–8 weeks as well as for discontinuations due to AEs. o ESK-NS vs augmentation and vs combination: indirect comparative efficacy data presented for CFB MADRS at 4–6 weeks, response at 4–6 and 4–8 weeks, remission at 4–8 weeks, and discontinuations due to AEs • Combination, augmentation therapies and ECT were included in the model and a cost	with oral antidepressants with placebo with oral antidepressants, even though these will not be the only comparators in clinical practice.

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			effectiveness scenario was presented in Table 81 (Section B.3.4.4.9 of Company submission, p221 of Committee papers). The Odds Ratios (ORs) were consistently in favour of ESK-NS over every comparator in each outcome for which sufficient data were available to support the NMA. The analysis shows ESK-NS is cost-effective compared to all treatment options included in the NMA. As previously submitted in the original company submission, data show ECT is not a relevant comparator (p35 of Committee papers). ECT is used in [redacted] of eligible patients in UK clinical practice based on data from South London and Maudsley (SLaM). ECT is also generally used further down the treatment pathway than the proposed positioning for ESK-NS + OAD. Janssen have fulfilled the NICE scope through the submission of evidence compared to the most relevant comparators to NICE. Janssen previously submitted data to show the relevant comparators at TRD positioning in the UK (see p34 of Committee Papers). The data indicated that switching to newly initiated OAD monotherapy is the most relevant comparator for the licensed population for ESK-NS. We note the NICE positive guidance for vortioxetine, for which comparative evidence for all relevant comparators was not provided by the Company. The evidence for TA367 only considered direct comparison with agomelatine and an indirect comparison with sertraline, venlafaxine, bupropion and citalopram. No comparison was provided for vortioxetine compared to OAD augmentation or combination therapies, or ECT. **6.2 Psychological treatments should not be considered, as in the NICE Scoping workshop for ESK-NS it was agreed to exclude them as they have an additive effect to all pharmacological treatments** We note the Committee's conclusion regarding psychological treatments in the NICE ACD Section 3.5, p7-8: *"The patient expert explained that psychological therapy can help alleviate cognitive symptoms and with developing coping strategies. The NICE depression guideline expert noted that psychological therapies were not included as comparators or in combination treatments in the company's submission. The clinical expert explained that CBT is used alongside drug treatment to treat depression. However, not all people with depression can effectively engage with CBT because of the severity of their physical and cognitive symptoms. The patient expert suggested that treatment with esketamine may improve symptoms for enough time to allow people to have CBT. However, the clinical expert added that, because of the dissociative effects of esketamine treatment, someone would not be able to have psychological therapy immediately after having esketamine. This means that they could not have CBT at the same time as esketamine at their clinic visits. The committee concluded that CBT alongside oral antidepressant therapy and adjunctive therapy is a relevant part of the treatment pathway. But it had not seen any evidence on its effect when combined with esketamine or its comparators."* Psychological therapies were not included in the final Scope for ESK-NS as a comparator, as clinical experts involved in the NICE scoping process agreed that patients with TRD require	Comments noted. The committee concluded that psychological therapies are an adjunctive therapy and a relevant part of the treatment pathway, but that its effect would likely be variable depending on the treatment population and severity of depressive symptoms (see section 3.4). But it considered the effect of combining psychological therapies with esketamine treatment to be an unresolvable uncertainty with the evidence available. See section 3.6 of the updated ACD.

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			pharmacological treatments, and psychological treatments should be considered a potential add-on therapy. This was further validated by the clinical experts consulted by Janssen during the preparation of the submission. Clinical experts have stated that CBT is an additive therapy and would be expected to exert the same benefit regardless of which treatment it is co-administered with, including ESK-NS. The Committee have been inconsistent in their consideration compared to a previous NICE appraisal of TA367, which did not consider psychological therapies as comparator, and did not consider the combined effect of CBT plus pharmacological treatment. Note that in the ESK-NS clinical trials, if patients received CBT before ESK-NS, CBT could be continued whilst ESK-NS treatment was ongoing. **6.3 Conclusion** We urge the Committee to consider the evidence originally submitted by Janssen in the company submission regarding the relative effectiveness of ESK-NS versus all comparators in the NICE scope where there is available evidence. Both Janssen and the ERG noted the significant limitations of this comparative evidence, but when incorporated in the economic model demonstrated that the ESK-NS remains cost-effective. We would like to highlight to the Committee that the psychological treatments were not deemed relevant during the NICE scoping workshop and were not part of the NICE scope for the appraisal, as any effect would be additive to any pharmacological treatment. We also note that the Committee's conclusion is inconsistent with TA367 and it should not be considered as a relevant comparator for this appraisal.	
7	Consultee (company)	Janssen	**Section 7. Overall conclusion** The Committee have made an initial decision to reject ESK-NS as they believe it does not represent a cost-effective option for the treatment of TRD. Janssen urges the Committee to re-consider the previously submitted evidence and consider the additional evidence presented in our response to the ACD, which strongly supports the following: o Patients are able to discontinue ESK-NS once reaching the recovery health state with a limited impact on the risk of recurrence and hence on their HRQoL. As such, patients will discontinue ESK-NS for reasons other than lack of efficacy once reaching the recovery health state, which is aligned to evidence from different sources. Additional discontinuation guidance could be included in the ESK-NS recommendation to provide considerable certainty that patients will discontinue once reaching the recovery health state. o It is appropriate to include carer disutility in the base case analysis to account for the wide impact that TRD has on other people, and to be consistent with other NICE TAs. o The Committee should consider the evidence versus the relevant comparators that Janssen has previously provided, but consider the limitations previously highlighted	Comments noted. See responses above and the updated ACD.

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			by the Company and the ERG. ESK-NS has demonstrated impressive rates of response and remission in patients who have previously failed at least two OADs. ESK-NS is the first new antidepressant in 30 years with a novel mechanism of action, providing a much-needed new treatment option for patients with TRD in the NHS. In our revised base case ICER, upon considering the Committee's concerns, ESK-NS is a consistently cost-effective treatment option for use in the NHS. The wider economic burden of TRD on society increases the cost effectiveness of ESK-NS. Janssen therefore urge the Committee to reverse their initial decision, to allow patients routine access to this important new treatment. In the section below we provide further response to other issues and factual inaccuracies.	
8	Consultee (company)	Janssen	**Other issues and factual inaccuracies** There are a number of additional minor issues which Janssen wish to comment on. These include: • The population included in the ESK-NS clinical trials, despite the Committee's questions regarding its generalisability, is appropriate for decision making by NICE • Analyses show that unblinding was not an issue in the clinical trials • NHS stakeholders have indicated that significant investment is not needed for the introduction of ESK-NS to the NHS • The efficacy of subsequent treatments is based on a clinically validated and robust publication • Supervising multiple patients in the post-administration observation is clinically reasonable and based on extensive clinical input • Previously provided data on the dosing and frequency of administration shows ESK-NS remains cost effective • Other issues and factual inaccuracies in the ACD Each of these issues are described below. **8.1 The population included in the clinical trials, despite the Committee's questions regarding its generalisability, is appropriate for decision making by NICE** NICE ACD Section 3.7, p9: "*The committee concluded that the extent of the exclusion criteria and the lack of participants from England in the trials mean the evidence for esketamine is limited in generalisability to the NHS population with treatment-resistant depression."* The "extent of the exclusion criteria" in the ESK-NS trials are consistent with multiple other trials in depression and the clinical evidence from TA367. While it is acknowledged that the	Comments noted. The committee considered the consultation comments on this point. See section 3.14 of the updated ACD. The committee was aware of the comments in the European public assessment report (EPAR) about

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			trials excluded patients with moderate to severe alcohol abuse, psychiatric comorbidities and suicidal intent, the exclusion criteria applied in the ESK-NS trials are consistent to other antidepressant trials in depression. For example, the exclusion criteria are consistent with the trials in the appraisal of TA367 (vortioxetine for treating major depressive episodes), which excluded patients with a dual diagnosis, previous treatment with ECT, or those with suicidal ideation/behaviours. It is important to note that despite having no clinical evidence in the patient population in adults whose condition has responded inadequately to two antidepressants within the current episode, TA367 recommends vortioxetine for this patient population. As noted above in Section 4.4, Janssen intend to conduct a prospective observational study to collect the characteristics and the clinical outcomes of patients with TRD in the NHS. Janssen are willing to share the study protocol and data with NICE.	the precautions that need to be taken if people with psychiatric comorbidities take esketamine. The committee also noted that the population in the trial may not be in line with its expected clinical use (see section 3.4 of the ACD) and that patients with more severe symptoms may be more likely to be excluded using these criteria. The committee considered that the other exclusion criteria could inhibit the generalisability of the trial results but that this was an unresolvable uncertainty in this disease area with currently available data. It concluded that excluding people with recent suicidal ideation limits the generalisability of the trials to the NHS for people with treatment-resistant depression.
			8.2 Analyses show that unblinding was not an issue in the clinical trials NICE ACD, Section 3.6, 9: *"The committee acknowledged the company's attempts to blind the treatments but noted that blinding is difficult, given the dissociative symptoms experienced by people after they had esketamine."* As a result of a number of factors, unblinding was not an issue in the ESK-NS trials. Several measures were taken during study conduct to ensure blinding was maintained. This included having remote, independent, blinded MADRS assessments and using a bittering agent in the placebo nasal spray. The MADRS assessments were performed prior to dosing (if a dosing was planned for that visit) and, during the Optimisation and Maintenance Phases, they were performed weekly for all subjects regardless of dose frequency. Only ~26.1% of patients receiving ESK-NS experienced dissociative effects within the TRANSFORM-2 study. Furthermore, there were also reported cases of dissociation in the OAD+ PBO-NS arm. As previously noted in the Company Submission (p135 of Committee papers), a *post-hoc* analysis found dissociation not to be correlated with antidepressant treatment effect in the ESK-NS trials (4) and that dissociation also occurred in the OAD + PBO-NS arm. This shows that the dissociative effects did not result in unblinding of the studies.	Comments noted. The committee noted consultation comments on this issue. The committee concluded that the withdrawal design of SUSTAIN-1 may have biased results in favour of esketamine, if patients were unblinded to what treatment they were having. See section 3.11 of the ACD.
			8.3 NHS stakeholders have indicated that significant investment is not needed for the introduction of ESK-NS to the NHS.	Comments noted. The committee noted the commissioning expert

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			NICE ACD Section 3.17, p18*: "The committee noted the results of a survey conducted by the company which found that 18% of NHS Trusts had no specific plans on how they would adopt esketamine treatment. Therefore, the committee considered that some infrastructure costs may not be captured in the model. The committee acknowledged that the time needed to implement esketamine was unclear but that it is likely to be at least 6 months."* 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. The feedback was collected as part of the mandatory NHS advanced notification exercise, using semi-structured interview techniques 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 and 10 ECT managers and leads across the NHS. All NHS stakeholders interviewed indicated that there would be no requirement to invest in new infrastructure. Whilst it is apparent that the current staffing resource will need to change to implement ESK-NS, feedback from NHS at Trust level has clearly said that significant infrastructure investments are not required.	comments that these costs would be difficult to quantify. The committee also noted that the costs would depend on the expected population in clinical use (see section 3.4 of the ACD). The committee noted that NICE's guide to the methods of technology appraisal 2013 (section 5.5.8) states that if introduction of the technology needs changes in infrastructure, costs or savings should be included in the analysis. So, the committee concluded that there would need to be significant investment to use esketamine in the NHS, but considered that these costs could be difficult to quantify. See section 3.30 of the ACD.
			8.4 The efficacy of subsequent treatments is based on a clinically validated and robust publication NICE ACD, Section 3.11, p13: *"The ERG also noted that the modelled effectiveness of subsequent treatments appeared to be underestimated."* The source of the effectiveness of the best supportive care treatment efficacy was taken from a published NICE HTA monograph on augmentation with lithium or an AP in TRD. This data source was published by an ERG and validated as appropriate source with four UK psychiatrists. It was confirmed by the authors that the clinical experts considered STAR*D in their estimation of the Best Supportive Care (BSC) efficacy in the HTA monograph. NICE and the ERG have not validated their judgement that the efficacy of subsequent treatments is an underestimation with clinicians. In their judgement of the efficacy of subsequent therapies, the ERG has not considered that BSC is 7th treatment line and is applied for all subsequent lines. As acknowledged by the NICE Committee in TA367, STAR*D is the best evidence on the prognosis for people having subsequent lines of treatment. If using the ERG approach to model subsequent treatments, we note that the response and remission rates of 7th line MDD and subsequent lines are considerably higher (~38% and ~22%) than 4th line MDD in the STAR*D study (~29% and ~13%), at 14 weeks (Table 6). **Table 6: Remission and response rates applying the ERG method of subsequent treatment efficacy**	Comments noted. The ERG was unable to validate how the subsequent treatments were calculated but considered them to be considerably lower than the observed response and remission rates in STAR*D. The committee discussion on subsequent treatments in section 3.18 of the ACD.

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	ERG scenario method of implementing subsequent treatments		Comparison to STAR*D data	
	4-weekly Remission	4-weekly Response (excluding remission)	Remission at 14 weeks	Response at 14 weeks (excluding remission)
TRD Line 1 (3rd line MDD)			13.7%	16.8%
TRD Line 2 (4th line MDD)	25.2%	17.8%	13.0%	16.0%
TRD Line 3 (5th line MDD)	23.9%	17.3%		
TRD Line 4 (6th line MDD)	22.7%	16.8%		
BSC	21.5%	16.3%		

The above shows that the currently used assumptions in the company base case are appropriate, and the ERG scenario including clinically unreasonable and unvalidated assumptions on the efficacy of subsequent treatments should be considered inappropriate.

8.5 Supervising multiple patients in the post-administration observation is clinically reasonable and based on extensive clinical input

NICE ACD, Section 3.16,p 17: *"In its model, the company assumed a ratio of 2 nurses to 6 patients during the administration of esketamine and 1 nurse to 6 patients during the post-administration monitoring. The ERG preferred to model a 1:1 ratio throughout administration and monitoring because it considered this to be the most plausible in clinical practice. The NHS commissioning expert noted that because esketamine is a schedule 2 drug, it requires 2 healthcare professionals during part of the administration stage and it's subject to the full controlled drug requirements relating to prescriptions and storage. However, it may be reasonable to have a ratio of 1 nurse to 6 patients during the monitoring of esketamine. The clinical expert suggested that a ratio of 1:1 or 1:2 may be necessary when the service first starts, but that the ratio may increase to one nurse to a group of patients once the service becomes experienced and established. The patient expert, who was receiving treatment one to one, said that building a relationship with the healthcare professional was an important component for treatment and recovery. The company clarified that their model included a band 5 and a band 4 nurse to administer esketamine and a band 5 nurse for post-administration monitoring. The committee considered that more additional training or more experienced*

Comments noted. The committee concluded that the company's model may have underestimated the nurse experience and time required to safely administer, monitor, and manage the dissociative effects of esketamine, and that a 1 to 2 ratio of nurses to patients was appropriate. See section 3.29 of the ACD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			nurses may be needed to manage the dissociative effects of esketamine. The committee concluded that the company's model may have underestimated the nurse experience required to safely administer, monitor and manage people receiving esketamine. The committee also concluded that, without further evidence, incremental cost-effectiveness ratios (ICERs) should be estimated based on nurse to patient ratios across a range from 1:1 to 1:6 during the monitoring phase of administration." Janssen do not believe the 1:1 nurse: patient ratio for the post-administration observation as used as the lower bound by the Committee is appropriate. The rare occasions where a 1:1 nurse: patient ratio is expected to occur in clinical practice are included in the average ratio of 1:2 and 1:6 as included in the revised company base case, which is based on extensive clinical input. The totality of evidence from all interactions Janssen have had with NHS clinical experts shows that the monitoring of multiple patients simultaneously will occur when ESK-NS is used in NHS clinical practice. In an advisory board to discuss this topic, Janssen consulted with 6 clinical experts with first-hand experience in treating patients with TRD. These clinicians were consulted with and were in consensus with the assumptions that 1 nurse can observe 6 patients during the post-administration observation period based on the safety profile of ESK-NS. Additional market research of 59 UK psychiatrists showed that multiple patients can be monitored simultaneously (see p726 of Committee Papers). On average, clinicians estimated that one nurse would be able to monitor 4-6 patients concurrently. Furthermore, clinicians stated that the ratio of patients to nurses is likely to increase over time as clinical familiarity increases. The revised company base case now includes a range of ICERs from 1:2 to 1:6 to reflect this. In contrast with the company assumptions, the ERG/ NICE team have not validated their assumption of 1:1 nurse: patient ratio with any clinical experts familiar with ESK-NS or the nature of the monitoring required. As noted previously, nurse ratios of 1:1 or 1:2 ratios are recommended for intensive/critical care or neonatal care (3). The requirement of the nurse post-ESK-NS administration is predominantly hands-off patient observation. The nurse only requires monitoring blood pressure one or more times during post-administration observation. It seems unreasonable to assume that a nurse could only manage to observe a single patient who has received ESK-NS, especially when compared to these other, significantly more intensive care settings. A visual graphic (Figure 2) to further clarify the Committee's understanding of the administration model and assumptions is provided below. Throughout the post-administration observation, there are only 10-20 minutes where there are 6 patients observed by 1 nurse. For the remainder of the time in the clinic, there are 1-2 nurses with less than 6 patients. **Figure 2: Visual graph to display ESK-NS administration assumptions**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

Minutes after clinic started	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
10	Supervise self-administration					
20	Monitoring	Supervise self-administration				
30		Monitoring	Supervise self-administration			
40			Monitoring	Supervise self-administration		
50				Monitoring	Supervise self-administration	
60					Monitoring	Supervise self-administration
70	Discharge					Monitoring
80		Discharge				
90			Discharge			
100				Discharge		
110					Discharge	
120						Discharge

8.6 Previously provided data on the dosing and frequency of administration shows ESK-NS remains cost effective

NICE ACD Section 3.15, p17: *"The ERG confirmed that the dose of esketamine used in the model was an average from the trial evidence. The committee was concerned that it was unclear what proportion of people received the 56 mg or the 84 mg doses and that no dose response curve was presented. It also considered that the company model did not fully account for a scenario in which a greater proportion of people receive the more expensive 84 mg dose, or the proportion who would receive the dose once weekly compared with once every 2 weeks. The committee concluded that the model may underestimate the cost of a course of esketamine treatment. The committee would like to see evidence of the proportions of people on each dose and frequencies of administrations, and scenarios exploring the effects*

Comments noted. The committee concluded that the model may underestimate the cost of a course of esketamine treatment and would like to see the proportion of people having each dose, how often people

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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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<tr><td></td><td></td><td></td><td>
of these assumptions on the cost-effectiveness results."
As noted in the Company Submission, 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 (p191 of Committee Papers). Janssen previously provided an analysis considering variation of the dosing from the clinical trial data. This was already presented in a sensitivity analysis varying the dose in the original CS (Table 64 and Table 65 of CS, Page P207/876 of Committee papers). The number of devices per administration and administrations per week was varied to explore the impact on cost-effectiveness. The original company submission showed that the number of ESK-NS + OAD administrations per week during the continuation phase would need to nearly double to 1.32 for the ICER to reach £20,000. 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 for the ICER to reach £20,000, both of which are above the maximum dose limit of three per administration.
Similarly, using the revised base case assumptions (and conservatively assuming a 2:1 ratio of patients to nurse observation), the number of ESK-NS + OAD administrations per week during the continuation phase would need to increase by ~60% (1.07 vs 0.71 per week) for the ICER to reach £20,000. The number of ESK-NS devices per administration during the continuation phase would need to be 4.07 and during the acute phase (Weeks 1–4) would need to be 4.51 for the ICER to reach £20,000, both of which are above the maximum dose limit of three per administration.

8.7 Other issues and factual inaccuracies in the ACD:

Minor factual inaccuracies and/or errors are tabulated below:
<table>
<tr><th>Location of factual inaccuracy</th><th>Issue</th><th>Correction</th></tr>
<tr><td>Slide 8 of Committee Slides</td><td>SUSTAIN-1 is incorrectly described as a single arm, long term, follow up study</td><td>SUSTAIN-1 used a randomised withdrawal design to assess, in a double-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.</td></tr>
<tr><td>NICE ACD, Section 3.7</td><td>"TRANSFORM-3….were only used as supporting evidence, and the data were not included as part of the company's model."</td><td>The revised company model in response to the clarification questions includes data from TRANSFORM-3.
As the ERG note in P597 of the Committee papers: "In response to this request for clarification, the company submitted a</td></tr>
</table>
</td><td>
have esketamine (weekly or every 2 weeks), reasons for the dosing choices and scenarios exploring the effects of these assumptions on the cost-effectiveness results. See section 3.27 of the ACD.

Comments noted. Updated slides were presented to committee at the 2nd committee meeting. The ACD has been substantially updated where relevant. Please see updated ACD.
</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row			NICE Response Please respond to each comment
					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"	
			NICE ACD, Section 3.6 (multiple times)	Treatment included in ESK-NS clinical trials	When describing the clinical trials, the active treatment should be described as "esketamine nasal spray plus oral antidepressant" rather than "esketamine"	
			NICE ACD, Section 3.6:	The wording to describe the treatments in the TRANSFORM-2 and SUSTAIN-1 studies should be corrected to include a newly initiated OAD plus placebo, as per the study designs.	TRANSFORM-2 found significantly improved response rates (69.3% compared with 52%) and remission rates (52.5% compared with 31%) for esketamine **nasal spray plus a newly initiated OAD** over **a newly initiated** OAD **plus placebo nasal spray** SUSTAIN-1 found significantly lower relapse rates associated with esketamine **nasal spray plus a newly initiated OAD** compared with OAD **plus placebo nasal spray** for stable remitters (26.7% compared with 45.3%) and for stable responders (25.8% compared with 57.6%).	
			Committee papers, p 454-458	Patient experience whilst receiving treatment with IV ketamine was described instead of experience with ESK-NS	We appreciate the patients' perspective but note that IV ketamine is different from ESK-NS.	
			ACD Section 3.7, p 7	*"The committee heard from other clinical experts who noted that ECT should also be a comparator because the processes involved in administering ESK-NS are similar to those for ECT."*	This is not a relevant rationale for the definition of a comparator. Furthermore, the processes for administering ESK-NS and ECT are not similar, given the requirements for anaesthetics and a full day admission for ECT.	
			ACD Section 3.17, p18	*"The committee heard that adopting esketamine would result in displacement of other mental health treatments because of its cost"*	Other mental health treatments will be displaced because of the block contract funding system, not only due to the ESK-NS cost.	

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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th colspan="3">Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td colspan="3"><table>
<tr><td>ACD Section 3.17, p18</td><td>“The staff training to administer and monitor esketamine may not have been accounted for in the model because additional training is needed to manage dissociative effects.”</td><td>Janssen will provide additional educational materials for clinicians and patients. On request further training can be provided. Additional costs of training should therefore not be included in the model.</td></tr>
<tr><td>NICE ACD Section 3.8, p11</td><td>“However, the committee questioned whether the additional clinical contact involved in administering esketamine included psychological therapy”</td><td>Janssen would like to clarify that psychological therapy is not delivered during these clinic visits. The increased clinical contact as a result of the additional visits is not equivalent to receiving psychological therapy.</td></tr>
<tr><td>NICE ACD Section 3.8, p11</td><td>“Committee also recalled that CBT could not be given at the same time as esketamine”</td><td>Janssen would like to clarify that we are not proposing patients would have or not have CBT with ESK-NS. Patients are able to receive CBT prior to ESK-NS self-administration or at another day or timepoint. As noted above, in the clinical trials if patients received CBT before ESK-NS, CBT could be continued whilst ESK-NS + OAD treatment was ongoing.</td></tr>
<tr><td>NICE ACD Section 3.5, p7</td><td>“The clinical expert added that, because of the dissociative effects of esketamine treatment, someone would not be able to have psychological therapy immediately after having esketamine”</td><td>Janssen wish to clarify that it is possible to receive psychological therapy whilst also receiving ESK-NS treatment. The statement included in the ACD is not correct for two reasons:
Only 26.1% of patients receiving ESK-NS experienced dissociative effects within the TRANSFORM-2 study.
Whilst not able to have psychological therapy immediately after ESK, CBT could take place whilst the patient is not receiving ESK-NS, e.g., just before self-administration or at another time when the patient is not receiving ESK-NS</td></tr>
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<u>References</u></td><td></td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			1. NICE. Guide to the processes of technology appraisal. April 2018. [Available from: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/technology-appraisal-processes-guide-apr-2018.pdf] 2. NICE DSU, Modelling carer health-related quality of life in NICE technology appraisals and highly specialised technologies. April 2019. [Available from: http://nicedsu.org.uk/wp-content/uploads/2019/07/2019-04-03-NICE-carer-HRQL-v-2-0-clean.pdf] 3. Royal College of Nursing, 2011. Guidance on safe nurse staffing levels in the UK. 4. Chen et al, 2018. Relationship between antidepressant effects of esketamine nasal spray and perceptual disturbances. Presented at The American College of Neuropsychopharmacology (ACNP) 57th Annual Meeting, December 9-13, 2018, Hollywood, FL, USA	
1	Consultee (clinical expert)	Hamish McAllister-Williams	Context It is important to put discussions regarding esketamine for the treatment of depression into context. Depression is the leading cause of disability around the world (Friedrich MJ 2017 JAMA 317:1517). In the UK, it is the most common illness cited in benefit claims, being more than double the next most common – back pain (Dept of Work and Pensions, August 2010). Depression is associated with an increased risk of mortality from suicide. However, it is also associated with increased all cause mortality (UK standardised mortality ratio of 2.55 – Das-Munshi et al. 2019 Psychol. Med. 49:1639-1651). While there are a broad range of effective treatments for depression (psychotherapy, pharmacotherapy and neurostimulation), unfortunately a significant minority of patients either do not achieve remission, or fail to sustain remission, with current treatments despite multiple treatment trials. From the largest treatment study in depression ever conducted (Star*D), around of 1/3 of patients presenting with depression and treated systematically with up to 4 sequential treatments didn't achieve remission (Rush et al. 2006 Am J Psychiatry 163:1905-17). This group of patients have very poor outcomes. In a 5 year prospective follow up study, only around 40% of patients who were managed with conventional treatments in specialist services achieved response criteria (at least a 50% improvement in symptoms from baseline) at any point in time (Aaronson et al. 2017 Am J Psych. 174:640-648). Patients with difficult to treat depression have very poor outcomes. All cause mortality in patients defined as 'treatment resistant' is 29-35% higher than for non-treatment resistant depressed patients (Scherrer et al. 2012 Brit J Psychiatry 200:137-42). Data from a large health maintenance organisation in the USA suggested that patients with treatment resistant depression have all cause mortality rates higher than non depressed individuals who are 13 years older (Feldman et al. 2013 J Med Econ 16:62-74). There is also evidence of a strong	Comments noted. The committee considered the impact of treatment-resistant depression on people, families and their carers (see section 3.1 of the ACD), the unmet need for effective treatment (section 3.2 of the ACD). The committee considered the comments submitted at the first consultation and in addition patient and clinical experts attended the second appraisal committee meeting to ensure their perspective was heard following the consultation.

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			correlation between number of medication changes needed and health care costs (Russell et al. 2004 J Clin Psychiatry 65:341-347). Anecdotally, a number of CCGs have suggested that a high proportion of their health care spend (e.g. around 65%) occurs in relation to a small proportion of the population they cover (e.g. less than 5%). This small group of individuals with high health care costs are typified by the presence of multiple chronic health conditions, one of the most common of which is depression. These are the likely target population for esketamine, at least initially. Modern antidepressant treatments have been available since the mid-1950 when the broad groups of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) were serendipitously identified. Since then there has been an expansion of the number of antidepressants with the development of selective serotonin reuptake inhibitors (SSRIs), the serotonin and noradrenaline reuptake inhibitors (SNRIs) and a number of miscellaneous antidepressants (most recently vortioxetine). For patients who don't respond to antidepressant monotherapy, pharmacological augmentation is recommended, for example with lithium, quetiapine or aripiprazole (Cleare et al. 2015 J Psychopharm 29:459-525). The primary pharmacological mechanism of action of all current treatments, both monotherapies and augmentation strategies, relates to monoaminergic neurotransmission. Given that received wisdom is that depression is a heterogenous condition related to a number of different underlying pathologies, there is a perception that perhaps some patients have poor outcomes because current treatments are inadequately targeting their pathology. Given the very significant un-met burden of disease, there is great excitement amongst patients and clinicians when a treatment is developed that has a fundamentally different mechanism of action. It is for these reasons that the progress of esketamine has been followed so closely by patient groups and clinicians alike.	
2	Consultee (clinical expert)	Hamish McAllister-Williams	**Data related to ketamine.** It is disappointing that the Appraisal Committee did not consider the evidence base regarding the use of ketamine for the treatment of depression when reviewing esketamine. The drugs are pharmacological related and there is precedent for considering the evidence related to the racemic drug when reviewing a stereoisomer: This was done by NICE when reviewing escitalopram. In my opinion it is important to consider the number of RCTs versus placebo that suggest efficacy of ketamine for treatment resistant depression (Han et al. 2016 Neuropsychiatr Dis Treat 12:2859-2867). Whilst there is no data directly comparing intranasal esketamine with any formulation of ketamine, there is a study which compares the two drugs both administered intravenously in 63 patients. This non-inferiority study found comparable efficacy in treating treatment resistant depression, with both drugs well tolerated (Correia-Melo et al. 2020 J Affect Disorcer 264:527-534). There are other issues that I will raise below, where it is potentially helpful considering the literature around ketamine.	Comments noted. The committee was aware of the issue raised about using evidence for intravenous ketamine from the technical report. NICE seeks relevant evidence from several sources. The company submits the principal evidence. The evidence review group (ERG), an external academic organisation independent of NICE, produces a review of the evidence submission (see sections 3.3.8 and 3.3.9 of the NICE TA Process Guide). Consultees provide information and selected clinical experts, NHS commissioning experts and patient experts also give evidence (see section 3.4 of

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				the process guide).
3	Consultee (clinical expert)	Hamish McAllister-Williams	**Comparability** On page 3 of the ACD the following is stated “But how much benefit it provides over other oral antidepressants with adjunctive therapy or electroconvulsive therapy is unclear because these treatments have not been compared directly. Also, the available evidence did not include psychological therapies.” I have a number of concerns regarding this statement, foremost the implication of a hurdle that would prevent a favourable opinion ever being given to any potential new treatment for depression. There are currently around 30 antidepressants listed in the BNF. There are 7 pharmacological augmentation listed as first or second line option in national guidelines (Cleare et al. 2015 J Psychopharm 29:459-525). This gives around 240 different combinations of medication that might be used, assuming that patients are on monotherapy or augmentation with just a single agent. Frequently, for example, lithium AND an antipsychotic are added to an antidepressant, or an antipsychotic added to a combination of two antidepressants. By my reckoning, this means that there are at least 4-500 different medication combinations that might be used, not allowing for issues around different dosages. Currently there is next to no data directly comparing these treatments. Some antidepressants have been compared with other antidepressants as monotherapy. There is sufficient data to undertake a network metanalysis (Cipriani et al. 2018 Lancet 2018). While it is possible to rank the antidepressants included in order of efficacy, there is little in the way of clinically significant differences between them. Note, these data are not in populations of patients with treatment resistant depression. There is next to no data comparing pharmacological augmentation strategies in treatment resistant depression. This was highlighted by the NICE depression guideline group (CG90) and was a factor leading to the NIHR HTA panel funding a multicentre randomised comparison of quetiapine vs lithium augmentation in TRD (Marwood et al. 2017 BMC Psychiatry 17:231) that is still to report. This means that network meta-analysis of pharmacological augmentation involve networks that are immature and unstable (Zhou et al. 2015 Int J Neuropsychopharm 18:pyv060; Strawbridge et al. 2019 Br J Psychiatry 214:42-51). The consequence is that it is impossible at this time to have any confidence in identifying what should be the pharmacological comparator(s) that one would consider. The ACD also makes reference to ECT and psychotherapies in relation to the lack of comparator data for esketamine. The draft NICE clinical guidelines for depression listed around 10 different forms of formal psychotherapy. These might be used alone or in combination with medication (leading to thousands of potential combinations). However, a recent systematic review was only able to identify three trials of psychotherapy in patients with defined treatment resistant depression. None of these included a placebo arm that allowed comparison with medication (Strawbridge et al. 2019 Br J Psychiatry 214:42-51). So, while commonly used, there is a lack of data	Comments noted. Following consultation page 3 of the ACD has been updated. In section 3.5 of the updated ACD, the committee concluded that the results comparing esketamine with some of the relevant comparators listed in the scope, such as combination or augmentation therapy and ECT, were highly uncertain. So, it considered only the results from the trials. These compared esketamine with oral antidepressants with placebo with oral antidepressants, even though these will not be the only comparators in clinical practice.

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			supporting the efficacy of psychotherapies, or their comparison with pharmacotherapy, in the management of treatment resistant depression. Raising the issue of a lack of inclusion of psychotherapy in the studies of esketamine appears to be setting a hurdle that not a single currently recommended pharmacological treatment has surpassed. The issue of comparison with ECT is an interesting one. It should be noted that in the entire history of ECT, to my knowledge, there are only four small and old comparisons of it versus pharmacotherapy in patients with treatment resistant depression (RCPsych ECT Handbook). How comparable intranasal esketamine is with ECT is a reasonable question, though difficult to address. This is in part due to the problems in study design – it is ethically questionable to run a truly double blind study of ECT versus medication when patients would potentially be having repeated anaesthetics without treatment. This said, there are two small RCTs of IV ketamine vs ECT (Basso et al. 2020 J Psych Res 123:1-8; Kheirabadi et al. 2019 Adv Biomed Res) which found no difference between the treatments. A larger study (ELEKT-D) is currently planned (Matthew et al. 2019 Contemp Clin Trials). However, one of the major issues around the comparison with ECT is that the populations of patients treated with ECT and potentially with esketamine, while overlapping, are not the same. The primary indication for ECT is for patients with severe acute depression with psychosis and/or marked psychomotor retardation with decreased food and fluid intake (see NICE CG90). This is not the population of patients likely to be treated with esketamine. Rather, esketamine is likely to be used in the more chronic treatment resistant patient population. While it is recommended to consider ECT in such groups (e.g. Cleare et al. 2015), the reality is that it is rarely used in practice due to a previous, now superseded, NICE clinical guideline being very negative about the treatment. The ACD (page 7) states “The company did not provide evidence comparing esketamine with all relevant comparators”. Given the lack of consensus as to what the most appropriate comparator would be, or the population of patients in which to perform the study, it is hard to see how any company could ever provide evidence against “….all relevant comparators”. Such a requirement prior to the recommendation for use of a treatment in the UK will inevitably mean that companies decide that it is not economically viable to introduce treatments for TRD into the UK, especially when such hurdles are not present in other countries. This will not only be to the detriment of patients by also the health care economy (see point 1 above)	
4	Consultee (clinical expert)	Hamish McAllister-Williams	Generalisability The issue of the generalisability of the data is raised in the ACD (page 9): “The evidence for esketamine is limited in its generalisability to the NHS”. To my mind there are two different sides to the question of generalisability and the patient population in which esketamine might be used in the UK. Firstly, it is argued in the ACD that the esketamine data is not particularly generalisable due to the inclusion of very few UK NHS patients in the company trails, and the nature of the eligibility criteria. The lack of UK NHS patients is an issue that at least in part reflects the difficulty of	Comments noted. This issue is discussed in more detail in the updated ACD. The committee considered that the other exclusion criteria could inhibit the generalisability of the trial results but that this was an unresolvable uncertainty in this disease area with currently available data. The committee concluded that excluding

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			conducting studies in TRD in the UK despite its prevalence (an issue I am only too familiar with as a researcher in this area). It is disappointing that there were not more UK patients included. However, I would be extremely concerned if a situation arose where only drugs tested in UK populations were approved for use in this country. Japan has a policy of only approving drugs where there is a significant data set in patients of Japanese origin. This is of potentially more justification given data demonstrating pharmacokinetic differences in Asian populations. However, it has led to a significantly slower introduction of many modern psychopharmacological agents. The high suicide rate there (around 4X the rate in the UK) is probably rooted in societal differences. However, as a psychiatrist, I find it hard not to believe that the lack of psychopharmacological agents contributes to this high suicide rate, at least to some extent. The UK has an arguably more ethnically diverse population than Japan meaning that trials conducted in other countries are of more relevance. With regards to the eligibility criteria used in the esketamine studies, these are pretty standard across studies of this type. I am currently involved as PI or CI in five different trials in patients with treatment resistant depression – three NIHR funded and two industry funded. These all have similar eligibility criteria. It is critical to recognise that trials in mental health conditions, such as depression, present challenges that are not present in many other therapeutic areas. The symptoms of depression can not be assessed objectively – we are reliant on patient descriptions of symptoms and self-completed or observer-rated scales. There is inherently a great deal of noise in such measures. This means that it is even more critical to control confounding variables that in studies with more objective outcome measures. Patients with significant alcohol problems are excluded from most trials because there is an increased risk of non-adherence and because alcohol can exacerbate depression and make it more likely to be difficult to treat. Some psychiatric comorbidities may respond to the treatments for depression (for example generalised anxiety responds to many antidepressants), but some may be made worse (e.g. psychosis can worsen with antidepressants and there are theoretical reasons why we would have concerns giving ketamine or esketamine to a psychotic patient – ketamine leads to schizophrenic like symptoms in health subjects). It might be argued that randomisation should address these issues. However, it is nigh on impossible to achieve balance between treatment arms across many different comorbidities and there are far too many to use minimisation to ensure similar numbers in each treatment arm. This, plus the problems of low signal to noise ratios, means that to NOT exclude patients for significant alcohol problems or any psychiatric comorbidity would require unfeasible sample sizes in studies. Including a requirement that patients must have failed ECT would be a great concern to me – this would massively impede recruitment (see arguments above about differences in patient populations treated with ECT and ketamine) and prevent access to the trial to any patient who refused ECT. Failure to respond to ECT is an extremely bad prognostic factor generally in patients with TRD (Aaronson et al. 2017 Am J Psych. 174:640-648). This means that the power of the study would be reduced and required sample sized increased – not a good when combined with massively reducing the eligible population size.	people with recent suicidal ideation limits the generalisability of the trials to the NHS for people with treatment-resistant depression (see section 3.14 of the updated ACD.

