Esketamine for Treatment-Resistant Major Depressive Disorder: Effectiveness and Value

Modeling Analysis Plan

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1. Approach

This analysis plan details our approach to the cost-effectiveness model and a cost analysis evaluating esketamine for people diagnosed with treatment-resistant major depressive disorder. For the cost-effectiveness analysis, esketamine plus a newly initiated oral antidepressant will be compared to a newly initiated antidepressant alone. For the cost analysis, intranasal esketamine will be compared to intravenous ketamine. Refer to the research protocol for details on the systematic review of the clinical evidence on this topic.

The primary aim of the model will be to evaluate the cost-effectiveness of the addition of esketamine nasal spray compared to no additional treatment, in patients receiving a newly prescribed oral antidepressant, for the treatment of treatment-resistant major depressive disorder using a decision analytic model. For this aim, the base-case analysis will take a health care sector perspective (i.e., focus on direct medical care costs only), and a lifetime horizon. Productivity losses will be considered in a scenario analysis, if data allow. The model will be developed in Microsoft Excel 2016 (Redmond, WA).

A review of the literature of potential comparators to esketamine was conducted. When the available trials were reviewed, one trial comparing ketamine to placebo, with patients continuing any other antidepressant medications they were receiving at study entry, emerged for potential inclusion in a network meta-analysis (NMA). However, further evaluation of the trial revealed that while ketamine had similar rates of response and remission to studies evaluating esketamine, placebo response and remission were very different from esketamine placebo trials. These differences suggest that either the enrolled patient populations differed greatly, treatments were administered or evaluated in very different ways, and/or other factors affecting the placebo response may be present. The heterogeneity present in these trials was deemed too substantial to conduct an NMA from which to derive needed inputs for a cost-effectiveness model. However, given the similar, but non-comparable efficacy of ketamine and esketamine, a cost-analysis will be undertaken to provide payers and others with some estimate of differences in expected costs for each of these treatments.

Thus, as a secondary aim of this report, we will evaluate the one-year costs of treatment with esketamine nasal spray compared to intravenous ketamine for the treatment of treatment-resistant major depressive disorder. For this aim, the base-case analysis will take a health care sector perspective, focusing on direct medical care and patient out-of-pocket costs, with a one-year time-horizon. Productivity losses will be considered in a scenario analysis, if data allow. The model will be developed in Microsoft Excel 2016 (Redmond, WA).

2. Methods

2.1 Overview and Model Structure

For the cost-effectiveness analysis, we will develop a *de novo* decision analytic model informed by key clinical trials and prior relevant economic models. The base-case analysis will take a health care sector perspective and thus focus on direct medical care costs only. Costs and outcomes will be discounted at 3% per year.

The model will focus on an intention-to-treat analysis, with a hypothetical cohort of patients with TRD, all being treated with either a new oral antidepressant plus eskatamine or new oral antidepressant plus no additional treatment upon entry into the model. Model cycle length will be 3 months, based on the length of typical treatment initiation seen in trials for treatment-resistant depression.

As shown in the model schematic, Figure 1, and using definitions shown in Table 1, simulated patients enter the model with severe depression receiving an "Initial Treatment" (i.e. antidepressant + eskatamine or antidepressant + no additional treatment). Initial treatment may result in a considerable improvement in depression symptoms (Markov state "Initial treatment effective, remain on initial treatment, no depression"), a lesser improvement in depression symptoms (Markov state "Initial treatment partly effective, remain on initial treatment with augmentation, mild to moderate depression"), or an insufficient response (Markov states "Initial treatment not effective, switch to alternative treatment 1 (effective), no depression" or "Initial treatment not effective, switch to alternative treatment 1 (not effective), severe depression."

