**National Institute for Health and Care Excellence**

**Health Technology Evaluation – Review proposal**

### TA854 esketamine for treatment resistant depression

**Response to stakeholder organisation comments on the review proposal**

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Comments on the proposal

| Consultee/ Commentator | Comments [sic] | Response |
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| International Society for Affective Disorders (ISAD) | There are very few head to head studies of augmentation therapies in treatment resistant depression – just 9 according to Nunez et al (Journal of Affective Disorders, 2022, 302, 385-400). Crucially, until this year no head to head study had gone past a 12 week time point. We have now have in the literature two completed studies that are large, head to head, and long term - the ESCAPE study (industry funded, esketamine v quetiapine, 32 weeks; published) and the LQD Study (NIHR funded, Quetiapine v lithium, 52 weeks; presented in abstract and submitted for publication) that both add very significantly to the literature on long term effectiveness and cost-effectiveness of pharmacological augmentation. Both studies find superiority of one of the interventions over another. These new and much improved data suggest that a new look at the NICE recommendations for augmentation are needed, including TA854. This should help not only clarify the suggested order for augmentation therapy but help decide where esketamine may fit in. Augmentation remains very underused (Day et al, BJPsych Open, 2021, 7(3) E101, doi:10.1192/bjo.2021.59) and hence many people with TRD are failing to get the potential benefits from it. | Thank you for your comments. This proposal refers only to the review of Esketamine (TA854) and the ESCAPE study was considered as part of the proposal. |
| \*\*\*\*\*\*\*\*\*\*\*\* | As opposed to previous evidence the current study compares esketamine treatment with an established pharmacotherapeutic strategy and the evidence shows promising results. Keeping this in mind a review of proposal should be considered.  | Thank you for your comments, as noted in the proposal paper, the evidence did not show a relative benefit compared to currently available treatments that is greater than the benefit already considered by the committee in TA854. |
| \*\*\*\*\*\*\*\*\*\*\*\* | Several international studies corroborate this evidence and use of esketamine has surpassed experimental stage in several other countries.  | Comment noted. |
| \*\*\*\*\*\*\*\*\*\*\*\* | Use of esketamine can be a strong alternative for patients who are appropriate for Ketamine therapy, but cannot tolerate IV administration very frequently.  | Comment noted. Please note that IV ketamine was not considered established clinical management in the NHS. |
| \*\*\*\*\*\*\*\*\*\*\*\* | We are in crying need for treatments for patients who fail to multiple treatments and that end up costing the NHS a lot of resources in terms of service utilization, admissions to hospital and so on. | Comment noted. |
| \*\*\*\*\*\*\*\*\*\*\*\* | The evidence from the ESCAPE-TRD shows that esketamine could be useful for patients who fails to multiple treatments; therefore a deeper analysis of this trial could offer new insight and respond to some of the doubts raised by NICE. | Thank you for your comments, as noted in the proposal paper, the evidence did not show a relative benefit compared to currently available treatments that is greater than the benefit already considered by the committee in TA854. |
| \*\*\*\*\*\*\*\*\*\*\*\* | As a consultant neuropsychiatrist I work at interface between different disciplines and my impression is that the same opportunities (in terms of treatments) are not given to people with mental health needs compared to people with organic conditions.  | Comment noted. The disparity between mental health and organic conditions was considered as part of TA854. |
| British Association for Psychopharmacology | We recommend that a review of TA854 should be conducted and that this should include ALL relevant data from the ESCAPE-TRD study.In Technology appraisal guidance TA854, the committee described six “clinical uncertainties” in the data used to make a judgement regarding the use of intranasal esketamine in routine clinical practice in the NHS (section 3.17). The assumptions that had to be made to undertake the health economic modelling relating to these uncertainties were very influential with regards to the cost-effectiveness estimate and ultimately the final conclusion of the appraisal. The committee concluded that one of these “uncertainties” was unresolvable and three others only partially resolvable. However, two were described as “resolvable” with further data (with the company sponsored ESCAPE-TRD specifically named in this regard). These uncertainties related to a) the need for more data specifically related to the use of esketamine in patient’s whose depression had not responded to 3+ antidepressants, and b) a need for longer term data. An additional issue was the lack of comparison of esketamine with another treatment routinely used in patients with 3+ antidepressant non-responses.The ESCAPE-TRD study was a randomised controlled study comparing outcomes of patients with treatment resistant depression treated either with intranasal esketamine or quetiapine, both added to ongoing oral antidepressants. Quetiapine is the only licenced treatment for patients with a sub-optimal response to an antidepressants. It is recommended in both NICE NG222, and British Association for Psychopharmacology depression guidelines as an option for augmentation of a conventional oral antidepressant. Such augmentation is considered after 2+ antidepressant monotherapy failures. A recent (as yet unpublished) National Institute for Health Research Health Technology Assessment panel funded study comparing quetiapine augmentation with the use of another recommended (unlicensed) option, lithium, found quetiapine to be superior. This argues for quetiapine being the most appropriate comparator for intranasal esketamine in patients with treatment resistant depression.ESCAPE-TRD extends the follow up of patients from 28 days (in the initial TRANSFORM studies) to 32 weeks. In addition, the a-priori Statistical Analysis Plan for ESCAPE-TRD included a secondary analysis of patients who had not responded to 3+ antidepressants.The data from the ESCAPE-TRD therefore has the potential to significantly inform the decision regarding the appropriateness and place of intranasal esketamine in routine NHS practice. It is therefore surprising that the review proposal was considered in relation simply to the data from ESCAPE-TRD described in just one single poster. Neither the data in the primary peer reviewed publication (https://pubmed.ncbi.nlm.nih.gov/37792613/), nor the critical data in patients with 3+ antidepressant failures (so far only presented as a poster) have been considered. We understand that, in addition, no data was requested from the company regarding the fuller details of the ESCAPE-TRD study.Thus, all relevant data from the ESCAPE-TRD study should be considered in this new review.We would strongly argue that remission rates are an important way of considering the relative clinical benefit of esketamine over quetiapine.The review comments on the large difference in remission rates between patients treated with esketamine and quetiapine in the ESCAPE-TRD study. However, the review then refers back to TA854, section 3.14, arguing that remission rates are not the appropriate outcome to consider. TA854 states “Also, a consultee commented that splitting data into 2 groups, response or remission compared with no response or remission, can lead to an overestimation of differences between arms.” We are surprised by this comment, as often spurious statistical difference in mean score values do not translate into clinically-meaningful differences. Patients are not interested in whether there is a 2 or 3 point difference in rating scale scores when averaged across all participants in the two treatment arms. Rather, patients are interested in the relative chances of treatment 1 versus treatment 2 leading them to be symptom free (i.e., in remission). For this reason, many clinical guidelines and recommendation instead recommend the use of “response” and “remission” as more relevant quantification of the effects of an antidepressant (see, for example, Sforzini et al., A Delphi-method-based consensus guideline for definition of treatment-resistant depression for clinical trials. Mol Psychiatry. 2022 Mar;27(3):1286-1299). Considering all of the data from ESCAPE-TRD, rather than just that reported in a single poster, would also allow consideration across a range of outcome measures.We are concerned that not enough attention has been given to the data from the SUSTAIN-3 study, published in May 2023, after TA854.This phase 3, open-label, long-term extension study, present data for a average 31.5 months per participant, with cumulative data across the subsequent waves of SUSTAIN studies up to 64 months. The study, with the limitation of naturalistic observations, points to maintained efficacy and tolerability. These data should be considered as part the new appraisal.We are concerned about the statement in the review that “However, this trial [ESCAPE-TRD] represents only one augmentation therapy that may be used in clinical practice at this line”. In reality, only quetiapine is licenced for treatment-resistant depression in England and Wales; in Europe, quetiapine (and Esketamine); and in the USA, quetiapine aripiprazole, brexpiprazole and the combination of fluoxetine plus olanzapine (and Esketamine). We are concerned that an ever increasing and impossibly high hurdle appears to be being erected for Esketamine by NICE, including the need of comparing with multiple, unlicenced medications. This will prevent any new treatment for treatment resistant depression ever being approved in the England and Wales.With reference to the point above, we are also concerned that, in general, different and more stringent thresholds are used when assessing a new medication for people with mental disorders compared with physical disorders. There has been an embarrassing paucity of new medications in mental health, also due to disinvestment from pharmaceutical companies, and we would urge NICE to ensure that people with mental disorders have access to the largest possible range of medications. We also want to say that NICE should be particularly concerned about people with treatment-resistant depression as a disadvantaged group.Not only these people lack available medications, but also the risk of treatment-resistant depression is higher, in NICE own words, in “people with lower socio-economic status”. Thus, delaying NHS approval for a treatment that is routinely available in the private sector will only cement social inequalities.  | Thank you for your comments, as noted in the proposal paper, the evidence did not show a relative benefit compared to currently available treatments that is greater than the benefit already considered by the committee in TA854.As noted in the proposal paper, the new evidence may contribute to some reduction in uncertainty.Additional data from the full published paper from the ESCAPE-TRD was considered as part of consultation.The disparity between mental health and organic conditions and underserved groups was considered as part of TA854. |
| College of Mental Health Pharmacy (CMHP) | The proposal for not reviewing the original decision was based on data from a poster on Treatment-Resistant Depression (TRD) presented at a European conference. That was appropriate at the time as the full paper had yet to be published, but as it is now in the New England Journal of Medicine, this study must be taken into consideration. A paper in the NEJM is one of the highest accolades for research and illustrates that the data is of high quality.  | Thank you for your comment. Additional data from the full published paper from the ESCAPE-TRD was considered as part of this consultation. |