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			The point raised in the ACD regarding the exclusion criteria related to suicidal ideation is an important point. Suicidal ideation is part and parcel of depression. It is always a concern to me when this is included as an exclusion criteria. In independent (e.g. NIHR funded) trials we tend to try to keep inclusion as broad as possible and only exclude participants who are actively suicidal simply for safety reasons. However, industry funded studies always have tighter requirements in this regard. No company wants to have patients in their trials committing suicide, especially given all of the noise in the lay press regarding antidepressants and suicide. This does mean that we have great caution when using newly introduced drugs in patients with significant suicidality given the usual lack of data in this regard. However, the situation with esketamine is very different. Looking at the ketamine data is potentially helpful. There is increasing data suggesting that ketamine has anti-suicidal properties (e.g. Zhou et al. 2020 J Affect Disord 264:263-271). Similarly, there is also published data suggesting that intra-nasal esketamine has anti-suicidal effects (e.g. Canuso et al. 2019 Focus (Am Psychiatr Publ) 17:55-65). Indeed, I understand that Janssen are seeking a license for the use of esketamine in depressed patients with acute suicidality. I assume that the company have not provided this data to the Advisory Committee since this indication has not yet been approved. However, it does mean that as a clinician I am pretty relaxed with regards the exclusion of patients with suicidal ideation in the TRD trials. My second point regarding generalisability relates to something that it appears the Advisory Committee have not considered. All of the discussion and economic modelling has been done in relation to patients with treatment resistant depression defined using the standard definition of failure to response to two adequate trails of different antidepressants. This is the definition that the regulatory authorities use. However, this is certainly not a good definition of patients that might be given esketamine in the UK NHS. The reality is that patients do not follow a treatment pathway reflecting NICE recommendation in any shape or form. CG90 recommends that if a patient has failed to respond to two trials of antidepressant monotherapy, they should be referred into secondary care where they may receive pharmacological augmentation and/or the addition of specific psychotherapies. ECT is some what stuck out on a limb being recommended for those with severe depression plus psychosis or psychomotor retardation (as described above). However, the reality is very different from this. Patients may have three or four trials of antidepressant monotherapy before being referred into secondary care. Once referred, the most common intervention is either simply increasing the dose of the antidepressant the patient is on or switching to an alternate antidepressant. Only then are first line pharmacological augmentation strategies considered. In the vast majority of circumstances, at least one or two current standard augmentation options are tried before a clinician starts to consider newer or less conventional treatments. (Psychotherapies are usually considered in parallel with these various pharmacological steps). There would be a number of hurdles to the provision of esketamine in practice. Top amongst these will be pressures from pharmacies to not prescribe because of the drugs costs. In addition, clinicians would need to organise for patients to attend a hospital site twice a week	

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			and then weekly for a period of time, and patients would need to be agreeable to undertaking this. We know from experience that the smallest extra hassle around prescribing a treatment leads to low rates of prescribing (e.g. the need to undertake LFT checks in patients on agomelatine, or ECGs in patients on higher doses of escitalopram). As a result, there is no way that esketamine will be used as a third line treatment – indeed it would be surprising to me if it was used much earlier than 5th or 6th line. There are at least two implications from the observation above. 1. The studies so far conducted with esketamine have not been conducted in the sort of patients likely to be treated with it in practice and 2. The numbers of patients receiving esketamine will be much more limited than might otherwise be the case. I think there is a potential issue around generalisability of the current esketamine data, but it is not in relation to the issues raised in the ACD. Rather, the patients included in the Janssen studies are nowhere near as treatment resistant as those likely to be in practice. This is an issue in that the evidence suggests that there are decreasing response and remission rates with each treatment failure (Rush et al. 2006 Am J Psychiatry 163:1905-17). I do not think that this means the drug should not be recommended for use until studies in such populations are done. This is because the sample sizes needed would, once again, be unfeasible. I have designed a number of studies of treatments in TRD and the more I do, the more I feel the need to limit the degree of resistance in the sample population to stand any chance of detecting any effect of the treatment in a practical sample size. The other implication, though, is that the response and remission rates used in the economic modelling of esketamine, based on the trail data, are likely to be over-estimates. Adjusting for this would lead to reduced costs since more patients would stop treatment early on. When using IV ketamine, if a patient has had not therapeutic benefit from three administrations, I would very rarely continue the treatment. So, should esketamine be recommended for patients that are not exactly analogous to those included in the Janssen studies (i.e. patients who are more treatment resistant)? There is very strong precedent for NICE to make such a recommendation. The antidepressant vortioxetine was reviewed by NICE for the treatment of major depressive episodes in 2015 (TA367). The drug was recommended "…as an option for treating major depressive episodes in adults whose condition has responded inadequately to 2 antidepressants within the current episode". This was despite the Advisory Committee only reviewing evidence from one study where vortioxetine was trialed in patients who had failed a single antidepressant (Montgomery et al. 2014 Human Psychopharm 29:470-82). The argument was that SSRIs are much cheaper and so patients should be tried on a couple of these before being offered vortioxetine, despite a lack of evidence for efficacy in patients who have failed two treatments. It seems not an unreasonable extrapolation that if vortioxetine works in patients who have failed one antidepressant, then it is likely to work in patients who have failed two, albeit probably with a lower response and remission rate. I believe that a similar argument can be made with regards to esketamine, and I think that such an argument is important for NICE to make a recommendation that would be consonant with current clinical practice (see below).	

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5	Consultee (clinical expert)	Hamish McAllister-Williams	Cost effectiveness Modelling There seems to be great uncertainty with regards the economic modelling for esketamine, with the company arguing that the cost per QALY is in the order of £7,500, with the ERG coming up with figures in the order of £55-62,000. I am not a health economist, but I am not surprised by this discrepancy. The modelling is using so many estimates, not just due to lack of data regarding esketamine but also the lack of high quality data regarding the natural history and treatment of depression. I think such discrepancies would be evident in the review of any new treatment for depression. The ACD describes a number of issue and concerns regarding the health economic modelling. I am not sure that I agree with all of the points raised, but I shall focus on just one – the ERG's assumption of "no discontinuation by 2 years for reasons other than loss of efficacy" (section 3.19). The reasons for focusing on this one assumption is that a) it is the assumption with the most influence on the cost per QALY and b) it seems to me to be the hardest to justify. For the reasons described above, I suspect that in NHS clinical practice, response and remission rates with esketamine will be lower than seen in the trial data and used in the economic modelling. For those patients who do gain some benefit, there will be a massive spread with regards to the degree of improvement. Some will have minimal symptom improvement (not meeting criteria for response or remission), but still feel this is of significant benefit to their quality of life and hence want to continue treatment. Others will achieve the definition of remission (NB this does not necessarily mean being symptom free). There is evidence that patients with low enough levels of depressive symptoms to meet remission criteria can still experience significant psychosocial dysfunction (Demyttenaere et al. 2009 Prim Care Companion J Clin Psychiatry 11:307-15). Such patients may or may not want to continue treatment. So, whether a patient continues with treatment will only loosely correlate with degree of symptomatic improvement. All treatments carry some burden – even if this is simply remembering to take a table. Undergoing treatment with intranasal esketamine will carry a very significant burden. Patients will need to attend hospital for a couple of hours twice weekly for a few weeks, then weekly for a few more weeks and then possibly only every two weeks thereafter. These is no mean commitment, especially for patients with an illness characterised by anergia, amotivation and feelings of hopelessness. Taking esketamine or ketamine leads to dissociative symptoms. While some people use ketamine recreationally, my experience of using ketamine is that patients with depression are much more likely to experience the dissociation as aversive, rather than pleasurable. How long a patient takes any treatment for will depend on their perception of the balance between benefit and burden. I can't think of any clinical situation, certainly not in mental health, where all patients keep taking a treatment indefinitely despite responding to it. This is certainly the case with regards to experience of using IV ketamine. Some patients do continue taking it long term, but some choose to at least take a pause from treatment, even if they are	Comments noted. Section 3.25 and 3.26 of the updated ACD discuss these points in more detail.

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			responding. One published study of maintenance ketamine for TRD found that the reasons for stopping treatment were varied, including loss of efficacy, adverse effects, treatment burden and so on (Archer et al. 2018 J Clin Psychopharm 38:380-384). So, I think that there will be multiple reasons for stopping treatment other than simply lack of efficacy. Most of the patients stopping for lack of efficacy would do so very early on – probably earlier than modelled. However, some will drop out because of lack of efficacy periodically because of their perception of the degree of response not justifying the level of burden. On the other side of the coin, there are also likely to be patients who do really well with esketamine who just start questioning whether they need to keep having treatments. It is vey common for patients who have been well on treatments for months or years to question whether they need to keep taking them. We don't have evidence to guide us as to what might happen to patients who have gone into full remission for a prolonged period if they stop treatment. There is a small study that looked at patients discontinuing maintenance ketamine, and this found some patients remaining well for up to around 6 months (Diamond et al. 2014 J Psychopharmacol 28:536-44). Given this uncertainty, it would seem reasonable for clinicians to be provided with guidance as to how to manage such patients. For example, if patients go into full remission and this is sustained for say 9-12 months, it may be reasonable to consider at least pausing the treatment, possibly while exploring other management options. If there was a clear psychosocial precipitant to the episode of depression and this is now resolved and the patient is in remission, again it would not seem unreasonable to consider discontinuing treatment. In summary, there are so many reasons why a patient might discontinue treatment other than lack of efficacy, that it does not seem possible to justify this as being the only reason for discontinuing. As a result, I do not think the ERG's position on this point is defensible.	
6	Consultee (clinical expert)	Hamish McAllister-Williams	Summary Making recommendations regarding the use of esketamine for treatment resistant depression, when the generic evidence basis for treatments in this area is so poor, is extremely challenging. Economic modelling is fraught by the number of assumptions being made and how sensitive the model is to some of these. The Advisory Committee is therefore in an invidious position given this coupled with the enormous unmet need in this therapeutic area and the impact of treatment resistant depression on individuals, the health care economy and wider society. In my opinion it is important to consider all sources of evidence, including that from studies of ketamine. It is certainly the case that there is less comparator data for esketamine than would be ideal, but this is no different from any other medication, psychotherapy or neurostimulatory treatment currently in use. Similarly, there are issues around generalisability of the data though, in my opinion, these relate to the level of treatment resistance of the patients included in the esketamine studies, rather than the issue raised in the ACD. I think that it is essential to cautiously extrapolate from these studies to populations where the drug is more likely to be used in the UK. To my mind, there are two major issues of concern if esketamine is introduced into clinical	Comments noted. Decisions made by the appraisal committee on the cost effectiveness of a new technology must include judgements on the implications for healthcare programmes for other patient groups that may be displaced by the adoption of the new technology. It therefore needs to take in to account the uncertainty around the clinical and cost effectiveness.

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			practice. The first is to guard against 'doctor shopping'. There is some anecdotal evidence of this happening with regards to IV ketamine in the USA. The Royal College of Psychiatrists has strongly advocated to the MHRA that all patients receiving esketamine should be entered onto a national registry that can be used to ensure that they are not receiving treatment from multiple clinics. The second issue is with regards to cost. Whatever the economic modelling, the raw acquisition costs are significantly higher than most other current treatments. I think this issue can be addressed in a number of ways. Firstly, I would suggest that esketamine is only recommended for patients with TRD who have failed to respond to at least two conventional augmentation strategies or ECT. In reality, I think this is where clinicians would be thinking of using it in any case. Making this restriction would limit the number of people receiving esketamine. Secondly, I would suggest clear guidelines with regards to ongoing treatment. I think that this should include two elements – one that the patient must be showing demonstrable benefit for treatment to continue, with this regularly assessed, and the other that there should be a recommendation to at least pause treatment if there is a period of sustained remission. Thirdly, I would suggest using a register to collect long term outcome from patients. These data could then be used to refine the cost effectiveness modelling for a review of the recommendations.	Comment noted. 3.16 of the ACD has been updated to discuss this issue. Comment noted. The potential position in the treatment pathway for esketamine is discussed in section 3.4 of the revised SPC. Comment noted. 3.16 of the ACD has been updated to discuss this issue regarding a registry.
1	Consultee (commissioning expert)	Peter Pratt	NICE requested further information from NHS England regarding the feasibility of the company plan and also any longer term costs for setting this up when no ECT suites are available and other costs, including costs of setting up a registry and the controlled status of the drug. In Peter's initial expert statement, he mentioned that the costs of implementation would involve: • 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 The company have included nursing and monitoring costs but have said there will initially be no additional implementation costs because ECT suites can be turned into esketamine clinics at no cost and monitoring equipment/ equipment for medical complications borrowed using the same criteria. They also have stated they will provide additional training for post dose complications. I have not surveyed all mental health trusts to validate the company's view. The only way would be a detailed interrogation of all stakeholders within all mental health trusts to establish	Comments noted. The committee considered and acknowledged these points at the second committee meeting. With regard to the investment needed to implement use of esketamine, the committee concluded that there would need to be significant investment to use esketamine in the NHS, but considered that these costs could be difficult to quantify. See section 3.30 of the updated ACD.

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			whether or not this would be the case – or not & I am afraid I do not have the capacity to undertake that level of enquiry. However 1) It is entirely feasible that some trusts could turn their ECT suits into Esketamine administration and monitoring facilities – however I am not convinced that this will be the case for all/the majority of trusts. 2) If this drug receives a positive opinion from NICE - I do not think it reasonable to expect all patients to travel – perhaps large distances to an ECT suite. My expectation is that trusts would /should establish/convert/adapt their community mental health facilities to enable the safe administration and monitoring in such a way that minimises travel for patients 3) I am not aware that all mental health trusts have an ECT suite – if this is the case - some patients would have to travel further distances and/or additional costs associated with travel would need to be made available 4) I am not convinced that there will be sufficient space/capacity in all current ECT mental health trusts to accommodate the esketamine administration and monitoring – For example I suspect that the medicines storage facilities of current ECT suits would need upgrading to enable stocks of this schedule 2 controlled drug to be held/administered and post dose devices destroyed.	
2	Consultee (commissioning expert)	Peter Pratt	Other comments mentioned that a reclining chair and a quiet room is all that would be needed. 5) "a reclining chair and a quiet room is all that would be needed." I disagree, As I mentioned in my initial comments - This drug is a schedule 2 controlled drug – therefore there will need to be adequate staffing and governance processes established in order to ensure the Adequate storage, checking, transportation, disposal in relation to the controlled drug status of this drug. It is unlikely that there will be adequate storage, transport etc facilities in all mental health Trust ECT suits that will meet the approval of the Trust CD accountable officer. I appreciate Mental health Trust are able to establish safe and appropriate systems, but these will take time to implement. (e.g. they are able to arrange methadone (a schedule 2 controlled drug) supply and administration in community facilities) Adequate "medical" equipment to monitor and deal with the immediate management of any post dose medical complications will be required.– it is possible that such facilities may be available within some trusts existing ECT suits- however as mentioned previous this is unlikely to be the case for all MH trusts.	Comments noted. See section 3.30 of the updated ACD.
3	Consultee (commissioning expert)	Peter Pratt	6) I am not aware of the relationships between all mental health trusts and the supporting infrastructure that they use to perform ECT – It may be that there are contractual relationships between the Trust and anaesthetists/and /or acute general hospitals that would require review/ re-negotiation to enable the ECT facilities option to be considered – However as mentioned previously I am not aware that this will be a viable option for all mental health trusts – and if this drug receives a positive opinion - it would be wrong to limit the use/availability to those trusts that have an ECT suit that can be "easily" converted to allow esketamine administration and post dose monitoring.	Comments noted. See above and section 3.30 of the updated ACD.

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			I am sorry, but I am not able to offer any guidance on the detailed "costing" associated with establishing an appropriate infrastructure – There are just to many variables to consider – not least the starting point/existing trust infrastructure arrangements. The key issue from my perspective is that Trusts are allowed adequate time to review their existing estate and infrastructure so that a fit for purpose solutions can be developed. There is considerable heterogeneity within and across mental health trusts which means a ONE size will not fit all – There may be some trusts with relatively small geographical footprints and good transport infrastructure where the ECT suit option may be viable – however there are many other MH trusts including those which may span 5 or more CCG's and large – possibly rural geographical locations where an ECT adaptation would be impractical/unviable. In some Trusts for example those who do not operate an In-house pharmacy service there may be additional complexities to negotiate the mechanisms of supply through their third-party pharmacy dispensing and supply arrangement. I appreciate that the company may be offering some sort of direct delivery system – (which may avoid VAT) but it will be for each trust CD accountable officer and chief pharmacist to be assured of the governance arrangements before this could be adopted by the Trust. I have seen some of the feedback to the consultation which indicates the infrastructure to support the adoption of the technology is "not a problem" – however I am not convinced that the respondents have considered all the factors – transport, storage, governance etc in addition to the direct clinical factors for someone to support administration and monitor post dose (and intervene in the event of a medical emergency) – To ensure the safe use of this drug it will require joined up agreements that cross medical, nursing, pharmacy ,estates, transport, governance, CD accountable officer as well as finance and contracting departments. I think the comment "a reclining chair and a quiet room is all that would be needed" highlights this narrow perspective. On the national registry front – I know that there is some strong support for this from some people. I also know that they are pressing the MHRA to host such a registry and it may be that the people pushing for this have a more detailed plan for the practicalities of implementing such a system. At one level I can understand that there may be concern about patients traveling from place to place simply to get access to the drug (or increased doses) – However if the drug has little/no liability for misuse (as I thought the company had previously mentioned? – then the concerns about patients hoping from one place to another would be unfounded – on the other hand If there is a possibility of misuse (my personal view is that there is) then such a register would only work if it was directly tied to the supply of the drug – and my guess is that could only be facilitated on a national basis (including Scotland & Wales) if the register was held by the company and the drug was supplied against a named patient/unique hospital number. The company would have to have a real time live system which restricted supply to those patients who have been "registered" onto the system.	Comment noted. The committee discussed the consultation comments about registries and safety considerations at the second committee meeting. See section 3.15 and 3.30 of the updated ACD.

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			Other options could be that individuals offer to Host such a system on a commercial basis and/or, manage the whole supply arrangements linked to a major research program to follow use against outcomes Overall I think the only viable option if a registration system is felt to be necessary that this would have to be managed in real time through a single source of supply – to both the NHS and the private/independent sector. I can see the merits of such a system – but I am unsure if this should be a requirement. Another option would be to require all prescribing to be uploaded against a patients summary care record – and local governance processes established to verify any existing prescribing – however I am not convinced that the current spine/summary care records would be workable mechanism as a register for all patients in all circumstances. I hope this is helpful and I am sorry I cannot be more definitive about infrastructure costs, but please do get in touch if you require any further information/discussion	
4	Consultee (commissioning expert)	Peter Pratt	Please see below a list of ECT suits on the RCPsych website As far as I can tell this suggests that all of the following 54 mental health trusts have at least one ECT suite 2gether NHS Foundation trust Avon & Wiltshire Mental Health Partnership NHS Trust Barnet, Enfield & Haringey Mental Health Trust Berkshire Healthcare NHS Foundation Trust Birmingham & Solihull Mental Health NHS Foundation Trust Black Country Partnership NHS Foundation Trust Cambridgeshire & Peterborough NHS Foundation Trust Camden & Islington NHS Foundation Trust Central & North West London NHS Foundation Trust Cheshire & Wirral Partnership NHS Foundation Trust Cornwall Partnership NHS Foundation Trust Coventry & Warwickshire Partnership NHS Trust Derbyshire Healthcare NHS Foundation Trust Devon Partnership NHS Trust Dorset Healthcare University NHS Foundation Trust Dudley & Walsall Mental Health Partnership NHS Trust East London Foundation NHS Trust East Sussex Healthcare NHS Trust Essex Partnership University NHS Foundation Trust Greater Manchester Mental Health NHS Foundation Trust Hertfordshire Partnership University NHS Foundation Trust	Comments noted. The committee acknowledged that if esketaimine is recommended for routine use in the NHS, it will take and resource for it to become part of clinical practice. See section 3.31 of the updated ACD.

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			Humber Teaching NHS Foundation Trust Isle of Wight NHS Trust Kent & Medway NHS & Social Care Partnership Trust Lancashire Care NHS Foundation Trust Leeds & York Partnership NHS Foundation Trust Leicestershire Partnership NHS Trust Lincolnshire Partnership NHS Foundation Trust Livewell Southwest Mersey Care NHS Foundation Trust Midlands & East England Midlands Partnership NHS Foundation Trust Norfolk & Suffolk NHS Foundation Trust North East London Foundation Trust North Staffordshire Combined Healthcare NHS Trust North West Boroughs Healthcare NHS Foundation Trust Northamptonshire Healthcare NHS Foundation Trust Northumberland, Tyne & Wear NHS Foundation Trust Nottinghamshire Healthcare NHS Foundation Trust Oxford Health NHS Foundation Trust Oxleas NHS Foundation Trust Pennine Care NHS Foundation Trust Rotherham Doncaster & South Humber NHS Foundation Trust Sheffield Health & Social Care NHS Foundation Trust Somerset Partnership NHS Foundation Trust South London and Maudsley NHS Foundation Trust South West London & St George's Mental Health NHS Trust South West Yorkshire Partnership NHS Foundation Trust Southern Health NHS Foundation Trust Surrey & Borders Partnership NHS Foundation Trust Sussex Partnership NHS Foundation Trust Tees, Esk & Wear Valleys NHS Foundation Trust West London NHS Trust Worcestershire Health & Care NHS Trust However I think my points about the logistics of patient travel , upgrading of the facility , transport (of medication), storage of medication and cross trust /third party suppliers are still valid – and whilst negotiating ypdrage and use of EXT facilities may be straight forward for some trusts I do not think this will be the case for all trust – as you will see from the list of ECT suits – some of these facilities appear to be housed in a different trust (see https://www.rcpsych.ac.uk/improving-care/ccqi/quality-networks-accreditation/ectas/ectas-membersm)	

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			Schedule 2 controlled drugs will require a controlled drug storage cabinet of sufficient size to hold the esketamine nasal spray (s) – There will be additional governance arrangements over the siting of these cupboards depending on whether or not the "room" is staffed 24 hours a day – or not. A secure audit trail for the transportation and receipt/ storage of controlled drugs will need to be established - This will be more straightforward where the trust in-house pharmacy supplies the medication and the Trust owns the building where the ECT suit is sited.	
1	Consultee (professional group)	Royal College of Psychiatrists	'***When considering the efficacy….as these have not been compared directly.*** We would ask that NICE further consider the robustness of the evidence that they draw upon for the efficacy of alternative adjunctive treatments (such as antipsychotic drugs or lithium) in treatment of resistant depression. We believe that it might not be as strong as reflected in the document and would in particular refer NICE to the meta-analysis reported by Strawbridge et al 2019.	Comments noted. The committee noted the uncertainties with the clinical evidence that inform the economic model and transitions between health states (see sections 3.7 to 3.13 and section 3.21). It also noted the clinical trial evidence did not include people with recent suicidal behaviour, which limits the generalisability of the results (see section 3.14)
2	Consultee (professional group)	Royal College of Psychiatrists	***The NICE Committee comments that the features of the considered studies with esketamine are such that the findings may not be applicable to the wider patient population seen in UK clinical practice (e.g. the exclusion of patients with comorbid substance use disorders and high risk of suicide).*** We would ask that NICE reconsider their reliance on this as a rationale for their decision. If this approach were to be widely adopted, most NICE guidelines in patients with mental illness would potentially have little 'generalisability' to current practice. For example, NICE could make very few recommendations on psychological therapies (as patients with such problems are usually excluded from treatment studies). Furthermore, the evidence for esketamine indicates a beneficial effect on reducing suicidal thoughts, suggesting its potential application in clinical practice for patients who have intense and risky suicidal thoughts.'	Comments noted. Comments received at consultation confirmed that uncertainty introduced by excluding these patients is common in trials in this disease area. See section 3.14 of the updated ACD.
3	Consultee (professional group)	Royal College of Psychiatrists	***The NICE Committee contends that findings relating to IV ketamine cannot be used to provide a background for considering the findings relating to esketamine.*** We would ask that NICE revisit this decision not to take account of findings relating to IV ketamine as ketamine and esketamine are pharmacologically the same and have similar pharmacokinetics. In other NICE deliberations, findings relating to citalopram were considered relevant when considering enantiomer escitalopram so think some consistency in approach is needed or a clearer rationale as to why it is not appropriate in this case.	Comments noted. The committee was aware of the issue raised about using evidence for intravenous ketamine from the technical report.. The company submission stated that, "esketamine is the S-enantiomer and more potent form of ketamine". It is also delivered via a

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				different pathway (nasal vs. IV). This could mean any results from such studies might not be generalisable to esketamine. NICE seeks relevant evidence from several sources. The company submits the principal evidence. The evidence review group (ERG), an external academic organisation independent of NICE, produces a review of the evidence submission (see sections 3.3.8 and 3.3.9 of the NICE TA Process Guide). Consultees provide information and selected clinical experts, NHS commissioning experts and patient experts also give evidence (see section 3.4 of the process guide).
4	Consultee (professional group)	Royal College of Psychiatrists	**Page 3 – ECT as a comparator** The comparison with electroconvulsive therapy (ECT) does not seem appropriate. ECT is largely restricted to depressed patients with profound psychomotor retardation or psychotic features, whereas such patients were **excluded** from studies with esketamine. ECT is a specialist and costly procedure, requiring an anaesthetic, muscle relaxant, an anaesthetist, a recovery suite with nursing staff, second opinions (etc.) and carries a negative stigma. The patient group likely to receive esketamine is markedly different to the patient group which currently receives ECT. As a result of previous NICE TA59, ECT is reserved for the most severe and intractable cases of depression. In addition, with increasing concerns among the public and media, the numbers receiving ECT has dropped significantly. The main clinical barrier to use of ECT is fear of inducing cognitive side-effects. We are not aware of evidence that exists for ESKNS that shows cognitive or other enduring side effects. It would not be possible to conduct a long term RCT comparing ECT with esketamine with follow-up over more than a year in the UK. The numbers coming for ECT are simply too small. Of the 1600 annual ECT cases, half are on a section and half are over 65 years. Even in the highly unlikely event that an adequately powered trial was funded and recruited to completion, the results would not be generalizable to routine practice because such a high proportion of potential participants would refuse to be randomized to ECT.	Comments noted. The committee concluded that the results comparing esketamine with some of the relevant comparators listed in the scope, such as combination or augmentation therapy and ECT, were highly uncertain. So, it considered only the results from the trials. These compared esketamine with oral antidepressants with placebo with oral antidepressants, even though these will not be the only comparators in clinical practice. See section 3.5 of the updated ACD.
5	Consultee (professional	Royal College of Psychiatrists	'***The available evidence did not include psychotherapy'***	Comment noted. The committee concluded that psychological

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	group)		This is correct but the evidence for psychological interventions in treatment-resistant depression (TRD) is too limited to make reliable comparisons: and only one low quality study (of cognitive behaviour therapy) employed the robust definition of TRD of failure to respond to two antidepressant medicines. The same point relating to the absence of comparisons to psychotherapy could also be levelled at studies in TRD with lithium or antipsychotic medicines, but these are considered to be valid comparators: some consistency in approach or a clearer explanation to the different approaches is needed.	therapies are an adjunctive therapy and a relevant part of the treatment pathway, but that its effect would likely be variable depending on the treatment population and severity of depressive symptoms (see section 3.4) of the updated ACD. But it considered the effect of combining psychological therapies with esketamine treatment to be an unresolvable uncertainty with the evidence available. See section 3.6 of the updated ACD.
6	Consultee (professional group)	Royal College of Psychiatrists	***The NICE Committee preferred that consideration of outcome in the cost-effectiveness analysis was placed within the context of a twenty-year period***. We were not convinced by the arguments for this. Yes, depression tends to recur and can run a protracted course, but on the individual level there is much variability in clinical outcomes, and prediction of outcome in a given patient is notoriously inaccurate. It seems excessive to withhold a potentially effective treatment from a currently severely ill patient, on the supposition that treatment might have limited cost-effectiveness over twenty years: the same could be said for many other treatments in clinical practice. We recommend that the NICE Committee request the sponsoring company to provide additional data, based on differing acquisition costs of esketamine, to allow a more nuanced consideration of potential cost-effectiveness.	Comments noted. The committee noted uncertainty about long-term outcomes (see section 3.17) but concluded that a shorter time horizon may not solve this issue. See section 3.19 of the updated ACD.
7	Consultee (professional group)	Royal College of Psychiatrists	***The Committee have quite correctly stated that 'the effectiveness of current treatments for treatment-resistant depression is limited and that there is a need for new treatment options for this condition'***. However, the Committee appears reluctant to accept that a reduction in suicide risk is appropriate when considering potential interventions for patients with TRD: but patients, relatives and clinicians would undoubtedly welcome treatments with such a property. TRD is associated with suicide and effective treatment of depression reduces risk of suicide. This suggests the Committee is making decisions based on inappropriate comparisons to other interventions with reliance on contestable economic models, when considering a potentially life-saving medical treatment with a novel mechanism of action.	Comments noted. The committee concluded that the treatment burden, combined with the safety concerns (see section 3.16), would mean esketamine is used later in the treatment pathway. This would be after 1 or 2 augmentation therapies have been trialled. See also section 3.4 of the updated ACD.
1	Commentator (joint response)	All Party Parliamentary	We have come together to express our support for the findings and conclusions of the NICE appraisal committee concerning the clinical and cost effectiveness of esketamine for treatment resistant depression. We are highly supportive of recommendation 1.1 that esketamine is not	Comments noted. The committee discussed consultation comments at the committee meeting in August 2020. An updated ACD has been

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		Group Prescribed Drug Dependence*, Dr Anne Guy (Secretariat Coordinator) Association for Family Therapy and Systemic Practice in the UK, Dr Reenee Singh (CEO) Association of Clinical Psychologists UK, Che Rosebert (Director External Communications) Association for Psychoanalytic Psychotherapy in the NHS (APP): Andrew Soutter, Chair British Psychoanalytic Council, Gary Fereday (CEO) British Psychotherapy Foundation, Mike Owen (CEO) Council for Evidenced Based Psychiatry, National Counselling Society, Psychotherapy	recommended. We fully support NICE in taking an evidence based approach to the appraisal of esketamine, in contrast to the approach taken by the FDA and MHRA. A number of stakeholders have expressed their concerns directly to the MHRA and documented the lack of evidence of efficacy for esketamine. Unfortunately the lack of evidence of efficacy appears not to have impacted on the MHRA decision. As you are aware, numerous stakeholders came together recently concerning the NICE guideline on Recognition and Management of Depression in Adults and expressed a number of methodological concerns about the draft guideline. One of these was the lack of analysis of long-term outcomes. Stakeholders were advised in December 2019 that NICE will now be looking for long-term outcome data and will take these into account in the next draft of the guideline. We would urge you to continue to apply this and other methodological principles raised by stakeholders in relation to all new as well as existing treatments for depression and to ensure that long-term efficacy as well as long-term avoidance of harm remains the paramount consideration in any decision formulated by NICE.	issued.

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		Foundation, Tavistock Relations, Tavistock & Portman NHS Foundation Trust, University of Essex, Wish.		
1	Consultee (patient group)	SANE	With regard to evidence, not all treatment comparators were included in the appraisal, in our view limiting the confidence that can be placed in the decision on the clinical effectiveness of esketamine in treatment-resistant depression.	The committee concluded that the results comparing esketamine with some of the relevant comparators listed in the scope, such as combination or augmentation therapy and ECT, were highly uncertain. So, it considered only the results from the trials. These compared esketamine with oral antidepressants with placebo with oral antidepressants, even though these will not be the only comparators in clinical practice. Se section 3.5 of the updated ACD.
2	Consultee (patient group)	SANE	With regard to costs, we are particularly concerned that the episodic nature of treatment-resistant depression has not been adequately taken into account by the committee in their preference for a 20-year time horizon for the calculation of quality-adjusted life years and treatment costs. SANE knows from our 25-year contact with callers to our helpline and those who use our call-back service that depression can be highly episodic, with a good success rate when patients are compliant with treatment. Relapse can happen, but there can be long periods when a patient is 'in remission', and some can recover from depression with the right treatments and clinical support. It cannot be assumed that patients with treatment-resistant depression will need to stay on medication, including esketamine, for such a long period. The consultation document states: "The clinical expert explained that it is difficult to determine when an episode of depression begins or ends and characterized the 'waxing and waning' nature of the condition." The decision to regard treatment-resistant depression as "a chronic condition requiring a longer time horizon" is described as having been made "on balance". In view of the high variability in individual experience and the scale of difference between 5 and 20 years in calculating value and costs, we believe that work should be done to arrive at more reliable estimates of treatment value and costs for esketamine over a patient's lifetime.	Comments noted. The committee agreed that the company model does not reflect the course of the disease. It concluded that the model does not reflect the episodic nature of the condition. This is discussed in more detail in section 3.17 of the updated ACD.
3	Consultee (patient group)	SANE	Uncertainty about the investment needed to adopt esketamine treatment in the NHS is another factor inhibiting an accurate judgement on the possible costs of its introduction. We would like to see a closer examination of the range of options for adopting eskatamine as a treatment, in	Comments noted. This is further discussed in t section 3.30 of the updated ACD.

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			order to provide a fuller assessment of the range of possible additional service requirements, taking account of the range of differing local circumstances, such as the availability of an ECT suite.	
4	Consultee (patient group)	SANE	There are currently believed to be around 2.7 million people in the UK with treatment-resistant depression (when using the NICE definition of those who have not responded to two or more anti-depressants). As SANE stated in our submission to the committee, those living with treatment-resistant depression - both patients and carers - are impacted heavily in most aspects 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.	Comments noted. Patient experts were invited back to the second committee meeting to share their knowledge and experience with the committee. See sections 3.1 and 3.2 of the updated ACD.
5	Consultee (patient group)	SANE	People with depression have to rely on medications that are 30 years old. Although these drugs can be life-saving for many people, they can have unpleasant side-effects and do not work for everyone. Esketamine is the first new compound that works in a fundamentally different way from other medications and, compared with other anti-depressants which can take as much as six to eight weeks to take full effect, can have an effect within 24 to 48 hours of being administered, potentially saving patients weeks or months of uncertainty. In our view this makes it important that a more robust view is formed on the clinical and cost-effectiveness of eskatamine. We consider it premature to disallow this innovative treatment to those for whom other treatments have proved ineffective, without a more comprehensive evidence base and a more positive view of the cost-benefiit ratio.	Comments noted. The committee took into account the unmet need for effective treatment options and the innovative nature of esketamine. But, based on the committee's most plausible assumptions, the costs and benefits of esketamine were very uncertain. See 3.35 of the updated ACD for more detail.
6	Consultee (patient group)	SANE	In the light of patient and clinical expert evidence, the appraisal committee concluded that treatment-resistant depression has a negative effect, including on families and carers, and "acknowledged that the effectiveness of current treatments for treatment-resistant depression is limited and that there is an unmet need for new treatment options for the condition." In the press release announcing the decision, Meindert Boysen, the director of the centre for health technology evaluation at NICE said: "Our independent committee very much recognizes the impact treatment-resistant depression has on people, their families and carers, the clear need for effective treatment options, and the priority of addressing mental health challenges for the NHS." We hope the appraisal committee will examine further the basis of its decision and take these observations as its watchword in doing so.	Comments noted. The ACD has been updated to reflect discussion of the comments received at consultation. The committee took into account the unmet need for effective treatment options and the innovative nature of esketamine. But, based on the committee's most plausible assumptions, the costs and benefits of esketamine were very uncertain.
1	Commentator (web comments)	Member of public	after 2 years for reasons other than lack of efficacy Clinical experience with esketamine and ketamine suggests that many people do stop the treatment after entering stable remission. Experience with other treatments is similar. In particular, whilst we will often suggest long term treatment with antidepressant medication to reduce the risk of relapse, we often suggest the add-on medication is the first to be reduced after stable remission. By way of example, we followed up a group of NHS patients we had treated with very severe TRD. We found that in long term follow up (1-7 years, median 3 years) patients with TRD generally maintained their improvements seen at the end of acute treatment, and indeed on average improved further, whilst at the same time 43% of patients were able to reduce the number of medications they were taking compared to the end of acute treatment. So improvement in TRD is often maintained whilst reducing medication. (Wooderson SC, Fekadu A, Markopoulou K, Rane LJ, Poon L, Juruena MF, Strawbridge R, Cleare AJ (2014) Long-term symptomatic and functional outcome following an intensive	Comments noted. The ACD has been substantially updated to reflect the committee consideration of the comments received at consultation. Please see the update ACD.

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			inpatient multidisciplinary intervention for treatment-resistant affective disorders. Journal of Affective Disorders, 166, 334-342.) Has all of the relevant evidence been taken into account? I have listed in the comments where I think some additional evidence in terms of the long term treatment of TRD could be taken into account. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? I have listed in the comments reasons I believe that some of the committee's assumptions are flawed. Are the recommendations sound and a suitable basis for guidance to the NHS? I think this may represent a lost opportunity for the NHS to give some of its most disabled patients, who are already suffering from disparities in care, access to a novel treatment option. Comment on Esketamine is unlikely to be cost effective for treatment-resistant depression It seems inconceivable that 1:1 nursing would be needed. Established clinics I have seen work on far lower ratios. Comment on the company did not provide evidence comparing esketamine with all relevant comparators virtually none of the available treatments for treatment resistant depression (TRD) have been compared in this way. The first line treatments recommended in guidelines such as the British Association for Psychopharmaology and the Maudsley Prescribing Guidelines (eg Lithium, quetiapine and aripiprazole) do not have good evidence of efficacy against one another - but all are better than placebo when added to an antidepressant, which is why clinicians use them. This should not mean that none of these should be available to clinicians to treat a clearly sever and disabling condition such as TRD. Comment on the effect of psychological therapy in addition to drug treatments is not clear Exactly the same lack of evidence applies to the other first line treatments for TRD mentioned above. We know that ideally all patients with TRD should have both medication and a psychological therapy. I cannot see how this is relevant as to whether esketamine should be one of the medications used in TRD. Comment on it is not appropriate to include an effect of esketamine on mortality Our long term follow up of NHS patients with TRD shows clearly that entering remission is associated with reduced all cause mortality during long term follow up. (Fekadu A, Wooderson S, Rane L, Markopoulou K, Poon L, Cleare AJ (2012) Prediction of longer-term outcome of treatment-resistant depression in tertiary care. British Journal of Psychiatry, 201, 369-375.)	

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			If patients treated with esketamine are more likely to enter remission, extrapolating this (NHS) data would suggest that mortality is likely to be lower. Comment on Esketamine is not recommended As a clinician specialising in TRD, this is disappointing, and I do feel that several of the assumptions leading to this conclusion may be incorrect. I of course support that the treatment must be cost effective. Notwithstanding this, I would just like to say that if some of the requirements mentioned (need to study the additional effects of CBT, need to compare to other add-on treatments rather than to placebo, need to assume indefinite usage of the drug) are applied, then this will provide a powerful disincentive to industry in making further investments in developing new treatments. Many companies have already pulled out of the area, which is inherently a challenging field. Esketamine has a novel mechanism of action, in a field that has not seen such developments for many decades. Our patients have a potentially treatable condition, are already subject to a disparity of resources, and I fear that we will merely exacerbate this if we do not evaluate new treatments in a less draconian fashion.	
1	Commentator (web comments)	Member of public	General Comment: "1. The appraisal committee. We are surprised that members of this appraisal committee chosen by NICE have little or no professional experience, including usual pathways of care, of prescribing this treatment. In fact, the SmPC states that “the decision to prescribe Spravato should be determined by a psychiatrist”. We acknowledge that that the principles of evidence-based medicine mean such a committee ought to be able to make decisions based purely on RCTs, it must be an almost impossible job when you do not have day-to-day practical knowledge and clinical experience of the type of people we are trying to help. Treatment options in TRD: The committee needs to consider the options for clinicians when faced with someone with TRD. The definition of treatment-resistant depression as used by the FDA and DSM-V is a neat classification but is a little misleading. In practice UK clinicians would not classify someone as TRD until they had received probably at least 3 different antidepressants, and probably more. Thus, we think the committee may be being misled into thinking esketamine will become a much earlier treatment than it actually will be in real life. Hence we urge the committee to reconsider its position statement. 2: 3.4 (p7): “The committee heard from other clinical experts who noted that ECT should also be a comparator because the processes involved in administering esketamine are similar to those for ECT.” The comparison with ECT is difficult to comprehend because it does not reflect clinical practice and does not quite match reality. ECT differs from esketamine in most respects. ECT requires a qualified anaesthetist present throughout, specific equipment (to buy and maintain), a team of clinicians, and a custom-built ECT suite using several rooms (reception, ECT room and recovery; to which service users often need to travel), injection and resuscitation equipment. ECT has many contraindications, a different mode of action and, as “electric shock treatment“, creates a degree of fear amongst potential patients. It has had a bad press over the years.	Comments noted. The ACD has been substantially updated to reflect the committee consideration of the comments received at consultation. Please see the update ACD.

