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EMA/141382/2021
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Spravato

International non-proprietary name: esketamine

Procedure No. EMEA/H/C/004535/II/0001/G

## Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted

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# List of abbreviations

| | |
|---|---|
| ΔMADRS | change from baseline in MADRS total score |
| ADR | adverse drug reaction |
| AE | adverse event |
| ALT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| ANOVA | Analysis of variance |
| ASA | American Society of Anesthesiologists |
| ATC | Anatomical Therapeutic Chemical |
| $AUC_{inf}$ | Area under the plasma concentration vs time curve from time 0 to infinity |
| BDNF | Brain-derived neurotrophic factor |
| BHS | Beck Hopelessness Scale |
| BOCF | baseline observation carried forward |
| BP | blood pressure |
| BQL | Below Quantification Limit |
| CADSS | Clinician Administered Dissociative States Scale |
| C-CASA | Columbia Classification Algorithm for Suicide Assessment |
| CGI-SR-I | Clinical Global Impression – Imminent Suicide Risk |
| CGI-SR-LT | Clinical Global Impression – Long-term Suicide Risk |
| CGI-SS | Clinical Global Impression – Severity of Suicidality |
| CGI-SS-R | Clinical Global Impression – Severity of Suicidality - Revised |
| CI | confidence interval |
| CIOMS | Council for International Organization of Medical Sciences |
| CL | Clearance |
| CLn/F | Apparent clearance of noresketamine |
| $C_{max}$ | Maximum concentration |
| CrI | credible interval |
| CSR | clinical study report |
| CV | Coefficient of variation |
| CWRES | Conditional weighted residuals |
| DB | Double-blind |
| eCRF | electronic case report form(s) |
| DBP | diastolic blood pressure |
| DF | Degree of freedom |
| DNA | deoxyribonucleic acid |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders (5th edition) |
| EBE | Empirical Bayes Estimates |
| ECG | electrocardiogram |
| ER | Emergency Room |
| EQ-5D-5L | European Quality of Life Group, 5-Dimension, 5-Level |
| EQ-VAS | European Quality of Life Group, Visual Analogue Scale |
| EU | European Union |
| FDA | Food and Drug Administration |
| FOCE | First-order conditional estimation |
| FoST | frequency of suicidal thinking |
| FRn | Esketamine absorbed partly directly through the nasal cavity |
| GAMP | Good Automated Manufacturing Practice |

| | |
|---|---|
| GCP | Good Clinical Practice |
| GOF | Goodness of fit |
| HP3 | High Performance Pharmacometrics Platform |
| HRUQ | Healthcare Resource Use Questionnaire |
| ICH | International Conference on Harmonisation |
| IDMC | Independent Data Monitoring Committee |
| IEC | Independent Ethics Committee |
| IIV | Inter-individual variability |
| IM | Intramuscular |
| IN | Intranasal |
| IPRED | Individual predited concentration |
| IRB | Institutional Review Board |
| IRT | item response theory |
| IWRS | interactive web response system |
| kel | Esketamine metabolism rate-constant |
| -2LL | -2 Log-likelihoodLOCF last observation carried forward |
| LS | least squares |
| MAA | Marketing Authorisation Application |
| MADRS | Montgomery Asberg Depression Rating Scale |
| MAP | Maximum a posteriori |
| MDD | major depressive disorder |
| MDSI | MDD in patients assessed to be at imminent risk for suicide |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MINI | Mini International Psychiatric Interview |
| MMRM | mixed-effects model for repeated measures |
| MOAA/S | Modified Observer's Assessment of Alertness/Sedation |
| NDA | New Drug Application |
| NMDA | N-methyl-D-aspartate |
| NONMEM® | Nonlinear mixed effects modeling |
| NPC | Numerical predictive check |
| NPDE | Normalized prediction distribution errors |
| OFV | Objective function value |
| OL | open-label |
| PADER | Periodic Adverse Drug Experience Report |
| pcVPC | Prediction corrected visual predictive check |
| PD | pharmacodynamic(s) |
| PK | pharmacokinetic(s) |
| PKPD | Pharmacokinetic-pharmacodynamic |
| PO | Per os |
| PopPK | Population pharmacokinetics |
| PRED | Population predicted concentration |
| PRO | patient-reported outcome |
| Qh | Hepatic liver blood flow |
| QLDS | Quality of Life in Depression Scale |
| QQ | Quantile-Quantile |
| QTc | corrected QT |
| QTcB | QT corrected according to Bazett's formula |
| QTcF | QT corrected according to Fridericia's formula |
| RSE | Relative standard error |

| | |
|---|---|
| RUV | Residual unknown variability |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SBP | systolic blood pressure |
| SD | standard deviation |
| SE | standard error |
| SIBAT | Suicide Ideation and Behavior Assessment Tool |
| SmPC | Summary of Product Characteristics |
| SNRI | Serotonin and Norepinephrine Reuptake Inhibitors |
| SOC | standard of care |
| SSRI | Selective Serotonin Reuptake Inhibitors |
| TEAE | treatment-emergent adverse event |
| TEMA | treatment-emergent markedly abnormal |
| TRD | treatment-resistant depression |
| TSMQ-9 | Treatment Satisfaction Questionnaire for Medication |
| ULN | upper limit of normal |
| US | United States |
| V | Volume of distribution |
| VPC | Visual predictive check |
| Vss/F | Apparent steady state volume |
| WHO | World Health Organization |

# 1. Background information on the procedure

## *1.1. Type II group of variations*

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International N.V. submitted to the European Medicines Agency on 14 January 2020 an application for a group of variations.