| College of Mental Health Pharmacy (CMHP) | The quetiapine-esketamine study above is one of, if not the, longest and largest comparisons in TRD. The study used a clearly treatment-resistant population, and at the level that esketamine would be used in the UK i.e. fourth line. Esketamine was demonstrated to be very effective in this study.  | Thank you for your comments, as noted in the proposal paper, the evidence did not show a relative benefit compared to currently available treatments that is greater than the benefit already considered by the committee in TA854. |
| College of Mental Health Pharmacy (CMHP) | Our last submission made it clear that we felt that the appraisal committee showed a lack of real understanding of Treatment-Resistant Depression as a serious condition. To list the other standard antidepressants available as alternatives for a treatment-resistant depression showed a lack of comprehension. We have no practical options other than ECT. We ask that the group recognise that TRD is a potentially fatal condition. As a chronic unremitting illness with limited treatment options and suicide as an outcome in many cases, to make esketamine only available in England via private clinics degrades the ability of the NHS services to help people at high risk of premature death. There are a number of studies which describe the impact to patients of treatment resistant depression which we feel need to be considered when reviewing the evidence of esketamine such as: <https://pubmed.ncbi.nlm.nih.gov/37734244/> The lived experience of major and treatment-resistant depression in England: a mixed-methods study And those that describe the patient experience of esketamine <https://pubmed.ncbi.nlm.nih.gov/37891860/> The Patient's Perspective on the Effects of Intranasal Esketamine in Treatment-Resistant Depression. | Comment noted. The treatment pathway and patient experience of treatments with treatment resistant depression were extensively considered as part of TA854. |
| College of Mental Health Pharmacy (CMHP) | England is now an outlier in the world for the use of esketamine. Other countries have recognised its role in TRD and are using it carefully in selected people for whom there are no good evidence-based options left. Colleagues outside England and Wales report that esketamine is effective in treatment-resistant depression.  | Comment noted. |
| College of Mental Health Pharmacy (CMHP) | There are other studies that we feel may also be relevant to include as evidence that certain patients may benefit more from esketamine. This may help guide those patient groups in which esketamine is likely to be more cost-effective and supports the role of esketamine in treatment-resistant depression. These include:<https://pubmed.ncbi.nlm.nih.gov/37738705/> Early effects predict trajectories of response to esketamine in treatment-resistant depression <https://pubmed.ncbi.nlm.nih.gov/37568081/> Esketamine versus placebo on time to remission in major depressive disorder with acute suicidality<https://pubmed.ncbi.nlm.nih.gov/37558912/> Efficacy and Safety of Esketamine Nasal Spray in Patients with Treatment-Resistant Depression Who Completed a Second Induction Period: Analysis of the Ongoing SUSTAIN-3 Study<https://pubmed.ncbi.nlm.nih.gov/37449831/> Reduction in Cognitive Symptoms Following Intranasal Esketamine Administration in Patients With Chronic Treatment-resistant Depression: A 12-Week Case Series. | Thank you for your comments. The additional studies provided offer important context that would be considered in a full appraisal, but the substantial evidence on relative benefit comes from the ESCAPE trial which did not show a relative benefit compared to currently available treatments that is greater than the benefit already considered by the committee in TA854.  |
| \*\*\*\*\*\*\*\*\*\*\*\* | Given that the only therapy for treatment resistant depression with a specific license in that indication is Quetiapine, and the new evidence here suggests superiority, it surprises me that more emphasis is not being placed on it. New treatments, specifically for TRD, are urgently needed. I think this evidence warrants further review by NICE. | Thank you for your comments, as noted in the proposal paper, the evidence did not show a relative benefit compared to currently available treatments that is greater than the benefit already considered by the committee in TA854. |
| \*\*\*\*\*\*\*\*\*\*\*\* | The differences between the quetiapine and esketamine groups at 8 weeks (2.8 points) and 32 weeks (2.2 points) were statistically significant, on the 60-point MADRS scale, but were less than the minimum clinically important difference. The remission figures provided are unreliable because dichotomised data can inflate small differences between treatments. Discontinued patients were classified as having had an unfavourable outcome which might have artificially improved the outcome for esketamine (with less drop-outs than quetiapine). A “retrieved dropout analysis” is only presented at 8 weeks and lacks transparency. The esketamine group also had increased hours of contact with staff (for safety monitoring) which can reduce depression scores and impact attrition. Esketamine may induce short-term euphoria which reduces depression scores but may not modify the condition in the long-term. The difficulties that patients may have in stopping esketamine due to withdrawal effects, recently highlighted,5 as well as longer term tolerance effects, were not examined. Adverse events occurred to almost all esketamine participants (91.9%), with as many serious adverse events for esketamine (19) as quetiapine (17), mostly psychiatric. | Thank you for your comments. These points were considered as part of the review paper. |
| \*\*\*\*\*\*\*\*\*\*\*\* | Esketamines intra-nasal potentially offers a quicker relief than other antidepressive medications. | Comment noted. |
| \*\*\*\*\*\*\*\*\*\*\*\* | Esketamines intra-nasal potentially can facilitate improvement of symptoms for patients otherwise suffering from treatment resistant depression. | Comment noted. |
| \*\*\*\*\*\*\*\*\*\*\*\* | Esketamines intra-nasal offers an innovative action mechanism through NMDA . | Comment noted. |
| \*\*\*\*\*\*\*\*\*\*\*\* | Its administration could be translated in specialist clinics in the community. | Comment noted. |
| \*\*\*\*\*\*\*\*\*\*\*\* | Is already established as therapeutic modality in other country at the risk of patients in the UK falling behind treatments at the leading edge of science.  | Comment noted. |
| \*\*\*\*\*\*\*\*\*\*\*\* | Esketamines intra-nasal brings an addition to the therapeutic arsenal for an index patient population representing some 30% of client groups in secondary services.  | Comment noted. |
| Rethink Mental Illness | We are concerned that this proposal will represent another barrier to new mental health treatments becoming available. The mental health clinical research landscape faces many challenges, such as under-investment, difficulties with recruiting patients and the difference between mental and physical healthcare pathways. These are explored in more detail below. These challenges have resulted in a paucity of new treatments for severe mental illness (SMI) and so people living with these conditions are not getting the help they need. People with SMI live on average 15 to 20 years shorter than the general population, often due to conditions such as cardiovascular disease or respiratory disorders. Some current drugs for SMI increase the risk of these conditions and so new treatments that do not exacerbate the life expectancy gap between people living with SMI and the general population are desperately needed (NHS, 2019).  | Comment noted. The disparity between mental health and physical conditions was considered as part of TA854, |
| Rethink Mental Illness | Rethink Mental Illness is now prioritising clinical research as an area of focus as people with lived experience of mental illness have told us that this is a significant area that needs more attention. We are beginning to gather evidence around what is needed to address challenges in this area and what needs to be done to address them. | Comment noted. |
| Rethink Mental Illness | There has been a historic lack of parity between mental and physical health research; a study by MQ Research found that while £228 was spent per person on cancer research, only £9 was spent per person affected by mental illness (MQ Research, 2017). As the International Alliance of Mental Health Research Funders found, much of the funding that mental health research does receive goes into basic research, which can be unpredictable and may not lead to the development of new treatments (IAMHRF, 2020). As a result, there has been insufficient funding for testing new treatments with people who may benefit from them. Esketamine is a pathfinder treatment and we are concerned that NICE’s proposal will negatively impact on other innovative new treatments that may be coming down the research pipeline, further impacting on people with SMI’s chances of getting the right treatment. | Comments noted. The disparity between mental health and physical conditions was considered as part of TA854. |
| Rethink Mental Illness | Recruitment onto mental health clinical trials can also be particularly challenging. There are general challenges faced by mental and physical health clinical trials alike, such as lack of time, patient mistrust around data usage and clinicians’ lack of understanding around research (DHSC, 2017). However, there are additional barriers to patient participation in mental health research, such as stigma around mental health, some patients’ inability to grant informed consent (i.e. at times of crisis) and clinicians’ unwillingness to offer research opportunities due to perceptions of patient vulnerability (Jones H, Cipriani A., 2019). This has made it challenging to recruit enough people onto mental health clinical trials to produce robust evidence on the efficacy of new treatments. | Comments noted. The issues around generating evidence for mental health research were considered as part of TA854. |
| Rethink Mental Illness | We note that NICE has flagged the uncertainty of the treatment line and clinical pathway. However, this reflects the reality of mental health treatment; compared to physical health treatments, there is a lack of care pathways for mental health conditions. Applying the same criteria to mental health studies as used for physical health may prevent new technologies from gaining approval. In 2019, we conducted a focus group with nine people living with treatment resistant depression, to understand more about their experiences of living with the condition and how it impacts on their quality of life. We heard that current treatment and support options are inadequate and that care is often disjointed. People with lived experience of treatment resistant depression told us that more research is needed, so that people are able to receive treatments that work.  | Comment noted. The disparity between mental health and physical conditions was considered as part of TA854. |
| Rethink Mental Illness | Overall, in order for people living with mental illness to receive new treatments that meet their needs, a different approach needs to be taken with regards to mental health clinical trials and appraisal of evidence from such trials compared to physical health. We are concerned that the current process for appraising new technologies is preventing people from getting access to new technologies and getting the help they need.  | Comment noted. This point is beyond the remit of the review of new evidence that may change the recommendation for TA854. |
| Brain and Cognition Discovery Foundation | Major depressive disorder (MDD) is a highly prevalent condition which, according to the World Health Organisation, is the single largest contributor to loss of healthy life. Other important points from World Psychiatric Association (WPA) publication *Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions (World Psychiatry 2023; 22:394–412)*, published on 15 September 2023, are:* A substantial proportion of individuals with MDD fail multiple antidepressant interventions, resulting in what is described as Treatment-resistant depression (TRD). TRD is often stated to affect approximately 30% of persons receiving antidepressant treatment. However, the prevalence in real-world practice is reported to range between 6-55%.