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			We envisage that esketamine nasal spray will need a single HCP (to welcome, supervise and be available during recovery to measure BP and assess when the person is safe to leave), a quiet room, and a sphygmomanometer. A quiet room for an hour or two for the recovery period would not need to be custom built or permanently equipped but will need to be carefully chosen, as would any clinical setting. 3: 3.12 (p14) "The company assumed that people would not stop taking oral antidepressants for any reason other than lack of response. But it assumed that people would stop esketamine treatment for other reasons, in line with the criteria in the SPC and additional discontinuation guidance provided by the company". The assumption that people will only stop esketamine due to lack of effect is unrealistic. Esketamine may be an on-going treatment for some, involving a day, a visit to a clinic (possibly many miles away, especially in the many rural areas), the need for an accompanying person or taxis, a treatment that is rather more than just popping a pill, and a significant routine. People might think about trying without esketamine as soon as they have recovered sufficiently from their acute symptoms, especially if they know there is an option to restart should symptoms return. 4. p3 "Electroconvulsive therapy can be used if oral treatments do not work. " This is true but it is important to understand the context in real clinical practice. In clinical practice, ECT tends to be offered to patients who are more clinically unwell; they frequently are unable to function normally, for example are unable to go to work and may even have stopped eating and drinking. ECT can indeed be used in some people but many people decline this old and crude treatment for personal reasons, it has many contraindications and relapse is common even with continued treatment. 5. p3 "Drug treatment can also be combined with psychological therapy." Indeed it can, but again this may not be effective. People may be too depressed to be able to take the strategies on board or into practice. Furthermore, the actual evidence for psychological therapies in TRD is minimal. 6. p3 Clinical trials suggest that esketamine with an oral antidepressant may be more effective at relieving the symptoms of depression than placebo and an oral antidepressant. But how much benefit it provides over other oral antidepressants with adjunctive therapy or electroconvulsive therapy is unclear because these treatments have not been compared directly. This is true but we already know the outcomes from sequential treatments in TRD from the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study. This was the largest independent RCT study carried out on remission from depression, over 6 years using real-world patients. Stage 1: A first line therapy (citalopram) was tried to the optimum dose (mean 42mg/d, remission using QIDS = 37%). Non-remitters then went to: Stage 2: A switch (patient choice) to venlafaxine, bupropion, sertraline or CBT (Cognitive	

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			Behavioural Therapy) or augmentation with bupropion, buspirone or CBT (overall remission using QIDS 31%). Non-remitters (who would now be considered treatment-resistant) then went to: Stage 3: A switch (patient choice) to mirtazapine (remission 12%), nortriptyline (remission 20%), or augmentation with lithium (remission 16%) or triiodothyronine (remission 24%). CBT (overall remission using QIDS 14%) Non-remitters then went to stage 4: Stage 4: A switch (patient choice) to tranylcypromine (remission 7%), or venlafaxine plus mirtazapine (remission 14%). (overall remission using QIDS 13%) Whilst not a direct comparison with esketamine this does give the background to response rates in TRD. It is true the therapies you list can be used but the group of people with TRD will almost certainly have tried many other treatments in the past, with STAR*D showing that there is a considerable drop-off in remission rates after the second stage as people get more desperate for relief from their symptoms. We feel that the place in therapy for esketamine might be aligned to stage 4 of STAR*D. Clinical trials to date with esketamine have shown some efficacy but there is currently insufficient data to extrapolate into clinical practice. The current draft document outlines the various unknowns, but the proposed position statement by NICE might limit opportunities for organisations to trial the use of esketamine to help answer them. Furthermore, it might limit availability to this medication for those who may genuinely benefit from it. To put this into context, alternatives such as deep brain or vagal nerve stimulation are rarely available even via specialist mental health NHS Trusts. We suggest that NICE might reconsider this position statement and allow organisations, especially specialist mental health services to trial use of esketamine in patients who they deem to be suitable. Such patient would receive a thorough assessment and data about efficacy and side-effects would be collected. This real-life experience and data collected could then guide future wider roll-out for use in clinical practice. STAR*D references include Trivedi et al, Am J Psychiatry 2006;163:28-40, (n=727, RCT, 14/52, Rush et al, N Engl J Med 2006, 354, 1231-42. 7.p3 “Also, the available evidence did not include psychological therapies.” The criticism of the lack of comparison with psychotherapy is unfair and inappropriate as no other therapy had been asked for this before. A recommendation that this carried out would, however, be welcomed. Perhaps this is based on the NICE depression guidelines which are now 11 years old and well out-of-date. It is relevant to highlight that the evidence base for any psychotherapy in TRD is almost entirely lacking. 8. p3 “There is uncertainty about the effect of stopping esketamine treatment. It is unclear if any improvements in symptoms will be maintained after a course of treatment and whether this will improve someone’s quality of life. The costs of repeated courses of treatment with esketamine are unknown, as are the costs of providing the clinic service for esketamine.”	

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			This is true but it is something we will find out over time as we gain more clinical experience with using esketamine. 9: 3.17 (p18) The committee acknowledged that introducing esketamine would probably represent a change in managing people with treatment-resistant depression in the NHS. We welcome this statement. We think that offering this treatment to the right, but fairly small population of desperately ill people, who have often exhausted most treatment options, might help obtain more experience and data about efficacy and tolerability to guide future practice. 10: 3.17 (p18) "The NHS commissioning expert advised that esketamine would require a significant investment to become part of NHS clinical practice." We do not recognise this. On a practical basis esketamine intranasal administration would need: 1. A quiet room for 60-120 minutes, capable of being made reasonably dark 2. A reclining chair to allow the head to tip back to 45o 3. A blood pressure monitoring machine An HCP available to welcome the person, supervise the administration, carry out the blood pressure check at 40 minutes, be available to reassure or help the person, and assess them after one or two hours. There will be a need for some staff commitment but this does not seem to us to be a significant investment, particularly if you care to compare this with other new technologies. 11: 3.17 (p18) The committee heard that adopting esketamine would result in displacement of other mental health treatments because of its cost. We feel this that there is insufficient evidence about whether this will be the case; it is too early day. We do not recommend widespread use initially, but instead trial in a small number of patients as described above. Other treatments could be replaced if the evidence that emerges shows that this treatment is more effective in TRD than comparators. If some treatments are displaced because another treatment is more effective then that is to be welcomed not cautioned about. If this did not happen in medicine then treatments would never improve. We would like to point out the human side of this devastating and life-threatening condition and this statement from NICE could deny some people a potentially life-saving medicine . We appreciate that cost has to be a consideration but this will always be an issue for Trusts, who will have to limit its use. We would welcome comparative and robust trials, with proper placebo groups, full randomisation and blinding, and for adequate duration, properly costed but this should not delay any approval of esketamine. 12. We would welcome a full economic review, but not at the expense of delaying a positive decision. It should include: Changes in bed days from use of oral treatments, esketamine and ECT	

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			Societal costs of TRD (being off work, poor productivity, family costs, carers, stress)"	
1	Commentator (web comments)	Member of public	I was unaware that esketimine was already being used by the NHS? Your recommendations state, ""...In addition there is uncertainty about the effect of stopping esketamine treatment."" How do you propose to learn more about the effect of stopping esketimine treatment given that the clinical trials were short in duration?"	Comments noted. The ACD has been substantially updated to reflect the committee consideration of the comments received at consultation. Please see the update ACD.
1	Commentator (web comments)	Member of public	Has all of the relevant evidence been taken into account? no, the costs of delivery ECT were not considered. this is the current next step in treatment beyond oral pharmacotherapy - as per CG90. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? given the nature of this new treatment (method of administration, CD status) it is not surprising that there are minimal trials and none in the UK, as there are so many barriers in the UK to conducting such trials. however non UK data should not necessarily be considered to be not applicable to the UK. the evidence for esketmine is building on that for the racemic mixture of the UK licensed IV ketamine - which does not appear to have been considered. Are the recommendations sound and a suitable basis for guidance to the NHS? the recommendations have not considered a sub-population for whom this treatment may be suitable. General comment Technically true, but the manner in which this is written implies that ECT would be considered after an antidepressant and a "Second drug". which is not true and not in line with the NICE guidance on ECT. phrasing should be altered to show that ECT is only considered as a last resort when both psychological treatments have been explored and several drug treatment with antidepressants alone, and more than one augmentation strategy attempted, and all failed. CG90 " consider it if their depression has not responded to multiple drug treatments and psychological treatment." Otherwise it makes ECT sound like the third step option that should be taken, which contradicts CG90. Comment on price please state what you mean here by "course" - single treatment? 6 months treatment of twice weekly? please also state whether you mean solely the purchase cost of the product (I assume not), or whether the "course" includes the cost of delivery - similar to the cost of delivering ECT.	Comments noted. The ACD has been substantially updated to reflect the committee consideration of the comments received at consultation. Please see the update ACD.

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			Comment on current clinical practice includes several different types of treatments this is a very important point, and given the expert nature of this NICE committee there should be consideration of this implications, and not simply go along with the application for "TRD" as per the license. The committee should be more nuanced to see sub-populations within this where there is need. similarly the ECT NICE guidelines do not use this term, but expect it to only be used: "Consider ECT for acute treatment of severe depression that is life-threatening and when a rapid response is required, or when other treatments have failed. " Comment on the company did not provide evidence comparing esketamine with all relevant comparators ECT could not be a direct comparator. even as per CG90 that should only be used for life threatening and very severe depression, which is not the same category of patient as this is licensed for. however the committee should consider the potential place of esketamine within the pathway, and many expert clinicians consider this to be a step before ECT - which has proven efficacy, and very speedy efficacy, that make the (considerable) risks of a general anaesthetic twice weekly for about 6 weeks, worth the risk. to Comment on Safety must be taken into account when administering and monitoring esketamine A registry of treated patients would seem a very good idea for this and many other reasons. e.g. gathering real life data to track patient response in real life scenarios. Comment on there are substantial limitations to the structure of the company's model Agreed, given the nature of the illness, and the that all other treatments for depression are used repeatedly when episodes relapse, and oral antidepressants are even used continuously in a subpopulation to keep people in remission. Comment on A range of ICERs is needed to estimate resource use costs associated with administering esketamine firstly it need to specify "Mental health" nurse, or RMN. secondly why are you advocating band 5? Why this grade? in an NHS NH Ward 1:1 or "Close" observations would usually be undertaken by a band 3 MH Health Care Assistant (HCA) under the supervision of a registered MH nurse (RMN). I would expect the same to occur here. Comment on Esketamine is not recommended Agree, given that there is no working definition for TRD. however i think NICE should be able to use their expertise to recommend the subset of patients to whom this new treatment may be of benefit - acknowledging the uncertainly around some aspects of the data. Esketamine may be of benefit to a sub-population. i.e. a tighter criteria for treatment than "TRD". eg offer to those who would otherwise be considered for ECT : CG90: "1.10.4.2 ....consider it	

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			[ECT] if their depression has not responded to multiple drug treatments and psychological treatment." a mandatory register should be required of treated patients (as is required for other treatments e.g. clozapine) to collect real life treatment data and outcomes from the UK setting. Esketamine is likely to be worthwhile for the population who would otherwise receive ECT, given the associated risks of twice weekly general anaesthetic and costs of the setting and the staff required (anaesthetist and ECT expert) to deliver the treatment and monitor immediately afterwards (MH nursing staff for 1:1 "close" observations).	
1	Commentator (web comments)	Member of public	Has all of the relevant evidence been taken into account? We acknowledge that NICE's decision not to recommend esketamine is based on limited data, including information provided by the manufacturer. However, Drug Science kindly requests that NICE consider a wider range of evidence, not just from RCTs. This is particularly important for clinical conditions such as treatment resistant depression and for medication such as esketamine, where the requirement for RCTs limits the ability to review more 'real world data'. The current draft document outlines numerous 'unknowns'; however as the Technology Appraisal does not provide 'research recommendations' this will further limit opportunities for providers to create cases for trialling the use of esketamine to help answer them. Perhaps most importantly, NICE's proposed position will further limit availability to this medication for those who may genuinely benefit and for a clinical condition for which an individual will have very limited (if any) alternative treatment options. To put this into context, alternatives such as deep brain or vagal nerve stimulation are rarely available even via specialist mental health NHS Trusts. It would perhaps be more useful if the current position could be amended to be more supportive of organisations (specialist mental health services) being able to trial the use of esketamine and therefore allow a greater opportunity for it's use in clinical practice to be better assessed before reaching such a conclusive decision. Are the recommendations sound and a suitable basis for guidance to the NHS? We acknowledge that NICE's decision not to recommend esketamine is based on limited data, including information provided by the manufacturer. However, Drug Science kindly requests that NICE consider a wider range of evidence, not just from RCTs. This is particularly important for clinical conditions such as treatment resistant depression and for medication such as esketamine, where the requirement for RCTs limits the ability to review more 'real world data'. The current draft document outlines numerous 'unknowns'; however as the Technology Appraisal does not provide 'research recommendations' this will further limit opportunities for providers to create cases for trialling the use of esketamine to help answer them. Perhaps most importantly, NICE's proposed position will further limit availability to this medication for those who may genuinely benefit and for a clinical condition for which an individual will have very limited (if any) alternative treatment options. To put this into context, alternatives such as deep brain or vagal nerve stimulation are rarely available even via specialist mental health NHS Trusts. It would perhaps be more useful if the current position could be amended to be more supportive of organisations (specialist mental health services) being able to trial the use of esketamine and therefore allow a greater opportunity for it's use in	Comments noted. The ACD has been substantially updated to reflect the committee consideration of the comments received at consultation. Please see the update ACD.

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			clinical practice to be better assessed before reaching such a conclusive decision.	
1	Commentator (web comments)	Member of public	Has all of the relevant evidence been taken into account? Yes Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Can only comment on clinical - yes. Are the recommendations sound and a suitable basis for guidance to the NHS? Absolutely not. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Discrimination against people with severe resistant depression by denying them an effective treatment General comment In my trust it took about 6 weeks. We use oral, IM, SC and intranasal. It really isn't that difficult. It is implied here and elsewhere that ECT is an alternative to esketamine. ECT requires a GA and is not without risk. ECT causes significant memory disturbance. Treatment in the acute phase is usually twice weekly for 4-6 weeks. Each treatment requires a GA given by an anaesthetist. ECT often has to be given longer term. These factors make ECT rather less preferable to esketamine. Patients would certainly think so. This is true of any treatment, including ECT. The NICE assessment of vortioxetine (recommended as third line Tx) does not mention this aspect. This is true of any treatment. There is no mention of the costs of the nominated alternative - ECT I think everyone agrees that resistant depression is that that does respond at all to two antidepressants in the current episode. The favourable decision on vortioxetine was based on one comparator trial. I can't believe anyone said this or believed it to be true. Esketamine is given by nasal spray under supervision and then the patient is allowed home shortly afterwards. ECT involves	Comments noted. The ACD has been substantially updated to reflect the committee consideration of the comments received at consultation. Please see the update ACD.

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			giving the patient an intravenous anaesthetic and a muscle relaxant and then causing them to have a grand mal seizure. The patient is often drowsy and confused for several hours afterwards. Not mentioned in the vortioxetine decision The 'current' NICE Guideline is 11 years old. Out of date by any standards. It is difficult to know what to say here. Is this standard applied to all medicines evaluated by NICE - that the trials need to include some English people? How are 'participants from England' known to differ from, say, France? Comment on It is not appropriate to adjust the efficacy estimates of the placebo arm in the trials This is true but the reasoning is sound - there is evidence to suggest that the number of visits enhances placebo response. General comment We have dozens of Schedule 2 Controlled Drugs that are much more liable to misuse, and for which no registry is required. Examples include methadone, diamorphine and fentanyl. A registry for esketamine would be pointless because it would have no effect on diversion (for which there is limited scope because esketamine is administered on site). This must therefore apply to all treatments including ECT. The implication is that ECT needs to be considered a 20 year Tx. This is not sensible. ECT suites are ideal for esketamine administration. There are already in situ. Surely not allowing its use anywhere in the UK would represent an 'equalities consideration'. This misses the point completely. TRD is a condition that is currently very poorly treated and one for which different treatments are sorely needed. Either it is efficacious or it isn't. If you agree it is then it should be recommended, at the very least, as an alternative to ECT. The patient could be asked to decide - a nasal spray or a grand mal seizure under GA?	
1	Commentator (web comments)	Member of public	Has all of the relevant evidence been taken into account? No. 1. Esktamine does not take weeks to work, which improves it's cost effectiveness. 2. Esktamine is not physically addictive, with no risk of seizures or long term brain change. 3. You have not addressed use of Esktamine for patients for whom SSRI's are contraindicated. 4. Esktamine does not have to be tapered off, which improves it's cost effectiveness. 5. Esktamine does not have as many interaction problem to worry about compared to classical anti-depressants.	Comments noted. The ACD has been substantially updated to reflect the committee consideration of the comments received at consultation. Please see the update ACD.

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			6. Esktamine as s-isomer ketamine, is already freely available and being used off-label in all towns and cities and many villages in the UK. The long approx. 58 year history of clinical use of this drug has taught people of it's benefits, but they are being forced to buy impure and potentially dangerous forms of the drug from untaxed criminal gangs. 7. Esktamine has no risk of suicidal ideation in the initial period of clinical use. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Categorically no. How can the costs be £163 for 28mg of s-isomer ketamine, when 1000mg of 100% pure s-isomer ketamine can be bought by anyone for approximately £20-30, or as low as £6 if bought in bulk. The figures given are hugely inflated compared to what the public knows pure esketamine can be produced for. Let's be clear here. Pure s-isomer ketamine hydrochloride has been used off-label for treating depression for as long as 58 years. The costs you are quoting are complete fantasies, and it seems, an invented excuse for not proceeding with this important evolution of our approach to depression. Are the recommendations sound and a suitable basis for guidance to the NHS? No, they are not, see previous answers as for why. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? No	
1	Commentator (web comments)	Member of public	Has all of the relevant evidence been taken into account? Yes Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes Are the recommendations sound and a suitable basis for guidance to the NHS? Yes General comments We (12 clinicians/researchers, including 8 psychiatrists) are writing in support of the NICE recommendation not to approve esketamine for use in the NHS. We have grave concerns about the use of a dissociative anaesthetic agent, and known street drug of abuse, being marketed as a treatment for people with complex emotional difficulties, which are often based on social adversities.	Comments noted. The ACD has been substantially updated to reflect the committee consideration of the comments received at consultation. Please see the update ACD.

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			As you are aware, there have been no trials of the efficacy of esketamine in the medium or long term. The majority of the studies of this drug (almost entirely conducted by the drug company attempting to license the drug, Janssen) are only four weeks in duration. Most of these studies find no benefit for esketamine versus placebo, and multiple adverse effects. The one positive efficacy study finds a difference between esketamine and placebo that is small and not clinically meaningful. Esketamine is the only antidepressant that has been approved by the FDA with only one successful efficacy trial. The longest study to date is a 16 week trial using a discontinuation design, which is almost certain to confound withdrawal effects with relapse of depression. This trial design also increases the likelihood of patients breaking blind in the drug condition. As noted in the FDA statistical review, "perception of their treatment assignment may have been influenced by acute side effects (dissociation, sedation, etc.). FDA's exploratory analysis suggested that changes in these side effects were associated with time relapse." Notably, there were six deaths in the esketamine studies, including three suicides, all in the esketamine group, with none in those assigned to placebo. Although these deaths were dismissed as unrelated by Janssen we do not believe that this worrying signal of danger should be ignored. These suicides may well be consistent with a severe withdrawal reaction from the medication, known to occur in other medications such as antidepressants and opiates. Short term apparent benefits of using esketamine are unsurprising, given its similarities to drugs of abuse, and no basis for approving a drug. One could achieve similar results, short term euphoria or dissociation, with various other street drugs. Indeed, we are as shocked by this recent development as we would have been had es-cocaine been submitted for approval. If esketamine is approved for public use in the UK, there is no impediment to doctors prescribing this drug for weeks, months and beyond, which is precisely what we now see occurring in the US since FDA approval. We are aware of the public statements made by Janssen spokespersons about the NICE recommendation, parts of which seem to border on bullying. We trust that an evidence-based approach will be taken to your decision and, therefore, that no approval fir NHS use will be granted until multiple, successful, independent trials (i.e. not industry sponsored) of at least a year, and preferably longer, have been conducted. Yours Sincerely Dr John Read Professor of Clinical Psychology, University of East London. Dr Pat Bracken Consultant Psychiatrist, Ireland Dr James Davies Medical Anthropology, University of Roehampton Dr Peter J Gordon,	

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			Retired Consultant Psychiatrist for Older Adults Dr Rex Haigh Consultant Psychiatrist in Medical Psychotherapy, Berkshire NHS Dr Peter Kinderman Professor of Clinical Psychology, University of Liverpool Dr Irving Kirsch Associate Director, Program in Placebo Studies, Harvard Medical School; Professor Emeritus, Psychology: University of Connecticut (USA) & University of Hull (UK) Dr Hugh Middleton Psychiatrist, University of Nottingham Dr Clive Sherlock Psychiatrist, Oxford Dr Derek Summerfield Consultant Psychiatrist; Hon. Senior Clinical Lecturer - Institute of Psychiatry, Psychology & Neuroscience, King's College, London Dr Philip Thomas Formerly Professor of Philosophy, Diversity & Mental Health, University of Central Lancashire; Formerly Consultant Psychiatrist Dr Sami Timimi Consultant Child and Adolescent Psychiatrist, UK	
1	Commentator (web comments)	Member of public	Has all of the relevant evidence been taken into account? Evidence of deaths in the esketamine group were not fully appraised in this document in its assessment of safety (see comment below for further information). Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? The clinical effectiveness of the drug was over-estimated by use of dichotomised data (response and remission rates) that exaggerate the small differences between placebo and esketamine on the primary MADRS measure. The efficacy trials only ran for 4 weeks with little relevance to treatment of depression. The discontinuation trial was flawed in design (withdrawal effects were likely to confound measures of relapse). See comment below for further information. Are the recommendations sound and a suitable basis for guidance to the NHS?	Comments noted. The ACD has been substantially updated to reflect the committee consideration of the comments received at consultation. Please see the update ACD.

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			The final recommendation is sound and a suitable basis for guidance for the NHS, but critical evaluation of the studies presented should be more rigorous to prevent lowering of the threshold for what constitutes a safe, and effective treatment option. General comment Division of Psychiatry, Maple House, 149, Tottenham Court rd, London W1T 7NF 12th February 2020 Dear NICE committee for esketamine Re: Approval of esketamine for treating treatment-resistant depression As psychiatric doctors with extensive experience of treating people diagnosed with depression we welcome NICE's draft guidance that esketamine should not be recommended for the treatment of treatment-resistant depression, given that the evidence of benefits over harms is not clear. We think the committee was wise to carefully evaluate the claims made by the manufacturer rather than uncritically accepting inflated claims of efficacy and minimisation of safety issues by the manufacturer. We are writing to highlight a number of points that were not emphasised by the committee when coming to its decision that further demonstrate both the lack of evidence for effectiveness of the drug, its danger and the lack of long-term studies. In the appraisal document, it was stated: "Clinical trials suggest that esketamine with an oral antidepressant may be more effective at relieving the symptoms of depression than placebo and an oral antidepressant." (page 3 of 23). The thinking underlying this summary is outlined in Section 3.6 We suggest this conclusion is not warranted by the data. Janssen performed three efficacy trials that lasted for 28 days. Two of these trials showed no significant difference between esketamine and placebo 1,2. These trials were appraised in the NICE document in terms of response and remission rates. However, this does not take into account the raw data, which was measured using the MADRS. Methodological experts are unanimous in advising the use of primary data (the MADRS) rather than dichotomised versions of the data (response or remission rates) because dichotomised data tends to inflate the differences between groups especially when the differences between groups are small on the primary data 3. When the data are appraised based on their primary measures evidence for superiority of esketamine over placebo is not clinically significant. The single positive study found a	

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			difference of 4 points on the MADRS favouring esketamine over placebo 4. The MADRS scale goes from 0 to 60; average score for patients at baseline was 37. The response to placebo treatment (a nasal spray with embittering agent) was a 17-point reduction on the MADRS score. The response to esketamine was 21 points. A 7 to 9 point reduction on the MADRS has been found to correspond to a clinically noticeable ("minimally improved") change on the Clinical Global Impressions scale (CGI) 5; "much improved" requires a reduction of 16-17 points. A 4-point difference therefore corresponds to less than "minimal" change, and was less than one quarter the size of the placebo response, suggesting doubtful clinical relevance 6. Furthermore, participants would have been unblinded by the noticeable psychoactive effects of esketamine (dissociation was reported by the majority of participants); expectation effects might therefore inflate the apparent difference between placebo and esketamine. Moreover, the time period of 28 days has little bearing on the treatment for depression, as treatment for depression is often continued for many months or years. Based on both the sub-clinical effects produced by the drug and the irrelevant time period for which these drugs were trialled it seems premature to conclude that esketamine is more effective than placebo for treating depression. The problematic discontinuation design study (SUSTAIN 1) used by Janssen as a second 'positive' trial is discussed in the below section. It is further stated that "There is uncertainty about the effect of stopping esketamine treatment" (Page 3). To the contrary it is widely recognised that ketamine is an addictive drug and withdrawal symptoms are experienced when stopping ketamine in recreational use. Stopping regular use causes a withdrawal syndrome characterised by anxiety, dysphoria, shaking, sweating and palpitations, and craving the drug 7,8. Frequent users report using the drug compulsively until supplies run out 7. The addictive nature of ketamine has been linked by some authors to its activation of opioid receptors 7,9, amongst numerous receptor targets 10. There is no reason to think that esketamine will have any different effects than ketamine – indeed (S)-ketamine, or esketamine, is twice as potent an anaesthetic agent as ketamine 10, meaning its addictive properties might be even more marked. Notably, withdrawal effects were not reported in the discontinuation trial design (SUSTAIN-1) used by Janssen in its second 'positive' trial. Although the study reports suggests there was no evidence of a withdrawal syndrome using the Physician Withdrawal Checklist, scores for the different groups are not reported, and it is not clear how items in the checklist such as 'insomnia', 'anxiety-nervousness', 'dysphoric mood-depression', 'difficulty concentrating, remembering', 'fatigue', 'lack of appetite' were distinguished from almost identical items in the MADRS (e.g. MADRS items 'apparent sadness', 'reported sadness', 'inner tension' 'reduced sleep', 'reduced appetite', 'concentration difficulties', 'lassitude'). Consequently, it is possible that some of the 'relapses' detected were in fact due to mis-classification of withdrawal effects	

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			As half (48.7%) of relapses occurred in the first four weeks following esketamine cessation, the time most likely for withdrawal effects to occur, and as the relapse rate in the placebo group became “closer to esketamine with each week” as highlighted by the FDA, confounding of ‘relapse’ by withdrawal seems likely 2. Further evidence of a withdrawal effect is also suggested by the marked ‘relapse prevention’ effect of a drug with minimal antidepressant effects in the short term. This pattern is similar to what might be seen in a trial of a benzodiazepine for anxiety: modest effects in the short-term, but marked ‘relapse prevention’ effects on discontinuation, if confounding by withdrawal effects are ignored. The FDA also highlighted another problem with this study design: “functional unblinding”2, as in the acute efficacy studies. The absence of esketamine’s psychoactive effects would be noticed by participants randomised to placebo and consequent negative expectations would tend to increase their chance of relapse 2. Higher dissociation scores while on treatment were correlated with shorter time to relapse, consistent with this hypothesis. Importantly, the FDA also raised the concern that the positive results of the study were driven by a single site where there was 100% relapse rate in the placebo arm 2. It has been demonstrated that if this outlier site is excluded there is no difference between esketamine and placebo (the p value changes from 0.012 to 0.48)6, leading to the conclusion that the findings are “not robust”. It is unclear if any improvements in symptoms will be maintained after a course of treatment and whether this will improve someone’s quality of life. Safety considerations: It is not appropriate to include an effect of esketamine on mortality (p.15) In this section, it was outlined how Janssen attempted to estimate an effect of esketamine on mortality, suggesting that esketamine would improve overall mortality. It is of concern that Janssen presented this conjectural analysis, based on questionable assumptions, while downplaying the fact that there were six deaths in the esketamine arm and none in the placebo arm of the Phase 2 and Phase 3 clinical trials 2, out of about 1200 patients enrolled in these studies. We suggest that these deaths are highly relevant and should be regarded as a signal of potential serious harm. Three of these deaths were suicides. The three suicides occurred in participants 4, 12 and 20 days after the last dose of esketamine 9. Janssen attributed these deaths to ‘the severity of the patients’ underlying illness’ 2. However, two of the patients who died by suicide showed no previous signs of suicidal ideas during the study, either at entry to the study or at the last visit (data was not available for the third patient) 2. The FDA accepted Janssen’s assessment that the suicides were not drug-related” 2.	

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			However, others have argued that these cases fit with a pattern of a severe withdrawal reaction, consistent with other reports of suicide from ketamine 11,12, and are significant enough in number to constitute a worrying signal 9. An increase in depression and suicidality was also observed during esketamine treatment. In one 4-week trial 6 patients in the esketamine group became more depressed, compared to only one on placebo; 4 patients expressed new onset suicidal ideas in the esketamine group, compared to only one on placebo 2. The drug will be marketed with a 'black box' warning including a risk of suicidal ideas and behaviour 13, but it is not clear that this measure is stringent enough. In summary, the evidence for the benefits of esketamine is not strong, and there is a lack of long-term studies that can establish the benefits and harms of long-term use, even though we know that drug treatments for depression tend to be taken on a long-term basis by many users. We urge NICE to maintain its current position on the suitability of this drug for use for depression in the NHS and require higher quality longer term studies that carefully evaluate all aspects of its safety and efficacy before considering recommending this drug in the future. Yours sincerely, Professor Joanna Moncrieff Dr Mark Horowitz 1 Fedgchin M, Trivedi M, Daly EJ, et al. Efficacy and Safety of Fixed-Dose Esketamine Nasal Spray Combined With a New Oral Antidepressant in Treatment-Resistant Depression: Results of a Randomized, Double-Blind, Active-Controlled Study (TRANSFORM-1). Int J Neuropsychopharmacol 2019; 40: 1–30. 2 FDA. Efficacy, safety, and risk-benefit profile of New Drug Application (NDA) 211243, esketamine 28 mg single-use nasal spray device, submitted by Janssen Pharmaceuticals, Inc., for the treatment of treatment-resistant depression. 2019; : 1–135. 3 Kirsch I, Moncrieff J. Clinical trials and the response rate illusion. Contemp Clin Trials 2007; 28: 348–51. 4 Popova V, Daly EJ, Trivedi M, et al. Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: A randomized double-blind active-controlled study. Am J Psychiatry 2019; 176: 428–38. 5 Leucht S, Fennema H, Engel RR, Kaspers-Janssen M, Lepping P, Szegedi A. What does the MADRS mean? Equipercentile linking with the CGI using a company database of mirtazapine studies. J Affect Disord 2017; 210: 287–93. 6 Turner EH. Comment Esketamine for treatment-resistant depression : seven concerns about efficacy and FDA approval. The Lancet Psychiatry 2019; : 1–2. 7 Morgan CJA, Curran HV. Ketamine use: A review. Addiction 2012; 107: 27–38.	

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			8 Chen WY, Huang MC, Lin SK. Gender differences in subjective discontinuation symptoms associated with ketamine use. Subst Abus Treat Prev Policy 2014; 9: 1–7. 9 Schatzberg AF. A word to the wise about intranasal esketamine. Am J Psychiatry 2019; 176: 422–4. 10 Zanos P, Moaddel R, Morris PJ, et al. Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. Pharmacol Rev 2018; 70: 621–60. 11 Schifano F, Corkery J, Oyefeso A, Tonia T, Ghodse AH. Trapped in the 'K-hole': Overview of Deaths Associated With Ketamine Misuse in the UK (1993-2006). J Clin Psychopharmacol 2008; 28. 12 Cheng JYK, Chan DTW, Mok VKK. An epidemiological study on alcohol/drugs related fatal traffic crash cases of deceased drivers in Hong Kong between 1996 and 2000. Forensic Sci Int 2005; 153: 196–201. 13 Cristea I, Naudet F. US Food and Drug Administration approval of esketamine and brexanolone. The Lancet Psychiatry 2019; : 1–3.	
1	Commentator (web comments)	Member of public	Has all of the relevant evidence been taken into account? No I don't believe so as demonstrated in the comments Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? No I don't believe so as demonstrated in the comments Are the recommendations sound and a suitable basis for guidance to the NHS? No I don't believe so as demonstrated in the comments General Comments: Comment on Recommendations This recommendation is not based on a reasonable interpretation of the clinical and cost effectiveness of the evidence; and the provisional recommendations are not a sound and a suitable basis for guidance to the NHS? In the Star-D study at tier 3 which is failure of 2 anti-depressants the rate of remission with a new strategy varied: mirtazapine (8%), nortriptyline (12%), or Lithium (13%), all of which might be common strategies in the UK. The rate of remission with Esketamine at tier 3 (failure of 2 anti-depressants) is 50%. That is an absolute risk difference of at least 37% between treatments or on the face of it esketamine is 3 times as effective at tier 3 that other anti-depressants or augmentation strategies. Whilst they have not been directly compared this is the best comparative evidence that is available. I wonder how far the demand for a comparison with ECT is clinically valid. The two interventions are entirely different treatments. Whilst effective, a large number of people will not be willing to have ECT because of stigma or concern about it. Also, resources needed for	Comments noted. The ACD has been substantially updated to reflect the committee consideration of the comments received at consultation. Please see the update ACD.

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			ECT, involve significant medical (including anaesthetist) and nursing time, stringent governance procedures including second opinions and safeguards. It doesn't seem correct to be equating the two treatments in forming a judgement. The clinical reality is that ECT is only really offered to people when they have failed multiple treatments, probably because of its acceptability. Comment on Current clinical practice includes several different types of treatments On what basis did the committee conclude this.? Trainee psychiatrists from core training year 1 learn the widely accepted definition described above. It doesn't seem correct to say that there is no widely accepted definition Whilst there are differing academic and research based ideas about how this should be defined the definition within the licence is the widely accepted clinical definition, at least in the UK. It should be noted that the depression guidance is now over a decade old and it is debateable whether that guidance can be relied upon as a reasonable reference point for treatment and care pathways. Comment on The company did not provide evidence comparing esketamine with all relevant comparators I have made comments about the STAR-D study above, which could be used as a comparison (though not perfect) the evidence to suggest combining anti-depressants in comparison to a single anti-depressant is poor Comment on The effect of psychological therapy in addition to drug treatments is not clear I find this puzzling. As far as I am aware there are 2 trials of psychotherapy for treatment resistant depression, one of which is limited by its methodology. The level of skill to provide that type of therapy (in a manualised form) is not widespread in the NHS in my clinical experience. Also in my experience most people with TRD either do not want psychotherapy or are not able to use it because of the cognitive symptoms (e.g. poor attention, concentration, poor memory) that the illness causes. The NICE guidelines for depression are more than 10 years out of date. This would not seem a reasonable evidence based comparison for Esketamine. Comment on the evidence for esketamine is limited in its generalisability to the NHS This is a common exclusion in mental health trials This would suggest the panel wanted esketamine to be assessed in people with a greater degree of resistance-is that the case, if this is an issue? This would not usually be the population who were in the Esketamine trials and would to my mind have a greater degree of	

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			resistance. This would seem a very high bar to set for a trial. I would be interested to know whether similar bars have been set for assessment of psychotherapy or other treatments for depression or infact other treatments in mental health. It is difficult to understand how the committee came to this conclusion Comment on Safety must be taken into account when administering and monitoring esketamine I believe this would be outside the licence if it is substance misuse the clinical expert was referring to Comment on a longer time horizon for the economic model is preferred Whilst depression can have a waxing and waning nature is the clinical expert referring to the 10-15% of people with depression who follow a "chronic course". In my clinical experience (and from the perspective of having been a Consultant Psychiatrist for 15 years) it is not difficult to understand when an episode of depression has ended. Clinicians have to do this day in day out to decide how long to advise patients to continue to take anti-depressants for. Comment on There are substantial limitations to the structure of the company's model Though within that future episode the patient would have needed to try 2 previous anti-depressants for the Esketamine to be given within its licence Comment on it is not appropriate to include an effect of esketamine on mortality This text and thinking is difficult to follow. The committee appear to think that Esketamine could impact on suicide, but then say because people with acute suicidal risk were excluded this cannot be the case. Suicidal risk is not a static phenomenon, and lack of suicidal risk with intent in the last 6 months would not exclude people with severe suicidal behaviour previously; and previous suicidal behaviour at any time increases future suicidal risk. Purely from a clinical view the committee's lack of acceptance that treatment of TRD now could reduce suicide risk in the future (even if people with acute suicidal intent are excluded from a current sample) is of concern. In doing so the committee appear to be refuting evidence indicating that a] TRD is associated with suicidal thinking and suicide; and b] that treating TRD will reduce the risk of completed suicide (or at least risk), a basic tenet of mental health care. Comment on significant investment will be needed to adopt esketamine into clinical practice Should we assume that new mental health treatments cannot be sanctioned because they might displace other mental health treatments or need new investment? How does this fit with the continuous announcements of more money towards mental health treatment. The underlying assumption here is that if new treatments for TRD are available we cannot benefit from them, because they will need investment. This is of concern and I doubt very much a similar argument would be made in other therapeutic areas.	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Yes it would and that would be a very good thing, given the difficulties that this population currently face in access to effective treatment. Comment on 5 Appraisal committee members and NICE project team There was no Psychiatrist on the NICE committee-why is this? There seemed to be a representative of a very wide range of other healthcare professionals, but just not Psychiatrists. To my mind this shows and will sit as odd to many people in the field and the wider community. The committee has made a decision without professionals in the room who are actually faced with the condition day in day out. This is a lost opportunity for the committee and doesn't seem correct.	
1	Commentator (web comments)	Member of public	General comment Whilst I appreciate the comments about lack of evidence about the effect of TRD on carers and families, and how esketamine could help them, I can't help but feel that this is being passed over and is bordering on being insulting to them. The sustained impact on family and carers, whilst living with and trying to keep patients with TRD safe, is phenomenal and can continue for years. This can impact on their health, their lives and employment, and affects them socioeconomically. There are limited options available for patients with TRD and often patients are offered numerous versions and combinations of oral antidepressants that are purely based around the monoamine hypothesis. The chances of these working following several attempts are low. Often antidepressant's are augmented with antipsychotics that bring numerous additional side effects and therefore unpalatable to patients. Access to psychological treatments are sadly lacking. ECT can be effective for patients, but tend to be held back for more poorly patients and have many side effects related, such as memory impact. In short, by not recommending esketamine, you are limiting options for patients that are already sadly lacking and withholding a new, potentially, life changing treatment. Work on treating depression via the Glutamate Hypothesis is novel and could bring hope to patients who have sadly been neglected by new innovative ways of treating them.	Comments noted. The ACD has been substantially updated to reflect the committee consideration of the comments received at consultation. Please see the update ACD.

Document processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments

Esketamine nasal spray for treatment resistant depression (ID1414)

Janssen response to NICE appraisal consultation determination (ACD)

18th February 2020

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
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
Name of commentator person completing form:	Tom Denee

Overview

Janssen welcomes the opportunity to comment on the preliminary recommendation detailed in the appraisal consultation document (ACD). We are disappointed the Appraisal Committee's preliminary decision is that esketamine nasal spray (ESK-NS) is not recommended for patients with treatment resistant depression (TRD) in the NHS; however, we are committed to working with NICE in order to address all the Committee's key concerns outlined in the ACD.

ESK-NS is the first new antidepressant in 30 years with a novel mechanism of action, demonstrating additional benefit over the standard of care and providing a much-needed new treatment option for patients with TRD in the NHS. ESK-NS has a substantial evidence base, including five completed phase 3 trials and several additional complementary research projects.

The main points outlined in this response to the ACD are as follows:

- We wish to address the committee's considerations on the previous approach to economic modelling including retreatment. We have included a retreatment scenario but suggest that this should be considered only a scenario for decision making, given the significant uncertainties associated with the retreatment model and its inconsistency with previous NICE decision making in NICE TA 367 *[vortioxetine for treating major depressive disorder]* and NICE CG90 *(Depression in adults: recognition and management)*. It is also inconsistent with the advice previously received from NICE PRIMA on the economic model. Regardless, under this scenario, the cost-effectiveness of ESK-NS improves compared to not including retreatment, ranging from being dominant to an ICER of £8,348 (see Table 1 below, Section 1).

- We provide a revised company base case which does not include retreatment, and which addresses some of the Committee's other concerns raised in the ACD.

    - The revised company base case includes the committee's preferred assumptions on excluding treatment adjustment effect, removing excess mortality for the Major Depressive Episode (MDE) health state, and extending the time horizon to 20 years, although available data do not support these assumptions.
    - The revised company base case maintains ESK-NS treatment discontinuation for non-efficacy reasons for patients in recovery, based upon market research provided during the technical engagement step. This is the single most important determinant of the cost-effectiveness of ESK-NS. As such, we have further explained how the model currently considers the reduction in health-related quality of life (HRQoL) following discontinuation for non-efficacy reasons, and provided additional scenarios exploring the impact of discontinuing ESK-NS.
    - The revised base case also continues to include carer disutility for the MDE health state. We note that the Committee acknowledged the impact on carers of people with TRD in the ACD and that the ERG and NICE technical team concluded that the evidence provided was of good quality. The evidence is also significantly stronger than compared to previous appraisals in both mental and physical health conditions where carer utilities have been included.

Although we do not agree on the Committee's preferred assumptions for excluding treatment adjustment effect, removing excess mortality for the Major Depressive Episode (MDE) health state, and extending the time horizon to 20 years, we have incorporated these Committee preferred assumptions into our revised base case (see Section 2 for the revised company base case). Based on

the previously provided evidence, we suggest that these three assumptions should be considered conservative. The revised base case company ICERs demonstrate that, even with all the Committee's other preferred conservative assumptions, apart from treatment discontinuation in recovery, ESK-NS remains cost effective option for TRD with an ICER range of between £10,790 - £12,26 per QALY.

Finally, the Committee have not considered all the evidence regarding comparators, as Janssen previously provided evidence comparing ESK-NS to all relevant comparators in the scope, including combination, augmentation and ECT. ESK-NS was cost-effective compared to all those comparators. Consideration of the combined effect of psychological and pharmacological treatment is also inconsistent with previous NICE decision making and this should not be considered further.

A detailed comment for each of these key issues is provided below.

Section 1. Incorporating retreatment and a longer time horizon brings significant uncertainty to the analysis due to the lack of data to inform retreatment assumptions

ACD Section 3.11, p14: "The committee would like to see a new model with a longer time horizon that allows for repeat treatment."