Table 1. Treatment Response Definitions Used in the Model

Model State Description	Definition	Calculation from Clinical Trials
Treatment Effective	MADRS score of 12 or less or QIDS-SR_{16} of 5 or less	Proportion achieving remission
Treatment Partly Effective (applies only to initial treatments)*	50% reduction from baseline MADRS score, but not achieving a MADRS score of 12 or less or 50% reduction from baseline QIDS-SR_{16}, but not achieving a QIDS-SR_{16} of 5 or less	Proportion achieving response - Proportion achieving remission
Treatment Not Effective or Treatment Loses Effect	Less than a 50% reduction in MADRS or QIDS-SR_{16}, score when compared with baseline	Transform-2

Each cycle, patients whose initial treatment was effective may continue to experience effective treatment or may have loss of initial treatment effect. Those with continued effective treatment will typically remain in the same Markov state ("Initial treatment effective, remain on initial treatment, no depression"), although some patients with continued response may have the initial treatment discontinued and remain without depression. Those patients who respond to the the initial treatment, but subsequently have a loss of effect will move to one of two Markov states, depending on the effectiveness of the subsequent alternative treatment (Markov states "Initial treatment not effective, alternative treatment 1 (effective), no depression" or "Initial treatment not effective, alternative treatment 1 (not effective), severe depression").

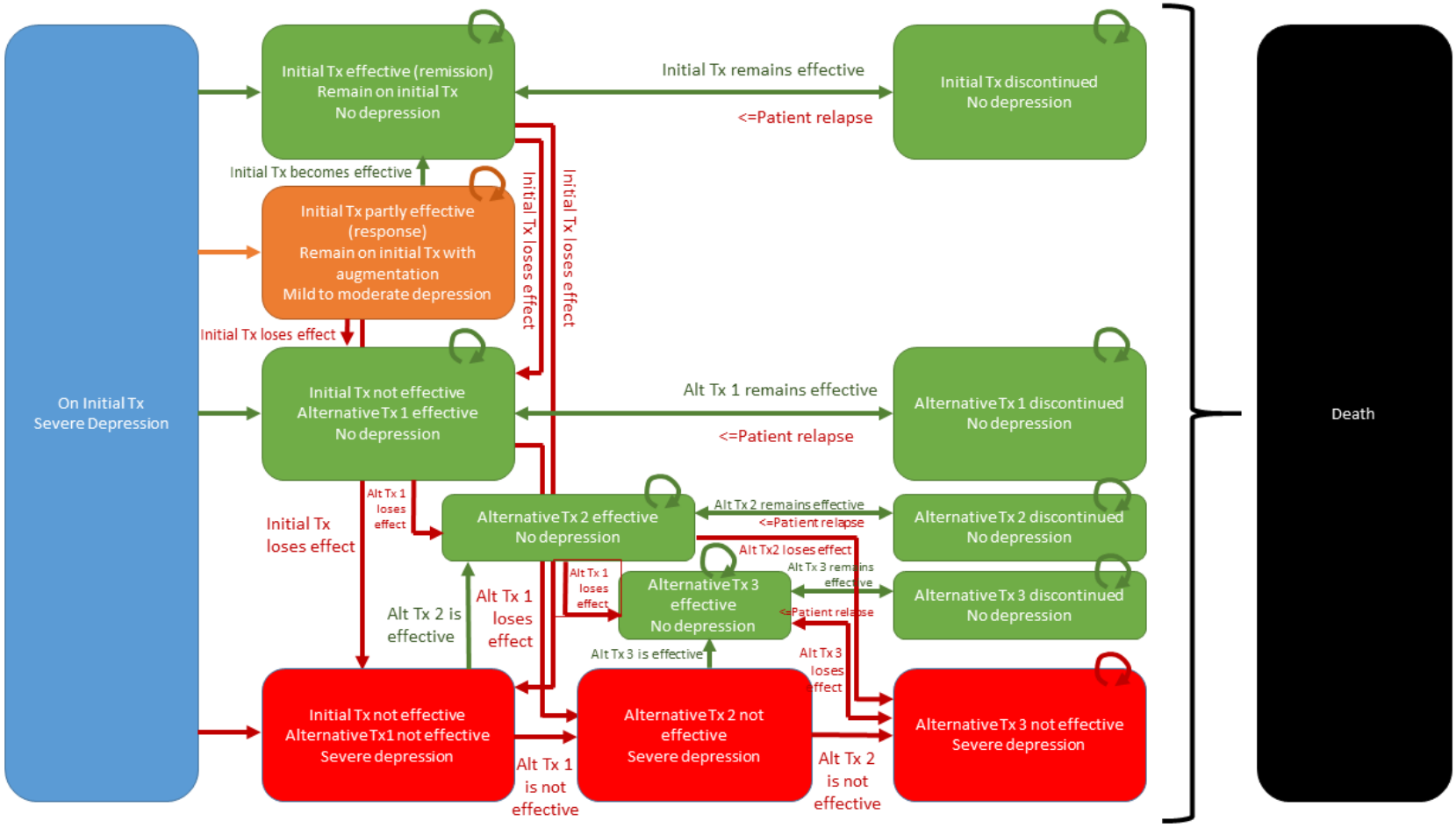
Patients whose initial treatment was partly effective will receive augmentation added to their initial treatment. Each cycle, patients whose initial treatment was partly effective may continue treatment with initial treatment plus augmentation (Markov state "Initial treatment partly effective, remain on initial treatment with augmentation, mild to moderate depression"), have initial treatment become more effective (Markov state "Initial treatment effective, remain on initial treatment, no depression"), or subsequently have a loss of treatment effect thereby moving to one of two Markov states depending on the effectiveness of the subsequent alternative treatment (Markov states "Initial treatment not effective, alternative treatment 1 (effective), no depression" or "Initial treatment not effective, alternative treatment 1 (not effective), severe depression"). Patients in whom the initial treatment was partly effective long-term will not be allowed to have their initial treatment discontinued while in this partial response Markov state.