The following variations were requested in the group:

| **Variations requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| B.II.e.5.a.2 | B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes | Type IB | None |
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I, II, IIIA, IIIB and IV |

The group of variations requested amendments to the Summary of Product Characteristics, Annex II, Labelling, Package Leaflet and addition to Annex IV and amendment to the Risk Management Plan (RMP).

C.I.6(a): Extension of Indication to include a new indication for Spravato for the rapid reduction of depressive symptoms in adult patients with a moderate to severe depressive episode of MMD who have current suicidal ideation with intent.

B.II.e.5.a.2: Addition of a new pack size (multipack) of 24 nasal spray devices (multipack of 8 packs of 3 nasal spray devices) corresponding to 4 weeks of treatment in the new indication.

As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 6.5 the SmPC are updated. The RMP version 2.1 has also been submitted.

The Package Leaflet and labelling are updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to clarify the wording in Annex II.D.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed and accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of Hungary.

## *Information on paediatric requirements*

Pursuant to Article 7 of Regulation (EC) No 1901/2006, this variation application includes the current EMA Decision (P/0238/2019 dated 16 July 2019) on the agreement of a paediatric investigation plan (PIP) (Mod 1.10/EMA PIP Decision) for esketamine.

At the time of submission of this application, the PIP has not yet been completed as some measures are deferred. On 23 March 2018 and in accordance with Articles 23 and 24 of the Paediatric Regulation, the applicant received confirmation from EMA of a positive partial compliance check for 2 PIP measures due to be completed prior to the variation submission date in January 2020: a non-clinical study measure (Study 1) and an extrapolation, modelling and simulation measure (Study 5). None of the remaining PIP measures are due to be completed until 2022 at the earliest.

**Table 1: An overview table of the PIP results is provided below**.

| | **Measure** | **Status** | **Location in dossier** |
|---|---|---|---|
| Non-clinical studies | Study 1:<br>Neurotoxicity study in juvenile rats to explore potential brain injury (TOX13050) | A partial compliance check on the non-clinical study measure was performed and adopted on 23 March 2018 (EMEA-C1-001428-PIP03-15) | Seq0000/Mod1.10 |
| Clinical studies | Study 2:<br>Double-blind, double-dummy, randomised dose-response study to evaluate the efficacy and safety of intranasal esketamine compared with psychoactive placebo in adolescents with major depressive disorder assessed to be at imminent risk for suicide, with an initial 8-week post-treatment follow-up as part of a full 6-month post-treatment follow-up<br>(ESKETINSUI2002). | Study 2 – completion deferred until February 2022 | |
| | Study 3:<br>Double-blind, double-dummy, randomised study to evaluate the efficacy and safety of intranasal esketamine compared with psychoactive placebo in adolescents with major depressive disorder (MDD) assessed to be at imminent risk for suicide, with an initial 8-week post-treatment follow-up as part of a full 6-month post-treatment follow-up (54135419SUI3003). | Study 3 – completion deferred until April 2026 | |
| | Study 4: | Study 4 – completion | |

| | | | |
|---|---|---|---|
| | Open-label study to evaluate the safety of repeated doses of intranasal esketamine in adolescents with major depressive disorder (MDD) assessed to be at risk for suicide. | deferred until August 2024 | |
| Extrapolation, modelling and simulation studies | Study 5:<br>Population PK modelling and simulation study<br>A partial compliance to identify possible covariates that have an influence on esketamine exposure after intranasal administration and to support dose selection for adolescents | A partial compliance check on the modelling and simulation study measure was performed and adopted on 23 March 2018 (EMEA-C1-001428-PIP03-15) | Seq0000/Mod1.10 |

The applicant is also currently developing esketamine for the treatment of adolescents (12 to <18 years) with major depressive disorder in patients assessed to be at imminent risk for suicide (MDSI). The Paediatric Investigational Plan (EMEA-001428-PIP03-15) was agreed with the Paediatric Committee (PDCO) in December 2016. The applicant is planning to complete 3 paediatric clinical studies in adolescents with MDSI, including 1 Phase 2 and 1 Phase 3 double-blind and psychoactive placebo-controlled studies and 1 open-label Phase 3 safety study. The entire paediatric program is expected to take approximately 8 years to complete. Approximately one-half of the planned 145 subjects have been randomized in the ongoing Phase 2 proof-of-concept study. As agreed with PDCO, the start of the two Phase 3 studies has been deferred pending completion of the Phase 2 study.