We acknowledge the Committee had concerns around the time horizon for the model, and specifically the lack of function to include retreatment in the model. We firmly believe, however, that by using a longer time horizon and including assumptions to inform retreatment brings additional uncertainty due to the lack of data to inform the analysis. Including retreatment is also inconsistent with previous NICE decision making in NICE TA 367 *[vortioxetine for treating major depressive episodes*] and NICE CG 90 *[Depression in adults: recognition and management],* where it has not been considered. Regardless, as this was explicitly requested by the Committee in the ACD, we have provided scenarios to show the impact of retreatment on the cost-effectiveness of ESK-NS. The scenarios show that retreatment improves the cost-effectiveness of ESK-NS.

Limitations of the retreatment model

As noted above, incorporating retreatment increases uncertainty in the analysis, which we believe is insufficient to offset the proposed benefits highlighted by the Committee. The retreatment option is incorporated in the previously submitted Markov model, which comes with a number of restrictions inherent with a Markov model. Further discussion of the limitations are below:

- In the retreatment model scenario, retreatment is only for patients treated with ESK-NS + OAD who had previously been in stable remission for at least 9 months, then discontinued ESK-NS, and subsequently experienced a recurrence while in the recovery health state.
- The positioning and sequencing of ESK-NS during retreatment of the new episode is uncertain and based on assumptions, since there are many factors that affecting whether a patient will be retreated with ESK-NS in NHS clinical practice, of which access to health care professionals is key.
- The data to inform the effectiveness of ESK-NS during retreatment are based on the assumptions taken from initial treatment of the first episode with ESK-NS.
- It is assumed similar health states (MDE, remission and recovery (but no response)) also apply to ESK-NS in retreatment of the new episode.
- The data to inform relapse and recurrence for ESK-NS are based upon assumptions taken from the initial treatment with ESK-NS.
- The dosage and frequency of ESK-NS (and hence treatment costs) are based upon initial ESK-NS treatment.
- The safety profile of ESK-NS retreatment is assumed to be consistent with initial treatment with ESK-NS.
- The proposed approach assumes that every episode of depression after an episode of TRD will be treatment-resistant and patients will receive ESK-NS retreatment in the absence of data.

Overall, the retreatment scenario significantly increases the uncertainty in the cost-effectiveness of ESK-NS, especially when these assumptions are projected over a 20-year time horizon. This was also recognised by NICE PRIMA, who stated the following about extending the time horizon beyond 5 years:

[redacted]

In addition, retreatment has not been considered previously in the other NICE decision making (CG 90 and TA367) in the disease area. We are concerned that the Committee are considering retreatment in the context of this appraisal only, as existing NICE guidance and guidelines have not made specific recommendation on the topic previously. This leads to inconsistency with the NICE guidance and guidelines where there are no recommendations given for retreatment for any other intervention. The above limitations show that the retreatment model should not be considered more than a scenario and should be interpreted with caution.

New scenarios incorporating retreatment improves the cost effectiveness of ESK-NS

Given the Committee's explicit request and despite our reservations highlighted above, we have developed a model which attempts to incorporate retreatment, presented below. It is important to note that based upon clinical opinion, retreatment will only be used in clinical practice if the active treatment was successful before, and the patient is no longer on that treatment, i.e. patients who have been in stable remission for at least 9 months and have discontinued ESK-NS will be eligible for ESK-NS retreatment. This is aligned to the modelling approach that we have taken in this exploratory scenario. These scenarios show that including repeat courses of ESK-NS treatment for patients who discontinue in recovery but subsequently have a recurrence improves the cost-effectiveness of ESK-NS. Even if assuming all the preferred NICE assumptions (excluding treatment discontinuation assumptions since patients have to discontinue before being eligible for retreatment), retreatment ranges in results from ESK-NS dominance, to ICERs of £8,348.

Table 1: Retreatment scenarios

	Revised company base case post ACD (see Section 2)*	Scenario with NICE preferred assumptions (excluding treatment discontinuation using market research data, see Section 4.2)
Original base case model (see Table 2), no retreatment	£10,790 - £12,264	£13,821 – £17,326
Retreatment model (using TRANSFORM-2 remission data)	£ 4,348 - £ 5,518	£ 5,568 - £ 8,348
Retreatment model (assuming 100% retreatment efficacy)	-£1,087 (Dominant) to £-174 (Dominant)	-£ 1,392 (Dominant) - £778

*range from 1:6 to 1:2 nurse: patient ratio

The analysis shows that including retreatment improves the cost effectiveness of ESK-NS. This is because recurrence (transition from recovery to the active MDE health state), increases the proportion of patients subsequently entering remission compared to the original model. In the original model, patients who had a recurrence moved to a subsequent treatment rather than being re-treated with ESK-NS. The increased proportion of patients entering remission reflects the additional clinical benefit of ESK-NS retreatment compared to the subsequent therapies, as well as

best supportive care treatment efficacy. Keeping more patients in the remission health state significantly reduces the disease management costs, which offsets the additional drug and administration costs of ESK-NS re-treatment.

Full assumptions used for the scenarios including retreatment are provided in Appendix A.

Conclusion: Given the uncertainty associated with the retreatment model, the existing company model is the most robust to base decision making on for ESK-NS

Due to the complex nature of depression, the frequency of recurrence, how these recurrent episodes manifest and are subsequently treated, and consistency with previous decision making used by NICE, Janssen propose that the scenarios including retreatment should be considered only as a scenario. The high level of uncertainty in the scenarios including retreatment should be considered when used to inform decision making. The rest of the response is therefore presented on the basis of the current economic model originally considered by the Committee, with a revised base case presented below.

Section 2. Janssen wish to present a revised company base case, which includes some of the Committee's preferred assumptions and should be considered a conservative estimate of ESK-NS cost-effectiveness

We have noted the Committee's preference for retreatment in Section 1 above. Given the Committee's other considerations in the ACD, Janssen wish to provide the below revised base case (Table 2). We do not agree with the Committee's judgement based on all the evidence provided, as we believe in some instances the Committee have been overly conservative given the evidence available. There are several topics which we have now included in the revised base case, based upon the Committee's preferred assumptions. This includes:

- Excluding the treatment adjustment effect on the TRANSFORM-2 OAD results based on the Posternak et al method
- Exclusion of additional mortality for the MDE health state, and
- Extending the time horizon of the economic model to 20 years.

If the unadjusted efficacy data are taken directly from the clinical trials, the cost-effectiveness analysis should be considered conservative for the reasons outlined previously (see p683-691 of Committee Papers). As noted in NICE CG90, it is widely accepted that social support plays an important part in a person's propensity to develop depression and his or her ability to recover from it. This was additionally recognised by the patient expert and patient advocacy group in their stakeholder responses to NICE (p454 and p433 of Committee Papers).

Similarly, if no excess mortality for MDE is included, the analysis should be considered conservative. We note that the Committee considered that it is plausible that ESK-NS could affect mortality. Although the guideline expert stated that "people with treatment resistant depression are likely to have an increased risk of suicide" (ACD section 3.7, P9). The committee have not included this assumption in the base case. The revised company base case assumes no excess mortality for MDE.

Even with these conservative assumptions and considering a nurse to patient: ratio of 1:2 – 1:6 for the post-administration observation, the ICER ranges between £10,790 - £12,264. This shows ESK-NS is a very cost-effective new treatment option for TRD to the NHS.

Table 2: Revised company base case

Parameter	Input	ICER
Treatment discontinuation	Data from market research from 25 UK psychiatrists*	£ 10,790- £ £12,264
Carer disutility	Applying a disutility to the MDE health state of [redacted] to represent carer disutility*	
Administration costs	1:2* - 1:6 nurse to patient ratio	
Other modelling topics	• No adjustment for clinic visits • No additional mortality in MDE health state • Time horizon extended to 20 years	

**Note: assumptions are different from NICE preferred model assumptions*

There remains, however, a number of Committee assumptions which are not implemented in the revised company base case. These include:

- Considering that no patients will discontinue ESK-NS for reasons other than lack of efficacy
- Excluding carer disutility
- Including a 1:1 ratio of nurse to patients for the post self-administration monitoring

The rationale and evidence for why we do not agree with these topics are provided below. In summary, we believe the Committee has insufficiently understood the episodic and/or chronic recurrent nature of the disease, not fully considered all previously submitted evidence, and displayed inconsistency with previous NICE decision making, when using these assumptions.

In particular, the key issue of treatment discontinuation for patients in recovery is further discussed below in Sections 3 and 4, as this is pivotal to the exploration of the cost-effectiveness of ESK-NS.

Section 3. Treatment discontinuation: Data submitted shows that patients who achieve recovery are likely to stop ESK-NS over time for reasons other than efficacy and are at continuous risk of recurrence, which captures the risk of a worsening of symptoms and HRQoL that the Committee believe is not captured in the model.

We welcome the Committee's statement that they believe people would stop ESK-NS for reasons other than lack of efficacy over a 2-year period (ACD section 3.12 p15). This is consistent with available evidence. We note, however, that the Committee decided to conservatively conclude that no patients in recovery would stop ESK-NS for reasons other than efficacy. We understand the main reason for the Committee's conclusion is the uncertainty regarding the impact of discontinuing ESK-NS on patient's symptoms or quality of life. We wish to highlight that even if patients discontinue treatment after achieving recovery from the depressive episode, in the model, *they remain at risk of recurrence and associated worsening of their depressive symptoms and quality of life*.

NICE ACD Section 3.12, p15:

"The company assumed that people would not stop taking oral antidepressants for any reason other than lack of response. But it assumed that people would stop esketamine treatment for other reasons, in line with the criteria in the SPC and additional discontinuation guidance provided by the company. In the company model, rates of discontinuation (for reasons other than lack of response) for esketamine varied by treatment phase. Based on advice from clinicians, the company modelled that 52% of people stopped treatment after 9 months in stable remission, with 16% expected to continue treatment for more than 2 years. Stopping treatment was assumed to stop incurring the cost of esketamine but have no effect on QALYs. The clinical experts suggested that a proportion of responders who were not in stable remission would discontinue. The committee were aware that in SUSTAIN-1 the rate of relapse increased when esketamine was stopped. The ERG highlighted that no evidence was submitted to determine the effect of discontinuation on symptoms or quality of life. The clinical expert explained that the decision to stop treatment would be done after a full discussion of all the circumstances associated with the individual patient. The patient expert noted that people would be concerned and worried about relapse. The committee recognised that people would be fully involved in the decisions around continuing treatment, and that decisions about how long treatment lasts and reasons for stopping it vary based on individual circumstances. Also circumstances are very different in people with comorbidities compared with those without. The committee considered that assuming an indefinite improvement in quality of life after stopping esketamine treatment was implausible. It recognised that people may have changes in MADRS score below the threshold for 'relapse' but that still affect quality of life. The clinical experts supported this view and explained that the MADRS is a non-linear scale, meaning that increases in score at the lower end of the scale represent a larger change in symptoms than at higher points of the scale. The ERG and clinical experts also highlighted that there were no data to accurately determine discontinuation rates. Because of this, the ERG preferred to assume no discontinuation for reasons other than lack of efficacy at 2 years. The committee considered that it's likely that people would stop esketamine for other reasons over a 2-year period, but that it's unclear how many. The committee recognised that, in practice, people who were 'responders' or 'stable remitters' and stopped treatment for reasons other than lack of efficacy could have repeat courses of esketamine, but that this was not accommodated in the model (see section 3.11). The committee concluded that, on balance, without data the least biased estimate of cost effectiveness would be to not include discontinuation of esketamine for reasons other than lack of efficacy."

Overview

The following provides clarification of how treatment is discontinued in the current model. In the acute treatment phase, the model assumes that patients who do not achieve response or remission to the active treatment discontinue, and then receive the next subsequent treatment. Patients can discontinue treatment due to two reasons in the continuation and maintenance treatment phases: loss of efficacy, and non-efficacy reasons.

In the continuation phase, patients who relapse (transition from remission to MDE) or lose response (transition from response to MDE) discontinue treatment and move to the subsequent treatment. Furthermore, patients can discontinue for reasons other than efficacy, based on the observed data from SUSTAIN-1. Similarly in the maintenance phase, whilst patients are in recovery, patients can discontinue due to efficacy reasons and reasons other than efficacy. We address the Committee's concerns on the impact of discontinuing ESK-NS on symptoms or patient's quality of life below.

Based on the Committee's consideration in the ACD, we believe that the discontinuation due to other reasons than efficacy of most concern in the recovery phase, as prior to that in the model reasons to discontinue is based on trial data. We refer the Committee to the previously provided data from a post-hoc analysis of SUSTAIN-1 (p697-698 of Committee papers) and now provide an additional post-hoc analysis of SUSTAIN-2 (see Section 3.2). Both of these data sources show there is a limited impact on risk of recurrence from discontinuing ESK-NS in recovery.

Recurrence is a simplifying assumption to capture the reduction in quality of life from returning to the MDE health state. The Committee have concluded that there may be sub-threshold reductions in quality of life where the person in recovery may not fully have a recurrence of the disease but may experience some worsening of the disease again. To try and account for this artefact, we have provided scenarios where the recurrence risk after discontinuation of ESK-NS is increased in recovery to take account of people experiencing a worsening of the disease again. This is likely to be a conservative assumption, as it assumes that people are not just having a slight worsening of the disease, i.e. a sub-threshold change in the disease, but they are having a full recurrence of the disease and have returned to the MDE health state. The scenario below shows that even with this conservative assumption, ESK-NS remains a cost-effective option for TRD to the NHS.

Overall, Janssen respectfully request the Committee to re-consider the totality of evidence and change their assumption that patients will not discontinue for reasons other than efficacy. The current model accurately captures the impact of discontinuing ESK-NS and resulting change in HRQoL. Considering all model parameters, ESK-NS is cost-effective once this conclusion is reached.

The points below provide further explanation.

3.1 Patients who achieve recovery are assumed to be at a continuous risk of recurrence, which accounts for a significant worsening of the disease in patients who discontinue for reasons other than efficacy

We understand from the ACD that the Committee are concerned about how many patients would be discontinuing treatment for other reasons than efficacy in the first two years. In order to provide context for our rationale below, it is important to clarify the company model transitions in each health state. There are three different treatment phases and associated treatment objectives upon which the cost-effectiveness model is built:

Treatment phase	**Treatment objective**
The induction phase (first 4 weeks after initiating ESK-NS treatment)	To achieve response/ remission of depressive symptoms.
The continuation phase (9 months for continuous stable remitters)	To prevent loss of response and relapse into the MDE health state. *Note that patients who relapse initiate a subsequent treatment. Patients have a continuous risk of relapse.*
The maintenance phase (from 9 months in stable remission onwards)	To prevent recurrence of a new episode of depression. *Note that recurrence is the risk of returning to the MDE health state and experience the associated reduction in HRQoL. Patients have a continuous risk of recurrence.*

As noted above in the overview, the relevant issue of discussion is the assumptions of treatment discontinuation in the maintenance treatment phase (when patients are in recovery). Currently when patients are in recovery, a continuous risk of recurrence (2.88% per 4 weeks) is assumed in the model for both the ESK-NS and the OAD treatment arm, which is applied whether the person is on treatment or off treatment. This is based on the pooled SUSTAIN-1 data from both study arms. This

was pooled in the model despite the ESK-NS arm showing a lower risk of recurrence than the OAD treatment arm in SUSTAIN-1 (see below).

Experiencing recurrence signifies a significant reduction in quality of life through returning to an active disease state. The inclusion of the recurrence risk means that patients in recovery have a constant risk of transitioning to the MDE health state and losing their quality of life. The utility score of patients in recovery is 0.866 and for patients in the MDE health state is 0.417 (Committee papers p184), which show the considerable impact on HRQoL when a patient has a recurrence. We believe that this *more than* accounts for the Committee's concern that there is no reduction or even an improvement in QALYs following discontinuation of ESK-NS in recovery.

The pooled recurrence risk of 2.88% per 4 weeks from both SUSTAIN-1 study arms is used for both ESK-NS + OAD as well as the OAD when patients are in recovery. This is an increase in recurrence risk versus the data from the SUSTAIN-1 ESK-NS + OAD arm, which was 2.43% per 4 weeks. The recurrence risk is 3.56% per 4 weeks from the OAD + PBO-NS arm of the SUSTAIN-1 trial shown in Table 3.

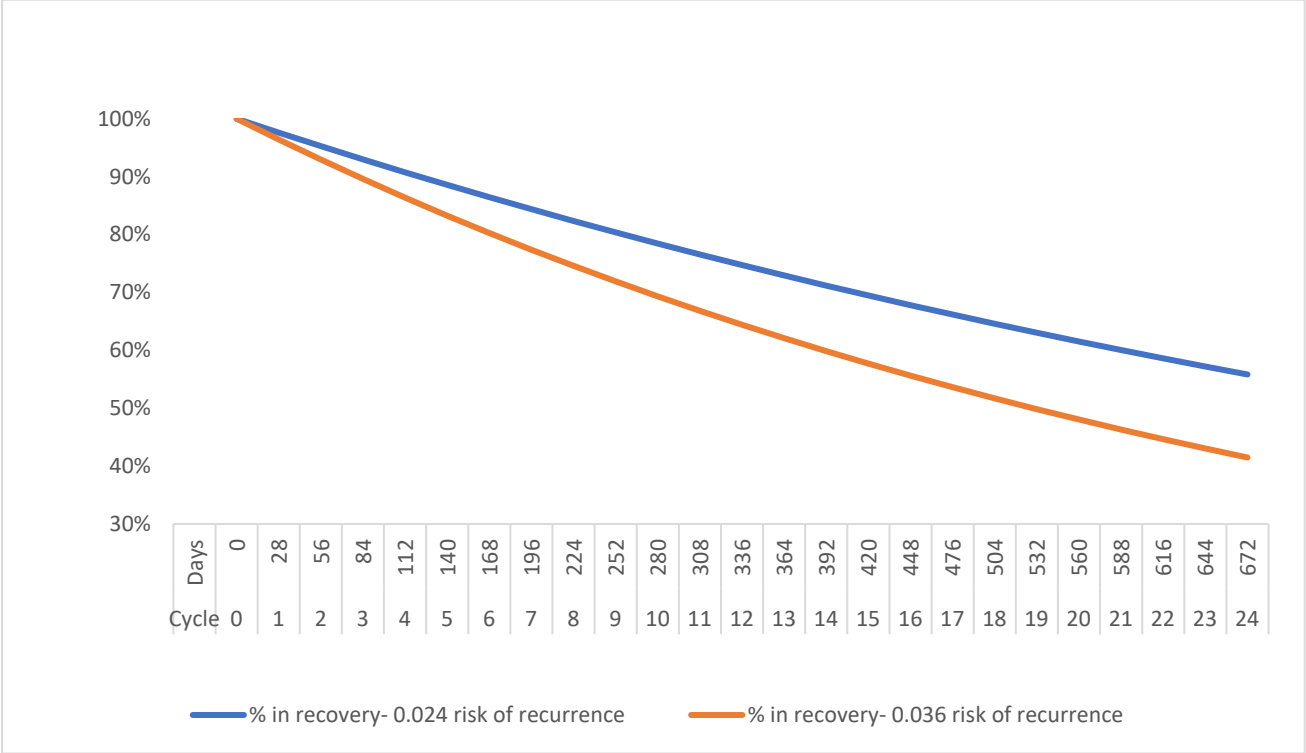
Table 3: Recurrence risk used in the model and from SUSTAIN-1

Recurrence risk used in base case model (pooled SUSTAIN-1 data)	**Recurrence risk from SUSTAIN-1 ESK-NS+OAD arm**	**Recurrence risk from SUSTAIN-1 OAD+PBO-NS arm**
2.88% per 4 weeks	2.43%	3.56%

Over the course of the model, this recurrence risk is cumulative and means that a significant number of patients are at risk of recurrence of the disease and a worsening of their depressive symptoms and quality of life (Figure 1). Over time, a large proportion of patients in recovery will have a recurrence, and hence start a new depressive episode with a significant worsening of quality of life. At the end of 2 years, approximately 40-50% of patients will have had a recurrence of the disease.

A visual graphic displaying the difference over time that this transition probability represents is displayed below.

Figure 1: Impact of recurrence risk over time



Taken cumulatively over the time frame of the model, the recurrence risk sufficiently accounts for the worsening of depressive symptoms and quality of life that may occur once ESK-NS treatment is stopped.

3.2 For patients who achieve recovery, previously submitted (SUSTAIN-1 post hoc) data show there is no impact of discontinuing ESK-NS

In the Response to the Draft Technical Engagement report, a *post-hoc* analysis of SUSTAIN-1 data was submitted showing there was no impact in the 2 weeks after discontinuing ESK-NS in patients who have been in remission for at least 9 months (range from 9 months- 1.5 years) (NICE ACD papers page 696-698). Longer follow-up is not available from the trial.

3.3 For patients who achieve recovery, additional evidence (SUSTAIN-2 *post hoc*) show the risk of recurrence does not increase after discontinuation of ESK-NS

We believe that the recurrence risk included in the model addresses the Committee's concern that there is no reduction in QALYs when patients discontinue treatment due to reasons other than lack of efficacy.

In addition, an additional *post-hoc* analysis of SUSTAIN-2, the long-term safety study, has been conducted and presented here. These data support the conclusion that there is a very limited increase in risk of recurrence after discontinuation of ESK-NS after 9 months in stable remission. The additional evidence shows the proportion of relapse in patients who have been in remission for at least 9 months was [redacted] at week 4 after discontinuing ESK-NS. This is similar to

the recurrence risk included in the company model (the pooled risk of 2.88% from both study arms of SUSTAIN-1) of when patients are on treatment. This demonstrates that, for patients who achieve recovery, the risk of recurrence/relapse does not increase substantially after discontinuing treatment. Together, these available data suggest patients are able to discontinue ESK-NS once reaching a recovery health state without increasing recurrence risk.

3.4 It is incorrect to use SUSTAIN-1 data to infer that the impact of discontinuing ESK-NS in terms of increased risk of relapse/recurrence during the continuation phase is equivalent to the impact of discontinuing ESK-NS in recovery the phase

We ask the committee to reconsider their comment in Section 3.12 of the ACD (p15) where the Committee appear to be applying the SUSTAIN-1 trial data, which was conducted during the continuation phase of treatment to the recovery phase in the model:

"Based on advice from clinicians, the company modelled that 52% of people stopped treatment after 9 months in stable remission, with 16% expected to continue treatment for more than 2 years. Stopping treatment was assumed to stop incurring the cost of esketamine but have no effect on QALYs. The clinical experts suggested that a proportion of responders who were not in stable remission would discontinue. The committee were aware that in SUSTAIN-1 the rate of relapse increased when esketamine was stopped."

In the treatment of depression, after discontinuation of an active treatment, the risk of relapse/recurrence is highest in the first 4 weeks. The relapse risk has been demonstrated to decrease over time, whether on or off ESK-NS (see SUSTAIN-1 KM curve, p122 of Committee Papers). Together, these show that the [redacted]% recurrence risk after 9 months in stable remission is higher than what is expected in the following 4-week periods.

The 2.7% recurrence risk is contrasted to the SUSTAIN-1 primary outcome analysis for patients who have been in stable remission for 12 weeks, where the proportion of patients who relapsed at 4 weeks after ESK-NS treatment discontinuation was [redacted]. Clearly, discontinuing ESK-NS after 9 months (after recovery), with a [redacted]% risk of recurrence after 4 weeks of follow-up compared to 12 weeks in SUSTAIN-1 with [redacted]% relapse after 4 weeks of follow up is very different (Table 4).

Table 4: Comparison of impact of discontinuation of ESK-NS

SUSTAIN-2 post hoc: Proportion of patients who relapse after discontinuation of ESK-NS after 9 months of treatment	**SUSTAIN-1 primary analysis: Proportion of patients who relapse after discontinuation of ESK-NS after 12 weeks of treatment**
[redacted]	[redacted]

The evidence from the trial clearly shows that the risk of relapse/recurrence of patients with TRD is dependent upon the health state, the timing and hence the treatment phase of when the treatment is discontinued. This is consistent with other trials and studies. Furthermore, it confirms the episodic nature of the disease. We therefore ask that the Committee consider that when a patient is in recovery, the impact of discontinuing ESK-NS is much lower than when a patient would be in remission and during the continuation treatment phase as seen in the SUSTAIN-1 trial.

3.5 New scenario: Increased risk of recurrence after discontinuation of ESK-NS

We believe the model adequately captures the worsening of quality of life using the recurrence risk from discontinuing ESK-NS treatment in recovery, but we recognise the Committee considered this a key topic of uncertainty and thus we have further tried to address the Committee's concerns regarding sub-threshold changes in quality of life.

To allow for this, the recurrence risk after discontinuation of ESK-NS can be varied. The recovery health state has a utility of 0.866 and the MDE health state has a utility of 0.417. Increasing the recurrence risk after discontinuation of ESK-NS results in a loss in quality of life due to the change in health state from recovery to MDE. This can be considered conservative as these patients transition fully from the recovery health state to the MDE health state, whereas in clinical reality, as the Committee has noted, some patients may not worsen to the threshold of recurrence.

The submitted model includes a new option to include a different risk of recurrence for patients in recovery when on or off ESK-NS treatment. Two new scenarios have been considered. The scenarios below include all the Committee's preferred assumptions apart from having no treatment discontinuation for reasons other than loss of efficacy. The first scenario uses a risk of recurrence after ESK-NS discontinuation taken from SUSTAIN-2. The constant recurrence risk used in this scenario ([redacted]) should be considered conservative given this is derived from the first 4 weeks after ESK-NS discontinuation in SUSTAIN-2, whilst in the following 4-week periods it is expected to be lower. A second scenario is using a recurrence risk of 3.6% per 4-weeks after discontinuation of ESK-NS is also presented taken from the SUSTAIN-1 OAD+PBO-NS arm. The scenario shows that ESK-NS remains cost-effective even when patients in the recovery state have a 50% relative increase in recurrence risk after discontinuation of ESK-NS. This scenario should be considered highly conservative give the constant risk of recurrence which is assumed over time.

Scenario 3.5: Increase risk of recurrence after discontinuation of ESK-NS

Key Parameters	**Revised base case assumptions**	**Inputs using SUSTAIN-2 post hoc**	**Inputs using OAD+PBO SUSTAIN-1 recurrence risk**
Treatment discontinuation	Data from market research from 25 UK psychiatrists	Data from market research from 25 UK psychiatrists	Data from market research from 25 UK psychiatrists
Recurrence risk ESK-NS + OAD	0.028 (pooled SUSTAIN-1 arms)	0.024 (SUSTAIN-1 ESK-NS arm)	0.024 (SUSTAIN-1 ESK-NS arm)
Recurrence risk OAD + PBO-NS	0.028 (pooled SUSTAIN-1 arms)	0.036 (SUSTAIN-1 OAD+PBO-NS arm)	0.036 (SUSTAIN-1 OAD+PBO-NS arm)
Recurrence risk after ESK-NS discontinuation	0.028	[redacted] (SUSTAIN-2 post hoc recurrence rate)	0.036 (SUSTAIN-1 OAD+PBO-NS arm)
Administration cost	1:6 – 1:2	1:6- 1:1	1:6- 1:1
Other key assumptions	• No adjustment for clinic visits • Including carer disutility • No excess mortality for	• No adjustment for clinic visits • No carer disutility • No excess mortality for	• No adjustment for clinic visits • No carer disutility • No excess mortality for

	MDE health state • 20-year time horizon	MDE health state • 20-year time horizon	MDE health state • 20-year time horizon
Retreatment	No	No	No
ICER	£ 10,790 - £12,264	£ 8,007 - £11,015	£ 18,484 - £22,386

Further details on this scenario are provided in Appendix B.

3.6 Conclusion

Overall, Janssen request the Committee to re-consider the totality of evidence provided, which demonstrate that patients in recovery (who have no depressive symptoms for at least 9 months) will be clinically justified to discontinue ESK-NS treatment for reasons other than lack of efficacy. Previously submitted and additional evidence (see Section 3.2 and Section 3.3) have shown there is only a very limited impact of discontinuing ESK once in recovery and that the impact on HRQoL of discontinuing ESK-NS is adequately capture in the model through the recurrence risks. Scenarios have shown that even conservatively increasing the recurrence risk results in ESK-NS remaining cost-effective (Section 3.5) to take account of sub-threshold changes in HRQoL.

Section 4. Previous submitted data on the rate of discontinuation consistently shows a similar proportion of patients discontinuing ESK-NS over time and if applied in the economic model shows ESK-NS to be cost-effective.

Overview

We welcome the Committee's original conclusion that it is likely patients will discontinue for reasons other than efficacy, as noted in Section 3.15 of the ACD (p15):

"The committee considered that it's likely that people would stop esketamine for other reasons over a 2-year period."

We note that this is aligned to previous NICE decision-making in NICE TA267 and NICE CG90 and consistent with the three sources of data that Janssen has previously submitted. We believe that the additional evidence and clarification provided above in Section 3, regarding the impact on quality of life that results from discontinuing ESK-NS, is sufficient to consider the discontinuation of ESK-NS in the recovery period. If this is the case, we would like to remind the Committee of the consistency in the data regarding discontinuation rates for patients of ESK-NS in recovery. When using the various sources of data in the economic model, ESK-NS remains a cost-effective option for treating TRD.

4.1 The Committee's initial conclusion, that it is likely that patients will discontinue for reasons other than efficacy, is consistent with the judgement of the ERG and NICE Technical Team, and previous NICE decision making in NICE TA367 and NICE CG90.

We note and thank the Committee for acknowledging the previously submitted evidence on ESK-NS discontinuation based on market research from 25 UK psychiatrists. The use of this evidence was agreed with the NICE technical team during the technical engagement call on the 6th November 2019. We believe this is the best evidence to inform the discontinuation of ESK-NS for those people who are in recovery. We note that after the Technical Engagement Step, the ERG also considered this market research data to be sufficiently robust to develop a model scenario in their response to the technical engagement (p825 of Committee papers). Based on the market research data input for the expected treatment duration of combination OADs (p826 of Committee papers), the ICER for the ERG scenario changed to £25,827. We also note that after receiving the data, the NICE technical team decided to incorporate treatment discontinuation into the model (p856 of Committee Papers).

NICE have previously accepted similar assumptions used in the model for TA367. These assumed that patients discontinued treatment after 6-22 months. Furthermore, the economic model used in NICE CG90 assumed that:

"patients who responded to treatment and did not relapse during follow up, it was assumed that no further additional treatment or mental health and social care resources beyond the 6-month maintenance period were required' (p407 of NICE CG90)."

The model assumptions used in NICE CG90 and TA367 are therefore inconsistent with the current final conclusion by the Committee that patients in recovery continue ESK-NS treatment in recovery until loss of efficacy. If the concerns of the Committee are addressed in Section 3, we request the market research data previously submitted on the numbers of patients in recovery discontinuing ESK-NS treatment over time can be used as part of the Committee's decision making. As NICE note, in the absence of clinical data, clinical expert opinion should subsequently be considered, as indicated by the NICE Process Guide:

"Evidence is obtained from a range of sources, including randomised controlled trials, observational studies and expert opinion (of clinical professionals and/or patients/carers)" (1)

4.2 Multiple sources provide clear estimates on how many patients will discontinue due to other reasons than efficacy and if any of these sources are included in the model, ESK-NS is cost-effective

The market research data are included in the revised base case which generate robust estimates of the ESK-NS rate of discontinuation for patients who have been in stable remission for 9 months (p702-705 and 742-748 of Committee papers). The market research data are aligned to the feedback on the survey with four UK clinical trialists (p705-707 and 749-751 of Committee papers), and the feedback of four UK clinical experts involved in an advisory board who have validated the assumptions on ESK-NS treatment duration in the initial base case (p178, 701 and 702 of Committee papers).

The clinical expert opinions from all methods consistently suggest that the initial conclusion by the Committee, that patients are likely to discontinue ESK-NS for reasons other than efficacy, are appropriate. The opinions are not aligned to the final conclusion from the Committee that no patients in recovery would discontinue ESK-NS for other reasons than efficacy.

A summary of the data and the impact on the ICER with varying model assumptions are presented in Table 5 below.

Table 5: Scenarios using different sources of discontinuation data

Data source	Proportion of stable remitters discontinuing at 9 months	Proportion of stable remitters continuing beyond 24 months#	4-weekly discontinuation rate after 9 months in stable remission	ICER using company revised base case assumptions* (£/QALY)	ICER using ERG/NICE base case assumptions** (£/QALY)
Market research - 25 UK psychiatrists	52.0%	16.0%	10.7%	£ 10,790-£12,264	£13,821 – £17,326
Survey - four UK clinical experts involved in ESK-NS trials	61.3%	26.0%	8.0%	£10,904-£12,383	£13,967-£17,484
Advisory board - 4 UK clinical experts and 2 HE experts	35.4%	1%	25.0%	£9,246-£10,649	£11,815–£15,146
NICE Committee preferred assumptions	0%	100%	0%	N/A	£55,027-£62,078

*ICERs using company revised base case assumptions, range from 1:6 to 1:2 nurse patient ratio. **ICERs using NICE/ERG base case assumptions and 1:6 to 1:1 nurse: patient ratio, NICE ACD page 20. # for proportion of patients that do not get a relapse or recurrence

Using any of the three data sources for ESK-NS treatment duration of patients who have been in stable remission for at least 9 months, even when assuming all of the other NICE preferred model assumptions, results in ICERs consistently below £20,000 per QALY.

4.3 The previously submitted discontinuation guidance provides additional certainty for the Committee that patients will discontinue treatment in recovery for reasons other than lack of efficacy if included in the recommendation by NICE

The previously submitted discontinuation guidance is a key item of consideration for the Committee. We propose for NICE to include the ESK-NS discontinuation guidance explicitly in the NICE ESK-NS recommendation to the NHS.

At the NICE technical engagement meeting on 6th November 2019, the NICE team stated that guidance on discontinuation of ESK-NS would help to mitigate the uncertainty around the treatment duration of ESK-NS in NHS clinical practice. Subsequently, Janssen reached out to 10 clinical experts in the field of treatment resistant depression, including five UK clinical experts.

The 25 UK clinicians who participated in the market research also indicated that discontinuation guidance for ESK-NS as recommended by NICE in any guidance would be the most important factor for informing the duration of treatment of ESK-NS in NHS clinical practice.

Together with the clinical community, and based on the available evidence, Janssen submitted practical and clinically relevant discontinuation guidance for ESK-NS to NICE in the response to the Draft Technical Report.

The proposed clinical guidance on discontinuing ESK-NS was developed and is presented below:

ESK-NS treatment discontinuation guidance

- **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**
- **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**
- **Exceptions will occur based on clinical judgement (e.g., some patients may exceptionally require longer treatment as is seen with Electroconvulsive Therapy (ECT)**

Janssen propose that NICE include the discontinuation guidance in their recommendation of ESK-NS to the NHS. The full rationale for each of the discontinuation guidance recommendations are found on pages 709-710 of the Committee papers. The discontinuation guidance is in addition to the current recommendations on treatment (dis-) continuation in the SmPC. Note that the discontinuation guidance is not modelled in the company base case economic model. The discontinuation guidance provides additional certainty that the discontinuation rates implemented in the model will occur in NHS clinical practice.

NICE have precedent to consider similar discontinuation guidance in several other TAs. Some examples include:

- TA342: Vedolizumab for treating moderately to severely active ulcerative colitis
- TA260: Botulinum toxin type A for the prevention of headaches in adults with chronic migraine

We therefore ask the Committee to consider the discontinuation guidance in their decision making for ESK-NS. In addition, Janssen have planned to collect real world evidence on ESK-NS, and specifically the discontinuation rate and impact of discontinuing of patients who have been at least 9 months in stable remission treated within NHS clinical practice. This will help to inform any future re-assessment of ESK-NS.

4.4 Conclusion

The Committee recognised that it is likely some patients will discontinue for reasons other than efficacy. This is aligned to the conclusions of extensive and representative clinical expert consultation. In addition, the previously submitted discontinuation guidance is a key item of

consideration for the Committee to reduce the uncertainty. We propose for NICE to include the ESK-NS discontinuation guidance explicitly in the NICE ESK-NS recommendation to the NHS.

Overall, Janssen request the Committee to reconsider their conclusion that no patients will discontinue due to reasons other than efficacy and consider the evidence submitted on the discontinuation guidance provided for ESK-NS.

Section 5. Carer disutility: The Committee decision to exclude carer disutility is inconsistent with previous appraisals and the determination of the ERG and NICE, who concluded that there was evidence and that it was of good quality.

Overview

We are concerned that the Committee have acknowledged the impact on people with TRD, families and their carers in the ACD, but have then concluded that there is insufficient data to include carer disutility. This is not consistent with previous appraisals and the level of evidence accepted by previous Committees. It is also in contrast to the view from the ERG: "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" (p866 Committee Papers) and NICE technical team: "The technical team prefer the method used by the ERG for calculating and incorporating carer disutility" (p866 Committee Papers). Both the ERG and NICE technical team concluded there are sufficient data and the evidence provided is of good quality and applicable to the decision problem. Janssen have therefore included a disutility for the MDE health state to represent carer disutility in the revised base case.

We note in the NICE ACD Section 3.14, p16 regarding the Committee conclusion on carer disutilities:

"However, the committee considered that there was uncertainty about the appropriateness of including a carer disutility because of the lack of data on the direct effect on carers of people with treatment-resistant depression. It is also noted the lack of evidence on any direct benefit to carers after treatment with esketamine. The committee also noted that adjusting for carer disutility was not part of any other NICE technology appraisals in mental health and may lead to inequities across disease areas."

In this technology appraisal, it is appropriate for the Committee to consider inclusion of carer disutility. In response to each of the reasons included in the ACD for not considering carer disutility in the base case, Janssen would like to highlight the following points in the sections below.

5.1 Contrary to the statement in the ACD, there are several previous NICE TAs where carer HRQoL was included. By not including carer HRQoL, NICE are being inconsistent with previous decision making.

The ACD states that a reason for not including carer disutility is to avoid inequalities across disease areas. We would like to point the Committee to the NICE DSU report published in April 2019 (2), which undertook a review of carer disutility across TAs. Of 422 appraisals, the DSU found 12 TAs and four HSTs where carer QALYs had been included in the economic evaluation, either by the submitting company or the Evidence Review Group (ERG)/Assessment Group (AG), either in the base case or scenario analyses.

The NICE DSU states that *"In the appraisals where quantitative analysis including carer QALYs were presented, the committee felt that they should be included in decision-making in most cases".*

In these appraisals, we note that carer disutility were included when a person caring for a patient with more severe disease may have to spend more time performing caring tasks or worry more about the patient, and so the HRQL impact would be higher. Treatment resistant depression has a similar significant impact on the patient and carer, as was explained by the patient expert and clinical expert at the Appraisal Committee meeting:

ACD, section 3.1, p5: "*The patient expert explained that treatment resistant depression is associated with a significant burden on all aspects of life, with a range of symptoms. The patient expert emphasised that people living with treatment resistant depression often have feelings of hopelessness, fear and despair. This can affect the person's family and carers. The clinical expert noted that there is also an impact on the lives of children of people with treatment resistant depression. The committee concluded that the condition has a negative effect on people, their families and their carers."*

The approach of including carer QALYs but modelling a disutility by patient's disease severity for ESK-NS is also aligned to the approach taken in TA493 (Cladribine tablets for treating relapsing–remitting multiple sclerosis) and TA527 (Beta interferons and glatiramer acetate for treating multiple sclerosis). The evidence provided for ESK-NS is of a similar and arguably higher quality. We would ask the Committee to consider the previous appraisals in the field of neuroscience, TA127, TA254, TA312, TA303, TA320, TA533 (all Multiple Sclerosis), and TA217 (Alzheimer's), which all modelled carer disutility by disease severity. It is important to note that the ERG method of incorporating carer disutility assumes a carer utility once patients achieve remission. This is not aligned to previous approaches, as it is appropriate to apply the full disutility based on the severity of the MDE health state.

Since the NICE DSU was published in April 2019, a number of other appraisals have included carer disutility in their decision making, such as TA614 (Cannabidiol with clobazam for treating seizures associated with Dravet syndrome). Janssen were aware of the precedence from NICE in including carer disutility in other TAs. As such, in the Scoping workshop conducted in September 2018, Janssen explicitly asked NICE if carer quality of life should be added to the Decision Problem, to which the NICE Committee co-chair agreed, given the impact that TRD has on patients and their carers. The above shows that the Committee's decision is inconsistent with previous NICE precedent from other therapeutic areas.

5.2 Carer disutility was previously included by NICE technical team and ERG during Technical Engagement and at all stages prior to Appraisal Committee meeting

By excluding carer disutility from the base case, the Committee are being inconsistent with the approach taken by the ERG and NICE technical team at previous stages of the appraisal. It has been recognised by the patient expert, the company, ERG, NICE Technical Team and the Committee at all previous stages of the NICE process that TRD has a substantial impact on wider society.