* TRD is associated with relatively higher costs of illness due to higher healthcare utilisation and the need for higher intensity treatments. Higher indirect costs are also reported in TRD as a consequence of relatively greater impairment in psychosocial function, greater need for disability benefits, higher workplace disability and absenteeism, as well as the negative impact on carers. Moreover, the rate of suicidality, including completed suicide, is disproportionately higher in TRD populations.
* Additional public health implications of TRD relate to the established association between MDD and multiple common and chronic non- communicable physical diseases. For example, it is established that MDD is a risk factor for cardiovascular disease, obesity and type 2 diabetes mellitus, and this is especially apparent in individuals with more severe and/or persistent depressive syndromes, which are over-represented in TRD populations.
* The extraordinary public health burden of TRD will unlikely be extinguished in the near future, but the proportion of individuals with debilitating symptoms of depression and dissatisfaction with treatment may be reasonably expected to be decreased with successful targeting of modifiable factors, reducing the knowledge- implementation gap, and rapid adoption of innovations across therapeutic modalities.
 | Comments noted. The burden of MDD and TRD were considered as part of TA854. |
| Brain and Cognition Discovery Foundation | Intranasal esketamine combined with an antidepressant is the most rigorously evaluated pharmacologic strategy in the acute and maintenance treatment of adults with TRD. Other important points from World Psychiatric Association (WPA) publication *Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions (World Psychiatry 2023; 22:394–412)*, published on 15 September 2023, are:* Notwithstanding the foregoing public health implications of TRD, relatively few interventions have been established as efficacious for persons having multiple failed trials with conventional antidepressants. Instead, the emphasis of treatment development in depressive disorders has been on non- TRD populations. In addition, prevention of TRD is not a national health policy priority in any country worldwide, nor is progress in its management a quality outcome measure in any national public healthcare system.
* Current treatment tactics for TRD include extending the current antidepressant trial, switching antidepressants, combining antidepressants, neurostimulation modalities and psychotherapy.
* The evidence supports select SGAs, as well as rTMS and manual- based psychotherapies (in combination), as proven strategies in adults who have failed one prior antidepressant. For individuals with TRD (failing multiple antidepressants), evidence is best for ketamine, esketamine, adjunctive psychotherapy, ECT and rTMS. Psychotherapeutic interventions in combination with antidepressants may offer partial symptomatic relief in persons with TRD, but their efficacy as monotherapy is not established. Combination antidepressants, switching antidepressant treatment, dose optimization and the use of a host of augmentation strategies (e.g., lithium, thyroid hormone) have mixed data supporting their usefulness.

Intranasal esketamine combined with an antidepressant is the most rigorously evaluated pharmacologic strategy in the acute and maintenance treatment of adults with TRD. In addition to demonstrating acute efficacy, it has established relapse prevention, tolerability and safety in persons with TRD, with more than three years of maintenance data.  | Comment noted. |
| Royal College of Psychiatrists | We agree that “quetiapine as a third line or more treatment is likely to be a more appropriate comparator than oral antidepressants at second line or more”. We agree that quetiapine ‘only represents one augmentation strategy’ but think that this objection needs to be contextualised appropriately. Olanzapine, risperidone and aripirazole are also referred to in NICE guidance as augmentation strategies, but only quetiapine and flupentixol are licensed for this indication. Flupentixol is almost never used because it is a ‘typical’ antipsychotic with the associated risks of extrapyramidalism. The other commonly used non-antipsychotic augmentation strategy, lithium, has recently been compared with quetiapine in the NIHR HTA ‘LQD’ study. The primary outcomes of this study were recently presented at British Association of Psychopharmacology conference in Manchester: quetiapine was clearly more effective and safer than lithium. The new LQD data therefore suggests that quetiapine is the appropriate comparator. The large number of other antidepressant augmentation agents available means that it would not be feasible to run the necessary number of large head-to-head trials to resolve their differences.Remission is used as an outcome because there is a clinical consensus that remission is a more clinically relevant than differences in scores on eg the MADRS scales. Whilst we understand the statistical point that is being made, we think that there is no perfect analytical strategy and prefer the binary outcome of the current, clinically-directed consensus. Disutilities. ESCAPE TRD shows that quetiapine has more long-term side effects than esketamine NS. Weight gain and sedation with quetiapine are serious clinical problems which limit the utility of quetiapine. The new evidence allows the quantification and incorporation of disutilities into the model. SUSTAIN3 (Zaki, 2023 PMID: 37173512) partially addresses one of NICE’s key resolvable issues: the necessary duration of treatment. SUSTAIN3 suggests that patients who continue to take esketamine continue to benefit from it.We are concerned that uncertainty in the cost of current treatment of TRD may remain unresolvable because the major sources of variability in the cost of treatment of TRD are structural. First, the variability in the costs of TRD are determined by the availability of services such as hospitals and crisis resolution teams, rather than by the cost or effectiveness or duration of the drugs used. Second, local policies that limit the repertoire of antidepressants available for use in primary care or access to secondary care introduce variability because many but not all patients who are not at immediate risk of suicide remain on ineffective first or second line treatments. This uncertainty means that, unlike with physical illnesses where this uncertainty of current costs does not apparently exist, there is currently no mechanism for new treatments for resistant depression to be introduced into the NHS. This raises issues of parity of esteem.Resolution of this impasse would be possible if NHS approval was limited to settings where the relevant cost and QoL data can be routinely collected before, during and after esketamine NS treatment in those who had and had not tried quetiapine. These data could then be compared with cost and QOL data from the quetiapine arm of the LQD study. | Comments noted. In TA854, the committee concluded that multiple further lines of treatment are considered for treatment-resistant depression (see section 3.3 of the final guidance). The review paper has been updated to recognise the positioning of treatment in a highly heterogeneous and personalised pathway.The committee recognised the limitation of using this binary outcome in the final guidance.The committee recognised the difficulty in assessing structural cost changes in the system as part of TA854 (see section 3.33-3.34). No additional evidence or policy changes have been presented for this uncertainty, Managed access was not considered appropriate for this appraisal in TA854. |
| SANE | We are concerned that the results from the ESCAPE-TRD trial are not considered sufficient to justify updating the existing recommendations in relation to the use of esketamine for treatment-resistant depression.  | Comment noted. The evidence did not show a relative benefit compared to currently available treatments that is greater than the benefit already considered by the committee in TA854. |
| SANE | It is estimated that there are around 2.7 million people in the UK with treatment-resistant depression (using the NICE definition of those who have not responded to two or more antidepressants). SANE conducted a study of 100 patients and 90 carers affected by treatment-resistant depression which showed that it impacts many aspects of the lives of both patients and carers. It has a major negative effect on the quality and social life of patients, and a harmful effect on their physical health. Nine out of ten carers reported that looking after someone with treatment-resistant depression impacted their own quality of life, affecting their relationships and mental health. The detailed findings of the study are set out in SANE’s submission on the use of esketamine for treatment-resistant depression (ID1414).  | Comments noted. The unmet need for treatment was considered in TA854. |
| SANE | 84% of patients in SANE’s study reported treatment-resistant depression having an impact on employment, with 45% having to stop work completely; just over half reported a negative financial impact. 43% of carers reported treatment-resistant depression affecting their work or study performance, and 47% their finances. | Comments noted. The unmet need for treatment was considered in TA854. |
| SANE | In SANE’s study, 92% of patients reported side-effects from taking antidepressants, most significantly increased fatigue and insomnia. 56% of patients and carers regarded their treatment as ineffective, with only 57% believing the benefits of antidepressants outweighed the side-effects. | Comments noted. The current treatment landscape was considered in TA854. |