Patients not responding to the initial treatment will move from the initial treatment state to one of two Markov states, depending on the effectiveness of the alternative treatment. Those responding to the first alternative treatment will be in the "Initial treatment not effective, alternative treatment 1 (effective), no depression" Markov state in the second model cycle. Those not responding to the alternative treatment will be in the "Initial treatment not effective, alternative treatment 1 (not effective), severe depression" Markov state. In subsequent cycles, patients can transition to up to three alternative treatments if they experience loss of treatment effect with current treatment. As with effective initial treatment, most patients with effective treatment over the longer term will continue to take the alternative treatment and remain in the Markov state "Initial treatment not effective, switch to alternative treatment 1-3 (effective), no depression" corresponding to which alternative treatment was effective. A small number of patients experiencing continued effect to the respective alternative treatment may move to a state where the alternative treatment is discontinued with no depression (Markov states "Alternative treatment 1-3 discontinued, no depression."

Any patient with continued response to initial treatment or any alternative treatment, and for whom treatment was discontinued, there is a possibility of relapse in depression. These patients will move to their most recent effective treatment.

Patients remain in the model until they die. All patients can transition to death from all causes from any of the alive health states.

Figure 1. Model Schematic



Blue = initial treatment; Green = treatment effective; Orange = treatment partly effective; Red = treatment not effective

2.2 Key Model Choices and Assumptions

Our model includes several assumptions stated in Table 2 below.

Table 2. Model Assumptions and Rationale

Assumption	Rationale
Some patients with effective treatment long-term will have their treatments discontinued.	In the treatment of major depressive disorder, patients with sustained response to treatment often have their treatments discontinued. There is limited information regarding the frequency of this practice in patients with treatment-resistant depression. We will assume that some patients will have their treatments discontinued, with the probability based on expert opinion. This input will be subjected to a robust sensitivity analysis.
Patients who have had their treatments discontinued for effectiveness and have a relapse of their depression will restart their last effective treatment and receive benefit from that treatment	There is limited information regarding practice treatment patterns in patients with treatment-resistant depression. Restarting patients on therapies that were previously effective is a common practice in major depressive disorder.
Patients in whom initial treatment is only partly effective have mild to moderate depression.	In the TRANSFORM 1 and 2 trials, the minimum starting MADRS score was 28 or greater. Response was defined as at least a 50% reduction in the MADRS score without achieving remission (defined as a MADRS score of less than 12).[1,2] Given a maximum MADRS score of 60 and a mean MADRS score of 37 - 38, patients with response without achieving remission would have scores between 12 and 30, which correspond to mild (scores 9-17) or moderate (scores 18-34).[1,2]
Patients in whom initial treatment is only partly effective will continue treatment with their initial treatment and receive augmentation.	There is limited information regarding practice treatment patterns in patients with treatment-resistant depression. The STAR*D study allowed patients to receive augmentation or switch antidepressants for patients in whom treatment was only partly effective and depression was still present.[3] As we did not have probabilities for the proportion of patients likely to choose augmentation versus switch treatment and since esketamine was generally well tolerated in its key trials.[1,2,4] we assumed that patients would remain on partly effective treatments with augmentation.