The patient expert emphasised that TRD can affect the person's family and carers (ACD Section 3.1, p5). This was also evidenced in the survey results from the submission from SANE, which included 100 patients and 90 carers with TRD from the UK. As previously noted in the company submission, NICE CG90 recognises the additional significant impact on carers of people with depression. The ERG also included the carer disutility in a scenario (p866 of Committee Papers), which was also incorporated by the NICE Technical team (p866 of Committee Papers).

The Committee themselves '*acknowledged that there is an impact on the families and carers of people with treatment-resistant depression'* (ACD Section 3.1, p5). It is therefore not clear why the Committee has now decided to exclude carer disutility when the submitted evidence, as the NICE technical team, ERG, NICE CG90 have shown it to be relevant.

5.3 Direct robust evidence was provided previously in the TRD carer HRQoL study which demonstrates impact on carers of patients with TRD (p758-808 of Committee papers)

ACD Section 3.14, p16: "*The committee considered that there was uncertainty about the appropriateness of including a carer disutility because of the lack of data on the direct effect on carers of people with treatment-resistant depression"*

It is unclear where the uncertainty regarding the carer disutility has come from for the Committee, as we note that the ERG have judged the TRD HRQoL study to be well conducted and provides robust evidence on the effect on carers of people with TRD.

"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" (p866 of Committee papers).

This is in contrast to the evidence that was previously used by NICE to incorporate carer QALYs in previous appraisals, which had severe limitations. For example, in seven of the MS TAs, the carer disutility was not even taken from carers of patients who had MS, but from a study conducted in patients with Alzheimer's (NICE TA217: Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease). Carer utility in NICE TA217 (MS) was based on an unpublished Short-Form 36 data, and a non-comparative study measuring the quality of life of carers of Alzheimer's patients using the Health Utilities Index. For TA254, TA312, TA303, TA320 and TA533 (all MS), these all subsequently used the same caregiver disutilities and approach as TA127 in the base case analyse. The ERGs for these five TAs did not challenge the inclusion of, or data source for, caregiver disutilities. In two of the MS appraisals, the use of the Alzheimer's data were included in the final decision making (TA320 and TA303).

The robust data provided by the TRD HRQoL study (p758-808 of Committee Papers) show there is a difference in utility of [redacted] between carers of patients with symptomatic TRD and carers of patients with TRD in remission. The evidence from the TRD HRQoL study is more robust than that used in previous NICE appraisals. The TRD HRQoL study provides direct evidence of carers of patients with TRD in the UK to show there is a disutility associated with caring for a patient with TRD who is symptomatic.

5.4 Conclusion

Overall, we ask the Committee to reconsider their conclusions on the topic of carer disutility for the following reasons:

- It is appropriate and consistent with Committee decisions in other TAs to include carer disutility in the base case analysis.
- Carer disutility was previously included by the NICE technical team and ERG during Technical Engagement and at all stages prior to the Appraisal Committee meeting.

- Direct evidence was provided previously from the TRD HRQoL study, which the ERG have judged to be robust and is of a higher quality than previous appraisals.
- TRD has a substantial impact on society including carers. The current approach is conservative given that it is likely that multiple family members will be impacted by one patient with TRD.

Section 6. The Committee have not considered all the evidence regarding comparators, as Janssen previously provided evidence comparing ESK-NS to all relevant comparators in the NICE Final Scope. Consideration of the combined effect of psychological and pharmacological treatment is inconsistent with previous NICE decision making.

Overview

The Committee have not considered all evidence submitted by Janssen on the comparators included in the NICE scope ahead of the first Appraisal Committee meeting. In the ACD Section 3.4, (p7), the Appraisal Committee have incorrectly concluded that Janssen did not submit evidence comparing ESK-NS with all relevant comparators :

"The company submission included oral antidepressants as comparators, stating that these were the most common oral treatments for the condition. The clinical expert highlighted that other oral antidepressants as included in the esketamine appraisal scope, sometimes combined, are also used in clinical practice. The committee acknowledged that different treatments are used at different points in the pathway (see section 3.3). The committee heard from other clinical experts who noted that ECT should also be a comparator because the processes involved in administering esketamine are similar to those for ECT. The committee noted that oral antidepressants augmented with lithium or antipsychotic medicines were also included as a comparator in the esketamine appraisal scope, and included in the NICE guideline on depression. The committee acknowledged the company did not provide evidence comparing esketamine with all the relevant comparators listed in the scope, such as combination or augmentation treatments and ECT, were not included as comparators in the company's model."

The data comparing ESK-NS to all relevant comparators was reported in both the company submission (p127 of Committee Papers) and the ERG report (p601 of Committee Papers). The data shows that ESK-NS was compared to all relevant comparators in the scope, including combination, augmentation and ECT, and that ESK-NS is a cost-effective option for TRD. Please note that psychological treatments were not a comparator in the NICE Scope, and psychological treatments have an additive effect that could be applied to all pharmacological treatments, including ESK-NS. The Committee's conclusions are also inconsistent with the Committee's considerations in TA367, as they did not consider psychological therapies as comparator, and did not consider the combined effect of CBT plus pharmacological treatment.

6.1 The Committee have not considered all the evidence regarding comparators, as Janssen previously provided evidence comparing ESK-NS to all relevant comparators in the scope, including combination, augmentation and ECT, which showed ESK-NS is cost effective.

Janssen have previously submitted a network meta-analysis (NMA) which compared to augmentation/ combination treatments and ECT. The clinical systematic literature review (SLR) and NMA conducted for ESK-NS demonstrate that there is only limited evidence available for the

treatments used for TRD. This shows the unmet need and lack of evidence-based treatments for this patient population. Nevertheless, the original results of the indirect comparison to augmentation/ combination treatments and ECT can be found in:

- Page 127 of committee papers (B2.9) of company submission NMA scenario, with the results of indirect comparison presented in Section B.2.9.2 (p130 of Committee papers). The following comparisons were conducted:
    - ESK-NS vs ECT: indirect comparative efficacy data presented for response at 4–6 weeks and 4–8 weeks as well as for discontinuations due to AEs.
    - ESK-NS vs augmentation and vs combination: indirect comparative efficacy data presented for CFB MADRS at 4–6 weeks, response at 4–6 and 4–8 weeks, remission at 4–8 weeks, and discontinuations due to AEs
- Combination, augmentation therapies and ECT were included in the model and a cost effectiveness scenario was presented in Table 81 (Section B.3.4.4.9 of Company submission, p221 of Committee papers).

The Odds Ratios (ORs) were consistently in favour of ESK-NS over every comparator in each outcome for which sufficient data were available to support the NMA. The analysis shows ESK-NS is cost-effective compared to all treatment options included in the NMA.

As previously submitted in the original company submission, data show ECT is not a relevant comparator (p35 of Committee papers). ECT is used in [redacted] of eligible patients in UK clinical practice based on data from South London and Maudsley (SLaM). ECT is also generally used further down the treatment pathway than the proposed positioning for ESK-NS + OAD.

Janssen have fulfilled the NICE scope through the submission of evidence compared to the most relevant comparators to NICE. Janssen previously submitted data to show the relevant comparators at TRD positioning in the UK (see p34 of Committee Papers). The data indicated that switching to newly initiated OAD monotherapy is the most relevant comparator for the licensed population for ESK-NS.

We note the NICE positive guidance for vortioxetine, for which comparative evidence for all relevant comparators was not provided by the Company. The evidence for TA367 only considered direct comparison with agomelatine and an indirect comparison with sertraline, venlafaxine, bupropion and citalopram. No comparison was provided for vortioxetine compared to OAD augmentation or combination therapies, or ECT.

6.2 Psychological treatments should not be considered, as in the NICE Scoping workshop for ESK-NS it was agreed to exclude them as they have an additive effect to all pharmacological treatments

We note the Committee's conclusion regarding psychological treatments in the NICE ACD Section 3.5, p7-8:

"The patient expert explained that psychological therapy can help alleviate cognitive symptoms and with developing coping strategies. The NICE depression guideline expert noted that psychological therapies were not included as comparators or in combination treatments in the company's submission. The clinical expert explained that CBT is used alongside drug treatment to treat depression. However, not all people with depression can effectively engage with CBT because of the severity of their physical and cognitive symptoms. The patient expert suggested that treatment with esketamine may improve symptoms for enough time to allow

people to have CBT. However, the clinical expert added that, because of the dissociative effects of esketamine treatment, someone would not be able to have psychological therapy immediately after having esketamine. This means that they could not have CBT at the same time as esketamine at their clinic visits. The committee concluded that CBT alongside oral antidepressant therapy and adjunctive therapy is a relevant part of the treatment pathway. But it had not seen any evidence on its effect when combined with esketamine or its comparators."

Psychological therapies were not included in the final Scope for ESK-NS as a comparator, as clinical experts involved in the NICE scoping process agreed that patients with TRD require pharmacological treatments, and psychological treatments should be considered a potential add-on therapy. This was further validated by the clinical experts consulted by Janssen during the preparation of the submission. Clinical experts have stated that CBT is an additive therapy and would be expected to exert the same benefit regardless of which treatment it is co-administered with, including ESK-NS.

The Committee have been inconsistent in their consideration compared to a previous NICE appraisal of TA367, which did not consider psychological therapies as comparator, and did not consider the combined effect of CBT plus pharmacological treatment. Note that in the ESK-NS clinical trials, if patients received CBT before ESK-NS, CBT could be continued whilst ESK-NS treatment was ongoing.

6.3 Conclusion

We urge the Committee to consider the evidence originally submitted by Janssen in the company submission regarding the relative effectiveness of ESK-NS versus all comparators in the NICE scope where there is available evidence. Both Janssen and the ERG noted the significant limitations of this comparative evidence, but when incorporated in the economic model demonstrated that the ESK-NS remains cost-effective. We would like to highlight to the Committee that the psychological treatments were not deemed relevant during the NICE scoping workshop and were not part of the NICE scope for the appraisal, as any effect would be additive to any pharmacological treatment. We also note that the Committee's conclusion is inconsistent with TA367 and it should not be considered as a relevant comparator for this appraisal.

Section 7. Overall conclusion

The Committee have made an initial decision to reject ESK-NS as they believe it does not represent a cost-effective option for the treatment of TRD. Janssen urges the Committee to re-consider the previously submitted evidence and consider the additional evidence presented in our response to the ACD, which strongly supports the following:

- Patients are able to discontinue ESK-NS once reaching the recovery health state with a limited impact on the risk of recurrence and hence on their HRQoL. As such, patients will discontinue ESK-NS for reasons other than lack of efficacy once reaching the recovery health state, which is aligned to evidence from different sources. Additional discontinuation guidance could be included in the ESK-NS recommendation to provide considerable certainty that patients will discontinue once reaching the recovery health state.
- It is appropriate to include carer disutility in the base case analysis to account for the wide impact that TRD has on other people, and to be consistent with other NICE TAs.

- The Committee should consider the evidence versus the relevant comparators that Janssen has previously provided, but consider the limitations previously highlighted by the Company and the ERG.

ESK-NS has demonstrated impressive rates of response and remission in patients who have previously failed at least two OADs. ESK-NS is the first new antidepressant in 30 years with a novel mechanism of action, providing a much-needed new treatment option for patients with TRD in the NHS.

In our revised base case ICER, upon considering the Committee's concerns, ESK-NS is a consistently cost-effective treatment option for use in the NHS. The wider economic burden of TRD on society increases the cost effectiveness of ESK-NS. Janssen therefore urge the Committee to reverse their initial decision, to allow patients routine access to this important new treatment.

In the section below we provide further response to other issues and factual inaccuracies.

Other issues and factual inaccuracies

There are a number of additional minor issues which Janssen wish to comment on. These include:

- The population included in the ESK-NS clinical trials, despite the Committee's questions regarding its generalisability, is appropriate for decision making by NICE
- Analyses show that unblinding was not an issue in the clinical trials
- NHS stakeholders have indicated that significant investment is not needed for the introduction of ESK-NS to the NHS
- The efficacy of subsequent treatments is based on a clinically validated and robust publication
- Supervising multiple patients in the post-administration observation is clinically reasonable and based on extensive clinical input
- Previously provided data on the dosing and frequency of administration shows ESK-NS remains cost effective
- Other issues and factual inaccuracies in the ACD

Each of these issues are described below.

8.1 The population included in the clinical trials, despite the Committee's questions regarding its generalisability, is appropriate for decision making by NICE

NICE ACD Section 3.7, p9: "*The committee concluded that the extent of the exclusion criteria and the lack of participants from England in the trials mean the evidence for esketamine is limited in generalisability to the NHS population with treatment-resistant depression."*

The "extent of the exclusion criteria" in the ESK-NS trials are consistent with multiple other trials in depression and the clinical evidence from TA367. While it is acknowledged that the trials excluded patients with moderate to severe alcohol abuse, psychiatric comorbidities and suicidal intent, the exclusion criteria applied in the ESK-NS trials are consistent to other antidepressant trials in depression. For example, the exclusion criteria are consistent with the trials in the appraisal of TA367 (vortioxetine for treating major depressive episodes), which excluded patients with a dual diagnosis, previous treatment with ECT, or those with suicidal ideation/behaviours.

It is important to note that despite having no clinical evidence in the patient population in adults whose condition has responded inadequately to two antidepressants within the current episode, TA367 recommends vortioxetine for this patient population.

As noted above in Section 4.4, Janssen intend to conduct a prospective observational study to collect the characteristics and the clinical outcomes of patients with TRD in the NHS. Janssen are willing to share the study protocol and data with NICE.

8.2 Analyses show that unblinding was not an issue in the clinical trials

NICE ACD, Section 3.6, 9: *"The committee acknowledged the company's attempts to blind the treatments but noted that blinding is difficult, given the dissociative symptoms experienced by people after they had esketamine.*"

As a result of a number of factors, unblinding was not an issue in the ESK-NS trials. Several measures were taken during study conduct to ensure blinding was maintained. This included having remote, independent, blinded MADRS assessments and using a bittering agent in the placebo nasal spray. The MADRS assessments were performed prior to dosing (if a dosing was planned for that visit) and, during the Optimisation and Maintenance Phases, they were performed weekly for all subjects regardless of dose frequency.

Only ~26.1% of patients receiving ESK-NS experienced dissociative effects within the TRANSFORM-2 study. Furthermore, there were also reported cases of dissociation in the OAD+ PBO-NS arm. As previously noted in the Company Submission (p135 of Committee papers), a *post-hoc* analysis found dissociation not to be correlated with antidepressant treatment effect in the ESK-NS trials (4) and that dissociation also occurred in the OAD + PBO-NS arm. This shows that the dissociative effects did not result in unblinding of the studies.

8.3 NHS stakeholders have indicated that significant investment is not needed for the introduction of ESK-NS to the NHS.

NICE ACD Section 3.17, p18*: "The committee noted the results of a survey conducted by the company which found that 18% of NHS Trusts had no specific plans on how they would adopt esketamine treatment. Therefore, the committee considered that some infrastructure costs may not be captured in the model. The committee acknowledged that the time needed to implement esketamine was unclear but that it is likely to be at least 6 months."*

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. The feedback was collected as part of the mandatory NHS advanced notification exercise, using semi-structured interview techniques 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 and 10 ECT managers and leads across the NHS. All NHS stakeholders interviewed indicated that there would be no requirement to invest in new infrastructure. Whilst it is apparent that the current staffing resource will need to change to implement ESK-NS, feedback from NHS at Trust level has clearly said that significant infrastructure investments are not required.

8.4 The efficacy of subsequent treatments is based on a clinically validated and robust publication

NICE ACD, Section 3.11, p13: *"The ERG also noted that the modelled effectiveness of subsequent treatments appeared to be underestimated."*

The source of the effectiveness of the best supportive care treatment efficacy was taken from a published NICE HTA monograph on augmentation with lithium or an AP in TRD. This data source was published by an ERG and validated as appropriate source with four UK psychiatrists. It was confirmed by the authors that the clinical experts considered STAR*D in their estimation of the Best Supportive Care (BSC) efficacy in the HTA monograph.

NICE and the ERG have not validated their judgement that the efficacy of subsequent treatments is an underestimation with clinicians. In their judgement of the efficacy of subsequent therapies, the ERG has not considered that BSC is 7th treatment line and is applied for all subsequent lines. As

acknowledged by the NICE Committee in TA367, STAR*D is the best evidence on the prognosis for people having subsequent lines of treatment. If using the ERG approach to model subsequent treatments, we note that the response and remission rates of 7th line MDD and subsequent lines are considerably higher (~38% and ~22%) than 4th line MDD in the STAR*D study (~29% and ~13%), at 14 weeks (Table 6).

Table 6: Remission and response rates applying the ERG method of subsequent treatment efficacy

	ERG scenario method of implementing subsequent treatments		**Comparison to STAR*D data**	
	4-weekly Remission	4-weekly Response (excluding remission)	Remission at 14 weeks	Response at 14 weeks (excluding remission)
TRD Line 1 (3rd line MDD)			13.7%	16.8%
TRD Line 2 (4th line MDD)	25.2%	17.8%	13.0%	16.0%
TRD Line 3 (5th line MDD)	23.9%	17.3%		
TRD Line 4 (6th line MDD)	22.7%	16.8%		
BSC	21.5%	16.3%		

The above shows that the currently used assumptions in the company base case are appropriate, and the ERG scenario including clinically unreasonable and unvalidated assumptions on the efficacy of subsequent treatments should be considered inappropriate.

8.5 Supervising multiple patients in the post-administration observation is clinically reasonable and based on extensive clinical input

NICE ACD, Section 3.16,p 17: *"In its model, the company assumed a ratio of 2 nurses to 6 patients during the administration of esketamine and 1 nurse to 6 patients during the post-administration monitoring. The ERG preferred to model a 1:1 ratio throughout administration and monitoring because it considered this to be the most plausible in clinical practice. The NHS commissioning expert noted that because esketamine is a schedule 2 drug, it requires 2 healthcare professionals during part of the administration stage and it's subject to the full controlled drug requirements relating to prescriptions and storage. However, it may be reasonable to have a ratio of 1 nurse to 6 patients during the monitoring of esketamine. The clinical expert suggested that a ratio of 1:1 or 1:2 may be necessary when the service first starts, but that the ratio may increase to one nurse to a group of patients once the service becomes experienced and established. The patient expert, who was receiving treatment one to one, said that building a relationship with the healthcare professional was an important component for treatment and recovery. The company clarified that their model included a band 5 and a band 4 nurse to administer esketamine and a band 5 nurse for post-administration monitoring. The committee considered that more additional training or more experienced nurses may be needed to manage the dissociative effects of esketamine. The committee concluded that the company's model may have underestimated the nurse experience required to safely administer, monitor and manage people receiving esketamine. The committee also concluded that, without further evidence, incremental cost-effectiveness ratios (ICERs) should be estimated based on nurse to patient ratios across a range from 1:1 to 1:6 during the monitoring phase of administration."*

Janssen do not believe the 1:1 nurse: patient ratio for the post-administration observation as used as the lower bound by the Committee is appropriate. The rare occasions where a 1:1 nurse: patient ratio is expected to occur in clinical practice are included in the average ratio of 1:2 and 1:6 as included in the revised company base case, which is based on extensive clinical input. The totality of evidence from all interactions Janssen have had with NHS clinical experts shows that the monitoring of multiple patients simultaneously will occur when ESK-NS is used in NHS clinical practice.

In an advisory board to discuss this topic, Janssen consulted with 6 clinical experts with first-hand experience in treating patients with TRD. These clinicians were consulted with and were in consensus with the assumptions that 1 nurse can observe 6 patients during the post-administration observation period based on the safety profile of ESK-NS.

Additional market research of 59 UK psychiatrists showed that multiple patients can be monitored simultaneously (see p726 of Committee Papers). On average, clinicians estimated that one nurse would be able to monitor 4-6 patients concurrently. Furthermore, clinicians stated that the ratio of patients to nurses is likely to increase over time as clinical familiarity increases. The revised company base case now includes a range of ICERs from 1:2 to 1:6 to reflect this.

In contrast with the company assumptions, the ERG/ NICE team have not validated their assumption of 1:1 nurse: patient ratio with any clinical experts familiar with ESK-NS or the nature of the monitoring required. As noted previously, nurse ratios of 1:1 or 1:2 ratios are recommended for intensive/critical care or neonatal care (3). The requirement of the nurse post-ESK-NS administration is predominantly hands-off patient observation. The nurse only requires monitoring blood pressure one or more times during post-administration observation. It seems unreasonable to assume that a nurse could only manage to observe a single patient who has received ESK-NS, especially when compared to these other, significantly more intensive care settings.

A visual graphic (Figure 2) to further clarify the Committee's understanding of the administration model and assumptions is provided below. Throughout the post-administration observation, there are only 10-20 minutes where there are 6 patients observed by 1 nurse. For the remainder of the time in the clinic, there are 1-2 nurses with less than 6 patients.

Figure 2: Visual graph to display ESK-NS administration assumptions

<table>
<tr><th>Minutes after clinic started</th><th>Patient 1</th><th>Patient 2</th><th>Patient 3</th><th>Patient 4</th><th>Patient 5</th><th>Patient 6</th></tr>
<tr><td>10</td><td>Supervise self-administration</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>20</td><td rowspan="4">Monitoring</td><td>Supervise self-administration</td><td></td><td></td><td></td><td></td></tr>
<tr><td>30</td><td rowspan="3">Monitoring</td><td>Supervise self-administration</td><td></td><td></td><td></td></tr>
<tr><td>40</td><td rowspan="3">Monitoring</td><td>Supervise self-administration</td><td></td><td></td></tr>
<tr><td>50</td><td rowspan="3">Monitoring</td><td>Supervise self-administration</td><td></td></tr>
<tr><td>60</td><td rowspan="3">Monitoring</td><td rowspan="4">Monitoring</td><td>Supervise self-administration</td></tr>
<tr><td>70</td><td>Discharge</td><td rowspan="3">Monitoring</td></tr>
<tr><td>80</td><td></td><td>Discharge</td></tr>
<tr><td>90</td><td></td><td></td><td>Discharge</td><td rowspan="3">Monitoring</td></tr>
<tr><td>100</td><td></td><td></td><td></td><td>Discharge</td></tr>
<tr><td>110</td><td></td><td></td><td></td><td></td><td>Discharge</td></tr>
<tr><td>120</td><td></td><td></td><td></td><td></td><td></td><td>Discharge</td></tr>
</table>

8.6 Previously provided data on the dosing and frequency of administration shows ESK-NS remains cost effective

NICE ACD Section 3.15, p17: *"The ERG confirmed that the dose of esketamine used in the model was an average from the trial evidence. The committee was concerned that it was unclear what proportion of people received the 56 mg or the 84 mg doses and that no dose response curve was presented. It also considered that the company model did not fully account for a scenario in which a greater proportion of people receive the more expensive 84 mg dose, or the proportion who would receive the dose once weekly compared with once every 2 weeks. The committee concluded that the model may underestimate the cost of a course of esketamine treatment. The committee would like to see evidence of the proportions of people on each dose and frequencies of administrations, and scenarios exploring the effects of these assumptions on the cost-effectiveness results."*

As noted in the Company Submission, 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 (p191 of Committee Papers). Janssen previously provided an analysis considering variation of the dosing from the clinical trial data. This was already presented in a sensitivity analysis varying the dose in the original CS (Table 64 and Table 65 of CS, Page P207/876 of Committee papers). The number of devices per administration and administrations per week was varied to explore the impact on cost-effectiveness. The original company submission showed that

the number of ESK-NS + OAD administrations per week during the continuation phase would need to nearly double to 1.32 for the ICER to reach £20,000. 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 for the ICER to reach £20,000, both of which are above the maximum dose limit of three per administration.

Similarly, using the revised base case assumptions (and conservatively assuming a 2:1 ratio of patients to nurse observation), the number of ESK-NS + OAD administrations per week during the continuation phase would need to increase by ~60% (1.07 vs 0.71 per week) for the ICER to reach £20,000. The number of ESK-NS devices per administration during the continuation phase would need to be 4.07 and during the acute phase (Weeks 1–4) would need to be 4.51 for the ICER to reach £20,000, both of which are above the maximum dose limit of three per administration.

8.7 Other issues and factual inaccuracies in the ACD:

Minor factual inaccuracies and/or errors are tabulated below:

Location of factual inaccuracy	**Issue**	**Correction**
Slide 8 of Committee Slides	SUSTAIN-1 is incorrectly described as a single arm, long term, follow up study	SUSTAIN-1 used a randomised withdrawal design to assess, in a double-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.
NICE ACD, Section 3.7	*"TRANSFORM-3….were only used as supporting evidence, and the data were not included as part of the company's model."*	The revised company model in response to the clarification questions includes data from TRANSFORM-3. As the ERG note in P597 of the Committee papers: "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"

NICE ACD, Section 3.6 (multiple times)	Treatment included in ESK-NS clinical trials	When describing the clinical trials, the active treatment should be described as "esketamine nasal spray plus oral antidepressant" rather than "esketamine"
NICE ACD, Section 3.6:	The wording to describe the treatments in the TRANSFORM-2 and SUSTAIN-1 studies should be corrected to include a newly initiated OAD plus placebo, as per the study designs.	TRANSFORM-2 found significantly improved response rates (69.3% compared with 52%) and remission rates (52.5% compared with 31%) for esketamine **nasal spray plus a newly initiated OAD** over **a newly initiated** OAD **plus placebo nasal spray** SUSTAIN-1 found significantly lower relapse rates associated with esketamine **nasal spray plus a newly initiated OAD** compared with OAD **plus placebo nasal spray** for stable remitters (26.7% compared with 45.3%) and for stable responders (25.8% compared with 57.6%).
Committee papers, p 454-458	Patient experience whilst receiving treatment with IV ketamine was described instead of experience with ESK-NS	We appreciate the patients' perspective but note that IV ketamine is different from ESK-NS.
ACD Section 3.7, p 7	*"The committee heard from other clinical experts who noted that ECT should also be a comparator because the processes involved in administering ESK-NS are similar to those for ECT."*	This is not a relevant rationale for the definition of a comparator. Furthermore, the processes for administering ESK-NS and ECT are not similar, given the requirements for anaesthetics and a full day admission for ECT.
ACD Section 3.17, p18	*"The committee heard that adopting esketamine would result in displacement of other mental health treatments because of its cost"*	Other mental health treatments will be displaced because of the block contract funding system, not only due to the ESK-NS cost.
ACD Section 3.17, p18	*"The staff training to administer and monitor esketamine may not have been accounted for in the model because additional training is needed to manage dissociative effects."*	Janssen will provide additional educational materials for clinicians and patients. On request further training can be provided. Additional costs of

		training should therefore not be included in the model.
NICE ACD Section 3.8, p11	*"However, the committee questioned whether the additional clinical contact involved in administering esketamine included psychological therapy"*	Janssen would like to clarify that psychological therapy is not delivered during these clinic visits. The increased clinical contact as a result of the additional visits is not equivalent to receiving psychological therapy.
NICE ACD Section 3.8, p11	*"Committee also recalled that CBT could not be given at the same time as esketamine"*	Janssen would like to clarify that we are not proposing patients would have or not have CBT with ESK-NS. Patients are able to receive CBT prior to ESK-NS self-administration or at another day or timepoint. As noted above, in the clinical trials if patients received CBT before ESK-NS, CBT could be continued whilst ESK-NS + OAD treatment was ongoing.
NICE ACD Section 3.5, p7	*"The clinical expert added that, because of the dissociative effects of esketamine treatment, someone would not be able to have psychological therapy immediately after having esketamine"*	Janssen wish to clarify that it is possible to receive psychological therapy whilst also receiving ESK-NS treatment. The statement included in the ACD is not correct for two reasons: • Only 26.1% of patients receiving ESK-NS experienced dissociative effects within the TRANSFORM-2 study. • Whilst not able to have psychological therapy immediately after ESK, CBT could take place whilst the patient is not receiving ESK-NS, e.g., just before self-administration or at another time when the patient is not receiving ESK-NS

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3. Royal College of Nursing, 2011. Guidance on safe nurse staffing levels in the UK.
4. Chen et al, 2018. Relationship between antidepressant effects of esketamine nasal spray and perceptual disturbances. Presented at The American College of Neuropsychopharmacology (ACNP) 57th Annual Meeting, December 9-13, 2018, Hollywood, FL, USA

Esketamine nasal spray for treatment resistant depression (ID1414)

Janssen additional response to NICE appraisal consultation determination (ACD)

01st April 2020

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
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
Name of commentator person completing form:	Tom Denee

Follow up on Janssen's 18th February response to the ACD of esketamine nasal spray for treatment resistant depression (TRD) (ID1414)

In addition to our response to the ACD submitted on 18th February, Janssen have been advised to submit additional scenario analyses as discussed with Meindert Boysen and Helen Knight on 20th February.

We understand that the Committee are concerned that indefinite improvement in quality of life could lead to undue benefit accruing to esketamine nasal spray (ESK-NS) over time, particularly in light of the clinical experts' description of the disease. As such, despite the Committee's statement that they believe people **would** discontinue ESK-NS over a 2-year period (for reasons other than a lack of efficacy), the Committee concluded that the least biased estimate of cost effectiveness was that no patients will discontinue ESK-NS due to reasons other than efficacy. We note in the ACD (Section 3.12):

"The committee considered that assuming an indefinite improvement in quality of life after stopping esketamine treatment was implausible. It recognised that people may have changes in MADRS score below the threshold for 'relapse' but that still affect quality of life. The clinical experts supported this view and explained that the MADRS is a non-linear scale, meaning that increases in score at the lower end of the scale represent a larger change in symptoms than at higher points of the scale. The ERG and clinical experts also highlighted that there were no data to accurately determine discontinuation rates. Because of this, the ERG preferred to assume no discontinuation for reasons other than lack of efficacy at 2 years. The committee considered that it's likely that people would stop esketamine for other reasons over a 2-year period, but that it's unclear how many……The committee concluded that, on balance, without data the least biased estimate of cost effectiveness would be to not include discontinuation of esketamine for reasons other than lack of efficacy."

In our previous response to the ACD we have explored scenarios with an increase in recurrence rate after discontinuation of ESK-NS following successful treatment (section 3.5 of previous ACD response). Experiencing recurrence is associated with a significant worsening of quality of life as patients re-enter the depression health state. After successful treatment, the rates of recurrence are equivalent for both the ESK-NS + oral antidepressant (OAD) arm and the OAD arm i.e. a Hazard Ratio of 1 is applied. This means that in the base case model there is no additional treatment effect of ESK-NS + OAD over the OAD arm when patients are in recovery. As such, there is no indefinite improvement in quality of life after stopping ESK-NS as stated in the ACD (Section 3.12).

Over and above this, based upon discussions during the follow up meeting on the 20th February, in this additional response we have explored the remaining issues:

1) The rate of treatment discontinuation of ESK-NS for patients in recovery following successful treatment considering the previously submitted ESK-NS discontinuation guidance
2) The impact of discontinuing ESK-NS following successful treatment on QALYs for patients worsening but not reaching the threshold of recurrence (i.e., introducing a 'waning effect')

These two areas are explored individually in Section 1.0 and Section 2.0 respectively. In Section 3.0, a combined analysis of both areas is provided for additional clarity on the cost-effectiveness of ESK-NS. Overall, these additional analyses provide support for the Committee to accept their preferred assumption that patients would discontinue ESK-NS due to reasons other than lack of efficacy, whilst

ensuring that cost-effectiveness estimates are not biased by an over accrual of QALYs for patients treated with ESK-NS + OAD.

In all scenarios presented, and when using the Committee's preferred assumptions, ESK-NS remains a cost-effective use of NHS resources for the treatment of TRD. In addition, a new patient access scheme (PAS) - [redacted] - has been proposed that further improves the cost effectiveness of ESK-NS, with the majority of these highly conservative analyses below the £20,000 per QALY threshold.

Section 1.0: The treatment discontinuation guidance and market research from 25 UK clinicians provide strong evidence of the likely rate of discontinuation of ESK-NS in clinical practice and should form the basis for the Committee's decision on this area of uncertainty.

We note that the rate of ESK-NS discontinuation in recovery was an area of uncertainty for the Committee:

'The Committee considered that it's likely that people would stop esketamine for other reasons over a 2-year period, but that it's unclear how many.'

1.1 Previously submitted discontinuation guidance provides additional certainty on treatment discontinuation in recovery

As noted in Section 4.3 of the Response to the ACD (18th Feb), the previously submitted discontinuation guidance provides additional certainty for the Committee that patients in recovery will discontinue treatment for reasons other than lack of efficacy.

The 25 UK clinicians who participated in a market research also indicated that discontinuation guidance for ESK-NS as recommended by NICE in any guidance would be the most important factor for informing the treatment duration of ESK-NS in NHS clinical practice.

At the NICE technical engagement meeting on 6th November 2019, the NICE team stated that guidance on discontinuation of ESK-NS would help to mitigate the uncertainty around the treatment duration of ESK-NS in NHS clinical practice. Together with the clinical community, and based on the available evidence, Janssen submitted practical and clinically relevant discontinuation guidance for ESK-NS to NICE in the response to the Draft Technical Report.

The proposed clinical guidance on discontinuing ESK-NS is below:

ESK-NS treatment discontinuation guidance

- **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**
- **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**
- **Exceptions will occur based on clinical judgement (e.g., some patients may exceptionally require longer treatment as is seen with Electroconvulsive Therapy (ECT))**

This is also aligned with the discontinuation recommendations for current antidepressants in NICE CG90: Depression in Adults: recognition and management. The recommendations state: *'Review with the person with depression the need for continued antidepressant treatment beyond 6 months after remission'* and '*Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse'* (1).

1.2 Scenarios to explore rates of treatment discontinuation of ESK-NS in recovery

In this section we have further explored the impact of the rate of discontinuing ESK-NS for patients in recovery. The market research from 25 UK psychiatrists represents the most robust source of data

to inform the discontinuation of ESK-NS in NHS clinical practice. The market research data included patients at high risk and low of relapse, which is reflective of clinical practice.

The results of the market research data are similar to findings from the literature and NICE clinical guidelines for antidepressant treatment discontinuation. A published UK study on treatment duration of antidepressants in NHS clinical practice found a median duration of 56 days for antidepressant therapy, with 14.42% of patients continuing antidepressant treatment beyond two years (2).

In the scenarios below in Table 1, we have based the rates of treatment discontinuation on the market research data and the recommendations in the discontinuation guidance. Scenario A is based on the likely discontinuation of patients as per the discontinuation guidance. Scenario B is based on the market research data, which is more conservative than Scenario A. Scenario C is the most conservative scenario and shows that even when the proportion of patients continuing treatment beyond two years is almost doubled (to 30% from the 16% used in the market research data) and no patients discontinue at 9 months, ESK-NS remains cost effective at a threshold of £20,000 per QALY.

Table 1: Impact of treatment discontinuation scenarios on ICER

Treatment discontinuation input	**ICER (£/QALY) using ERG/NICE model assumptions***
No discontinuation for other reasons than efficacy	[redacted]
Scenario A: **50% will discontinue after 9 months in remission and 1% remain on treatment after 2 years**	[redacted]
Scenario B (base case): **Data from market research from 25 UK psychiatrists: 52% will discontinue after 9 months in remission, 32% between nine months and two years, and 16% remain on treatment after 2 years**	[redacted]
Scenario C: **0% discontinue at 9 months, 70% of patients discontinue by 2 years and 30% continue treatment beyond 2 years**	[redacted]

**The range of ICERs (£/QALY) reflects range of administration cost assumptions (1:6 – 1:1 for post self-administration nurse : patient ratio). ICERs are all based on NICE/ERG preferred assumptions (no excess mortality, no treatment adjustment, 20-year time horizon, no carer disutility)*

Section 2.0: The waning effect explores the committee's key concerns around patients worsening but not reaching the threshold of recurrence following ESK-NS treatment discontinuation and demonstrates that ESK-NS remains cost effective even with a waning effect included in the model

We note specifically that the Committee: *'recognised that people may have changes in MADRS score below the threshold of relapse but that still affect quality of life'* (ACD section 3.12 p15).

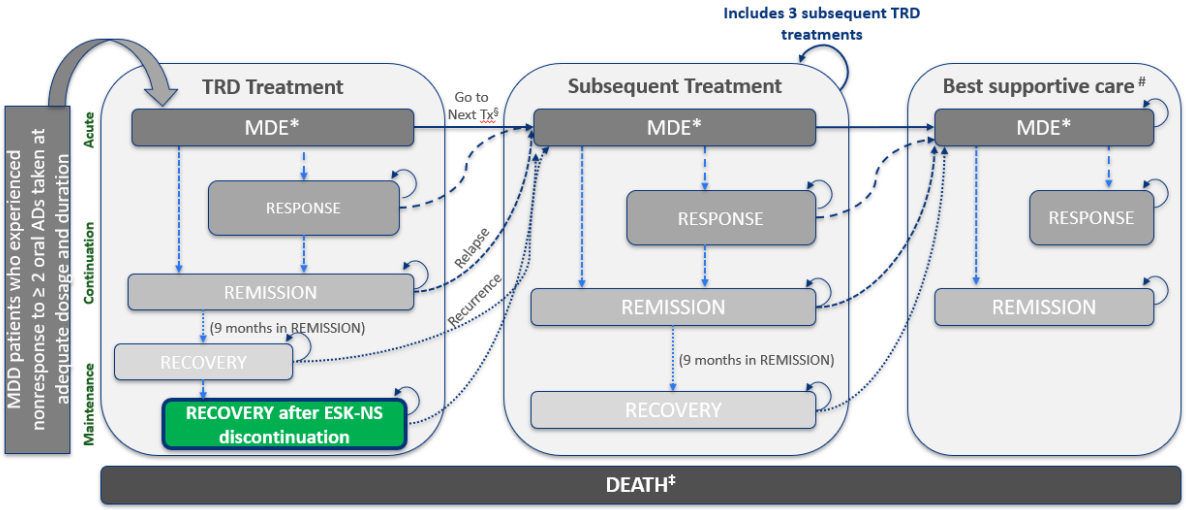
Below, we have therefore explored the impact of discontinuing ESK-NS on a patient's quality of life, beyond the rate of recurrence that we explored in our previous response to the ACD, to address the Committee's concerns. For simplicity we have called this a 'waning effect'.

This waning effect reflects the Committee's observation that there are likely to be changes in symptoms ('sub-threshold changes') measured via the MADRS scale that do not lead to the patient crossing the threshold of recurrence and entering a new depressive episode. For example, a patient may have an increase, in reduced sleep, one of the 10 symptoms captured in the MADRS. This, however, is insufficient to cause a recurrence of depression, but this will have an impact on quality of life.

In order to implement the waning effect, a new health state has been added to the Markov model to whom patients will move if they discontinue ESK-NS after successful treatment; see Figure 1 for the model diagram including the new health state 'Recovery after ESK-NS discontinuation'.

Note that in the model scenarios, the waning effect (and resulting impact on the total QALYs over the time horizon) is purely due to a change in the utility of the health state of patients after discontinuing ESK-NS in recovery. There are no changes in incremental Life Years Gained in these scenarios, given the Committee's preference for exclusion of the excess mortality for the MDE health state.

Figure 1: Markov Model diagram including a new health state following 'waning': recovery after ESK-NS discontinuation



**MDE = major depressive episode. Green box reflects the new recovery health state following ESK-NS discontinuation when patients are in recovery.*

We acknowledge the clinical expert's statement during the Appraisal Committee meeting that it can be '*difficult to determine when an episode of depression begins or ends'* and that the condition is characterised by *'waxing and waning'* [ACD 3.10]. It is important to note that although patients may

have a waning of the disease at certain times, equally, patients may also have an improvement of their symptoms at other times. The continuous deterioration and improvement in symptoms are difficult to characterise in the economic model. As a result, we have focused exclusively and conservatively on waning effect to explore the impact of this on cost-effectiveness.

2.1 *Post-hoc* analyses from the ESK-NS trials suggest there is a minimal waning effect after discontinuing ESK-NS in recovery

The literature states that there is a 'paucity of psychometric studies addressing the phenomenology of depressed patients after benefiting from treatment' (3). There exists only limited evidence on the existence of a waning effect after discontinuation of ESK-NS in recovery. The only data available, from the ESK-NS long term studies SUSTAIN-1 and SUSTAIN-2 showed a very limited impact of discontinuing ESK-NS in recovery on a patient's quality of life. This is therefore the best evidence available to inform this waning effect.

Previously, Janssen have submitted a *post-hoc* analysis of SUSTAIN-1 (see Table 3 of Technical Engagement response, p39/40), the randomised double-blind long-term relapse prevention study. The SUSTAIN-1 data showed that, 2 weeks after discontinuing ESK-NS in recovery, stable remitters had a mean disutility of [redacted] (n=25). In summary, the SUSTAIN-1 *post-hoc* data show there is a very minimal waning effect on quality of life after discontinuation of ESK-NS once a patient reaches recovery following successful treatment.