| SANE | Of the 74% of patients in the study offered access to treatments other than antidepressants, only 10% initially found talking therapies to be very effective. 35% stopped feeling the benefits of non-drug treatment within a month of it ending.  | Comment noted. |
| SANE | As evidenced in SANE’s study, we believe that those affected by treatment-resistant depression are disproportionately disadvantaged by the condition compared with those others with depression who are able to respond to treatment. The condition causes a wide range of symptoms for patients on a daily basis, with 80% in SANE’s study reporting suicidal thoughts within the previous year. This combined with the side-effects and perceived ineffectiveness of antidepressants results in a loss of hope that any treatments might be helpful or effective. In our view this makes it essential that all means are explored to find treatments that will reduce this disadvantage.  | Comment noted. |
| SANE | People diagnosed with depression are having to rely on medications developed over 30 years ago. Esketamine is the first new compound that works in a fundamentally different way from other medications and, compared with other antidepressants that 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. The review proposal reports an improved rate of remission in treatment-resistant depression from the use of esketamine compared with quietamine. It also states that some issues may be partially addressed by the ESCAPE-TRD evidence.  | Comment noted.  |
| SANE | SANE knows of patients who have benefited from the administration of esketamine and as a result have been able to renew activities, including work, which had not been possible before being treated with esketamine. Successful treatment with esketamine meant there was an alternative to electro-convulsive therapy and improved mental health, social interaction and economic activity.  | Comment noted. |
| SANE | Being able to resume former activities is particularly beneficial in relation to work, where loss or reduction of paid employment is harmful to the patient’s standard of living and quality of life. We note from the review proposal that people with lower socio-economic status are more likely to have treatment-resistant depression. For those in this group, loss or reduction of paid work might have a particularly harmful effect. This could be compounded if as a consequence of the patient’s condition, the carer had to give up or reduce the amount of paid work they undertook.  | Comment noted. |
| SANE | There is a paucity of weapons in the arsenal available to doctors to combat depression, especially when a person does not respond to medication or cannot tolerate the side-effects, and for whom talking therapies do not provide relief. Given the acknowledgement by NICE of the limited effectiveness of current treatments for treatment-resistant depression, and its recognition of “the clear need for effective treatment options”, we believe that it should examine the results from the ESCAPE-TRD trial with a view to updating the existing recommendation in TA854. Failure to bring relief to this disadvantaged patient group has consequences not only for their quality of life and that of their carers but for society and the economy as a whole, where their condition hinders or prevents them from making a contribution. | Comment noted. The disparity between mental health and organic conditions was considered as part of TA854. |
| \*\*\*\*\*\*\*\*\*\*\*\* | I am writing in support of the Review proposal of Esketamine, especially in lights of emerging clinical trial data. Major depressive disorder (MDD) is a leading cause of global disability with many patients developing treatment-resistant depression (TRD). It is well established, that there is a substantial individual and economic burden associated with MDD and particularly TRD across both primary and secondary care settings.  Findings suggest that evidence-based treatment optimisation, availability and timely access to newer therapies as well as the development of stratified care pathways and specialist services could improve patients’ outcomes and cost-effectiveness. Augmentation strategies is often applied in the management of MDD/TRD and quetiapine is one of the most common and effective add-on options. It was shown to perform better than Lithium in the recent LQD study but worse than Esketamine in the ESCAPE study. Esketamine, has a novel mechanism that may benefit a number of patients that do not respond to currently available treatments. Even if only a small proportion were to profit from its use, it would still be a significant gain for individual patients but also in terms of overall healthcare usage and costs. Therefore, in advancing the field in terms of availability of new specialist treatments and address considerably patient heterogeneity and unmet need, I’d strongly advocate for the above Review proposal. | Comments noted, the difficulty of generating evidence in mental health conditions was considered as part of TA854. |
| \*\*\*\*\*\*\*\*\*\*\*\* | Dear Committee Members,I am writing to express my concern over the decision to not undertake a full update of this current guidance. I believe this has been made without consideration of significant new evidence that has been recently published (1, 2).These publications clearly show that a significantly greater proportion of patients achieved remission at Week 8 with esketamine nasal spray versus quetiapine. Additionally, the evidence demonstrates that a greater proportion of patients were relapse-free through Week 32 after remission at Week 8 with esketamine nasal spray versus quetiapine. Treatment-resistant depression (TRD) represents a major challenge in the clinical management of depression. Patients with TRD experience more severe depression symptoms, more impairment in social functioning, and lower work productivity than patients with non-TRD. More recent data has also shown that patients with TRD episodes had higher prevalence of psychiatric comorbid conditions, twice the utilisation of outpatient health care resources, 3 times the number of inpatient bed-days, and 23% higher all-cause mortality. (3) This subgroup of patients also experienced decreased acute remission rates with each Sequenced Treatment Alternatives for resistant Depression (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 and tolerance. Furthermore, patients with TRD experience relapse at a higher rate than those with treatment-responsive Major Depressive Disorders. Even when patients with TRD respond to treatment, the overall relapse rate while continuing treatment with the same antidepressant is high after 2 (65%; within 3.1 months) and 3 failed trials (71.1%; within 3.3 months). (4, 5) Taking these negative results into consideration, the data provided by Reif et. al and Young et. al is encouraging. New treatments are very much necessary. There is a substantial unmet need for effective treatments that can sustain antidepressant benefits for patients affected by TRD. I therefore urge you to reconsider your current proposal and very much hope this decision is changed, in order to alleviate our patients’ suffering.  | Thank you for your comments, as noted in the proposal paper, the evidence did not show a relative benefit compared to currently available treatments that is greater than the benefit already considered by the committee in TA854. |
| World Psychiatric Association Affective Disorders Section | We would like to endorse the proposal regarding the evaluation of effectiveness and practicality of esketamine within both acute and long-term treatment contexts. Nevertheless, the precise positioning of the esketamine within the hierarchy of depression treatment steps, particularly compared to alternative treatment strategies, rather remains ambiguous. | Thank you for your comments. The remit of this review is to consider whether any evidence presented would change the current recommendation. |
| World Psychiatric Association Affective Disorders Section | A notable concern may also arise from the fact that relying exclusively on depression rating scale scores for evaluating the treatment response may prove inadequate, given the inherent heterogeneity of depression. Therefore, it is imperative that the assessment extends beyond mere numerical evaluations. Furthermore, a comprehensive evaluation of esketamine’s effectiveness, particularly in terms of its impact on suicidal ideation, should be another point of discussion. | Thank you for your comments. The limitations of the depression rating scales were considered in TA854. |
| World Psychiatric Association Affective Disorders Section | The accessibility and cost-effectiveness of treatment option is crucial due to the substantial economic and personal burden of depression. Hence, esketamine might be positioned as the final resort between other treatment regimens. Antidepressant combinations and/or augmentation strategies may take precedence in terms of cost-benefit balance. Therefore, the significance of this approach can be further highlighted in the proposal. | Comment noted. The cost-effectiveness of treatment was the remit of the decision |