Assumption	Rationale
Patients in whom treatment is not effective will have treatment discontinued and receive an alternative treatment.	There is limited real-world evidence regarding treatment patterns in patients with treatment-resistant depression, especially as it relates to patients who receive some benefit, but experience a suboptimal response to a new treatment. Clinical trials, including TRANSFORM 1 and 2 and STAR*D, consider non-response as those patients who do not achieve "remission" nor "response." In the STAR*D, some patients who achieved response switched treatment[3]. To simplify the model, we have assumed that only those patients who do not achieve "remission" or "response" would receive a different treatment.
The Markov state "Alternative treatment 3 not effective, severe depression" represents the third and all future treatments that are not effective. Simulated patients will remain in that state long-term if all future therapies are not effective or move to the Markov state "Alternative treatment 3 effective, no depression" if a future alternative treatment is effective.	Costs were not evaluated for patients requiring beyond eight regimen changes. Probabilities for treatment failure were not available beyond four therapies. Since patients were entering the model already having failed an average of three therapies (with the new treatment being at least the third treatment), failing more than three additional alternative therapies would result in the same costs for each additional failed treatment. Therefore, we decided to limit the number of alternative treatments in the model to three.
Treatment does not directly affect mortality.	Treatments were not shown to decrease mortality in clinical trials. However, depression has been linked with a higher mortality rate. Provided data is available, we will consider adjusting mortality rates for those with treated versus untreated depression.
Modeled costs are associated with number of previous therapies and not directly with depression severity.	Cost data was not available evaluating the total costs of treating treatment-resistant depression by disease severity. Cost data was available according to number of failed therapies. The model was developed to incorporate data that was available from the literature.
Patients with effective depression treatment will have medical costs (not including pharmaceuctical costs) equivalent to those with three prior treatment failures (i.e. on their fourth treatment).	Cost data was not available for patients with treated depression from the same source as those who had failed multiple therapies. We therefore assumed that the lowest available cost from Russell et al.[5] should apply to all patients on effective treatment with initial treatment.

2.3 Populations

The population of focus for the economic evaluation will include adults aged 18 to 64, with a mean age of 46 years. Patients will enter the model with a single espisode or recurrent major depressive disorder without psychotic features that is treatment-resistant (Table 3). Treatment-resistance is defined as non-response to two or more adequate trials of antidepressant treatment in the current depressive episode.[6] Baseline patient characteristics are presented in Table 3.

Table 3: Baseline Population Characteristics

Baseline Characteristics	Value	Source
Mean Age, years (SD)	46 years	TRANSFORM 1 and 2
Female, %	67%	TRANSFORM 1 and 2
Number of previous antidepressant trials, % **1 or 2** **≥3**	 63% 37%	TRANSFORM 1 and 2
MADRS score at baseline, mean	37.4	TRANSFORM 1 and 2

2.4 Interventions and Comparators

Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which drugs to include. The full list of interventions is as follows:

- Esketamine (investigational, Janssen) 56 mg or 84 mg intranasally twice weekly, reduced to once weekly or every other week
- Unspecified new oral antidepressant agent

Comparators

- (Placebo intranasally twice weekly)
- Unspecified new oral antidepressant agent

Based on the judgement of clinical experts, esketamine treatment is viewed as an option for later-line treatment after patients had failed numerous oral anti-depressants. Potential comparators included electroconvulsive treatment, transcranial magnetic stimulation, and ketamine. However,

systematic differences in study design, heterogeneity between patient populations, and inconsistency in the outcomes assessed by clinical trials evaluating these therapies precluded the inclusion of these comparators in an NMA. As a result, it was not possible to generate effect estimates for other therapies compared to esketamine. Therefore, the model will compare esketamine plus a new oral antidepressant to a new oral antidepressant alone (i.e. the placebo comparison arms of the TRANSFORM 1 and 2 studies.[1,2]

2.5 Input Parameters

Clinical Inputs

Short-term clinical inputs of the relative risk of depression remission and response for esketamine and the comparator will be derived from a meta-analysis of the esketamine clinical trials TRANSFORM 1 and 2.[1,2] Long-term clinical inputs related to continued response of esketamine will be derived from the SUSTAIN 1 study.[4] Long-term clinical inputs related to alternative oral antidepressant treatments will be derived from the STAR*D trial.[3]