SUSTAIN-2 is a long-term single-arm safety study of ESK-NS, where discontinuation of ESK-NS occurred when the study was terminated. The study included a considerable number of patients (n=74) who have been receiving ESK-NS + OAD and been in stable remission for at least 9 months when the study was terminated. The follow up period after study termination was 4 weeks, which allowed to assess the impact of discontinuing ESK-NS treatment when patients are in recovery. A *post-hoc* analysis of SUSTAIN-2 suggests only a minimal waning effect after discontinuing ESK-NS, which is supportive of SUSTAIN-1 previously submitted. Patients from the SUSTAIN-2 study who achieved recovery with ESK-NS + OAD, then discontinued ESK-NS whilst in recovery had a change in utility of [redacted] 4 weeks after discontinuation.

In order to implement this in the model, a disutility of [redacted] is applied indefinitely in the 20-year time horizon in Scenario 1, below. In Scenario 2 and 3, the disutility based on SUSTAIN-2 has been doubled and tripled respectively, and applied indefinitely once patients discontinue ESK-NS in recovery.

Please note that patients in SUSTAIN-1 and SUSTAIN-2 had to discontinue treatment abruptly when the study terminated, which might increase the impact of discontinuing. This does not reflect how the treatment will be discontinued in NHS clinical practice.

As noted above, patients in the model also remain at risk of recurrence throughout 20-year time horizon and are at risk of moving back to the MDE health state and subject to a significant worsening of quality of life (with a subsequent impact on QALYs) as a result.

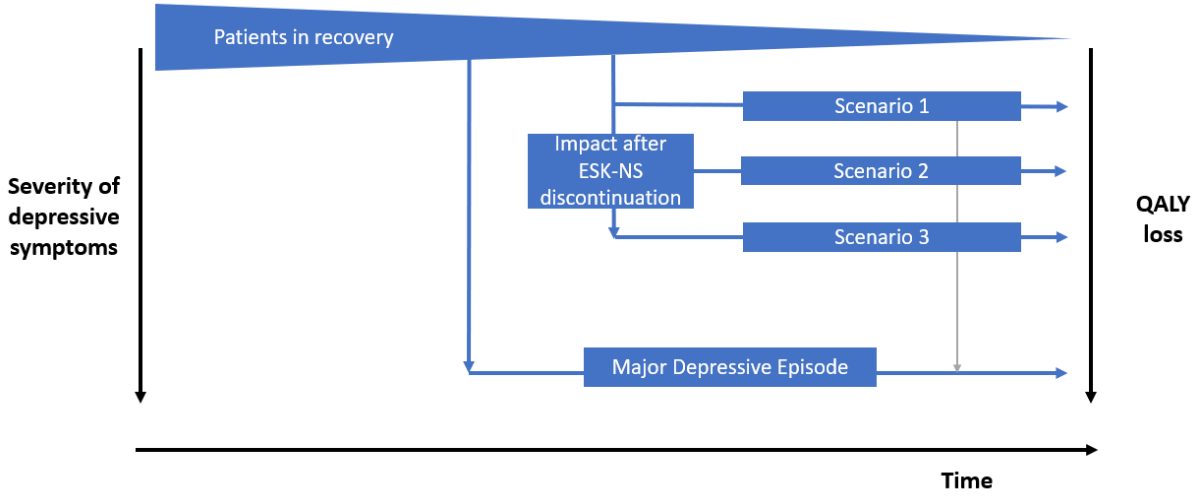
2.2 Scenarios to explore impact waning after ESK-NS discontinuation in recovery

For the exploration of waning after stopping ESK-NS, three additional scenarios are presented using the SUSTAIN-2 data as a basis to explore this uncertainty:

- Scenario 1: Applying a waning effect based on data from discontinuing ESK-NS in the SUSTAIN-2 *post hoc* analysis (disutility of [redacted]). This scenario provides the most robust data to inform this topic, given it represents observed data from people discontinuing ESK-NS in recovery following successful treatment.
- Scenario 2: Applying double the waning based on the SUSTAIN-2 *post hoc* analysis (disutility of [redacted])
- Scenario 3: Applying double the waning based on the SUSTAIN-2 *post hoc* analysis (disutility of [redacted])

The scenarios are depicted in Figure 2 below.

Figure 2: Visual representation of scenarios to represent a waning effect after ESK-NS discontinuation



In all three scenarios, the decrease in quality of life is assumed to exist indefinitely, as long as the patient remains in the recovery health state after discontinuation of ESK-NS. This is likely to be conservative, given that any change in quality of life (waning impact) of antidepressant discontinuation is largest in the first 4 weeks and is expected to reduce over time (4,5).

The three scenarios presented above include all of the Committee's preferred assumptions, apart from having no treatment discontinuation for reasons other than loss of efficacy, which has been explored in Section 1 of the response above. The company's market research data is used to inform the treatment discontinuation for reasons other than loss of efficacy. This is because of the Committee's statement that they believed people would discontinue ESK-NS for reasons other than lack of efficacy over a 2-year period.

To put this additional change into perspective, the impact of implementing these scenarios is a reduction in the total incremental QALYs over the time horizon by 9% - 27% compared to the ERG/NICE base case (see Table 2 below). Even when tripling the disutility from SUSTAIN-2, the cost effectiveness of ESK-NS is below the £20,000 per QALY threshold (including the new PAS price). Other assumptions used in these scenarios can be found in Appendix A.

Table 2: Scenarios to demonstrate a waning effect of discontinuation of ESK-NS in recovery

Scenario	Utility after ESK-NS discontinuation in recovery (disutility applied in recovery)	Total Incremental QALYs over model time horizon	Incremental QALY difference vs base case (%)	ICER (£/QALY) using ERG/NICE model assumptions* (apart from MR**

				data for ESK-NS discontinuation)
ERG/NICE model assumptions* but using MR data for discontinuing. No impact of discontinuing on QALYs**	0.862 (0)	0.249	0	[redacted]
Scenario 1: Waning based on SUSTAIN-2 *post hoc* analysis	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Double the waning based on SUSTAIN-2 *post hoc* analysis	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Triple the waning based on SUSTAIN-2 *post hoc* analysis	[redacted]	[redacted]	[redacted]	[redacted]

**The range of ICERs (£/QALY) reflects range of administration cost assumptions (1:6 – 1:1 for post self-administration nurse : patient ratio). ICERs are all based on NICE/ERG preferred assumptions (no excess mortality, no treatment adjustment, 20-year time horizon, no carer disutility).*
***MR is Market Research data providing treatment discontinuation estimates based on feedback of 25 UK psychiatrists*

Section 3.0 Combining the scenarios for treatment discontinuation and waning effect, alongside the PAS, demonstrates that ESK-NS remains a cost-effective use of NHS resources to treat patients with TRD.

We have combined the treatment duration (section 1.0) and waning effect scenarios (section 2.0) to illustrate the combined impact of varying these two areas of uncertainty, which are the most significant factors in determining the cost effectiveness of ESK-NS. In this analysis, shown in Table 3 below, the majority of ICERs are under £20,000 per QALY and all under £30,00 per QALY, even when the most conservative assumptions are combined and applied.

Table 3: Scenarios demonstrating cost effectiveness of ESK-NS when varying waning effect of ESK-NS discontinuation and rates of ESK-NS discontinuation in recovery (with PAS)

Treatment discontinuation	**Waning effect**			
	No waning	**Scenario 1: Waning based on SUSTAIN-2 *post hoc* analysis**	**Scenario 2: Double the waning based on**	**Scenario 3: Triple the waning based on**

			SUSTAIN-2 *post hoc* analysis	**SUSTAIN-2 *post hoc* analysis**
No discontinuation for other reasons than efficacy	[redacted]	N/A		
Scenario A: 50% after 9 months in remission and 1% beyond 2 years	[redacted]	[redacted]	[redacted]	[redacted]
Scenario B: MR data - 52% discontinue after 9 months in remission and 16% continue beyond 2 years**	[redacted]	[redacted]	[redacted]	[redacted]
Scenario C: 0% discontinue at 9 months and 30% continue beyond 2 years	[redacted]	[redacted]	[redacted]	[redacted]

The range of ICERs (£/QALY) reflects range of administration cost assumptions (1:6 – 1:1 for post self-administration nurse : patient ratio). ICERs are all based on NICE/ERG preferred assumptions (no excess mortality, no treatment adjustment, 20-year time horizon, no carer disutility).
***MR is Market Research data providing treatment discontinuation estimates based on feedback of 25 UK psychiatrists*

4.0 Conclusion of additional analyses

In conclusion, we have provided additional scenarios looking at the combined impact of both the rate of ESK-NS discontinuation and a waning effect. The inclusion of the new PAS for ESK-NS ensures that the majority of ICERs are below £20,000 per QALY and that all scenarios remain below £30,000 per QALY, representing a cost-effective use of NHSE resources for patients with TRD.

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Appendix A: Other assumptions used to explore impact of waning effect after ESK-NS discontinuation in recovery

Key Parameters	**Revised base case assumptions**	**Scenario 1: Waning based on SUSTAIN-2 *post hoc* analysis**	**Scenario 2: Double the waning based on SUSTAIN-2 *post hoc* analysis**	**Scenario 3: Triple the waning based on SUSTAIN-2 *post hoc* analysis**
Treatment dis-continuation	Data from market research from 25 UK psychiatrists			
Recurrence risk ESK-NS + OAD	0.028 (pooled SUSTAIN-1 arms)			
Recurrence risk OAD + PBO-NS	0.028 (pooled SUSTAIN-1 arms)			
Recurrence risk after ESK-NS dis-continuation	0.028 (pooled SUSTAIN-1 arms)			
Administration cost	1:6 – **1:2**	1:6 - 1:1		
Other key assumptions	• No adjustment for clinic visits • No excess mortality for MDE health state • 20-year time horizon			
	• **Including carer disutility**	• No carer disutility		
Retreatment	No			
	[redacted]	[redacted]	[redacted]	[redacted]

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	With regard to evidence, not all treatment comparators were included in the appraisal, in our view limiting the confidence that can be placed in the decision on the clinical effectiveness of esketamine in treatment-resistant depression.
2	With regard to costs, we are particularly concerned that the episodic nature of treatment-resistant depression has not been adequately taken into account by the committee in their preference for a 20-year time horizon for the calculation of quality-adjusted life years and treatment costs. SANE knows from our 25-year contact with callers to our helpline and those who use our call-back service that depression can be highly episodic, with a good success rate when patients are compliant with treatment. Relapse can happen, but there can be long periods when a patient is 'in remission', and some can recover from depression with the right treatments and clinical support. It cannot be assumed that patients with treatment-resistant depression will need to stay on medication, including esketamine, for such a long period. The consultation document states: "The clinical expert explained that it is difficult to determine when an episode of depression begins or ends and characterized the 'waxing and waning' nature of the condition." The decision to regard treatment-resistant depression as "a chronic condition requiring a longer time horizon" is described as having been made "on balance". In view of the high variability in individual experience and the scale of difference between 5 and 20 years in calculating value and costs, we believe that work should be done to arrive at more reliable estimates of treatment value and costs for esketamine over a patient's lifetime.
3	Uncertainty about the investment needed to adopt esketamine treatment in the NHS is another factor inhibiting an accurate judgement on the possible costs of its introduction. We would like to see a closer examination of the range of options for adopting eskatamine as a treatment, in order to provide a fuller assessment of the range of possible additional service requirements, taking account of the range of differing local circumstances, such as the availability of an ECT suite.
4	There are currently believed to be around 2.7 million people in the UK with treatment-resistant depression (when using the NICE definition of those who have not responded to two or more anti-depressants). As SANE stated in our submission to the committee, those living with treatment-resistant depression - both patients and carers - are impacted heavily in most aspects 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.
5	People with depression have to rely on medications that are 30 years old. Although these drugs can be life-saving for many people, they can have unpleasant side-effects and do not work for everyone. Esketamine is the first new compound that works in a fundamentally different way from other medications and, compared with other anti-depressants which can take as much as six to eight weeks to take full effect, can have an effect within 24 to 48 hours of being administered, potentially saving patients weeks or months of uncertainty. In our view this makes it important that a more robust view is formed on the clinical and cost-effectiveness of eskatamine. We consider it premature to disallow this innovative treatment to those for whom other treatments have proved ineffective, without a more comprehensive evidence base and a more positive view of the cost-benefiit ratio.
6	In the light of patient and clinical expert evidence, the appraisal committee concluded that treatment-resistant depression has a negative effect, including on families and carers, and "acknowledged that the effectiveness of current treatments for treatment-resistant

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	depression is limited and that there is an unmet need for new treatment options for the condition." In the press release announcing the decision, Meindert Boysen, the director of the centre for health technology evaluation at NICE said: "Our independent committee very much recognizes the impact treatment-resistant depression has on people, their families and carers, the clear need for effective treatment options, and the priority of addressing mental health challenges for the NHS." We hope the appraisal committee will examine further the basis of its decision and take these observations as its watchword in doing so.

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	table.
Example 1	We are concerned that this recommendation may imply that ……..
1	"But how much benefit it (esketamine) provides over other oral antidepressants with adjunctive therapy or electroconvulsive therapy is unclear because these treatments have not been compared directly (p3, Summary) "**The company did not provide evidence comparing esketamine with all relevant comparators." (Section 3.4, p7)** The evidence for adjunctive therapies such as lithium, or oral antipsychotics is not as strong as that reported in the recent trials of esketamine. These studies are highlighted in a recent systematic review and meta-analysis, that used the criteria of failure of depression to respond to two or more antidepressants (Strawbridge *et al.*, 2019). Furthermore, it is noted that comments were made on generalisability of esketamine studies to the UK population of people with Treatment Resistant Depression, these studies excluding people with co-morbid substance misuse and/or suicidal ideation. We note that using this approach, a number of NICE guidelines in mental illness would be obsolete, including recommendations from the 2009 Depression guideline that are cited by the ERG. Furthermore, virtually every recommendation for psychosocial interventions, based on evidence, would be rejected. Regarding suicide, evidence from trials of IV ketamine suggest beneficial effects of the compound on suicidal ideation, highlighted in a recent systematic review (Wilkinson *et al.*, 2018). The ERG stated that results of IV ketamine could not be extrapolated to esketamine. Though mode of administration is different, we consider that, because ketamine is the same broad class of drug, it is reasonable to make inferences about effects, in much the same way one would do for beta-blockers-and thus makes the point regarding generalisability and suicidality difficult to comprehend. The comparison with electroconvulsive therapy is puzzling- these are two entirely different treatments, and many people will not wish to have ECT, for reasons such as stigma, as well as medical or psychiatric co-morbidity. Clinically, people offered ECT for Treatment Resistant Depression are presenting more acutely unwell, have co-morbid psychosis (for which esketamine is contraindicated), and have more medical morbidity, e.g. have stopped eating or drinking. This is a very different cohort to those people entering the esketamine trials.
2 Also, the available evidence did not include psychological therapies.	"Also, the available evidence did not include psychological therapies. (p3, Sumary) **The effect of psychological therapy in addition to drug treatments is not clear" (Section 3.4, p7)** Whilst this is true, the ERG appears to have derived their conclusions about efficacy of psychotherapy in this population from a prior NICE guideline, as opposed to any empirical data. As highlighted in the systematic review above (Strawbridge et al, 2019) there are only two trials of psychotherapy in people with Treatment Resistant Depression, and only one in which a strict definition of failure of response to two antidepressants was used

	(Hauksson *et al.*, 2017). This CBT trial had a number of methodological limitations, including self-report of the outcome measure, and would not constitute high level of evidence, using any accepted criteria. Therefore, it is puzzling as to why use of psychotherapy should have any bearing here- especially given that this criterion was never placed on the evidence base for adjunctive therapies such as lithium or antipsychotic medication, mentioned above regarding generalisability.
3	**"Esketamine is unlikely to be cost effective for treatment-resistant depression" (p20)** **The committee's preferred modelling assumptions were reflected in the ERG's base-case analysis:** **A time horizon of 20 years** **The ERG had a preference of 20 years for analysis of outcome for the cost-effectiveness analysis, the question being "is TRD episodic or chronic in nature?"** This modelling appears instrumental to the overall decision, and both perspectives are difficult to understand. The literature cited by the ERG appears to not be generalisable to this clinical population, or to the esketamine trials, and both the ERG and drug company appear to be unaware of naturalistic studies of people with treatment resistant depression within the NHS. In terms of evidence presented, the ERG cites a meta-analysis of relapse in depression, which showed increased relapse upon discontinuation of antidepressant therapy versus placebo (Geddes *et al.*, 2003). It is questionable as to how generalisable this data is to people with treatment-resistant depression. The longest follow-up meta-analysed is up to three years (the ERG gives a 20-year time horizon), and the comparator in the meta-analysis is placebo, not continued antidepressant therapy, as per the esketamine maintenance trial. There is no citation of literature on treatment resistant depression outcome studies within an NHS setting. A follow-up study of people within a tertiary treatment-resistant depression service within the NHS examined mortality, and found, "Mortality is one of the indicators of unfavourable outcome in depression. Thirteen participants died during follow-up: eight from natural causes (primarily cardiovascular) and five from unnatural causes (suicide, n= 3; accidental deaths, n= 2). There was a significant trend for association between discharge status and mortality (Chi^2 = 8.03; p= 0.01). Thus, only two individuals who were discharged in remission died."(Fekadu *et al.*, 2012) Therefore, remission appears to reduce all-cause mortality within the NHS, naturalistically. The prediction of treatment resistant depression outcome is dependent on initial response, though the overall course is difficult to predict. Clinical data from the same tertiary service above indicated that, post-discharge, over a mean of 3 years, 35% of people with TRD had a poor outcome, treatment to remission being associated with dichotomised good, versus poor outcome (Fekadu *et al.*, 2011). Further analysis of discontinuation within this patient group found that in long term follow up (1-7 years, median 3 years) patients with TRD generally maintained their improvements seen at the end of acute treatment, and even on average improved further, whilst at the same time 43% of patients were able to reduce the number of medications they were taking compared to the end of acute treatment (35% were taking the same number, 22% more) (Wooderson *et al.*, 2014). Therefore, improvement in treatment resistant depression is often maintained whilst reducing medication. There is

	no reason to doubt this will occur with esketamine.
4	**"no discontinuation by 2 years for reasons other than loss of efficacy…There is no evidence on the effect of stopping esketamine after 2 years for reasons other than lack of efficacy…The committee concluded that, on balance, without data the least biased estimate of cost effectiveness would be to not include discontinuation of esketamine for reasons other than lack of efficacy"** The stark reality in clinical practice is that a lot of people do not take psychotropic medication as prescribed. People tend to stop treatment for a variety of reasons other than lack of efficacy. For people with depression these include feeling better, and adverse events (Mitchell, 2006). It is difficult to understand how a cost-effective analysis could be informed by people with treatment resistant depression hypothetically discontinuing medication solely on the basis of lack of efficacy. <u>References</u> Fekadu, A. *et al.* (2011) 'Long-term impact of residual symptoms in treatment-resistant depression', *Canadian Journal of Psychiatry. Revue Canadienne De Psychiatrie*, 56(9), pp. 549–557. doi: 10.1177/070674371105600906. Fekadu, A. *et al.* (2012) 'Prediction of longer-term outcome of treatment-resistant depression in tertiary care', *The British Journal of Psychiatry*, 201(5), pp. 369–375. doi: 10.1192/bjp.bp.111.102665. Geddes, J. R. *et al.* (2003) 'Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review', *Lancet (London, England)*, 361(9358), pp. 653–661. doi: 10.1016/S0140-6736(03)12599-8. Hauksson, P. *et al.* (2017) 'Effectiveness of cognitive behaviour therapy for treatment-resistant depression with psychiatric comorbidity: comparison of individual versus group CBT in an interdisciplinary rehabilitation setting', *Nordic Journal of Psychiatry*, 71(6), pp. 465–472. doi: 10.1080/08039488.2017.1331263. Mitchell, A. J. (2006) 'Depressed patients and treatment adherence', *The Lancet*, 367(9528), pp. 2041–2043. doi: 10.1016/S0140-6736(06)68902-2. Strawbridge, R. *et al.* (2019) 'Augmentation therapies for treatment-resistant depression: systematic review and meta-analysis', *The British Journal of Psychiatry*, 214(1), pp. 42–51. doi: 10.1192/bjp.2018.233. Wilkinson, S. T. *et al.* (2018) 'The Effect of a Single Dose of Intravenous Ketamine on Suicidal Ideation: A Systematic Review and Individual Participant Data Meta-Analysis', *The American Journal of Psychiatry*, 175(2), pp. 150–158. doi: 10.1176/appi.ajp.2017.17040472. Wooderson, S. C. *et al.* (2014) 'Long-term symptomatic and functional outcome following an intensive inpatient multidisciplinary intervention for treatment-resistant affective

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	disorders', *Journal of Affective Disorders*, 166, pp. 334–342. doi: 10.1016/j.jad.2014.05.013.
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Esketamine for treatment-resistant depression [ID1414]

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**The following person who contributed to the College response has declared the following potential Conflicts of Interest. These are detailed below:** [redacted] **Commercial:** He has sat on advisory boards for Janssen and is principal investigator for several esketamine for TRD trials. His Trust is participating in the Janssen Named Patient Programme which provides early access to esketamine treatment ahead of licensure. He has been approached for advice by approximately 20 private and NHS providers seeking to provide ketamine and esketamine services. Any funding arising from the provision of such advice goes towards the costs of the clinic. The ketamine clinic runs under the auspices of his employer (Oxford Health NHS Foundation Trust) and may gain or lose referrals if NICE finds esketamine is or is not cost effective. He is not paid extra for running this clinic. Academic: He was involved in the NICE scoping for this TA and also the TA for esketamine for suicidality. He has drafted Royal College Psychiatry guidance on ketamine for TRD and chair the committee responsible for ketamine and esketamine. He has written several pieces advocating monitoring of ketamine and esketamine prescribing through a single platform. He ran NIHR-funded studies about the use of ketamine in TRD and about the attitudes of patients and carers to the use of ketamine. He ran an international conference about ketamine and related compounds for psychiatric disorders in March 2018 and is running a similar event in April 2020 and expects the event to be supported by unrestricted educational grants from pharma including, but not restricted to, Janssen.
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	'***When considering the efficacy….as these have not been compared directly.*** We would ask that NICE further consider the robustness of the evidence that they draw upon for the efficacy of alternative adjunctive treatments (such as antipsychotic drugs or lithium) in treatment of resistant depression. We believe that it might not be as strong as reflected in the document and would in particular refer NICE to the meta-analysis reported by Strawbridge et al 2019.
2	***The NICE Committee comments that the features of the considered studies with esketamine are such that the findings may not be applicable to the wider patient population seen in UK clinical practice (e.g. the exclusion of patients with comorbid substance use disorders and high risk of suicide).*** We would ask that NICE reconsider their reliance on this as a rationale for their decision. If this approach were to be widely adopted, most NICE guidelines in patients with mental illness would potentially have little 'generalisability' to current practice. For example, NICE could make very few recommendations on psychological therapies (as patients with such problems are usually excluded from treatment studies). Furthermore, the evidence for esketamine indicates a beneficial effect on reducing suicidal thoughts, suggesting its potential application in clinical practice for patients who have intense and risky suicidal thoughts.'

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3	***The NICE Committee contends that findings relating to IV ketamine cannot be used to provide a background for considering the findings relating to esketamine.*** We would ask that NICE revisit this decision not to take account of findings relating to IV ketamine as ketamine and esketamine are pharmacologically the same and have similar pharmacokinetics. In other NICE deliberations, findings relating to citalopram were considered relevant when considering enantiomer escitalopram so think some consistency in approach is needed or a clearer rationale as to why it is not appropriate in this case.
4	**Page 3 – ECT as a comparator** The comparison with electroconvulsive therapy (ECT) does not seem appropriate. ECT is largely restricted to depressed patients with profound psychomotor retardation or psychotic features, whereas such patients were **excluded** from studies with esketamine. ECT is a specialist and costly procedure, requiring an anaesthetic, muscle relaxant, an anaesthetist, a recovery suite with nursing staff, second opinions (etc.) and carries a negative stigma. The patient group likely to receive esketamine is markedly different to the patient group which currently receives ECT. As a result of previous NICE TA59, ECT is reserved for the most severe and intractable cases of depression. In addition, with increasing concerns among the public and media, the numbers receiving ECT has dropped significantly. The main clinical barrier to use of ECT is fear of inducing cognitive side-effects. We are not aware of evidence that exists for ESKNS that shows cognitive or other enduring side effects. It would not be possible to conduct a long term RCT comparing ECT with esketamine with follow-up over more than a year in the UK. The numbers coming for ECT are simply too small. Of the 1600 annual ECT cases, half are on a section and half are over 65 years. Even in the highly unlikely event that an adequately powered trial was funded and recruited to completion, the results would not be generalizable to routine practice because such a high proportion of potential participants would refuse to be randomized to ECT.
5	'***The available evidence did not include psychotherapy'*** This is correct but the evidence for psychological interventions in treatment-resistant depression (TRD) is too limited to make reliable comparisons: and only one low quality study (of cognitive behaviour therapy) employed the robust definition of TRD of failure to respond to two antidepressant medicines. The same point relating to the absence of comparisons to psychotherapy could also be levelled at studies in TRD with lithium or antipsychotic medicines, but these are considered to be valid comparators: some consistency in approach or a clearer explanation to the different approaches is needed.
6	***The NICE Committee preferred that consideration of outcome in the cost-effectiveness analysis was placed within the context of a twenty-year period***. We were not convinced by the arguments for this. Yes, depression tends to recur and can run a protracted course, but on the individual level there is much variability in clinical outcomes, and prediction of outcome in a given patient is notoriously inaccurate. It seems excessive to withhold a potentially effective treatment from a currently severely ill patient, on the supposition that treatment might have limited cost-effectiveness over twenty years: the same could be said for many other treatments in clinical practice. We recommend that the NICE Committee request the sponsoring company to provide additional data, based on differing acquisition costs of

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	esketamine, to allow a more nuanced consideration of potential cost-effectiveness.
7	***The Committee have quite correctly stated that 'the effectiveness of current treatments for treatment-resistant depression is limited and that there is a need for new treatment options for this condition'***. However, the Committee appears reluctant to accept that a reduction in suicide risk is appropriate when considering potential interventions for patients with TRD: but patients, relatives and clinicians would undoubtedly welcome treatments with such a property. TRD is associated with suicide and effective treatment of depression reduces risk of suicide. This suggests the Committee is making decisions based on inappropriate comparisons to other interventions with reliance on contestable economic models, when considering a potentially life-saving medical treatment with a novel mechanism of action.
8	***Approach for introduction of prescribing on the NHS*** In November 2019, the College President, together with the Chairs of the Psychopharmacology Committee and ECT and related treatments Committee, wrote to the psychiatry expert on the Commission on Human Medicines, stating 'we believe it vital that the MHRA mandate the development of a national registry to track the use of ketamine and esketamine as an important safeguard for patient safety'. We also stated 'should esketamine be licensed for use and approved as a treatment by NICE, the College Centre for Quality Improvement (CCQI) would consider developing a proposal for a network for esketamine services, analogous to the 20 other networks which CCQI operate. This would involve the Academy of Royal Medical Colleges and other stakeholders (including anaesthetists, general practitioners, and general physicians). Under existing regulation, participation in this network could not be mandatory, but for participating clinics completion of any MHRA mandated registry would clearly be necessary for accreditation. **This remains the College position on how best to monitor esketamine prescribing. We would only support the introduction of prescribing on the NHS with these appropriate safeguards for patients in place.**

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright

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reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	I have previously received honoraria (paid to Newcastle University) for attendance at Janssen-Cilag advisory board meetings and speaking at Continuing Medical Education events. I was nominated by Janssen-Cilag as an Independent Expert to provide input to the Appraisal Committee. I attended the committee's meeting on the 7th January in Manchester.
Name of commentator person completing form:	Prof R. Hamish McAllister-Williams

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**Context** It is important to put discussions regarding esketamine for the treatment of depression into context. Depression is the leading cause of disability around the world (Friedrich MJ 2017 JAMA 317:1517). In the UK, it is the most common illness cited in benefit claims, being more than double the next most common – back pain (Dept of Work and Pensions, August 2010). Depression is associated with an increased risk of mortality from suicide. However, it is also associated with increased all cause mortality (UK standardised mortality ratio of 2.55 – Das-Munshi et al. 2019 Psychol. Med. 49:1639-1651). While there are a broad range of effective treatments for depression (psychotherapy, pharmacotherapy and neurostimulation), unfortunately a significant minority of patients either do not achieve remission, or fail to sustain remission, with current treatments despite multiple treatment trials. From the largest treatment study in depression ever conducted (Star*D), around of 1/3 of patients presenting with depression and treated systematically with up to 4 sequential treatments didn't achieve remission (Rush et al. 2006 Am J Psychiatry 163:1905-17). This group of patients have very poor outcomes. In a 5 year prospective follow up study, only around 40% of patients who were managed with conventional treatments in specialist services achieved response criteria (at least a 50% improvement in symptoms from baseline) at any point in time (Aaronson et al. 2017 Am J Psych. 174:640-648). Patients with difficult to treat depression have very poor outcomes. All cause mortality in patients defined as 'treatment resistant' is 29-35% higher than for non-treatment resistant depressed patients (Scherrer et al. 2012 Brit J Psychiatry 200:137-42). Data from a large health maintenance organisation in the USA suggested that patients with treatment resistant depression have all cause mortality rates higher than non depressed individuals who are 13 years older (Feldman et al. 2013 J Med Econ 16:62-74). There is also evidence of a strong correlation between number of medication changes needed and health care costs (Russell et al. 2004 J Clin Psychiatry 65:341-347). Anecdotally, a number of CCGs have suggested that a high proportion of their health care spend (e.g. around 65%) occurs in relation to a small proportion of the population they cover (e.g. less than 5%). This small group of individuals with high health care costs are typified by the presence of multiple chronic health conditions, one of the most common of which is depression. These are the likely target population for esketamine, at least initially. Modern antidepressant treatments have been available since the mid-1950 when the broad groups of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) were serendipitously identified. Since then there has been an expansion of the number of antidepressants with the development of selective serotonin reuptake inhibitors (SSRIs), the serotonin and noradrenaline reuptake inhibitors (SNRIs) and a number of miscellaneous antidepressants (most recently vortioxetine). For patients who don't respond to antidepressant monotherapy, pharmacological augmentation is recommended, for example with lithium, quetiapine or aripiprazole (Cleare et al. 2015 J Psychopharm 29:459-525). The primary pharmacological mechanism of action of all current treatments, both monotherapies and augmentation strategies, relates to monoaminergic neurotransmission. Given that received wisdom is that depression is a heterogenous condition related to a number of different underlying pathologies, there is a perception that perhaps some patients have poor outcomes because current treatments are inadequately targeting their pathology. Given the very significant un-met burden of disease, there is great excitement amongst patients and clinicians when a treatment is developed that has a fundamentally different mechanism of action. It is for these reasons that the progress of esketamine has been followed so closely by patient groups and clinicians alike.

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2	**Data related to ketamine.** It is disappointing that the Appraisal Committee did not consider the evidence base regarding the use of ketamine for the treatment of depression when reviewing esketamine. The drugs are pharmacological related and there is precedent for considering the evidence related to the racemic drug when reviewing a stereoisomer: This was done by NICE when reviewing escitalopram. In my opinion it is important to consider the number of RCTs versus placebo that suggest efficacy of ketamine for treatment resistant depression (Han et al. 2016 Neuropsychiatr Dis Treat 12:2859-2867). Whilst there is no data directly comparing intranasal esketamine with any formulation of ketamine, there is a study which compares the two drugs both administered intravenously in 63 patients. This non-inferiority study found comparable efficacy in treating treatment resistant depression, with both drugs well tolerated (Correia-Melo et al. 2020 J Affect Disorcer 264:527-534). There are other issues that I will raise below, where it is potentially helpful considering the literature around ketamine.
3	**Comparability** On page 3 of the ACD the following is stated “But how much benefit it provides over other oral antidepressants with adjunctive therapy or electroconvulsive therapy is unclear because these treatments have not been compared directly. Also, the available evidence did not include psychological therapies.” I have a number of concerns regarding this statement, foremost the implication of a hurdle that would prevent a favourable opinion ever being given to any potential new treatment for depression. There are currently around 30 antidepressants listed in the BNF. There are 7 pharmacological augmentation listed as first or second line option in national guidelines (Cleare et al. 2015 J Psychopharm 29:459-525). This gives around 240 different combinations of medication that might be used, assuming that patients are on monotherapy or augmentation with just a single agent. Frequently, for example, lithium AND an antipsychotic are added to an antidepressant, or an antipsychotic added to a combination of two antidepressants. By my reckoning, this means that there are at least 4-500 different medication combinations that might be used, not allowing for issues around different dosages. Currently there is next to no data directly comparing these treatments. Some antidepressants have been compared with other antidepressants as monotherapy. There is sufficient data to undertake a network metanalysis (Cipriani et al. 2018 Lancet 2018). While it is possible to rank the antidepressants included in order of efficacy, there is little in the way of clinically significant differences between them. Note, these data are not in populations of patients with treatment resistant depression. There is next to no data comparing pharmacological augmentation strategies in treatment resistant depression. This was highlighted by the NICE depression guideline group (CG90) and was a factor leading to the NIHR HTA panel funding a multicentre randomised comparison of quetiapine vs lithium augmentation in TRD (Marwood et al. 2017 BMC Psychiatry 17:231) that is still to report. This means that network meta-analysis of pharmacological augmentation involve networks that are immature and unstable (Zhou et al. 2015 Int J Neuropsychopharm 18:pyv060; Strawbridge et al. 2019 Br J Psychiatry 214:42-51). The consequence is that it is impossible at this time to have any confidence in identifying what should be the pharmacological comparator(s) that one would consider. The ACD also makes reference to ECT and psychotherapies in relation to the lack of comparator data for esketamine. The draft NICE clinical guidelines for depression listed around 10 different forms of formal psychotherapy. These might be used alone or in combination with medication (leading to thousands of potential combinations). However, a recent systematic review was only able to identify three trials

	of psychotherapy in patients with defined treatment resistant depression. None of these included a placebo arm that allowed comparison with medication (Strawbridge et al. 2019 Br J Psychiatry 214:42-51). So, while commonly used, there is a lack of data supporting the efficacy of psychotherapies, or their comparison with pharmacotherapy, in the management of treatment resistant depression. Raising the issue of a lack of inclusion of psychotherapy in the studies of esketamine appears to be setting a hurdle that not a single currently recommended pharmacological treatment has surpassed. The issue of comparison with ECT is an interesting one. It should be noted that in the entire history of ECT, to my knowledge, there are only four small and old comparisons of it versus pharmacotherapy in patients with treatment resistant depression (RCPsych ECT Handbook). How comparable intranasal esketamine is with ECT is a reasonable question, though difficult to address. This is in part due to the problems in study design – it is ethically questionable to run a truly double blind study of ECT versus medication when patients would potentially be having repeated anaesthetics without treatment. This said, there are two small RCTs of IV ketamine vs ECT (Basso et al. 2020 J Psych Res 123:1-8; Kheirabadi et al. 2019 Adv Biomed Res) which found no difference between the treatments. A larger study (ELEKT-D) is currently planned (Matthew et al. 2019 Contemp Clin Trials). However, one of the major issues around the comparison with ECT is that the populations of patients treated with ECT and potentially with esketamine, while overlapping, are not the same. The primary indication for ECT is for patients with severe acute depression with psychosis and/or marked psychomotor retardation with decreased food and fluid intake (see NICE CG90). This is not the population of patients likely to be treated with esketamine. Rather, esketamine is likely to be used in the more chronic treatment resistant patient population. While it is recommended to consider ECT in such groups (e.g. Cleare et al. 2015), the reality is that it is rarely used in practice due to a previous, now superseded, NICE clinical guideline being very negative about the treatment. The ACD (page 7) states “The company did not provide evidence comparing esketamine with all relevant comparators”. Given the lack of consensus as to what the most appropriate comparator would be, or the population of patients in which to perform the study, it is hard to see how any company could ever provide evidence against “….all relevant comparators”. Such a requirement prior to the recommendation for use of a treatment in the UK will inevitably mean that companies decide that it is not economically viable to introduce treatments for TRD into the UK, especially when such hurdles are not present in other countries. This will not only be to the detriment of patients by also the health care economy (see point 1 above)
4	**Generalisability** The issue of the generalisability of the data is raised in the ACD (page 9): “The evidence for esketamine is limited in its generalisability to the NHS”. To my mind there are two different sides to the question of generalisability and the patient population in which esketamine might be used in the UK. **Firstly**, it is argued in the ACD that the esketamine data is not particularly generalisable due to the inclusion of very few UK NHS patients in the company trails, and the nature of the eligibility criteria. The lack of UK NHS patients is an issue that at least in part reflects the difficulty of conducting studies in TRD in the UK despite its prevalence (an issue I am only too familiar with as a researcher in this area). It is disappointing that there were not more UK patients included. However, I would be extremely concerned if a situation arose where only drugs tested in UK populations were approved for use in this country. Japan has a policy of only approving drugs where there is a significant data set in patients of Japanese origin. This is of potentially more justification given data demonstrating pharmacokinetic differences in Asian populations. However, it has led to a significantly slower introduction of many modern psychopharmacological agents. The high suicide rate there (around 4X the rate in the UK) is probably rooted in societal differences. However, as a psychiatrist, I find it hard not to believe that the lack of psychopharmacological agents contributes to this high suicide rate, at least to some extent. The UK has an arguably more ethnically diverse population than Japan

	meaning that trials conducted in other countries are of more relevance. With regards to the eligibility criteria used in the esketamine studies, these are pretty standard across studies of this type. I am currently involved as PI or CI in five different trials in patients with treatment resistant depression – three NIHR funded and two industry funded. These all have similar eligibility criteria. It is critical to recognise that trials in mental health conditions, such as depression, present challenges that are not present in many other therapeutic areas. The symptoms of depression can not be assessed objectively – we are reliant on patient descriptions of symptoms and self-completed or observer-rated scales. There is inherently a great deal of noise in such measures. This means that it is even more critical to control confounding variables that in studies with more objective outcome measures. Patients with significant alcohol problems are excluded from most trials because there is an increased risk of non-adherence and because alcohol can exacerbate depression and make it more likely to be difficult to treat. Some psychiatric comorbidities may respond to the treatments for depression (for example generalised anxiety responds to many antidepressants), but some may be made worse (e.g. psychosis can worsen with antidepressants and there are theoretical reasons why we would have concerns giving ketamine or esketamine to a psychotic patient – ketamine leads to schizophrenic like symptoms in health subjects). It might be argued that randomisation should address these issues. However, it is nigh on impossible to achieve balance between treatment arms across many different comorbidities and there are far too many to use minimisation to ensure similar numbers in each treatment arm. This, plus the problems of low signal to noise ratios, means that to NOT exclude patients for significant alcohol problems or any psychiatric comorbidity would require unfeasible sample sizes in studies. Including a requirement that patients must have failed ECT would be a great concern to me – this would massively impede recruitment (see arguments above about differences in patient populations treated with ECT and ketamine) and prevent access to the trial to any patient who refused ECT. Failure to respond to ECT is an extremely bad prognostic factor generally in patients with TRD (Aaronson et al. 2017 Am J Psych. 174:640-648). This means that the power of the study would be reduced and required sample sized increased – not a good when combined with massively reducing the eligible population size. The point raised in the ACD regarding the exclusion criteria related to suicidal ideation is an important point. Suicidal ideation is part and parcel of depression. It is always a concern to me when this is included as an exclusion criteria. In independent (e.g. NIHR funded) trials we tend to try to keep inclusion as broad as possible and only exclude participants who are actively suicidal simply for safety reasons. However, industry funded studies always have tighter requirements in this regard. No company wants to have patients in their trials committing suicide, especially given all of the noise in the lay press regarding antidepressants and suicide. This does mean that we have great caution when using newly introduced drugs in patients with significant suicidality given the usual lack of data in this regard. However, the situation with esketamine is very different. Looking at the ketamine data is potentially helpful. There is increasing data suggesting that ketamine has anti-suicidal properties (e.g. Zhou et al. 2020 J Affect Disord 264:263-271). Similarly, there is also published data suggesting that intra-nasal esketamine has anti-suicidal effects (e.g. Canuso et al. 2019 Focus (Am Psychiatr Publ) 17:55-65). Indeed, I understand that Janssen are seeking a license for the use of esketamine in depressed patients with acute suicidality. I assume that the company have not provided this data to the Advisory Committee since this indication has not yet been approved. However, it does mean that as a clinician I am pretty relaxed with regards the exclusion of patients with suicidal ideation in the TRD trials. My **second** point regarding generalisability relates to something that it appears the Advisory Committee have not considered. All of the discussion and economic modelling has been done in relation to patients with treatment resistant depression defined using the standard definition of failure to response to two adequate trails of different antidepressants. This is the definition that the regulatory authorities use. However, this is certainly not a good definition of patients that might be given esketamine in the UK NHS. The reality