| Janssen (JNJ) | The decision taken by NICE not to re-appraise esketamine nasal spray does not take into consideration the full breath of evidence and substantial changes that would be made, resulting in a brand-new submission Janssen are disappointed and surprised with the decision by NICE not to re-appraise esketamine nasal spray (NS) for treatment-resistant depression (TRD), despite the significant body of evidence the ESCAPE-TRD trial adds to the disease area. Janssen would like to highlight that a significant number of countries have now reimbursed esketamine NS world-wide, (a number utilising the ESCAPE-TRD data). We believe the updates provided in this document, including details of the ESCAPE-TRD trial, which NICE did not have at the time of decision making, are sufficient to necessitate a re-appraisal of esketamine-NS by NICE for TRD patients in England/Wales. We will discuss throughout this document how the new evidence will have a meaningful impact on the overall certainty (and reduced uncertainty) of the data. In particular, the ESCAPE-TRD trial will provide new evidence to enable the Committee to give full consideration of the TRD population with the most unmet need, and will result in the following: • A new clinical trial in the relevant population in order to base the re-submission on for Committee decision making • Comparison of esketamine-NS to a directly relevant (and the most widely used) active comparator i.e., quetiapine • Updates to the economic model (inputs and structure)• Longer-term data in the most appropriate population i.e., pre-specified data in a more severe (later pathway) TRD population • Additional activities being carried out to support the uncertainties identified by the Committee during the last appraisal. These activities are in development; however, they relate to engagement with NHSE on the pathway and Real-World Evidence (RWE) regarding the management of esketamine NS • Evidence to reduce uncertainty in the safety of esketamine NS utilising the ASPIRE trials (raised by the Committee during the last appraisal; TA854). While a license for esketamine NS has been granted by the UKs’ Medicines and Healthcare products Regulatory Agency (MHRA) and European Medicines Agency (EMA), these data will reinforce the additional safety of esketamine relating to suicidal ideation with intent • Updated inclusion/exclusion criteria that improves generalisability of the trial population to NHS patients. ESCAPE-TRD included individuals with a more recent history of suicidal intention and behaviour than previous phase III clinical trials• Inclusion of long-term supplemental evidence from SUSTAIN-3 (a long-term follow-up trial) and safety data from the ASPIRE trials (in a population with major depressive disorder and suicidal ideation), which resolves a number of the issues the Committee raised in the original appraisal (TA854) • Two articles were published on 31st October 2023 relating to an adjusted indirect treatment comparison study of esketamine NS compared to observational cohort data (ICEBERG), this provides evidence that at 6-months, esketamine NS has a substantial and significant benefit over existing real-world treatments (Oliveira-Maia, 2023a), (Oliveira-Maia A. , 2023b). | Comments noted. Please see responses to individual points below. |
| Janssen (JNJ) | **There is a substantial unmet need for novel treatments for TRD; the ESCAPE-TRD study demonstrates the potential to reduce uncertainty and addresses many of NICE’s concerns regarding the use of esketamine amongst this patient population.**Treatment Resistant Depression (TRD), defined as a lack of clinically meaningful improvement despite the use of adequate doses of at least two antidepressant agents, prescribed for adequate duration with adequate affirmation of treatment adherence, is associated with significantly lower quality of life (Jaffe, 2019), a greater risk of all-cause mortality (Lundberg, 2022) and a two-fold and ten-fold increased rate of suicide completion and attempt, respectively (Bergfeld, 2018), than for those with depression without treatment-failure. By 2026, the direct service costs of depression to the NHS are estimated to be £3 billion (Kings Fund 2008). A consistent body of evidence has demonstrated that increasing treatment resistance is associated with increased direct medical costs (Johnston, 2019) (Denee T. , 2021a), (CRIS, Unpublished) (LEAF Dataset, In Publication Process). Moreover, indirect costs of depression are substantially higher than direct costs and associated with decreased functioning, productivity and quality of life of family and carers (Denee, 2023) (Mc Crone, 2008) A review of TRD patients in secondary healthcare settings in England found 58% to be unemployed or on long-term sick leave (Talbot, 2021).New and effective treatments for TRD are urgently needed. A European observational cohort of 306 patients with TRD across Europe demonstrated 54 different drugs used at baseline (defined as day one of the study), with the top 5 treatment types accounting for just 40% of patients. In the same cohort only 16.7% of patients achieved remission at 6 months and 19.2% at 12 months. These data indicate that treatments for TRD are heterogeneous and that there is no clear treatment pathway. These data also highlight poor outcomes, with standard of care treatments meaning patients are left with only sub-optimal treatment options. (K Heerlein, 2021). Overall, mental health and depression are highly underserved therapy areas, with very few treatments receiving mandatory funding through the technology appraisal process. For the very few appraisals that have been appraised by NICE, some appraisals were terminated and while there are a few in development for broader mental health conditions e.g., schizophrenia and post-natal depression, there is no guarantee of positive recommendations. There has, in general, been very little progress made in the mental health space as a whole over the last 20-30 years since NICE’s instigation in 1999, which highlights the increasing need for new treatments and an increased awareness of the lack of parity in mental health compared to physical health treatments. Esketamine nasal spray (NS) represents the first novel pharmacological treatment for depression in over 30 years. NICEs previous appraisal of esketamine NS (TA854) was the first ever appraisal for treatment resistant depression, since the majority of mental health treatments currently in use have not been appraised by NICE and are often prescribed without a license for TRD.For esketamine NS (TA854), the outcome of the appraisal, in December 2022 was that NICE concluded it to be not recommend, citing substantial uncertainties. This decision was despite the appeal submitted by Janssen being upheld September 2022. The NICE appeal panel upheld Janssen’s topic that NICE failed to act fairly because “*The Committee recognises that clinical uncertainties are inherent in clinical trials in mental health but provides no explanation of how (if at all) this situation has been taken into account in its decision making”.* Indeed, the Final Appraisal Document (FAD) for TA854 lists key uncertainties such as the heterogeneity in the treatment pathway and patient population, being able to collect long-term evidence (regulatory mandated duration in mental health), and the heterogeneity in treatments, which highlights the hurdles in place for appraisals of new innovations in mental health and for future access to patients with mental health conditions currently underserved with efficacious treatments. Since that appraisal, Janssen completed a multi-national, randomised, open-label, phase IIIb study, the ESCAPE-TRD trial (Reif A. , 2023). This study involved 676 patients with TRD to assess the efficacy and safety of esketamine NS plus an ongoing oral antidepressant (SSRI or SNRI) in comparison to quetiapine extended release (XR) plus an ongoing oral antidepressant (SSRI or SNRI). The ESCAPE-TRD trial represents a significant body of evidence against a directly relevant comparator and with relevant (later pathway pre-specified subgroups) in the field of depression and utilised many different design aspects to address issues identified in the previous trials (i.e., the TRANSFROM-2 and SUSTAIN 1 studies (Popova, 2019), (Daly, 2019)) and mitigate committee concerns in the last appraisal, including:* **Comparison versus a directly relevant active comparator**: ESCAPE-TRD compared esketamine NS to quetiapine XR. Augmentation with antipsychotic treatment was recognised by NICE as an appropriate comparator for TRD (Section 3.3 of TA854). The second-generation antipsychotic quetiapine XR is the only licensed add-on treatment option for major depressive disorder, is recommended by multiple clinical guidelines for use in TRD (Bauer, 2013), (Cleare A. , 2015), (NICE, NICE guideline: Depression in adults: treatment and management, 2022), (Psychiatry, 2010)) and the most commonly prescribed augmentation treatment for patients after 3 previous treatment trials in England (Denee T. , 2021b) Unpublished data from the NEMO study (K Heerlein, 2021).
* **Longer-term comparative evidence**: ESCAPE-TRD measured both acute (Week-8) and long-term (up to Week-32) efficacy in a single comparative trial. The primary endpoint was assessed at 8-weeks to align to the duration of clinical trials previously designed to establish efficacy of quetiapine with continued assessment of efficacy to 32-Weeks. This provides considerable improvement to the robustness of evidence for the comparable long-term outcomes of treatment.  Acute efficacy measured at Week 8 addresses NICE’s concern on the 4-Week duration of the TRANSFORM-2 study and comparative evidence up to Week 32 addresses the concern NICE had on longer-term data.
* **Reliable and clinically meaningful primary and secondary endpoints:** Unlike the previous TRANSFORM studies, which were the main basis for the decision of TA854 and for which the primary endpoint was MADRS total score change at Week-4 (Popova, 2019), the main endpoints of ESCAPE-TRD were designed to be directly relevant to clinical practice and the short- and longer-term goals of treating depression. The goal of acute depression treatment is remission and the primary endpoint of ESCAPE-TRD reflected this and was the proportion of patients in remission at Week-8 (defined as a MADRS score of ≤10) (Reif A. , 2023). The goal of longer term, maintenance depression treatment is to keep patients free of relapse. The key secondary endpoint of ESCAPE-TRD was designed to reflect this and was the proportion of patients in remission at Week-8 and relapse free at Week-32.