Transition Probabilities

The decision model will be evaluated over a lifetime time horizon with 3-month cycles. Patients will begin with severe depression and receive initial treatment with esketamine. The degree of response to esketamine will be based on clinical trials evaluating outcomes at four weeks, in which remission was defined as achieving a MADRS score of 12 or less at four weeks and response was defined as achieving a 50% or greater reduction in the MADRS score from baseline at four weeks. A selected list of inputs is shown in Tables 4 and 5 below. Since esketamine's treatment effect was similar at week four of the TRANSFORM 1[1] trial and three months after initiation (i.e. week four of the SUSTAIN 2[7] trial), four-week estimates for effective and partly effective treatment probabilities will be used to represent 3-month transition probabilities and will not be transformed. The probability of non-response to esketamine and subsequent effective treatment or ineffective treatment with alternative treatment will be calculated from the probability of non-response to esketamine from the TRANSFORM 1 and 2 trials[1,2] and the probability of achieving remission with an alternative treatment at the next treatment step, derived from the STAR*D trial.[3] The probability of discontinuing esketamine or the comparator after long-term treatment success will be obtained from expert opinion in the absence of data on this estimate.

For patients in whom esketamine or the comparator was effective or partly effective and who are continuing treatment, estimates of loss of effect will be obtained from the SUSTAIN 1 trial.[4] These probabilities will be multiplied by the probability of effective treatment with an alternative treatment at the next treatment step, derived from the STAR*D trial.[3]

For those in whom esketamine or the comparator was effective long-term and discontinued, the probability of losing effectiveness will be based on estimates from the STAR*D trial.[3] Patients will receive the last effective treatment (esketamine or the comparator), which will be assumed to be effective for the current cycle.

For those patients in whom esketamine or the comparator was partly effective, results from the SUSTAIN 1 trial will be used to estimate the probability of effective treatment (regression output from SUSTAIN 1 trial, results included in open input document) or loss of effect (stable responders who experienced relapse at 12 weeks)[4].

Where inputs are available only from Kaplan Meier curves or bar graphs, probabilities will be derived using a digitized estimate value on the Kaplan-Meier curve at the appropriate time point. Where probability estimates are not available at three months (i.e. the model's cycle length), all probabilities except the initial response to esketamine or the comparator (as described above) will be transformed to three-month probabilities using the appropriate form of the equation $P[t]=1-e^{-rt}$, where P[t] is the probability at time t, r is the corresponding constant rate, and t is the time period over which the probability was assessed.

Table 4. Treatment Dependent Transition Probabilities Used in the Model

Model Input	Esketamine + Antidepressant	Placebo + Antidepressant	Source
Remission, relative ratio (95% CI)	1.37 (0.99-1.91)	Comparator	Meta-analysis of Transform 1 and 2
Effective initial treatment, probability (95% CI)	42.5% (30.7% – 59.2%)	31.0%	Meta-analysis of Transform 1 and 2, calculated from RR
Partly effective treatment, relative ratio (95% CI)	1.30 (1.08-1.56)	Comparator	eta-analysis of Transform 1 and 2
Partly effective initial treatment, probability (95% CI)	36.6% (25.2% – 50.1%)	21.0%	Meta-analysis of Transform 1 and 2, calculated from RR

Table 5. Non-Treatment Dependent Transition Probabilities Used in the Model

Model Input	Value	Source
Probability of loss of initial treatment effectiveness each cycle	13.0%	SUSTAIN 1
Probability of effective treatment with alternative treatment	13.0-13.7%	STAR-D (steps 3 and 4 from table 3)
Probability of patients with initial partial response to esketamine achieving complete response	19.9%	SUSTAIN 1 (calculated from long-term relapse and remission rates)
Probability of patients with initial partial response to esketamine losing response	20.0%	SUSTAIN 1 (calculated from long-term relapse and remission rates)
Proportion of patients with long-term effectiveness discontinuing treatment	-	Currently seeking expert opinion
Proportion of patients dying	Age specific, adjusted for depression	CDC/NCHS National Vital Statistics System Olin B et al. PLoS One. 2012;7(10):e48002

Discontinuation

Discontinuation of esketamine due to treatment-emergent adverse events occurred in 9.5% of patients receiving esketamine and 4.1% of patients receiving antidepressants in the SUSTAIN 2 open label trial.[7] Discontinuation of treatment with alternative oral antidepressants varies by specific agent used. Discontinuation of esketamine, the comparator, or alternative treatments was assumed to be incorporated in loss of treatment effect from clinical trials. Therefore, treatment discontinuation specifically due to treatment-emergent adverse events was not explicitly incorporated into the model, but is implicitly captured through treatment changes due to loss of treatment effect.