	is that patients do not follow a treatment pathway reflecting NICE recommendation in any shape or form. CG90 recommends that if a patient has failed to respond to two trials of antidepressant monotherapy, they should be referred into secondary care where they may receive pharmacological augmentation and/or the addition of specific psychotherapies. ECT is some what stuck out on a limb being recommended for those with severe depression plus psychosis or psychomotor retardation (as described above). However, the reality is very different from this. Patients may have three or four trials of antidepressant monotherapy before being referred into secondary care. Once referred, the most common intervention is either simply increasing the dose of the antidepressant the patient is on or switching to an alternate antidepressant. Only then are first line pharmacological augmentation strategies considered. In the vast majority of circumstances, at least one or two current standard augmentation options are tried before a clinician starts to consider newer or less conventional treatments. (Psychotherapies are usually considered in parallel with these various pharmacological steps). There would be a number of hurdles to the provision of esketamine in practice. Top amongst these will be pressures from pharmacies to not prescribe because of the drugs costs. In addition, clinicians would need to organise for patients to attend a hospital site twice a week and then weekly for a period of time, and patients would need to be agreeable to undertaking this. We know from experience that the smallest extra hassle around prescribing a treatment leads to low rates of prescribing (e.g. the need to undertake LFT checks in patients on agomelatine, or ECGs in patients on higher doses of escitalopram). As a result, there is no way that esketamine will be used as a third line treatment – indeed it would be surprising to me if it was used much earlier than 5th or 6th line. There are at least two implications from the observation above. 1. The studies so far conducted with esketamine have not been conducted in the sort of patients likely to be treated with it in practice and 2. The numbers of patients receiving esketamine will be much more limited than might otherwise be the case. I think there is a potential issue around generalisability of the current esketamine data, but it is not in relation to the issues raised in the ACD. Rather, the patients included in the Janssen studies are nowhere near as treatment resistant as those likely to be in practice. This is an issue in that the evidence suggests that there are decreasing response and remission rates with each treatment failure (Rush et al. 2006 Am J Psychiatry 163:1905-17). I do not think that this means the drug should not be recommended for use until studies in such populations are done. This is because the sample sizes needed would, once again, be unfeasible. I have designed a number of studies of treatments in TRD and the more I do, the more I feel the need to limit the degree of resistance in the sample population to stand any chance of detecting any effect of the treatment in a practical sample size. The other implication, though, is that the response and remission rates used in the economic modelling of esketamine, based on the trail data, are likely to be over-estimates. Adjusting for this would lead to reduced costs since more patients would stop treatment early on. When using IV ketamine, if a patient has had not therapeutic benefit from three administrations, I would very rarely continue the treatment. So, should esketamine be recommended for patients that are not exactly analogous to those included in the Janssen studies (i.e. patients who are more treatment resistant)? There is very strong precedent for NICE to make such a recommendation. The antidepressant vortioxetine was reviewed by NICE for the treatment of major depressive episodes in 2015 (TA367). The drug was recommended "…as an option for treating major depressive episodes in adults whose condition has responded inadequately to 2 antidepressants within the current episode". This was despite the Advisory Committee only reviewing evidence from one study where vortioxetine was trialed in patients who had failed a single antidepressant (Montgomery et al. 2014 Human Psychopharm 29:470-82). The argument was that SSRIs are much cheaper and so patients should be tried on a couple of these before being offered vortioxetine, despite a lack of evidence for efficacy in patients who have failed two treatments. It seems not an unreasonable extrapolation that if vortioxetine works in patients who have failed one antidepressant, then it is likely to work in patients who have failed two, albeit probably with a lower response and remission rate. I believe that a similar argument can

	be made with regards to esketamine, and I think that such an argument is important for NICE to make a recommendation that would be consonant with current clinical practice (see below).
5	**Cost effectiveness Modelling** There seems to be great uncertainty with regards the economic modelling for esketamine, with the company arguing that the cost per QALY is in the order of £7,500, with the ERG coming up with figures in the order of £55-62,000. I am not a health economist, but I am not surprised by this discrepancy. The modelling is using so many estimates, not just due to lack of data regarding esketamine but also the lack of high quality data regarding the natural history and treatment of depression. I think such discrepancies would be evident in the review of any new treatment for depression. The ACD describes a number of issue and concerns regarding the health economic modelling. I am not sure that I agree with all of the points raised, but I shall focus on just one – the ERG's assumption of "no discontinuation by 2 years for reasons other than loss of efficacy" (section 3.19). The reasons for focusing on this one assumption is that a) it is the assumption with the most influence on the cost per QALY and b) it seems to me to be the hardest to justify. For the reasons described above, I suspect that in NHS clinical practice, response and remission rates with esketamine will be lower than seen in the trial data and used in the economic modelling. For those patients who do gain some benefit, there will be a massive spread with regards to the degree of improvement. Some will have minimal symptom improvement (not meeting criteria for response or remission), but still feel this is of significant benefit to their quality of life and hence want to continue treatment. Others will achieve the definition of remission (NB this does not necessarily mean being symptom free). There is evidence that patients with low enough levels of depressive symptoms to meet remission criteria can still experience significant psychosocial dysfunction (Demyttenaere et al. 2009 Prim Care Companion J Clin Psychiatry 11:307-15). Such patients may or may not want to continue treatment. So, whether a patient continues with treatment will only loosely correlate with degree of symptomatic improvement. All treatments carry some burden – even if this is simply remembering to take a table. Undergoing treatment with intranasal esketamine will carry a very significant burden. Patients will need to attend hospital for a couple of hours twice weekly for a few weeks, then weekly for a few more weeks and then possibly only every two weeks thereafter. These is no mean commitment, especially for patients with an illness characterised by anergia, amotivation and feelings of hopelessness. Taking esketamine or ketamine leads to dissociative symptoms. While some people use ketamine recreationally, my experience of using ketamine is that patients with depression are much more likely to experience the dissociation as aversive, rather than pleasurable. How long a patient takes any treatment for will depend on their perception of the balance between benefit and burden. I can't think of any clinical situation, certainly not in mental health, where all patients keep taking a treatment indefinitely despite responding to it. This is certainly the case with regards to experience of using IV ketamine. Some patients do continue taking it long term, but some choose to at least take a pause from treatment, even if they are responding. One published study of maintenance ketamine for TRD found that the reasons for stopping treatment were varied, including loss of efficacy, adverse effects, treatment burden and so on (Archer et al. 2018 J Clin Psychopharm 38:380-384). So, I think that there will be multiple reasons for stopping treatment other than simply lack of efficacy. Most of the patients stopping for lack of efficacy would do so very early on – probably earlier than modelled. However, some will drop out because of lack of efficacy periodically because of their perception of the degree of response not justifying the level of burden. On the other side of the coin, there are also likely to be patients who do really well with esketamine who just start questioning whether they need to keep having treatments. It is vey common for patients who have been well on treatments for months or years to question whether they need to

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	keep taking them. We don't have evidence to guide us as to what might happen to patients who have gone into full remission for a prolonged period if they stop treatment. There is a small study that looked at patients discontinuing maintenance ketamine, and this found some patients remaining well for up to around 6 months (Diamond et al. 2014 J Psychopharmacol 28:536-44). Given this uncertainty, it would seem reasonable for clinicians to be provided with guidance as to how to manage such patients. For example, if patients go into full remission and this is sustained for say 9-12 months, it may be reasonable to consider at least pausing the treatment, possibly while exploring other management options. If there was a clear psychosocial precipitant to the episode of depression and this is now resolved and the patient is in remission, again it would not seem unreasonable to consider discontinuing treatment. In summary, there are so many reasons why a patient might discontinue treatment other than lack of efficacy, that it does not seem possible to justify this as being the only reason for discontinuing. As a result, I do not think the ERG's position on this point is defensible.
6	**Summary** Making recommendations regarding the use of esketamine for treatment resistant depression, when the generic evidence basis for treatments in this area is so poor, is extremely challenging. Economic modelling is fraught by the number of assumptions being made and how sensitive the model is to some of these. The Advisory Committee is therefore in an invidious position given this coupled with the enormous unmet need in this therapeutic area and the impact of treatment resistant depression on individuals, the health care economy and wider society. In my opinion it is important to consider all sources of evidence, including that from studies of ketamine. It is certainly the case that there is less comparator data for esketamine than would be ideal, but this is no different from any other medication, psychotherapy or neurostimulatory treatment currently in use. Similarly, there are issues around generalisability of the data though, in my opinion, these relate to the level of treatment resistance of the patients included in the esketamine studies, rather than the issue raised in the ACD. I think that it is essential to cautiously extrapolate from these studies to populations where the drug is more likely to be used in the UK. To my mind, there are two major issues of concern if esketamine is introduced into clinical practice. The first is to guard against 'doctor shopping'. There is some anecdotal evidence of this happening with regards to IV ketamine in the USA. The Royal College of Psychiatrists has strongly advocated to the MHRA that all patients receiving esketamine should be entered onto a national registry that can be used to ensure that they are not receiving treatment from multiple clinics. The second issue is with regards to cost. Whatever the economic modelling, the raw acquisition costs are significantly higher than most other current treatments. I think this issue can be addressed in a number of ways. Firstly, I would suggest that esketamine is only recommended for patients with TRD who have failed to respond to at least two conventional augmentation strategies or ECT. In reality, I think this is where clinicians would be thinking of using it in any case. Making this restriction would limit the number of people receiving esketamine. Secondly, I would suggest clear guidelines with regards to ongoing treatment. I think that this should include two elements – one that the patient must be showing demonstrable benefit for treatment to continue, with this regularly assessed, and the other that there should be a recommendation to at least pause treatment if there is a period of sustained remission. Thirdly, I would suggest using a register to collect long term outcome from patients. These data could then be used to refine the cost effectiveness modelling for a review of the recommendations.

Insert extra rows as needed

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology. • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NHS England

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Direct – financial** (if you have no interests in this category, state 'None') None **Direct – non-financial** (if you have no interests in this category, state 'None') None **Indirect** (if you have no interests in this category, state 'None') none
Name of commentator person completing form:	John P Pratt (Peter Pratt)

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	NICE requested further information from NHS England regarding the feasibility of the company plan and also any longer term costs for setting this up when no ECT suites are available and other costs, including costs of setting up a registry and the controlled status of the drug. In Peter's initial expert statement, he mentioned that the costs of implementation would involve: • 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 The company have included nursing and monitoring costs but have said there will initially be no additional implementation costs because ECT suites can be turned into esketamine clinics at no cost and monitoring equipment/ equipment for medical

	complications borrowed using the same criteria. They also have stated they will provide additional training for post dose complications. I have not surveyed all mental health trusts to validate the company's view. The only way would be a detailed interrogation of all stakeholders within all mental health trusts to establish whether or not this would be the case – or not & I am afraid I do not have the capacity to undertake that level of enquiry. However 1) It is entirely feasible that some trusts could turn their ECT suits into Esketamine administration and monitoring facilities – however I am not convinced that this will be the case for all/the majority of trusts. 2) If this drug receives a positive opinion from NICE - I do not think it reasonable to expect all patients to travel – perhaps large distances to an ECT suite. My expectation is that trusts would /should establish/convert/adapt their community mental health facilities to enable the safe administration and monitoring in such a way that minimises travel for patients 3) I am not aware that all mental health trusts have an ECT suite – if this is the case - some patients would have to travel further distances and/or additional costs associated with travel would need to be made available 4) I am not convinced that there will be sufficient space/capacity in all current ECT mental health trusts to accommodate the esketamine administration and monitoring – For example I suspect that the medicines storage facilities of current ECT suits would need upgrading to enable stocks of this schedule 2 controlled drug to be held/administered and post dose devices destroyed.
2	Other comments mentioned that a reclining chair and a quiet room is all that would be needed. 5) "a reclining chair and a quiet room is all that would be needed." I disagree, As I mentioned in my initial comments - This drug is a schedule 2 controlled drug – therefore there will need to be adequate staffing and governance processes established in order to ensure the Adequate storage, checking, transportation, disposal in relation to the controlled drug status of this drug. It is unlikely that there will be adequate storage, transport etc facilities in all mental health Trust ECT suits that will meet the approval of the Trust CD accountable officer. I appreciate Mental health Trust are able to establish safe and appropriate systems, but these will take time to implement. (e.g. they are able to arrange methadone (a schedule 2 controlled drug) supply and administration in community facilities) Adequate "medical" equipment to monitor and deal with the immediate management of any post dose medical complications will be required.– it is possible that such facilities may be available within some trusts existing ECT suits- however as mentioned previous this is unlikely to be the case for all MH trusts.

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3	6) I am not aware of the relationships between all mental health trusts and the supporting infrastructure that they use to perform ECT – It may be that there are contractual relationships between the Trust and anaesthetists/and /or acute general hospitals that would require review/ re-negotiation to enable the ECT facilities option to be considered – However as mentioned previously I am not aware that this will be a viable option for all mental health trusts – and if this drug receives a positive opinion - it would be wrong to limit the use/availability to those trusts that have an ECT suit that can be "easily" converted to allow esketamine administration and post dose monitoring. I am sorry, but I am not able to offer any guidance on the detailed "costing" associated with establishing an appropriate infrastructure – There are just to many variables to consider – not least the starting point/existing trust infrastructure arrangements. The key issue from my perspective is that Trusts are allowed adequate time to review their existing estate and infrastructure so that a fit for purpose solutions can be developed. There is considerable heterogeneity within and across mental health trusts which means a ONE size will not fit all – There may be some trusts with relatively small geographical footprints and good transport infrastructure where the ECT suit option may be viable – however there are many other MH trusts including those which may span 5 or more CCG's and large – possibly rural geographical locations where an ECT adaptation would be impractical/unviable. In some Trusts for example those who do not operate an In-house pharmacy service there may be additional complexities to negotiate the mechanisms of supply through their third-party pharmacy dispensing and supply arrangement. I appreciate that the company may be offering some sort of direct delivery system – (which may avoid VAT) but it will be for each trust CD accountable officer and chief pharmacist to be assured of the governance arrangements before this could be adopted by the Trust. I have seen some of the feedback to the consultation which indicates the infrastructure to support the adoption of the technology is "not a problem" – however I am not convinced that the respondents have considered all the factors – transport, storage, governance etc in addition to the direct clinical factors for someone to support administration and monitor post dose (and intervene in the event of a medical emergency) – To ensure the safe use of this drug it will require joined up agreements that cross medical, nursing, pharmacy ,estates, transport, governance, CD accountable officer as well as finance and contracting departments. I think the comment "a reclining chair and a quiet room is all that would be needed" highlights this narrow perspective. On the national registry front – I know that there is some strong support for

	this from some people. I also know that they are pressing the MHRA to host such a registry and it may be that the people pushing for this have a more detailed plan for the practicalities of implementing such a system. At one level I can understand that there may be concern about patients traveling from place to place simply to get access to the drug (or increased doses) – However if the drug has little/no liability for misuse (as I thought the company had previously mentioned? – then the concerns about patients hoping from one place to another would be unfounded – on the other hand If there is a possibility of misuse (my personal view is that there is) then such a register would only work if it was directly tied to the supply of the drug – and my guess is that could only be facilitated on a national basis (including Scotland & Wales) if the register was held by the company and the drug was supplied against a named patient/unique hospital number. The company would have to have a real time live system which restricted supply to those patients who have been "registered" onto the system. Other options could be that individuals offer to Host such a system on a commercial basis and/or, manage the whole supply arrangements linked to a major research program to follow use against outcomes Overall I think the only viable option if a registration system is felt to be necessary that this would have to be managed in real time through a single source of supply – to both the NHS and the private/independent sector. I can see the merits of such a system – but I am unsure if this should be a requirement. Another option would be to require all prescribing to be uploaded against a patients summary care record – and local governance processes established to verify any existing prescribing – however I am not convinced that the current spine/summary care records would be workable mechanism as a register for all patients in all circumstances. I hope this is helpful and I am sorry I cannot be more definitive about infrastructure costs, but please do get in touch if you require any further information/discussion
4	Please see below a list of ECT suits on the RCPsych website As far as I can tell this suggests that all of the following 54 mental health trusts have at least one ECT suite 2gether NHS Foundation trust Avon & Wiltshire Mental Health Partnership NHS Trust Barnet, Enfield & Haringey Mental Health Trust

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	Berkshire Healthcare NHS Foundation Trust Birmingham & Solihull Mental Health NHS Foundation Trust Black Country Partnership NHS Foundation Trust Cambridgeshire & Peterborough NHS Foundation Trust Camden & Islington NHS Foundation Trust Central & North West London NHS Foundation Trust Cheshire & Wirral Partnership NHS Foundation Trust Cornwall Partnership NHS Foundation Trust Coventry & Warwickshire Partnership NHS Trust Derbyshire Healthcare NHS Foundation Trust Devon Partnership NHS Trust Dorset Healthcare University NHS Foundation Trust Dudley & Walsall Mental Health Partnership NHS Trust East London Foundation NHS Trust East Sussex Healthcare NHS Trust Essex Partnership University NHS Foundation Trust Greater Manchester Mental Health NHS Foundation Trust Hertfordshire Partnership University NHS Foundation Trust Humber Teaching NHS Foundation Trust Isle of Wight NHS Trust Kent & Medway NHS & Social Care Partnership Trust Lancashire Care NHS Foundation Trust Leeds & York Partnership NHS Foundation Trust Leicestershire Partnership NHS Trust Lincolnshire Partnership NHS Foundation Trust Livewell Southwest Mersey Care NHS Foundation Trust Midlands & East England Midlands Partnership NHS Foundation Trust Norfolk & Suffolk NHS Foundation Trust North East London Foundation Trust North Staffordshire Combined Healthcare NHS Trust North West Boroughs Healthcare NHS Foundation Trust

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	Northamptonshire Healthcare NHS Foundation Trust Northumberland, Tyne & Wear NHS Foundation Trust Nottinghamshire Healthcare NHS Foundation Trust Oxford Health NHS Foundation Trust Oxleas NHS Foundation Trust Pennine Care NHS Foundation Trust Rotherham Doncaster & South Humber NHS Foundation Trust Sheffield Health & Social Care NHS Foundation Trust Somerset Partnership NHS Foundation Trust South London and Maudsley NHS Foundation Trust South West London & St George's Mental Health NHS Trust South West Yorkshire Partnership NHS Foundation Trust Southern Health NHS Foundation Trust Surrey & Borders Partnership NHS Foundation Trust Sussex Partnership NHS Foundation Trust Tees, Esk & Wear Valleys NHS Foundation Trust West London NHS Trust Worcestershire Health & Care NHS Trust However I think my points about the logistics of patient travel , upgrading of the facility , transport (of medication), storage of medication and cross trust /third party suppliers are still valid – and whilst negotiating ypdrage and use of EXT facilities may be straight forward for some trusts I do not think this will be the case for all trust – as you will see from the list of ECT suits – some of these facilities appear to be housed in a different trust (see https://www.rcpsych.ac.uk/improving-care/ccqi/quality-networks-accreditation/ectas/ectas-members Schedule 2 controlled drugs will require a controlled drug storage cabinet of sufficient size to hold the esketamine nasal spray (s) – There will be additional governance arrangements over the siting of these cupboards depending on whether or not the “room” is staffed 24 hours a day – or not. A secure audit trail for the transportation and receipt/ storage of controlled drugs will need to be established - This will be more straightforward where the trust in-

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	house pharmacy supplies the medication and the Trust owns the building where the ECT suit is sited.
5	
6	

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Dear Appraisal Committee Members

As a clinician in the NHS, frequently treating patients with treatment resistant depression (TRD), I am extremely disappointed with your decision to not recommend Esketamine with a serotonin selective reuptake inhibitor (SSRI) for this patient group.

Approximately 30% of patients with a major depressive disorder (MDD) do not respond to antidepressant medication or psychotherapy. Compared with other patients with MDD those with TRD have decreased productivity, higher medical comorbidity and more suicide attempts (ref 1,2)

The most comprehensive study of MDD treatment resistance was the National Institute of Mental Health-funded Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial. (ref 3) In this study, patients with MDD underwent a series of sequential antidepressant treatments in monotherapy or combination, or psychotherapy trials using evidence based antidepressant treatment strategies.

Acute remission rates decreased with each STAR*D level (level one 37%, level two 31%, level three 14% and level four 13%). Resistance to treatment becomes markedly increased at level 3 (after failure of two treatments), and predicts a poor prognosis with respect to future treatment efficacy, tolerance, and relapse. All current conventional treatments do not improve the remission rates after this point.

Therefore, novel treatments with good evidence in short-term and in maintenance trials , such as Esketamine with a selective reuptake inhibitor (SSRI), are very much needed in the field in order to bring hope to our patients and alleviate their suffering.

The negative endorsement of novel treatments not only denies patients access to them, but may significantly decrease the incentive for investment in these kinds of treatments within mental health in the future.

I very much hope this decision is changed.

Best wishes

[redacted]

Conflict of Interest/Disclosures: I receive only a salary from a full-time NHS post. I have no shares or positions in the pharmaceutical industry. I have received in the past consultancy fees from most of the pharmaceutical companies based in the UK.

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3. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps. *Am J Psychiatry*. 2006;163(11):1905-1917.

[redacted]

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Bristol Recovery Service

Avon and Wiltshire Mental Health Partnership NHS Trust
Bristol, UK
[redacted]

Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Comments on the ACD:	

Comment on there is no evidence on the effect of stopping esketamine after 2 years for reasons other than lack of efficacy

Clinical experience with esketamine and ketamine suggests that many people do stop the treatment after entering stable remission. Experience with other treatments is similar. In particular, whilst we will often suggest long term treatment with antidepressant medication to reduce the risk of relapse, we often suggest the add-on medication is the first to be reduced after stable remission. By way of example, we followed up a group of NHS patients we had treated with very severe TRD. We found that in long term follow up (1-7 years, median 3 years) patients with TRD generally maintained their improvements seen at the end of acute treatment, and indeed on average improved further, whilst at the same time 43% of patients were able to reduce the number of medications they were taking compared to the end of acute treatment. So improvement in TRD is often maintained whilst reducing medication.
(Wooderson SC, Fekadu A, Markopoulou K, Rane LJ, Poon L, Juruena MF, Strawbridge R, Cleare AJ (2014) Long-term symptomatic and functional outcome following an intensive inpatient multidisciplinary intervention for treatment-resistant affective disorders. Journal of Affective Disorders, 166, 334-342.)

Has all of the relevant evidence been taken into account?
I have listed in the comments where I think some additional evidence in terms of the long term treatment of TRD could be taken into account.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
I have listed in the comments reasons I believe that some of the committee's assumptions are flawed.

Are the recommendations sound and a suitable basis for guidance to the NHS?
I think this may represent a lost opportunity for the NHS to give some of its most disabled patients, who are already suffering from disparities in care, access to a novel treatment option.

Comment on Esketamine is unlikely to be cost effective for treatment-resistant depression
It seems inconceivable that 1:1 nursing would be needed. Established clinics I have seen work on far lower ratios.

Comment on the company did not provide evidence comparing esketamine with all relevant comparators

virtually none of the available treatments for treatment resistant depression (TRD) have been compared in this way. The first line treatments recommended in guidelines such as the British Association for Psychopharmaology and the Maudsley Prescribing Guidelines (eg Lithium, quetiapine and aripiprazole) do not have good evidence of efficacy against one another - but all are better than placebo when added to an antidepressant, which is why clinicians use them. This should not mean that none of these should be available to clinicians to treat a clearly sever and disabling condition such as TRD.

Comment on the effect of psychological therapy in addition to drug treatments is not clear

Exactly the same lack of evidence applies to the other first line treatments for TRD mentioned above. We know that ideally all patients with TRD should have both medication and a psychological therapy. I cannot see how this is relevant as to whether esketamine should be one of the medications used in TRD.

Comment on it is not appropriate to include an effect of esketamine on mortality

Our long term follow up of NHS patients with TRD shows clearly that entering remission is associated with reduced all cause mortality during long term follow up. (Fekadu A, Wooderson S, Rane L, Markopoulou K, Poon L, Cleare AJ (2012) Prediction of longer-term outcome of treatment-resistant depression in tertiary care. British Journal of Psychiatry, 201, 369-375.)

If patients treated with esketamine are more likely to enter remission, extrapolating this (NHS) data would suggest that mortality is likely to be lower.

Comment on Esketamine is not recommended

As a clinician specialising in TRD, this is disappointing, and I do feel that several of the assumptions leading to this conclusion may be incorrect. I of course support that the treatment must be cost effective. Notwithstanding this, I would just like to say that if some of the requirements mentioned (need to study the additional effects of CBT, need to compare to other add-on treatments rather than to placebo, need to assume indefinite usage of the drug) are applied, then this will provide a powerful disincentive to industry in making further investments in developing new treatments. Many companies have already pulled out of the area, which is inherently a challenging field. Esketamine has a novel mechanism of action, in a field that has not seen such developments for many decades. Our patients have a potentially treatable condition, are already subject to a disparity of resources, and I fear that we will merely exacerbate this if we do not evaluate new treatments in a less draconian fashion.

Name	[redacted]
Comments on the ACD:	

General Comment:

"1. The appraisal committee. We are surprised that members of this appraisal committee chosen by NICE have little or no professional experience, including usual pathways of care, of prescribing this treatment. In fact, the SmPC states that “the decision to prescribe Spravato should be determined by a psychiatrist”. We acknowledge that that the principles of evidence-based medicine mean such a committee ought to be able to make decisions based purely on RCTs, it must be an almost impossible job when you do not have day-to-day practical knowledge and clinical experience of the type of people we are trying to help.

Treatment options in TRD: The committee needs to consider the options for clinicians when faced with someone with TRD. The definition of treatment-resistant depression as used by the FDA and DSM-V is a neat classification but is a little misleading. In practice UK clinicians would not classify someone as TRD until they had received probably at least 3 different antidepressants, and probably more. Thus, we think the committee may be being misled into thinking esketamine will become a much earlier treatment than it actually will be in real life. Hence we urge the committee to reconsider its position statement.

2: 3.4 (p7): “The committee heard from other clinical experts who noted that ECT should also be a comparator because the processes involved in administering esketamine are similar to those for ECT.”
The comparison with ECT is difficult to comprehend because it does not reflect clinical practice and does not quite match reality.
ECT differs from esketamine in most respects. ECT requires a qualified anaesthetist present throughout, specific equipment (to buy and maintain), a team of clinicians, and a custom-built ECT suite using several rooms (reception, ECT room and recovery; to which service users often need to travel), injection and resuscitation equipment. ECT has many contraindications, a different mode of action and, as “electric shock treatment“, creates a degree of fear amongst potential patients. It has had a bad press over the years.
We envisage that esketamine nasal spray will need a single HCP (to welcome, supervise and be available during recovery to measure BP and assess when the person is safe to leave), a quiet room, and a sphygmomanometer. A quiet room for an hour or two for the recovery period would not need to be custom built or permanently equipped but will need to be carefully chosen, as would any clinical setting.

3: 3.12 (p14) “The company assumed that people would not stop taking oral antidepressants for any reason other than lack of response. But it assumed that people would stop esketamine treatment for other reasons, in line with the criteria in the SPC and additional discontinuation guidance provided by the company”.

The assumption that people will only stop esketamine due to lack of effect is unrealistic. Esketamine may be an on-going treatment for some, involving a day, a visit to a clinic (possibly many miles away, especially in the many rural areas), the need for an accompanying person or taxis, a treatment that is rather more than just popping a pill, and a significant routine. People might think about trying without esketamine as soon as they have recovered sufficiently from their acute symptoms, especially if they know there is an option to restart should symptoms return.

4. p3 “Electroconvulsive therapy can be used if oral treatments do not work. “
This is true but it is important to understand the context in real clinical practice. In clinical practice, ECT tends to be offered to patients who are more clinically unwell; they frequently are unable to function normally, for example are unable to go to work and may even have stopped eating and drinking. ECT can indeed be used in some people but many people decline this old and crude treatment for personal reasons, it has many contraindications and relapse is common even with continued treatment.

5. p3 “Drug treatment can also be combined with psychological therapy.”
Indeed it can, but again this may not be effective. People may be too depressed to be able to take the strategies on board or into practice. Furthermore, the actual evidence for psychological therapies in TRD is minimal.

6. p3 Clinical trials suggest that esketamine with an oral antidepressant may be more effective at relieving the symptoms of depression than placebo and an oral antidepressant.
But how much benefit it provides over other oral antidepressants with adjunctive therapy or electroconvulsive therapy is unclear because these treatments have not been compared directly.
This is true but we already know the outcomes from sequential treatments in TRD from the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study. This was the largest independent RCT study carried out on remission from depression, over 6 years using real-world patients.
Stage 1: A first line therapy (citalopram) was tried to the optimum dose (mean 42mg/d, remission using QIDS = 37%). Non-remitters then went to:
Stage 2: A switch (patient choice) to venlafaxine, bupropion, sertraline or CBT (Cognitive Behavioural Therapy) or augmentation with bupropion, buspirone or CBT (overall remission using QIDS 31%). Non-remitters (who would now be considered treatment-resistant) then went to:
Stage 3: A switch (patient choice) to mirtazapine (remission 12%), nortriptyline (remission 20%), or augmentation with lithium (remission 16%) or triiodothyronine (remission 24%). CBT (overall remission using QIDS 14%)
Non-remitters then went to stage 4:
Stage 4: A switch (patient choice) to tranylcypromine (remission 7%), or venlafaxine plus mirtazapine (remission 14%). (overall remission using QIDS 13%)

Whilst not a direct comparison with esketamine this does give the background to response rates in TRD. It is true the therapies you list can be used but the group of people with TRD will almost certainly have tried many other treatments in the past, with STAR*D showing that there is a considerable drop-off in remission rates after the second stage as people get more desperate for relief from their symptoms.

We feel that the place in therapy for esketamine might be aligned to stage 4 of STAR*D. Clinical trials to date with esketamine have shown some efficacy but there is currently insufficient data to extrapolate into clinical practice. The current draft document outlines the various unknowns, but the proposed position statement by NICE might limit opportunities for organisations to trial the use of esketamine to help answer them. Furthermore, it might limit availability to this medication for those who may genuinely benefit from it. To put this into context, alternatives such as deep brain or vagal nerve stimulation are rarely available even via specialist mental health NHS Trusts. We suggest that NICE might reconsider this position statement and allow organisations, especially specialist mental health services to trial use of esketamine in patients who they deem to be suitable. Such patient would receive a thorough assessment and data about efficacy and side-effects would be collected. This real-life experience and data collected could then guide future wider roll-out for use in clinical practice.
STAR*D references include Trivedi et al, Am J Psychiatry 2006;163:28-40, (n=727, RCT, 14/52, Rush et al, N Engl J Med 2006, 354, 1231-42.

7.p3 “Also, the available evidence did not include psychological therapies.” The criticism of the lack of comparison with psychotherapy is unfair and inappropriate as no other therapy had been asked for this before. A recommendation that this carried out would, however, be welcomed. Perhaps this is based on the NICE depression guidelines which are now 11 years old and well out-of-date. It is relevant to highlight that the evidence base for any psychotherapy in TRD is almost entirely lacking.

8. p3 “There is uncertainty about the effect of stopping esketamine treatment. It is unclear if any improvements in symptoms will be maintained after a course of treatment and whether this will improve someone’s quality of life. The costs of repeated courses of treatment with esketamine are unknown, as are the costs of providing the clinic service for esketamine.”

This is true but it is something we will find out over time as we gain more clinical experience with using esketamine.

9: 3.17 (p18) The committee acknowledged that introducing esketamine would probably represent a change in managing people with treatment-resistant depression in the NHS.

We welcome this statement. We think that offering this treatment to the right, but fairly small population of desperately ill people, who have often

exhausted most treatment options, might help obtain more experience and data about efficacy and tolerability to guide future practice.

10: 3.17 (p18) “The NHS commissioning expert advised that esketamine would require a significant investment to become part of NHS clinical practice.”

We do not recognise this. On a practical basis esketamine intranasal administration would need:
1. A quiet room for 60-120 minutes, capable of being made reasonably dark
2. A reclining chair to allow the head to tip back to 45o
3. A blood pressure monitoring machine

An HCP available to welcome the person, supervise the administration, carry out the blood pressure check at 40 minutes, be available to reassure or help the person, and assess them after one or two hours.
There will be a need for some staff commitment but this does not seem to us to be a significant investment, particularly if you care to compare this with other new technologies.

11: 3.17 (p18) The committee heard that adopting esketamine would result in displacement of other mental health treatments because of its cost.
We feel this that there is insufficient evidence about whether this will be the case; it is too early day. We do not recommend widespread use initially, but instead trial in a small number of patients as described above. Other treatments could be replaced if the evidence that emerges shows that this treatment is more effective in TRD than comparators. If some treatments are displaced because another treatment is more effective then that is to be welcomed not cautioned about. If this did not happen in medicine then treatments would never improve.
We would like to point out the human side of this devastating and life-threatening condition and this statement from NICE could deny some people a potentially life-saving medicine . We appreciate that cost has to be a consideration but this will always be an issue for Trusts, who will have to limit its use.
We would welcome comparative and robust trials, with proper placebo groups, full randomisation and blinding, and for adequate duration, properly costed but this should not delay any approval of esketamine.

12. We would welcome a full economic review, but not at the expense of delaying a positive decision.
It should include:
Changes in bed days from use of oral treatments, esketamine and ECT
Societal costs of TRD (being off work, poor productivity, family costs, carers, stress)"

Name	[redacted]
Comments on the ACD:	
General comment	

"I was unaware that esketimine was already being used by the NHS?

Your recommendations state, ""...In addition there is uncertainty about the effect of stopping esketamine treatment.""

How do you propose to learn more about the effect of stopping esketimine treatment given that the clinical trials were short in duration?"

Name	[redacted]

Comments on the ACD:

Has all of the relevant evidence been taken into account?
no, the costs of delivery ECT were not considered.
this is the current next step in treatment beyond oral pharmacotherapy - as per CG90.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
given the nature of this new treatment (method of administration, CD status) it is not surprising that there are minimal trials and none in the UK, as there are so many barriers in the UK to conducting such trials. however non UK data should not necessarily be considered to be not applicable to the UK. the evidence for esketmine is building on that for the racemic mixture of the UK licensed IV ketamine - which does not appear to have been considered.

Are the recommendations sound and a suitable basis for guidance to the NHS?
the recommendations have not considered a sub-population for whom this treatment may be suitable.

General comment
Technically true, but the manner in which this is written implies that ECT would be considered after an antidepressant and a "Second drug". which is not true and not in line with the NICE guidance on ECT. phrasing should be altered to show that ECT is only considered as a last resort when both psychological treatments have been explored and several drug treatment with antidepressants alone, and more than one augmentation strategy attempted, and all failed.
CG90 " consider it if
their depression has not responded to multiple drug treatments and psychological treatment."
Otherwise it makes ECT sound like the third step option that should be taken, which contradicts CG90.

Comment on price
please state what you mean here by "course" - single treatment? 6 months treatment of twice weekly?
please also state whether you mean solely the purchase cost of the product

(I assume not), or whether the "course" includes the cost of delivery - similar to the cost of delivering ECT.

Comment on current clinical practice includes several different types of treatments
this is a very important point, and given the expert nature of this NICE committee there should be consideration of this implications, and not simply go along with the application for "TRD" as per the license. The committee should be more nuanced to see sub-populations within this where there is need.
similarly the ECT NICE guidelines do not use this term, but expect it to only be used: "Consider ECT for acute treatment of severe depression that is life-threatening
and when a rapid response is required, or when other treatments have failed. "

Comment on the company did not provide evidence comparing esketamine with all relevant comparators
ECT could not be a direct comparator. even as per CG90 that should only be used for life threatening and very severe depression, which is not the same category of patient as this is licensed for. however the committee should consider the potential place of esketamine within the pathway, and many expert clinicians consider this to be a step before ECT - which has proven efficacy, and very speedy efficacy, that make the (considerable) risks of a general anaesthetic twice weekly for about 6 weeks, worth the risk. to

Comment on Safety must be taken into account when administering and monitoring esketamine
A registry of treated patients would seem a very good idea for this and many other reasons. e.g. gathering real life data to track patient response in real life scenarios.

Comment on there are substantial limitations to the structure of the company's model
Agreed, given the nature of the illness, and the that all other treatments for depression are used repeatedly when episodes relapse, and oral antidepressants are even used continuously in a subpopulation to keep people in remission.

Comment on A range of ICERs is needed to estimate resource use costs associated with administering esketamine
firstly it need to specify "Mental health" nurse, or RMN.
secondly why are you advocating band 5? Why this grade? in an NHS NH Ward 1:1 or "Close" observations would usually be undertaken by a band 3 MH Health Care Assistant (HCA) under the supervision of a registered MH nurse (RMN). I would expect the same to occur here.

Comment on Esketamine is not recommended

Agree, given that there is no working definition for TRD.
however i think NICE should be able to use their expertise to recommend the subset of patients to whom this new treatment may be of benefit - acknowledging the uncertainly around some aspects of the data.
Esketamine may be of benefit to a sub-population. i.e. a tighter criteria for treatment than "TRD".
eg offer to those who would otherwise be considered for ECT : CG90: "1.10.4.2 ....consider it [ECT] if their depression has not responded to multiple drug treatments and psychological treatment."

a mandatory register should be required of treated patients (as is required for other treatments e.g. clozapine) to collect real life treatment data and outcomes from the UK setting.
Esketamine is likely to be worthwhile for the population who would otherwise receive ECT, given the associated risks of twice weekly general anaesthetic and costs of the setting and the staff required (anaesthetist and ECT expert) to deliver the treatment and monitor immediately afterwards (MH nursing staff for 1:1 "close" observations).

Name	[redacted]

Comments on the ACD:

Has all of the relevant evidence been taken into account?
We acknowledge that NICE's decision not to recommend esketamine is based on limited data, including information provided by the manufacturer. However, Drug Science kindly requests that NICE consider a wider range of evidence, not just from RCTs. This is particularly important for clinical conditions such as treatment resistant depression and for medication such as esketamine, where the requirement for RCTs limits the ability to review more 'real world data'. The current draft document outlines numerous 'unknowns'; however as the Technology Appraisal does not provide 'research recommendations' this will further limit opportunities for providers to create cases for trialling the use of esketamine to help answer them. Perhaps most importantly, NICE's proposed position will further limit availability to this medication for those who may genuinely benefit and for a clinical condition for which an individual will have very limited (if any) alternative treatment options. To put this into context, alternatives such as deep brain or vagal nerve stimulation are rarely available even via specialist mental health NHS Trusts. It would perhaps be more useful if the current position could be amended to be more supportive of organisations (specialist mental health services) being able to trial the use of esketamine and therefore allow a greater opportunity for it's use in clinical practice to be better assessed before reaching such a conclusive decision.

Are the recommendations sound and a suitable basis for guidance to the NHS?
We acknowledge that NICE's decision not to recommend esketamine is based on limited data, including information provided by the manufacturer. However, Drug Science kindly requests that NICE consider a wider range of

evidence, not just from RCTs. This is particularly important for clinical conditions such as treatment resistant depression and for medication such as esketamine, where the requirement for RCTs limits the ability to review more 'real world data'. The current draft document outlines numerous 'unknowns'; however as the Technology Appraisal does not provide 'research recommendations' this will further limit opportunities for providers to create cases for trialling the use of esketamine to help answer them. Perhaps most importantly, NICE's proposed position will further limit availability to this medication for those who may genuinely benefit and for a clinical condition for which an individual will have very limited (if any) alternative treatment options. To put this into context, alternatives such as deep brain or vagal nerve stimulation are rarely available even via specialist mental health NHS Trusts. It would perhaps be more useful if the current position could be amended to be more supportive of organisations (specialist mental health services) being able to trial the use of esketamine and therefore allow a greater opportunity for it's use in clinical practice to be better assessed before reaching such a conclusive decision.

Name	[redacted]

Comments on the ACD:

Has all of the relevant evidence been taken into account?
Yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Can only comment on clinical - yes.

Are the recommendations sound and a suitable basis for guidance to the NHS?
Absolutely not.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Discrimination against people with severe resistant depression by denying them an effective treatment

General comment
In my trust it took about 6 weeks. We use oral, IM, SC and intranasal. It really isn't that difficult.

It is implied here and elsewhere that ECT is an alternative to esketamine. ECT requires a GA and is not without risk. ECT causes significant memory disturbance. Treatment in the acute phase is usually twice weekly for 4-6 weeks. Each treatment requires a GA given by an anaesthetist. ECT often has to be given longer term.

These factors make ECT rather less preferable to esketamine. Patients would certainly think so.

This is true of any treatment, including ECT. The NICE assessment of vortioxetine (recommended as third line Tx) does not mention this aspect.