* **More robust data in the proposed restricted TRD population**: Randomisation into ESCAPE-TRD was stratified according to age (18-64 years; 65-74 years) and number of prior treatment failures (2, ≥3). This permitted a balancing of patient characteristics in each arm (according to age and prior treatment failures) and enables reliable, substantiative comparisons to be performed between esketamine NS and quetiapine XR in the groups of patients that failed ≥3 prior treatments. There were uncertainties in the outcomes of this group in the previous appraisal, which was the proposed population. Due to stratification ESCAPE-TRD provides more robust data for the proposed population of the appraisal and reduces those uncertainties.
* **Study treatments administered more in line with real-world clinical practice.** In TA854 the committee were concerned that patients were initiated on a new oral AD treatment at the same time as starting esketamine NS treatment. In contrast and more in line with clinical practice, in ESCAPE-TRD patients continued their existing oral antidepressant at the time of starting treatment with esketamine NS or quetiapine XR.
* **Excluded risk of functional unblinding**. NICE previously expressed concern of the risk of functional unblinding, due to the distinct adverse effect profile of esketamine NS. By utilising an open-label design, the risk of functional unblinding was removed. Furthermore, the open-label design removed the requirement for a double dummy design and meant dosing and administration of both esketamine NS and quetiapine XR were per product labels and as such allowed administration to more closely reflect as it is in clinical practice
* **Updated inclusion/exclusion criteria that improve generalisability of trial population to NHS populations.** ESCAPE-TRD included individuals with a more recent history of suicidal intention and behaviour than previous phase III clinical trials, and as such addresses NICE’s concern on the generalisability of evidence in those patients with TRD in the NHS.

There is no parity in access to innovation between physical and mental health, which further widens the gap in access to treatment options in England vs Europe and the rest of the world. Despite the inherent uncertainties in mental health as a field and the disparities between physical and mental health, the ESCAPE-TRD trial adds significant body to the clinical evidence in depression and is designed in such a way that is appropriate for this disease area. There have been a substantial number of positive reimbursement decisions made across the globe for esketamine NS, including 25 across Europe plus countries in the Middle East and Africa, which is why it is disappointing to see that NICE have concluded not to assess the new evidence from the ESCAPE-TRD trial in an appraisal, and do not appear to be supporting innovation in mental health. Especially since the ESCAPE-TRD trial in combination with supplemental evidence from SUSTAIN-3 (long-term follow-up) and the ASPIRE trials (in a population with major depressive disorder and suicidal ideation), resolves a number of the issues the Committee raised in the original appraisal (TA854) including those relating to population, positioning, longer-term data, comparator and placebo comparison, and therefore means that expectations on the submission and base case are wholly different while being more related to the patient population. Following the publication of the UK Government's Life Science Vision in 2021, there has been a welcome focus on advancing the ecosystem for translational research into novel treatments in mental health in the UK. Through the Mental Health Mission there is an ambitious programme of work to support the research, approval, and uptake of new treatments for patients in the UK and demonstrates real global leadership by a range of UK bodies, including NICE. The surveillance decision is not, in our view, in line with these ambitions.Throughout this document we will provide details why a re-submission is an appropriate route for esketamine NS and why evidence generated since the previous appraisal contributes to increased certainty in the evidence base for esketamine NS in light of previous committee comments.  | Comments noted. The unmet need for treatment was considered in TA854. The disparity between mental health and organic conditions was considered as part of TA854. |
|  | **It is inappropriate to assess the benefit of esketamine from a single poster; the ESCAPE-TRD trial is a significant step-change and enriches the data in depression.**We are encouraged to see that NICE recognise the ESCAPE-TRD trial contributes to a reduction in the uncertainties identified in TA854, including evidence later in the treatment pathway, relevant comparator evidence and regarding the longer-term effects of treatment. However, we are disappointed and concerned that NICE do not recognise the full extent of the evidence from ESCAPE-TRD, and in particular the independently recognised impact this body of evidence adds to the field of depression. NICE base their assessment on a single poster presented at the European Congress of Psychiatry (EPA) 2023 (Reif(2), 2023). The totality of evidence from ESCAPE-TRD and the associated impact on the uncertainties identified in TA854 should not be determined from a single poster. Since the EPA congress there have been several additional posters presented at numerous international conferences ( (Reif, 2022), (Young, 2023), (Reif(3), 2023), (Reif(4), 2023), (Young(2), 2023), (Reif(5), 2023), (Reif(6), 2023), (Young(3), 2023), (Vieta, 2023), (Reif A. , 2023)). Most relevant is the publication of the ESCAPE-TRD primary results in the New England Journal of Medicine on 5th October 2023 (Reif A. , 2023). Our position is that the full body of evidence must be considered when making a surveillance decision.We would like to further point out that the impact of the ESCAPE-TRD trial and evidence generated from it have been recognised by thought leading regulatory and clinical bodies including: * **UK Medicines and Healthcare products Regulatory Agency (MHRA)**: On 2nd October 2023 the MHRA approved the addition of results from the ESCAPE-TRD trial in the UK Summary of Product Characteristics (SmPC) for esketamine nasal spray (SmPC, n.d.)
* **World Psychiatric association (WPA)**: On 18th October 2023 the WPA published their consensus paper on TRD, including recommendations for treatment. For the first time esketamine NS was included in the list of recommended treatments. Furthermore, results from the ESCAPE-TRD trial are included in the paper and esketamine NS is recognised as “*the most rigorously evaluated pharmacologic treatment strategy in the acute and maintenance treatment of adults with TRD”.* (Mc Intyre, 2023)
* **Gemeinsamer Bundesausschuss (G-BA)**: On 21st September 2023 the G-BA announced their positive assessment for esketamine nasal spray in TRD, assigning the second highest rating of *“considerable added benefit*”, which means that esketamine NS is available for the TRD population in Germany. This assessment was largely based on the results of the ESCAPE-TRD trial. It is noteworthy that this is the highest ever benefit assessment granted by the G-BA for a psychiatry product. (G-BA, 2023)

Given the significance of these data, the reaction to these data from other decision-making bodies and the potential to inform the TRD treatment pathway, we believe that NICE should consider the evidence in full via a reappraisal. Nicola Greenhalgh, deputy chief pharmacist, Inpatient, Specialist and Secure Services at Essex Partnership University NHS Foundation Trust, said: “*Overall management of depression that isn’t responding to treatment is limited and often leaves patients in significant distress, with impacts not only to them but to their family, and to wider networks and the wider society. Having a good repertoire of treatment is important to allow clinicians to be able to work with patients to select the most appropriate options for the patient presenting to them and it is hoped that, as the evidence base for esketamine grows, there may be an opportunity to revisit the NICE position. “Unless NICE does relook at the evidence though, the position that trusts are in makes it very difficult to support the use of esketamine outside of a trial and may push more of them to seek treatments elsewhere. Without any change from NICE, whilst we can theoretically prescribe for individual patients, it’s not straightforward and our hands are almost tied”* (Janković, 2023) | NICE considers the remit of the review is not to reassess all available evidence, which would be the case if a full appraisal was considered, but to consider whether any evidence presented would change the current recommendation. The results of the ESCAPE-TRD trial are considered the pivotal new information on which to base the decision for review and the only evidence initially presented by Janssen. Further consideration of other sources of supporting evidence does not suggest evidence that would substantially change the decision or as important as the results of ESCAPE-TRD. |