Mortality

Table 6 shows mortality inputs used in the model. Gender and age-specific all-cause mortality will be sourced from the USA Human Mortality Database.[8] Mortality rates will be adjusted to reflect increased all-cause mortality for patient with treatment-resistant depression.[9]

Table 6: Mortality Inputs

Parameter	Value	Source
All-cause mortality in inadequately treated treatment-resitant depression	1002 per 100,000 person-years	Olin 2012
All-cause mortality in inadequately treated treatment-resitant depression	493 per 100,000 person-years	Olin 2012
All-Cause Mortality **Male, 45-54 years old** **Female, 45-54 years old**	Varies by age and gender 521.9 per 100,000 person-years 314.8 per 100,000 person years	USA Human Mortality Database

Adverse Events

Adverse events on esketamine, although common, were reported as being short-term post dose and resolved shortly after administration of the treatment episode.[4,7] Treatment-emergent adverse events appeared to be fewer in the flexible dose study[7] when compared with the fixed dose study.[4] As a result, adverse events will not be explicitly incorporated into the model. Adverse events leading to treatment discontinuation will be reflected in treatment failure rates, as described in the section above on discontinuation.

Health State Utilities

Table 7 shows health state utilities used in the model. Health state utilities will be derived from publicly available literature. We will use consistent health state utility values across treatments evaluated in the model. Utility gains from improvement in treatment-resistant depressive symptoms will be modeled based on utility estimates available in the literature of having no depression (effective treatment), mild to moderate depression (partly effective treatment), and severe depression (treatment not effective). Age-adjusted utilities will be derived from US adult population values for patients having no depression (effective treatment).[10] Utilities will be adjusted to reflect the presence of mild to moderate or moderately severe to severe depression based on results from a study assessing depression severity using the Patient Health Questionnaire (PHQ-9) and utility using the EQ-5D in patients with major depressive disorder and receiving transcranial magnetic stimulation using a crosswalk provided in the open input period (Janssen letter).[11]

Table 7: Health State Utilities

Parameter	Value	Source
No depression **Age 40-49 years old** **Male, not age specific** **Female, not age specific**	Varies by age and gender 0.87 0.88 0.85	Sullivan 2006
Mild to moderate (average of mild and moderate)	0.73	Janicak 2013
Severe (average of moderately severe and severe)	0.51	Janicak 2013

Drug Utilization

Esketamine drug utilization, used to determine costs, is shown in Table 8. The following inputs will be used to model drug utilization and associated costs:

- Duration of treatment
- Schedule of doses for each drug in each regimen
- Protocol dosage for the indication *(include information on vial sharing, dose wastage as applicable)*

Table 8. Treatment Regimen Recommended Dosage

Generic Name	Esketamine	Source
Brand name	Investigational	
Manufacturer	Janssen	
Route of administration	Intranasal (clinic use only)	
Initial Dosing	56 mg twice weekly (33% of patients) 84 mg twice weekly (67% of patients)	TRANSFORM 2
Maintenance Dosing	56 mg once weekly (14.2% of patients) 84 mg once weekly (28.7% of patients) 56 mg every other week (18.8% of patients) 84 mg every other week (38.2% of patients)	Weighted average of patients receiving 56 and 84 mg dose from TRANSFORM 2 and mean dosing frequency from Table 2 (averaging those who changed back and forth from weekly to every other week) in the SUSTAIN 2 trial.

Cost Inputs

Drug Costs

Pricing for esketamine is unknown because it is still under FDA review and a price has not been announced by the manufacturer. If pricing is not available at the time of the analysis, we will calculate annual prices required to reach thresholds between $50,000 and $150,000 per QALY gained. Costs for alternative treatment used in the model will be derived from Russell et al.,[5] using pharmaceutical-specific costs of the corresponding treatment line and inflated to 2018 USD, shown in Table 9.