This is true of any treatment.

There is no mention of the costs of the nominated alternative - ECT

I think everyone agrees that resistant depression is that that does respond at all to two antidepressants in the current episode.

The favourable decision on vortioxetine was based on one comparator trial.

I can't believe anyone said this or believed it to be true. Esketamine is given by nasal spray under supervision and then the patient is allowed home shortly afterwards. ECT involves giving the patient an intravenous anaesthetic and a muscle relaxant and then causing them to have a grand mal seizure. The patient is often drowsy and confused for several hours afterwards.

Not mentioned in the vortioxetine decision

The 'current' NICE Guideline is 11 years old. Out of date by any standards.

It is difficult to know what to say here. Is this standard applied to all medicines evaluated by NICE - that the trials need to include some English people? How are 'participants from England' known to differ from, say, France?

Comment on It is not appropriate to adjust the efficacy estimates of the placebo arm in the trials
This is true but the reasoning is sound - there is evidence to suggest that the number of visits enhances placebo response.

General comment
We have dozens of Schedule 2 Controlled Drugs that are much more liable to misuse, and for which no registry is required. Examples include methadone, diamorphine and fentanyl. A registry for esketamine would be pointless because it would have no effect on diversion (for which there is limited scope because esketamine is administered on site).

This must therefore apply to all treatments including ECT. The implication is that ECT needs to be considered a 20 year Tx. This is not sensible.

ECT suites are ideal for esketamine administration. There are already in situ.

Surely not allowing its use anywhere in the UK would represent an 'equalities consideration'.

This misses the point completely. TRD is a condition that is currently very poorly treated and one for which different treatments are sorely needed. Either it is efficacious or it isn't. If you agree it is then it should be recommended, at the very least, as an alternative to ECT. The patient could be asked to decide - a nasal spray or a grand mal seizure under GA?

Name	[redacted]

Comments on the ACD:

Has all of the relevant evidence been taken into account?
No.
1. Esktamine does not take weeks to work, which improves it's cost effectiveness.
2. Esktamine is not physically addictive, with no risk of seizures or long term brain change.
3. You have not addressed use of Esktamine for patients for whom SSRI's are contraindicated.
4. Esktamine does not have to be tapered off, which improves it's cost effectiveness.
5. Esktamine does not have as many interaction problem to worry about compared to classical anti-depressants.
6. Esktamine as s-isomer ketamine, is already freely available and being used off-label in all towns and cities and many villages in the UK. The long approx. 58 year history of clinical use of this drug has taught people of it's benefits, but they are being forced to buy impure and potentially dangerous forms of the drug from untaxed criminal gangs.
7. Esktamine has no risk of suicidal ideation in the initial period of clinical use.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Categorically no. How can the costs be £163 for 28mg of s-isomer ketamine, when 1000mg of 100% pure s-isomer ketamine can be bought by anyone for approximately £20-30, or as low as £6 if bought in bulk. The figures given are hugely inflated compared to what the public knows pure esketamine can be produced for.

Let's be clear here. Pure s-isomer ketamine hydrochloride has been used off-label for treating depression for as long as 58 years. The costs you are quoting are complete fantasies, and it seems, an invented excuse for not proceeding with this important evolution of our approach to depression.

Are the recommendations sound and a suitable basis for guidance to the NHS?
No, they are not, see previous answers as for why.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
No

Name	[redacted]

Comments on the ACD:

Has all of the relevant evidence been taken into account?
Yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Yes

Are the recommendations sound and a suitable basis for guidance to the NHS?
Yes

General comments

We (12 clinicians/researchers, including 8 psychiatrists) are writing in support of the NICE recommendation not to approve esketamine for use in the NHS.

We have grave concerns about the use of a dissociative anaesthetic agent, and known street drug of abuse, being marketed as a treatment for people with complex emotional difficulties, which are often based on social adversities.

As you are aware, there have been no trials of the efficacy of esketamine in the medium or long term. The majority of the studies of this drug (almost entirely conducted by the drug company attempting to license the drug, Janssen) are only four weeks in duration. Most of these studies find no benefit for esketamine versus placebo, and multiple adverse effects. The one positive efficacy study finds a difference between esketamine and placebo that is small and not clinically meaningful. Esketamine is the only antidepressant that has been approved by the FDA with only one successful efficacy trial.

The longest study to date is a 16 week trial using a discontinuation design, which is almost certain to confound withdrawal effects with relapse of depression. This trial design also increases the likelihood of patients breaking blind in the drug condition. As noted in the FDA statistical review, "perception of their treatment assignment may have been influenced by acute side effects (dissociation, sedation, etc.). FDA's exploratory analysis suggested that changes in these side effects were associated with time relapse."

Notably, there were six deaths in the esketamine studies, including three

suicides, all in the esketamine group, with none in those assigned to placebo. Although these deaths were dismissed as unrelated by Janssen we do not believe that this worrying signal of danger should be ignored. These suicides may well be consistent with a severe withdrawal reaction from the medication, known to occur in other medications such as antidepressants and opiates.

Short term apparent benefits of using esketamine are unsurprising, given its similarities to drugs of abuse, and no basis for approving a drug. One could achieve similar results, short term euphoria or dissociation, with various other street drugs. Indeed, we are as shocked by this recent development as we would have been had es-cocaine been submitted for approval.

If esketamine is approved for public use in the UK, there is no impediment to doctors prescribing this drug for weeks, months and beyond, which is precisely what we now see occurring in the US since FDA approval.

We are aware of the public statements made by Janssen spokespersons about the NICE recommendation, parts of which seem to border on bullying. We trust that an evidence-based approach will be taken to your decision and, therefore, that no approval fir NHS use will be granted until multiple, successful, independent trials (i.e. not industry sponsored) of at least a year, and preferably longer, have been conducted.

Yours Sincerely

Dr John Read
Professor of Clinical Psychology, University of East London.

Dr Pat Bracken
Consultant Psychiatrist, Ireland

Dr James Davies
Medical Anthropology, University of Roehampton

Dr Peter J Gordon,
Retired Consultant Psychiatrist for Older Adults

Dr Rex Haigh
Consultant Psychiatrist in Medical Psychotherapy, Berkshire NHS

Dr Peter Kinderman
Professor of Clinical Psychology, University of Liverpool

Dr Irving Kirsch
Associate Director, Program in Placebo Studies, Harvard Medical School; Professor Emeritus, Psychology: University of Connecticut (USA) & University of Hull (UK)

Dr Hugh Middleton
Psychiatrist, University of Nottingham

Dr Clive Sherlock
Psychiatrist, Oxford

Dr Derek Summerfield
Consultant Psychiatrist; Hon. Senior Clinical Lecturer - Institute of Psychiatry, Psychology & Neuroscience, King's College, London

Dr Philip Thomas
Formerly Professor of Philosophy, Diversity & Mental Health, University of Central Lancashire; Formerly Consultant Psychiatrist

Dr Sami Timimi
Consultant Child and Adolescent Psychiatrist, UK

Name	[redacted]

Comments on the ACD:

Has all of the relevant evidence been taken into account?
Evidence of deaths in the esketamine group were not fully appraised in this document in its assessment of safety (see comment below for further information).

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
The clinical effectiveness of the drug was over-estimated by use of dichotomised data (response and remission rates) that exaggerate the small differences between placebo and esketamine on the primary MADRS measure. The efficacy trials only ran for 4 weeks with little relevance to treatment of depression. The discontinuation trial was flawed in design (withdrawal effects were likely to confound measures of relapse). See comment below for further information.

Are the recommendations sound and a suitable basis for guidance to the NHS?
The final recommendation is sound and a suitable basis for guidance for the NHS, but critical evaluation of the studies presented should be more rigorous to prevent lowering of the threshold for what constitutes a safe, and effective treatment option.

General comment

Division of Psychiatry,
Maple House,
149, Tottenham Court rd,
London
W1T 7NF

12th February 2020

Dear NICE committee for esketamine

Re: Approval of esketamine for treating treatment-resistant depression

As psychiatric doctors with extensive experience of treating people diagnosed with depression we welcome NICE's draft guidance that esketamine should not be recommended for the treatment of treatment-resistant depression, given that the evidence of benefits over harms is not clear. We think the committee was wise to carefully evaluate the claims made by the manufacturer rather than uncritically accepting inflated claims of efficacy and minimisation of safety issues by the manufacturer.

We are writing to highlight a number of points that were not emphasised by the committee when coming to its decision that further demonstrate both the lack of evidence for effectiveness of the drug, its danger and the lack of long-term studies.

In the appraisal document, it was stated: "Clinical trials suggest that esketamine with an oral antidepressant may be more effective at relieving the symptoms of depression than placebo and an oral antidepressant." (page 3 of 23). The thinking underlying this summary is outlined in Section 3.6

We suggest this conclusion is not warranted by the data. Janssen performed three efficacy trials that lasted for 28 days. Two of these trials showed no significant difference between esketamine and placebo 1,2. These trials were appraised in the NICE document in terms of response and remission rates. However, this does not take into account the raw data, which was measured using the MADRS. Methodological experts are unanimous in advising the use of primary data (the MADRS) rather than dichotomised versions of the data (response or remission rates) because dichotomised data tends to inflate the differences between groups especially when the differences between groups are small on the primary data 3.

When the data are appraised based on their primary measures evidence for superiority of esketamine over placebo is not clinically significant. The single positive study found a difference of 4 points on the MADRS favouring esketamine over placebo 4. The MADRS scale goes from 0 to 60; average score for patients at baseline was 37. The response to placebo treatment (a nasal spray with embittering agent) was a 17-point reduction on the MADRS score. The response to esketamine was 21 points. A 7 to 9 point reduction on the MADRS has been found to correspond to a clinically noticeable ("minimally improved") change on the Clinical Global Impressions scale (CGI) 5; "much improved" requires a reduction of 16-17 points. A 4-point difference therefore corresponds to less than "minimal" change, and was less than one quarter the size of the placebo response, suggesting doubtful clinical relevance 6. Furthermore, participants would have been unblinded by the noticeable psychoactive effects of esketamine (dissociation was reported by the majority of participants); expectation effects might therefore

inflate the apparent difference between placebo and esketamine.

Moreover, the time period of 28 days has little bearing on the treatment for depression, as treatment for depression is often continued for many months or years. Based on both the sub-clinical effects produced by the drug and the irrelevant time period for which these drugs were trialled it seems premature to conclude that esketamine is more effective than placebo for treating depression.

The problematic discontinuation design study (SUSTAIN 1) used by Janssen as a second 'positive' trial is discussed in the below section.

It is further stated that "There is uncertainty about the effect of stopping esketamine treatment" (Page 3).

To the contrary it is widely recognised that ketamine is an addictive drug and withdrawal symptoms are experienced when stopping ketamine in recreational use. Stopping regular use causes a withdrawal syndrome characterised by anxiety, dysphoria, shaking, sweating and palpitations, and craving the drug 7,8. Frequent users report using the drug compulsively until supplies run out 7. The addictive nature of ketamine has been linked by some authors to its activation of opioid receptors 7,9, amongst numerous receptor targets 10.

There is no reason to think that esketamine will have any different effects than ketamine – indeed (S)-ketamine, or esketamine, is twice as potent an anaesthetic agent as ketamine 10, meaning its addictive properties might be even more marked.

Notably, withdrawal effects were not reported in the discontinuation trial design (SUSTAIN-1) used by Janssen in its second 'positive' trial. Although the study reports suggests there was no evidence of a withdrawal syndrome using the Physician Withdrawal Checklist, scores for the different groups are not reported, and it is not clear how items in the checklist such as 'insomnia', 'anxiety-nervousness', 'dysphoric mood-depression', 'difficulty concentrating, remembering', 'fatigue', 'lack of appetite' were distinguished from almost identical items in the MADRS (e.g. MADRS items 'apparent sadness', 'reported sadness', 'inner tension' 'reduced sleep', 'reduced appetite', 'concentration difficulties', 'lassitude'). Consequently, it is possible that some of the 'relapses' detected were in fact due to mis-classification of withdrawal effects

As half (48.7%) of relapses occurred in the first four weeks following esketamine cessation, the time most likely for withdrawal effects to occur, and as the relapse rate in the placebo group became "closer to esketamine with each week" as highlighted by the FDA, confounding of 'relapse' by withdrawal seems likely 2.

Further evidence of a withdrawal effect is also suggested by the marked 'relapse prevention' effect of a drug with minimal antidepressant effects in

the short term. This pattern is similar to what might be seen in a trial of a benzodiazepine for anxiety: modest effects in the short-term, but marked 'relapse prevention' effects on discontinuation, if confounding by withdrawal effects are ignored.

The FDA also highlighted another problem with this study design: "functional unblinding"2, as in the acute efficacy studies. The absence of esketamine's psychoactive effects would be noticed by participants randomised to placebo and consequent negative expectations would tend to increase their chance of relapse 2. Higher dissociation scores while on treatment were correlated with shorter time to relapse, consistent with this hypothesis.

Importantly, the FDA also raised the concern that the positive results of the study were driven by a single site where there was 100% relapse rate in the placebo arm 2. It has been demonstrated that if this outlier site is excluded there is no difference between esketamine and placebo (the p value changes from 0.012 to 0.48)6, leading to the conclusion that the findings are "not robust".

It is unclear if any improvements in symptoms will be maintained after a course of treatment and whether this will improve someone's quality of life.

Safety considerations: It is not appropriate to include an effect of esketamine on mortality (p.15)

In this section, it was outlined how Janssen attempted to estimate an effect of esketamine on mortality, suggesting that esketamine would improve overall mortality. It is of concern that Janssen presented this conjectural analysis, based on questionable assumptions, while downplaying the fact that there were six deaths in the esketamine arm and none in the placebo arm of the Phase 2 and Phase 3 clinical trials 2, out of about 1200 patients enrolled in these studies. We suggest that these deaths are highly relevant and should be regarded as a signal of potential serious harm.

Three of these deaths were suicides. The three suicides occurred in participants 4, 12 and 20 days after the last dose of esketamine 9. Janssen attributed these deaths to 'the severity of the patients' underlying illness' 2. However, two of the patients who died by suicide showed no previous signs of suicidal ideas during the study, either at entry to the study or at the last visit (data was not available for the third patient) 2. The FDA accepted Janssen's assessment that the suicides were not drug-related" 2.

However, others have argued that these cases fit with a pattern of a severe withdrawal reaction, consistent with other reports of suicide from ketamine 11,12, and are significant enough in number to constitute a worrying signal 9.

An increase in depression and suicidality was also observed during esketamine treatment. In one 4-week trial 6 patients in the esketamine

group became more depressed, compared to only one on placebo; 4 patients expressed new onset suicidal ideas in the esketamine group, compared to only one on placebo 2. The drug will be marketed with a 'black box' warning including a risk of suicidal ideas and behaviour 13, but it is not clear that this measure is stringent enough.

In summary, the evidence for the benefits of esketamine is not strong, and there is a lack of long-term studies that can establish the benefits and harms of long-term use, even though we know that drug treatments for depression tend to be taken on a long-term basis by many users. We urge NICE to maintain its current position on the suitability of this drug for use for depression in the NHS and require higher quality longer term studies that carefully evaluate all aspects of its safety and efficacy before considering recommending this drug in the future.

Yours sincerely,

Professor Joanna Moncrieff

Dr Mark Horowitz

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Name	[redacted]

Comments on the ACD:

Has all of the relevant evidence been taken into account?
No I don't believe so as demonstrated in the comments

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
No I don't believe so as demonstrated in the comments

Are the recommendations sound and a suitable basis for guidance to the NHS?
No I don't believe so as demonstrated in the comments

General Comments:

Comment on Recommendations
This recommendation is not based on a reasonable interpretation of the clinical and cost effectiveness of the evidence; and the provisional recommendations are not a sound and a suitable basis for guidance to the NHS?

In the Star-D study at tier 3 which is failure of 2 anti-depressants the rate of remission with a new strategy varied: mirtazapine (8%), nortriptyline (12%), or Lithium (13%), all of which might be common strategies in the UK. The rate of remission with Esketamine at tier 3 (failure of 2 anti-depressants) is 50%. That is an absolute risk difference of at least 37% between treatments or on the face of it esketamine is 3 times as effective at tier 3 that other anti-depressants or augmentation strategies. Whilst they have not been directly compared this is the best comparative evidence that is available.

I wonder how far the demand for a comparison with ECT is clinically valid. The two interventions are entirely different treatments. Whilst effective, a large number of people will not be willing to have ECT because of stigma or concern about it. Also, resources needed for ECT, involve significant

medical (including anaesthetist) and nursing time, stringent governance procedures including second opinions and safeguards. It doesn't seem correct to be equating the two treatments in forming a judgement. The clinical reality is that ECT is only really offered to people when they have failed multiple treatments, probably because of its acceptability.

Comment on Current clinical practice includes several different types of treatments

On what basis did the committee conclude this.? Trainee psychiatrists from core training year 1 learn the widely accepted definition described above. It doesn't seem correct to say that there is no widely accepted definition

Whilst there are differing academic and research based ideas about how this should be defined the definition within the licence is the widely accepted clinical definition, at least in the UK.

It should be noted that the depression guidance is now over a decade old and it is debateable whether that guidance can be relied upon as a reasonable reference point for treatment and care pathways.

Comment on The company did not provide evidence comparing esketamine with all relevant comparators
I have made comments about the STAR-D study above, which could be used as a comparison (though not perfect)

the evidence to suggest combining anti-depressants in comparison to a single anti-depressant is poor

Comment on The effect of psychological therapy in addition to drug treatments is not clear
I find this puzzling. As far as I am aware there are 2 trials of psychotherapy for treatment resistant depression, one of which is limited by its methodology. The level of skill to provide that type of therapy (in a manualised form) is not widespread in the NHS in my clinical experience. Also in my experience most people with TRD either do not want psychotherapy or are not able to use it because of the cognitive symptoms (e.g. poor attention, concentration, poor memory) that the illness causes. The NICE guidelines for depression are more than 10 years out of date. This would not seem a reasonable evidence based comparison for Esketamine.

Comment on the evidence for esketamine is limited in its generalisability to the NHS
This is a common exclusion in mental health trials

This would suggest the panel wanted esketamine to be assessed in people with a greater degree of resistance-is that the case, if this is an issue? This would not usually be the population who were in the Esketamine trials and would to my mind have a greater degree of resistance.

This would seem a very high bar to set for a trial. I would be interested to know whether similar bars have been set for assessment of psychotherapy or other treatments for depression or infact other treatments in mental health.

It is difficult to understand how the committee came to this conclusion

Comment on Safety must be taken into account when administering and monitoring esketamine
I believe this would be outside the licence if it is substance misuse the clinical expert was referring to

Comment on a longer time horizon for the economic model is preferred
Whilst depression can have a waxing and waning nature is the clinical expert referring to the 10-15% of people with depression who follow a "chronic course". In my clinical experience (and from the perspective of having been a Consultant Psychiatrist for 15 years) it is not difficult to understand when an episode of depression has ended. Clinicians have to do this day in day out to decide how long to advise patients to continue to take anti-depressants for.

Comment on There are substantial limitations to the structure of the company's model
Though within that future episode the patient would have needed to try 2 previous anti-depressants for the Esketamine to be given within its licence

Comment on it is not appropriate to include an effect of esketamine on mortality
This text and thinking is difficult to follow. The committee appear to think that Esketamine could impact on suicide, but then say because people with acute suicidal risk were excluded this cannot be the case. Suicidal risk is not a static phenomenon, and lack of suicidal risk with intent in the last 6 months would not exclude people with severe suicidal behaviour previously; and previous suicidal behaviour at any time increases future suicidal risk. Purely from a clinical view the committee's lack of acceptance that treatment of TRD now could reduce suicide risk in the future (even if people with acute suicidal intent are excluded from a current sample) is of concern. In doing so the committee appear to be refuting evidence indicating that a] TRD is associated with suicidal thinking and suicide; and b] that treating TRD will reduce the risk of completed suicide (or at least risk), a basic tenet of mental health care.

Comment on significant investment will be needed to adopt esketamine into clinical practice
Should we assume that new mental health treatments cannot be sanctioned because they might displace other mental health treatments or need new investment? How does this fit with the continuous announcements of more money towards mental health treatment. The underlying assumption here is

that if new treatments for TRD are available we cannot benefit from them, because they will need investment. This is of concern and I doubt very much a similar argument would be made in other therapeutic areas.

Yes it would and that would be a very good thing, given the difficulties that this population currently face in access to effective treatment.

Comment on 5 Appraisal committee members and NICE project team
There was no Psychiatrist on the NICE committee-why is this? There seemed to be a representative of a very wide range of other healthcare professionals, but just not Psychiatrists. To my mind this shows and will sit as odd to many people in the field and the wider community. The committee has made a decision without professionals in the room who are actually faced with the condition day in day out. This is a lost opportunity for the committee and doesn't seem correct.

Name	[redacted]

Comments on the ACD:

General comment
Whilst I appreciate the comments about lack of evidence about the effect of TRD on carers and families, and how esketamine could help them, I can't help but feel that this is being passed over and is bordering on being insulting to them. The sustained impact on family and carers, whilst living with and trying to keep patients with TRD safe, is phenomenal and can continue for years. This can impact on their health, their lives and employment, and affects them socioeconomically.

There are limited options available for patients with TRD and often patients are offered numerous versions and combinations of oral antidepressants that are purely based around the monoamine hypothesis. The chances of these working following several attempts are low.
Often antidepressant's are augmented with antipsychotics that bring numerous additional side effects and therefore unpalatable to patients.
Access to psychological treatments are sadly lacking.
ECT can be effective for patients, but tend to be held back for more poorly patients and have many side effects related, such as memory impact.
In short, by not recommending esketamine, you are limiting options for patients that are already sadly lacking and withholding a new, potentially, life changing treatment.
Work on treating depression via the Glutamate Hypothesis is novel and could bring hope to patients who have sadly been neglected by new innovative ways of treating them.

Name	[redacted]
Comments on the ACD:	
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? No. It is absolutely disgusting that you rejected the one hope for people with treatment-resistant depression. **Are the recommendations sound and a suitable basis for guidance to the NHS?** No	

Prof Gary McVeigh
National Institute for Health and Care Excellence
10 Spring Gardens
London
SW1A 28U

17th February 2020

Dear Prof McVeigh,

Re: Esketamine for treatment resistant depression

We have come together to express our support for the findings and conclusions of the NICE appraisal committee concerning the clinical and cost effectiveness of esketamine for treatment resistant depression. We are highly supportive of recommendation 1.1 that esketamine is not recommended.

We fully support NICE in taking an evidence based approach to the appraisal of esketamine, in contrast to the approach taken by the FDA and MHRA. A number of stakeholders have expressed their concerns directly to the MHRA and documented the lack of evidence of efficacy for esketamine. Unfortunately the lack of evidence of efficacy appears not to have impacted on the MHRA decision.

As you are aware, numerous stakeholders came together recently concerning the NICE guideline on Recognition and Management of Depression in Adults and expressed a number of methodological concerns about the draft guideline. One of these was the lack of analysis of long-term outcomes. Stakeholders were advised in December 2019 that NICE will now be looking for long-term outcome data and will take these into account in the next draft of the guideline. We would urge you to continue to apply this and other methodological principles raised by stakeholders in relation to all new as well as existing treatments for depression and to ensure that long-term efficacy as well as long-term avoidance of harm remains the paramount consideration in any decision formulated by NICE.

Yours sincerely,

All Party Parliamentary Group Prescribed Drug Dependence*, Dr Anne Guy (Secretariat Coordinator)
Association for Family Therapy and Systemic Practice in the UK, Dr Reenee Singh (CEO)
Association of Clinical Psychologists UK, Che Rosebert (Director External Communications)
Association for Psychoanalytic Psychotherapy in the NHS (APP): Andrew Soutter, Chair
British Psychoanalytic Council, Gary Fereday (CEO)
British Psychotherapy Foundation, Mike Owen (CEO)
Council for Evidenced Based Psychiatry, Dr James Davies (co-founder)
National Counselling Society, Meg Nunn (Acting CEO)
Psychotherapy Foundation, Dr Steve Buller (Chair)
Tavistock Relations, Andrew Balfour (CEO)
Tavistock & Portman NHS Foundation Trust, Paul Jenkins (CEO)
University of Essex, Dr Susan McPherson (Senior Lecturer)
Wish – a women's voice for mental health, Joyce Kallevik (Director)

*The APPG from the last parliament supported this and is in the process of reforming

Esketamine for treatment-resistant depression: ERG comment on Company ACD Response

Produced by Kleijnen Systematic Reviews Ltd (KSR)

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Declared competing interests of the authors
None.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.
Academic in confidence (AiC) data are highlighted in yellow throughout the report.

1. ERG comment on Company ACD Response

The Evidence Review Group (ERG) has reviewed the appraisal consultation document (ACD) response by Janssen and notes the production of a revised company base case.[1] The ERG has confirmed that this is based on the original company 'adults and elderly' model considered at the first appraisal committee meeting (ACM). Table 1 shows the assumptions that form this new base case and indicated whether they are in accordance with those stated to have been preferred in the ACD.

Table 1: Revised company base case assumptions

Assumption		Consistent with ACD preference?
1	Time horizon 20 years	Yes
2	No adjustment for placebo effect to OAD Acute response or remission transition probabilities	Yes
3a	52 % immediate discontinuation on recovery	No, no discontinuation for reasons other than lack of efficacy preferred.
3b	84% discontinuation up to 2 years in recovery state	
4	No excess mortality for MDE	No, no reduction in excess mortality preferred.
5	Cost of clinic visit for ESK-NS + OAD based on patient to nurse ratio of 6:1 to 2:1	Yes
6	Carer disutilities	No, no disutility

Source: Company ACD response[1]
ERG = Evidence Review Group; ESK = esketamine; MDE = major depressive episode; NS = nasal spray; OAD = oral antidepressant

As can be seen in Table 1, the company base case adopts the ACD preferences for three assumptions, time horizon, no adjustment for placebo effect, and the range of cost of clinic visits. However, it fails to adopt those for discontinuation due to lack of efficacy, excess mortality for major depressive episode (MDE) and carer disutilities. The ERG was also able to reproduce the base case incremental cost-effectiveness ratios (ICERs) of £10,790 with a nurse to patient ratio of 6:1. The ERG could not reproduce the value of £12,264, depending on a nurse to patient ratio of 2:1 because the cost associated with this ratio could not be found in any of the documents submitted by the company.

Discontinuation for reasons other than lack of efficacy

With regards to treatment discontinuation the company present additional evidence from SUSTAIN-2 that shows the proportion of relapse in patients who have been in remission for at least 9 months was [redacted] at week 4 after discontinuing esketamine nasal spray (ESK-NS). The ERG would like to highlight that SUSTAIN-2 included patients on a completely different basis to the trials used to inform the model parameters, TRANFORM-2 and SUSTAIN-1, i.e. it included patients transferred from TRANSFORM-3, who are all also at least 65 years of age, who had not responded to treatment.[2] The company goes on to make the point that this percentage is much lower than that for patients who have been in stable remission for 12 weeks, where the proportion of patients who relapsed at 4 weeks after ESK-NS treatment discontinuation was [redacted]. On this basis the company seem to argue that the rate of relapse on discontinuation of ESK-NS after at least 9 months of remission in clinical practice, i.e. in the so-called recovery phase would be nearer the lower figure. However, recognising that the rate of recurrence might increase on discontinuation of ESK-NS, it conducts a scenario (*"Inputs using OAD* [oral antidepressant]+*PBO* [placebo] *SUSTAIN-1 recurrence risk"*) whereby it increases to the same rate as observed in SUSTAIN-1 for the OAD+PBO-NS arm, i.e. 3.6%.

This contrasts with the value in both the revised and original company base case of 2.9% (apparently misreported as 2.8% in the company ACD response), which was reported to be the pooled estimate of recurrence from SUSTAIN-1 and used for both OAD only and ESK-NS both before and after its discontinuation. In this scenario, the company uses the estimate of 2.4% for ESK-NS + OAD from SUSTAIN-1 for ESK-NS pre-discontinuation and 3.6% for OAD. They also did not include a carer disutility, which means that the ICER would be lower if this had been included. The ERG were unable to reproduce precisely the results of £18,484-£22,386 shown in the table labelled Scenario 3.5: instead the values of £18,749-£22,674 were produced.

Scenario including retreatment with ESK-NS + OAD

The company also included a scenario whereby the revised company base case is adapted to include retreatment with ESK-NS + OAD only for those who had discontinued for reasons other than lack of efficacy and then had a recurrence. They argue that, given that patients who have a recurrence had already been in recovery (remission for at least 9 months), the effectiveness is likely to be at least that of those first treated and so they also include a scenario with 100% remission on retreatment. Given that retreatment improves overall effectiveness, it is not surprising that the results of these scenarios are for the ICER to decrease and even for ESK-NS + OAD to become dominant in the 100% remission scenario. Retreatment with ESK-NS + OAD up to five times in the model.[3]

The ERG considers that for those initially treated with ESK-NS + OAD retreatment on recurrence has some plausibility. However, it is unclear that just because retreatment would only occur in those who had experienced recovery on ESK-NS + OAD, such patients would have a chance of remission that was at least as high as on first treatment. The ERG would like to point out that if treatment with ESK-NS + OAD is permitted on recurrence after initial treatment with ESK-NS + OAD then there might seem to be no reason to not allow treatment with ESK-NS + OAD for those who suffer a recurrence following initial treatment with OAD only. This would lead to an improvement in effectiveness for the comparator and would probably imply an increase in the ICER. However, such comparator, i.e. OAD for an MDE followed by ESK-NS + OAD on recurrence of MDE would not constitute standard care since it involved ESK-NS.

Carer disutilities

The company provided argumentation that a carer disutility should be included based partly on precedent, i.e. it having been incorporated in previous NICE TAs and partly on clinical grounds, i.e. major depressive episode (MDE) is likely to have a detrimental effect on carers. As stated in the ERG comment on the company response to the technical engagement report, the company did produce a study that could be used to inform such a disutility, although the ERG would apply these data differently, as described in the ERG critique of response to technical report.[4] The effect of the ERG's preferred approach to applying the disutility would be to increase the ICER in the revised company base case from £10,790 to £12,339.

Other issues and factual inaccuracies

The company highlighted a number of minor issues for comment. These are highlighted in Table 2 alongside the ERG's response.

Table 2: Other issues and factual inaccuracies

Company Issue*		ERG response
1	The population included in the	No new evidence was presented.

Company Issue*		ERG response
	clinical trials, despite the Committee's questions regarding its generalisability, is appropriate for decision making by NICE	The exclusion from the ESK-NS trials of patients with moderate to severe alcohol abuse, psychiatric comorbidities and suicidal intent was justified by the company as being consistent with other trials and with TA367. The company has proposed an observational study to collect the characteristics and the clinical outcomes of patients with TRD in the NHS.
2	Analyses show that unblinding was not an issue in the clinical trials	No new evidence was presented. The company reiterated the measures taken to ensure blinding and reiterated that a post-hoc analysis found no correlation between treatment effect in the ESK-NS trials and disassociation. The ERG considers, as stated in the ERG report, that some unblinding due to disassociation could have occurred in the ESK-NS trials.
3	NHS stakeholders have indicated that significant investment is not needed for the introduction of ESK-NS to the NHS	No new evidence was presented.
4	The efficacy of subsequent treatments is based on a clinically validated and robust publication	The company make the point that the values for remission and response on subsequent treatment suggested by the ERG in their report are too high (see Table 6 of the company ACD response). Indeed, at TRD line 2 they are higher than those from STAR*D, particularly for remission. This is largely due to the TRD line 1 values for OAD (not included in Table 6) from TRANSFORM 2 being higher than those from STAR*D, i.e. 26.6% and 18.4% vs. 13.7% and 16.8% respectively for remission and response. Therefore, the ERG have adjusted the values for subsequent treatment by assuming only for the purpose of calculating these values that those at TRD line 1 are those from STAR*D, i.e. 13.7% and 16.8%. This change increases the ICER from £10,790 to £21,331.
5	Supervising multiple patients in the post-administration observation is clinically reasonable and based on extensive clinical input	The company provide a figure to show how, of the arrival of patients is staggered by 10 minutes between each patient, supervision of patients in a ratio of 6:1, as in the revised company base case, implies supervision of six patients simultaneously for only 10-20 minutes. The ERG would like to note that this still implies supervision of this number of patients for some non-negligible time. Also, it is assumed, according to this figure, that each patient is in the clinic for about 60-70 minutes. During this time, given that monitoring is required, it must be the case that an adverse event is possible, which would require the intervention of a nurse and which would presumably prevent the monitoring of other patients.
6	Previously provided data on the dosing and frequency of administration shows ESK-NS remains cost-effective	The company produce a new sensitivity analysis to show how great the number of ESK-NS OAD administrations would have to be in order to reach the ICER threshold of £20,000. However, the ERG were unable to reproduce these values because they were based on a patient: nurse ratio of 2:1 for which the cost has not been provided.

Company Issue*		ERG response
7	Other issues and factual inaccuracies in the ACD	This section of the company's response mainly related to factual inaccuracies and clarifications. No new evidence was presented. However in response to the ACD comment *"The staff training to administer and monitor esketamine may not have been accounted for in the model because additional training is needed to manage dissociative effects"* the company stated that additional costs of training should not be included in the model as the company will provide additional educational materials for clinicians and patients. On request, further training could be provided.
*The company issue numbering is as reported in the Company ACD Response for Section 8.[1] ACD = appraisal consultation document; ERG = Evidence Review Group; ESK = esketamine; ICER = incremental cost-effectiveness ratio; NHS = National Health Service; NICE = National Institute of Health and Care Excellence; NS = nasal spray; OAD = oral antidepressant; TA = technology appraisal; TRD = treatment-resistant depression		

Based on all considerations discussed in this ERG comment on the company ACD Response, the ERG constructed four additional scenarios using the revised model provided by the company. The base-case ICER in the company revised base case is £10,790. However, after implementation of the additional ERG scenarios the ICER with patient to nurse ratio 1:1 ranges from £15,839 to £40,900 and the ICER with patient to nurse ratio 6:1 ranges from £12,682 to £35,883. All the changes applied to the model are consistent with the ERG report and are described in Table 3.

Table 3: Additional ERG scenarios

ERG scenarios	ICER £/QALY Patient to nurse ratio 6:1	ICER £/QALY Patient to nurse ratio 1:1
Scenario 1: All changes*	£35,883	£40,900
Scenario 2: All changes* excluding decrease in response and remission at each line of subsequent therapy	£21,879	£25,827
Scenario 3: All changes* excluding assumptions that 0% of patients immediately discontinued treatment at recovery and 64% discontinued treatment in recovery after 2 years	£24,196	£28,207
Scenario 4: All changes* excluding decrease in response and remission at each line of subsequent therapy and assumptions that 0% of patients immediately discontinued treatment at recovery and 64% discontinued treatment in recovery after 2 years (see ERG critique of response to technical report).[4]	£12,682	£15,839
*All changes: Time horizon 20 years; no adjustment for placebo effect to OAD acute response or remission transition probabilities; 0% immediately discontinued treatment at recovery (was 52% in company base case); 64% discontinued treatment in recovery after 2 years (was 84% in company base case); no effect on mortality of ESK-NS + OAD; fixed carer disutilities; 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 as set out in Table 2 above (point 4). 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		

2. References

[1] Janssen. *Esketamine nasal spray for treatment-resistant depression [ID1414]. Company response to NICE appraisal consultation determination (ACD)*: Janssen, 2020 [accessed 19.2.20]. 34p.

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[3] Janssen. *Esketamine nasal spray for treatment-resistant depression [ID1414]. Company response to NICE appraisal consultation determination (ACD): Appendices*: Janssen, 2020 [accessed 19.2.20]. 4p.

[4] Kleijnen Systematic Reviews Ltd. *Esketamine for treatment-resistant depression [ID1414]. ERG critique of response to technical report*, 2019 [accessed 2.12.19]. 7p.

Esketamine for treatment-resistant depression: ERG comment on Additional Company Response to ACD

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Declared competing interests of the authors
None.
Commercial in confidence (CiC) data are highlighted in blue throughout the report.
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1. ERG comment on Company ACD Response

The Evidence Review Group (ERG) has reviewed the additional appraisal consultation document (ACD) response by Janssen and notes the production of a revised company base case ICER range (depending on patient to nurse ratio from 6:1 to 1:1) of [redacted], given a proposed commercial arrangement - [redacted].[1] According to Table 1 in the additional ACD response, this is based on the same assumptions as the base case in the original response to the ACD, i.e. those already presented in Table 1 of the ERG comment and reproduced below, apart from the exclusion of carer disutilities.[2, 3]

Table 1: Revised company base case assumptions

Assumption		Consistent with ACD preference?
1	Time horizon 20 years	Yes
2	No adjustment for placebo effect to OAD Acute response or remission transition probabilities	Yes
3a	52 % immediate discontinuation on recovery	No, no discontinuation for reasons other than lack of efficacy preferred.
3b	84% discontinuation up to 2 years in recovery state	
4	No excess mortality for MDE	No, no reduction in excess mortality preferred.
5	Cost of clinic visit for ESK-NS + OAD based on patient to nurse ratio of 6:1 to 2:1	Yes
6	No carer disutilities	Yes
Source: Company ACD response[2] ERG = Evidence Review Group; ESK = esketamine; MDE = major depressive episode; NS = nasal spray; OAD = oral antidepressant		

Therefore, one would expect that the only other reason for the difference between this base case ICER and the one in the previous company response of £10,790 - £12,264 would be the proposed commercial arrangement. Indeed, the ERG could reproduce these figures by applying the proposed commercial arrangement to the list price of £163 (per a single-use device that delivers a total of 28 mg of esketamine in two sprays (one spray per nostril)).

Also, the company have presented a set of scenarios based on the new company base case with proposed commercial arrangement. The company report that this is because they "…have been advised to submit additional scenario analyses as discussed with Meindert Boysen and Helen Knight on 20th February." (p.3) These relate to the effect of two sets of assumptions:

1) various assumptions regarding discontinuation for reasons other than lack of efficacy, i.e. in the recovery phase, with three additional scenarios shown in Table 1 of the company additional response.

The ERG can confirm that all of the results of Table 1 can be reproduced.

2) Adding a utility decrement post-discontinuation for reasons other than lack of efficacy.

The utility decrement was a multiple of [redacted]. This was reported to be the change in utility of 4 weeks after discontinuation of patients from the SUSTAIN-2 study who achieved recovery with ESK-NS + OAD and then discontinued ESK-NS whilst in recovery. Three scenarios were presented with decrements of [redacted], [redacted] or [redacted]. The results were presented in Table 2.

Finally, the effect of combinations of the two sets of assumptions was presented in Table 3.

The ERG can confirm that the results of Tables 2 and 3 could also be reproduced and that this was by incorporating a utility decrement in the model for only the part of the cohort that was off-treatment in the recovery phase, i.e. had discontinued ESK-NS for reasons other than lack of efficacy.

2. References

[1] Janssen. *Esketamine nasal spray for treatment resistant depression [ID1414]. Janssen additional response to NICE appraisal consultation determination (ACD)*: Janssen, 2020 [accessed 3.4.20]. 13p.

[2] Janssen. *Esketamine nasal spray for treatment-resistant depression [ID1414]. Company response to NICE appraisal consultation determination (ACD)*: Janssen, 2020 [accessed 19.2.20]. 34p.

[3] Wolff R, Armstrong N, Ryder S, Buksnys T, Fayter D, Swift S, et al. *Esketamine for treatment-resistant depression [ID1414]: ERG comment on Company ACD Response*. York: Kleijnen Systematic Reviews Ltd, 2020. 6p.

Esketamine for treatment-resistant depression: ERG analyses post-ACM 2

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1. Post-ACM 2 scenarios

The ERG were asked to provide ICERs for the following scenarios:

- The ERG scenario with proportional decrease in subsequent treatments
- stopping treatment as in scenario C of the company submission (0% immediately discontinue, 70% by 2 years)
- Administration costs of 2:1 patient:nurse ratio in the maintenance phase
- Equalising medical costs between arms
- Including the ERG method of implementing carer disutility and also sensitivity without any carer disutility (both these ICERs)
- Both those ICERs with and without the proposed commercial arrangement discount applied

With and without carer disutility plus with and without proposed commercial arrangement implies 4 scenarios in total, for which the ICERs are shown in Table 1.

Table 1: Post-ACM 2 scenarios

ERG scenarios	ICER £/QALY
Scenario 1: All changes with carer disutility, without proposed commercial arrangement	£ 64,554
Scenario 2: All changes without carer disutility, without proposed commercial arrangement	£ 72,158
Scenario 3: All changes with carer disutility, with proposed commercial arrangement	[redacted]
Scenario 4: All changes without carer disutility, with proposed commercial arrangement	[redacted]

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