| Janssen (JNJ) | **It is methodologically inappropriate to base the decision not to re-appraise esketamine on a naïve comparison of MADRS total score change from baseline in ESCAPE-TRD and TRANSFORM 2, since there are significant differences in the trial designs. Furthermore, the MADRS change from baseline is not a result that informs the economic model. By contrast the primary endpoint of ESCAPE-TRD (remission at Week 8) is a key result in informing the model.** While NICE mention the primary outcome of ESCAPE-TRD (remission at Week 8) in their evaluation, it is not adequately considered nor appears to be the main driver of the current decision. Instead, the focus of the assessment is on the MADRS total score change from baseline. This approach is incorrect and undermines the significance of the ESCAPE-TRD trial and the outcomes from the trial. Unlike the previous TRANSFORM studies, which were the main basis for the decision of TA854, where the primary endpoint was MADRS total score change at Week 4 (Popova, 2019) the primary endpoint of ESCAPE TRD was the proportion of patients in remission at Week 8 (defined as a MADRS score of ≤10) (Reif A. , 2023). While TA854 (section 3.14) expressed caution in the interpretation of remission (and response), the goal of acute depression treatment is remission and therefore remission at Week 8 is recognised as an important and clinically relevant endpoint. The primary endpoint of ESCAPE-TRD demonstrated esketamine NS’s superiority at achieving remission during acute treatment vs quetiapine XR, with 27.1% vs 17.6% of patients in remission at Week-8, respectively (p=0.003) (Reif A. , 2023). Furthermore, and not recognised in the current decision is the key secondary endpoint that reflects an additional and longer term clinically relevant endpoint, rarely measured in clinical trials, which was patients being relapse-free at Week 32, after remission at Week 8. The goal of maintenance depression treatment is to keep patients free of relapse. The key secondary endpoint of ESCAPE-TRD was designed to reflect this and was the proportion of patients in remission at Week 8 and relapse free at Week 32. Similar to the primary endpoint, ESCAPE-TRD demonstrated that esketamine NS was superior to quetiapine XR, with significantly more patients treated with esketamine NS relapse free at Week 32 after remission at Week 8 vs quetiapine XR (21.7% vs 14.1%, p=0.008). While these endpoints reflect more clinically meaningful, guideline led endpoints, they also reflect the main health states defined in the cost-effectiveness model for esketamine NS (remission and relapse). As such ESCAPE-TRD provides direct and robust evidence that will be incorporated into an updated cost effectiveness model if a re-submission takes place. The focus on the MADRS total score change from baseline and in particular the naïve comparison of the MADRS change in TRANSFORM 2 to ESCAPE-TRD, ignores the primary endpoints of ESCAPE-TRD and is not technically or methodologically robust. The naïve comparison conflicts with NICE’s own methods guidance (NICE, NICE health technology evaluations: the manual). It does not take into account the many differences between the two trials, which can contribute to different relative treatment effects (active comparator vs placebo comparison, continuing SSRI/SNRI vs newly initiated, 4-Week vs 32-Week trial). These differences should be examined properly and discussed by the Committee in an appraisal rather than assumed to be non-impactful.  | Comments noted. The decision paper has been updated to show the remission rates at week 4 that have already been considered by the committee in the TRANSFORM-2 subgroup analysis that formed the company’s base case analysis. In TA854, all stakeholders were in agreement that substantial heterogeneity in study design made results from indirect comparisons unreliable for decision making, and therefore the committee agreed to consider the naïve comparison in the trial in its decision making. NICE has not been presented with any evidence from an indirect comparison that would result in a different recommendation. It recognises there are uncertainties with this approach but considering it is appropriate to consider the magnitude of relative effect with the naïve comparison.  |
| Janssen (JNJ) | **Quetiapine XR is the most appropriate standard of care treatment available and is therefore the best comparator in a trial of esketamine** While NICE recognise quetiapine as a more appropriate comparator than oral antidepressant treatment, they state “*this trial represents only one augmentation therapy that may be used in clinical practice at this line*.” This implies evidence versus other augmentation therapies is needed. In physical health trials, it is common that the most appropriate comparator is selected, and indirect comparisons are conducted, since multiple comparison trials are difficult to conduct and highly expensive. The text written by NICE implies that they are holding mental health to unfair standards as opposed to physical health conditions. In line with NICE methods, we will however, (if a resubmission is permitted), be updating, and conducting indirect comparisons of relevant comparators (where possible). Furthermore, relating to this text, NICE continue to use terminology that is not appropriate for TRD as a condition, demonstrating a lack of understanding for the pathway; “*used in clinical practice at this line*” – once patients become treatment resistant, it is inappropriate to consider their treatment in “lines” since treatment does not follow an order and different treatments can be given in combination with one another. Whilst we appreciate the pathway is complex, we urge a greater understanding of the TRD pathway and appreciation of the intricacies of the disease area. It is our position that for esketamine NS, quetiapine is the most appropriate and reasonable comparator choice since it is the only treatment licensed for this population and is the most widely used. To note that not all treatments used in the mental health space are licensed and a majority of treatments that are used, either come with significant side effects or are sub-optimal for patients. Whilst we recognise other augmentation options are used, it is not feasible to conduct a clinical trial that includes multiple augmentation options, and it is irresponsible to promote the use of unlicensed treatments. It is evident the treatments used for TRD are heterogenous; a European observational cohort of 411 patients with TRD across Europe demonstrated 54 different drugs used at baseline (K Heerlein, 2021). This same cohort demonstrated that 9 different treatments were received by ≥10% of patients, all of these were oral antidepressants, except for quetiapine, which was the only augmentation strategy in the most frequently prescribed treatments (Heerlein, 2022). This indicates oral antidepressants remain the most frequent treatment for TRD and when augmentation is used, quetiapine is the most frequent therapy used, which supports the choice of quetiapine as the most appropriate augmentation comparator for TRD. Another guideline recommended augmentation treatment is lithium (Bauer, 2013) (Cleare A. , 2015) (NICE, NICE guideline: Depression in adults: treatment and management, 2022) (Psychiatry, 2010). A recent study has demonstrated the superiority of quetiapine to lithium, (Cleare, 2023), indicating quetiapine is likely a more clinically effective augmentation treatment for TRD and further evidence that it is the most appropriate comparator choice.  | Comments noted. In TA854, the committee concluded that multiple further lines of treatment are considered for treatment-resistant depression (see section 3.3 of the final guidance). The discussion of line of treatment has been redefined as position, which was extensively discussed as part of TA854. |
| Janssen (JNJ) | **While there are some disadvantages to open-label trial designs, an open-label design was the most appropriate and pragmatic design for this therapy area. NICE should consider the ESCAPE-TRD design in the context of mental health and the different mechanisms of actions and routes of administration of the two study treatments** We were pleased NICE recognise the risk of unblinding of treatment in the previous blinded studies (TRANSFROM 2 and SUSTAIN 1) was addressed by utilising an open-label design in ESCAPE-TRD. However, it is noted by NICE that the open-label design results should be “*interpreted with caution*.” While there can be challenges with open-label trial designs, we believe for this treatment and this indication, open-label is the most appropriate design. Beyond addressing the risk of functional unblinding, the open-label design also:* reduced the study burden for patients. Blinding would have required a double dummy design and therefore a placebo nasal spray or a placebo oral tablet up to Week 32 for all patients;
* more closely reflected routine clinical use in terms of number of visits, dosing, and observation times. As such permitted administration of the treatments according to their label instructions; and
* minimised the impact of placebo response on comparisons, which was an issue for the committee in the previous appraisal.