Table 9. Alternative Treatment Costs

Current Number of Depression Regimen Medication Changes*	Annual Cost (Inflated to Current USD)	Source
First alternative treatment (i.e. fifth treatment)	$4,389	Russell et al. J Clin Psychiatry. 2004; 65(3):341-7.
Second alternative treatment (i.e. sixth treatment)	$5,057	Russell et al. J Clin Psychiatry. 2004; 65(3):341-7.
Third alternative treatment (i.e. seventh treatment)	$5,635	Russell et al. J Clin Psychiatry. 2004; 65(3):341-7.

*Patients start in model beginning fourth treatment. Failing the fourth treatment results in first alternative treatment (fifth treatment in the current depression episode) being initiated.

Non-Drug Costs

Non-drug depression related costs will be represented by the level of treatment resistance defined by the number of depression medication regimen failures, inflated to 2018 USD and shown in Table 10.

Table 10. Alternative Treatment Costs

Current Number of Depression Regimen Medication Changes*	Annual Cost (Inflated to Current USD)	Source
Initial treatment with esketamine/new antidepressant or new antidepressant (i.e. fourth treatment)	$10,926	Russell et al. J Clin Psychiatry. 2004; 65(3):341-7.
First alternative treatment (i.e. fifth treatment)	$12,624	Russell et al. J Clin Psychiatry. 2004; 65(3):341-7.
Second alternative treatment (i.e. sixth treatment)	$13,437	Russell et al. J Clin Psychiatry. 2004; 65(3):341-7.
Third alternative treatment (i.e. seventh treatment)	$14,051	Russell et al. J Clin Psychiatry. 2004; 65(3):341-7.

*Patients start in model beginning fourth treatment. Failing the fourth treatment results in first alternative treatment (fifth treatment in the current depression episode) being initiated.

2.6 Model Outcomes

Model outcomes will include life years (LYs) gained, QALYs gained and total costs for each intervention over a lifetime time horizon. Costs and QALYs will also be reported by health state to better describe the costs and benefits of effective depression treatment on the treatment of treatment-resistant depression. All the costs and QALYs will be reported as discounted values, using a discount rate of 3% per annum.

2.7 Model Analysis

Cost-effectiveness will be estimated using incremental cost-effectiveness ratios, with incremental analyses comparing antidepressant + esketamine to new antidepressant + no additional treatment. The analyses will be conducted from a health care sector perspective in the base-case analyses. Additionally, we will present a cost per life-year gained and cost per depression-free year. A lifetime time horizon will be used.

Sensitivity Analyses

We will conduct one-way sensitivity analyses on all model inputs to identify the impact of parameter uncertainty and key drivers of model outcomes. Probabilistic sensitivity analyses will also be performed by jointly varying sensitive model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. We will also perform threshold analyses for drug costs across a range of incremental cost-effectiveness ratios (from $50,000 to $150,000 per QALY).

Scenario Analyses

If data allow, we will consider conducting scenario analyses that include:

1) Modified/restricted societal perspective that includes productivity losses.

Model Validation

We will use several approaches to validate the model. First, we will provide preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we will refine data inputs used in the model, as needed. Second, we will vary model input parameters to evaluate face validity of changes in results. We will perform model verification for model calculations using internal reviewers. As part of ICER's efforts in acknowledging modeling transparency, we will also share the model with the manufacturers for external verification around the time of publishing the draft report for this review. Finally, we will compare results to other cost-

effectiveness models in this treatment area. The outputs from the model will be validated against the trial/study data of the interventions and also any relevant observational datasets.

3. Cost Analysis Methods

3.1 Cost Analysis Overview

A network meta-analysis comparing esketamine to ketamine was not possible due to substantial heterogeneity in the patients involved in these studies. A cost-analysis will be conducted to compare the expected direct treatment costs for treatment with esketamine or ketamine. For the cost analysis, we will develop a *de novo* deterministic model, informed by an analysis of resources used by intravenous ketamine clinics and anticipated resources used delivering intranasal esketamine in a clinic setting. Costs will be applied to resources utilized, using published cost and fee structures. To estimate physician and clinic fees, we will utilize the CY 2019 Medicare Physician Fee Schedule.[12] Supplies for intravenous drug administration will be determined from a pricing source still to be determined. Labor costs for drug preparation will be included in the analysis, provided data is available to estimate these costs.

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