While we recognise there are limitations to open-label studies, to reduce the risk of bias and impact on efficacy results due to lack of blinding, independent MADRS raters were used. These raters only assessed MADRS scores, were blinded to the patient’s assigned study treatment and were not involved in any other study assessments, clinical care, or treatment decisions (Reif A. , 2023).It is therefore our position that the use of an open-label design is unavoidable. Where possible, the impact of an open-label design for decision making has been minimised. Hence, we believe that the prospects for patients to access this medicine should not be penalised as a result.  | Comments noted. In TA854, the committee recognised that blinding may contribute to the uncertainty of treatment effect (see section 3.13 of the guidance). The design of ESCAPE-TRD could bias in favour of esketamine because patients were unblinded and may have had expectations of a novel treatment mechanism. This contributes additional uncertainty to the ESCAPE-TRD treatment effect. |
| Janssen (JNJ) | **NICE do not appear to have considered the sub-population of patients with ≥3 prior treatment failures**NICE base their current decision on the full ESCAPE-TRD population, which includes patients with ≥2 prior treatment failures (the most frequently accepted definition of TRD). In the previous submission, the clinical experts proposed restricting the population to later in the treatment pathway, since this is where the greatest unmet need for the population sits. ESCAPE-TRD provides more robust evidence in the population of patients with ≥3 prior treatment failures (aligned to the later treatment pathway) than was available from the previous TRANFORM and SUSTAIN studies. Patients enrolled into ESCAPE-TRD were stratified based on number of prior treatment failures (≥2 vs ≥3 prior treatment failures), as such randomisation in these subgroups holds. As shown in the previous assessment the relevant treatment effect is greater in ≥3 prior treatment failure group vs the 2 prior treatment failures. At Week 8, 28.0% versus 10.9% (p=0.001) of patients in the ≥3 prior treatment failure group were in remission when treated with esketamine NS and quetiapine XR, respectively. This compares to 26.5% versus 21.8% (p=0.267) in the 2 prior treatment failure group (Young, 2023). These results confirm the greater relative treatment effect of esketamine NS later in the treatment pathway and in the proposed restricted population with more robust data. If NICE agree to reappraise esketamine NS, this ≥3 prior treatment failure group could form the basis of the new submission and would mitigate the Committee’s concerns of population and positioning. We therefore believe that the Committee would be assessing a new decision problem since TA854, which should be given due consideration.  | Comments noted. The company self-optimised the base case analysis in TA854 for the ≥3 prior treatment failures subgroup, therefore this is not a new decision problem. As with TRANSFORM-2, consideration of subgroups within this analysis substantially increases uncertainty of the results (see section 3.10 of the final guidance). It also does not change the conclusion that the relative treatment effect is less than what has already been considered by the committee. As Janssen note above, treatment line is not clearly defined and does not follow an order and different treatments can be given in combination with one another. |
| Janssen (JNJ) | **An updated cost effectiveness model has not been considered and would form part of the evidence package utilising ESCAPE-TRD data**NICE state that evidence from ESCAPE-TRD does “*not resolve many of the other substantial uncertainties with the evidence base or modelling concerns*”. We do not believe this, nor is any such conclusion appropriate, without a full review of the ESCAPE-TRD data and a revised economic model. Hence, it is our position that a full submission would be required for a full re-assessment of the additional evidence. Furthermore, there is no mention from NICE on the inherent uncertainties that remain as unresolvable in this disease area. We want to reassure NICE that we have carefully considered the modelling concerns outlined. The primary endpoint of the trials included in the previous submission (MADRS total score change from baseline) did not directly inform the economic model. In contrast the Primary endpoint of ESCAPE TRD (remission at Week 8) will directly inform the model. While ESCAPE-TRD cannot directly address some of those issues discussed, we are working on considerable changes based on the Committee’s feedback and in a new submission, NICE can anticipate appropriate updates to the cost-effectiveness model in line with Committee feedback.  | Comment noted. NICE does not consider that new analysis is required to assess whether the new evidence from ESCAPE-TRD would change the current recommendation. No new evidence for the other uncertainties in the model have been provided. |
| Janssen (JNJ) | **If NICE agree to re-appraise esketamine a new patient access scheme (PAS) would be submitted**NICE state that ‘*The company had a confidential discount through a patient access scheme, which would have applied if the technology had been recommended. This has since been withdrawn*.’ Whilst this statement is correct, we would like to clarify that the previous patient access scheme (PAS) aimed to facilitate access by committing to a net price likely to be cost-effective given the evidence base available for TA854. Given the appraisal process had completed, resulting in a negative recommendation, the PAS was withdrawn because there was no requirement for a PAS. A re-appraisal, however, allows a fresh approach, utilising the ESCAPE-TRD evidence and a revised model. To be clear, in the event that esketamine NS is re-appraised, Janssen will submit a patient access scheme to facilitate access by committing to a net price likely to be cost-effective given the evidence now available to inform appraisal. | Comment noted. No action required. |
| Janssen (JNJ) | **The totality of evidence from the esketamine trials has not been considered by NICE: In addition to the ESCAPE-TRD trial, Janssen would submit long-term safety data in the TRD population (SUSTAIN-3), as well as safety data from esketamine NS in major depressive disorder and suicidal ideation with intent (ASPIRE), and adjusted indirect treatment comparison data (ICEBERG), in response to Committee comments in TA854****SUSTAIN-3**Since NICE’s December 2022 recommendation the SUSTAIN 3 (Zaki, 2023), (Young(4), 2023) trial has been completed. SUSTAIN 3 was a long-term continuation of care study where the primary objective was to assess the long-term safety and tolerability of esketamine NS in patients with TRD. At completion of the study the total exposure to esketamine NS was 3,777 cumulative patient years. Results of the final analysis demonstrate there were no unexpected safety findings. The overall safety and tolerability profile remained consistent with the existing well-characterised safety profile of esketamine NS previously reported. While in TA854 the NICE committee recognise they are not a safety Committee and recognise the MHRA are responsible for assessing safety concerns, the long-term safety findings from the SUSTAIN-3 trial should help to address any residual concerns NICE may have on the longer-term safety of esketamine NS. **ASPIRE**Furthermore, results from the ASPIRE trials (Fu, 2020). (Ionescu, 2021) have not previously been considered. The ASPIRE trials (ASPIRE 1 and 2) were two double-blinded, randomised, placebo controlled, trials evaluating the efficacy and safety of esketamine NS in addition to comprehensive standard of care for the rapid reduction of the symptoms of major depressive disorder, including suicidal ideation, in adult subjects assessed to be at imminent risk for suicide. The primary endpoint of both trials was the change in MADRS total score at 24 hours. The change in MADRS total score at 24 hours was significantly greater in the esketamine + standard of care group than in the placebo + standard of care group in both trials; least square mean difference [95% confidence interval], −3.8 [−5.75 to −1.89], p=0.006 (ASPIRE 1) and -3.9 [1.39], 95% CI: -6.60, -1.11; p=0.006 (ASPIRE 2). Results from the ASPIRE studies, as well as the expanded inclusion criteria of ESCAPE-TRD (to include patients with more recent suicidal ideation), help address NICE’s concerns on the generalisability of evidence to the NHS, since they provide evidence for the significant proportion of patients with TRD that also present with suicide risk. Additionally, the ASPIRE trials will provide the safety data the Committee requested since they were in a population with major depressive disorder and suicidal ideation with intent.**ICEBERG**On the day of submitting the responses to the surveillance consultation (31st October 2023), two articles on the ICEBERG study were published, which will provide supplementary evidence to a new submission. The ICEBERG study is an adjusted indirect treatment comparison of data from the SUSTAIN-2 trial, a long-term, open-label study of esketamine NS plus SSRI/SNRI, compared to the European Observational TRD Cohort (EOTC), an observational study of routine clinical practice. Data were compared between patients receiving esketamine NS (SUSTAIN-2) and those from the EOTC treated with polypharmacy treatment strategies, either combination or augmentation (Oliveira-Maia, 2023a) (Oliveira-Maia A. , 2023b). Analyses were adjusted for potential confounders, using rescaled average treatment effect among treated estimates.Esketamine NS treatment resulted in a higher probability of 6-month response (49.7% [95% confidence interval (CI) 45.6–53.9]) and remission (33.6% [95% CI 29.7–37.6]) versus real-world polypharmacy (26.8% [95% CI 21.0–32.5] and 19.4%, [95% CI 14.2–24.6], respectively). Relative risk calculations showed esketamine NS was 1.859 (95% CI 1.474–2.345; p < 0.0001) times as likely to result in response and 1.735 (1.297–2.322; p = 0.0002) times as likely to result in remission versus real-world polypharmacy at 6-months (Oliveira-Maia A. , 2023b).  | Comments noted. It is unclear what uncertainty SUSTAIN-3 resolves for the appraisal.The results of the ASPIRE trials were not provided or considered as part of TA854 because they correspond to results from a different population within the marketing authorisation. The appraisal for this indication was terminated in TA899.The results of ICEBERG provide supplementary information that corresponds to a similar treatment effect size as ESCAPE-TRD with the additional. |
| Janssen (JNJ) | **We are working on activities to support wider uncertainties and if NICE agree to re-appraise esketamine, this will form part of the evidence package.**One of the uncertainties highlighted by the NICE Committee was based on the implementation of esketamine NS in the NHS. Janssen are currently furthering activities relating to supporting the wider challenges highlighted by the Committee, which would form part of the evidence submission if re-appraisal goes ahead. | Comments noted. |
| Janssen (JNJ) | **The ESCAPE-TRD data and changes to the economic model, in line with Real World practice will result in a new submission with considerably reduced uncertainty for Committee review and a meaningful impact on the ICERs.** There has been a significant update in the evidence base for esketamine-NS in TRD with the addition of the ESCAPE-TRD trial, as well as in the supporting evidence base with the completion of the SUSTAIN-3 trial and inclusion of safety data from the ASPIRE trial (in a population with current suicidal ideation and intent), which would culminate in a new technology appraisal submission. Furthermore, a new submission would focus on reducing the areas of uncertainty highlighted by the Committee in TA854, utilising the totality of evidence available for esketamine. As detailed throughout this document, a significant number of countries have reimbursed esketamine worldwide and we believe the updates provided in this document are sufficient to necessitate a re-appraisal of esketamine NS by NICE for TRD patients in England/Wales. The updates discussed will have a meaningful impact on the overall certainty (or reduced uncertainty) of the data and ultimately on the Incremental Cost-Effectiveness Ratio (ICER). | Comments noted. NICE considers the ESAPE-TRD trial could resolve some uncertainty in the relative treatment effect. It is unclear how this would be affect the cost-effectiveness results, because the committee have already considered ICERs that incorporate greater treatment effect that were presented without parameter uncertainty analysis. |

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