## *Information relating to orphan market exclusivity*

## Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

## Derogation(s) of market exclusivity

N/A

## *Scientific advice*

The applicant received scientific advice on the MDSI program from the CHMP on 19 December 2013 (EMEA/H/SA/2406/1/FU/1/2013/II), with follow-up scientific advice received on 10 November 2016 (EMEA/H/SA/2406/1/FU/4/2016/II). The applicant also received qualification advice for the Suicide Ideation and Behavior Assessment Tool (SIBAT) on 24 July 2014 (EMEA/H/SAB/051/1/QA/2014) and on 13 December 2018 (EMEA/H/SAB/051/1/FU/1/2018). The applicant has also received separate scientific

advice from the CHMP on quality (EMEA/H/SA/2406/1/FU/3/2015/I) and clinical pharmacology (EMEA/H/SA/2406/1/FU/5/ 2017/I) aspects of the development program for esketamine.

## *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Martina Weise Co-Rapporteur: Johann Lodewijk Hillege

| Timetable | Actual dates |
|---|---|
| Submission date | 14 January 2020 |
| Start of procedure: | 1 February 2020 |
| CHMP Co-Rapporteur Assessment Report | 30 March 2020 |
| CHMP Rapporteur Assessment Report | 27 March 2020 |
| PRAC Rapporteur Assessment Report | 2 April 2020 |
| Updated PRAC Rapporteur Assessment Report | 7 April 2020 |
| PRAC Outcome | 17 April 2020 |
| CHMP members comments | n/a |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 23 April 2020 |
| Request for supplementary information (RSI) | 30 April 2020 |
| CHMP Rapporteur Assessment Report | 21 September 2020 |
| PRAC Rapporteur Assessment Report | 21 September 2020 |
| Updated PRAC Rapporteur Assessment Report | 9 October 2020 |
| PRAC Outcome | 1 October 2020 |
| CHMP members comments | n/a |
| Updated CHMP Rapporteur Assessment Report | 9 October 2020 |
| 2nd Request for supplementary information (RSI) | 15 October 2020 |
| PRAC Rapporteur Assessment Report | 19 November 2020 |
| PRAC members comments | n/a |
| Updated PRAC Rapporteur Assessment Report | 19 November 2020 |
| CHMP Rapporteur Assessment Report | 25 November 2020 |
| PRAC Outcome | 26 November 2020 |
| CHMP members comments | n/a |
| Updated CHMP Rapporteur Assessment Report | n/a |
| Opinion | 10 December 2020 |

# 2. Scientific discussion

## *2.1. Introduction*

SPRAVATO (esketamine) nasal spray (hereafter referred to as "esketamine") is currently approved in the European Union (EU), the United States (US), and other markets for the treatment of adults with treatment-resistant depression (TRD). The applicant (Janssen Research & Development) has also investigated esketamine for the treatment of adults with Major Depressive Disorder (MDD) assessed to be at imminent risk for suicide (hereafter referred to in this document as MDSI).

Suicidal ideation and behaviour (SIB) is an umbrella term, which includes a range of passive and active thoughts about self-harm, with deliberate consideration or planning of possible techniques of causing one's own death, with or without suicidal intent (Posner, Oquendo et al., 2007). Suicidal ideation or behavior can be found in disorders such as schizophrenia, bipolar, depressive or anxiety. According to DSM-5, suicidal behavior disorder is defined when the individual has made a suicide attempt within the last 24 months and the attempt does not meet the criteria of a non-suicidal self-injury.

The ICD code R458 is used to code Suicidal ideation. Suicidal ideation, also known as suicidal thoughts, concerns thoughts about or an unusual preoccupation with suicide. The range of suicidal ideation varies greatly from fleeting thoughts, to extensive thoughts, to detailed planning, role playing (e.g., standing on a chair with a noose), and incomplete attempts, which may be deliberately constructed to not complete or to be discovered, or may be fully intended to result in death, but the individual survives (e.g., in the case of a hanging in which the cord breaks) (ICD-10 codes, accessed March 2020).

It should be noted that the term major depressive disorder in patients assessed to be at imminent risk for suicide (MDSI) does not currently exist in the literature or the clinical practice apart from data related to the investigation of esketamine in this specific group of depressed patients (identified by the answer yes to the questions B3 and B10 of the MINI, please see below). For the rest of the document it will be referred to as the so-called MDSI.

After discussions at CHMP it was considered more appropriate to avoid any reference to suicidal thoughts, suicidal ideation or behaviour in the therapeutic indication.

### 2.1.1. Problem statement

It has been estimated that nearly 45,000 people in the United States (CDC, 2018) and more than 800,000 worldwide die by suicide each year (GBD 2015).

It is suggested in the literature that 80% of the patients who committed suicide had contact with primary care clinicians within one year of their death and only 25% to 30% had contact with psychiatric clinicians within the year of their death (Stene-Larsen et al. 2019 and Walby et al 2018)

It has been also reported that there are no data to support that routine screening for suicide reduces mortality. In addition, it cannot be predicted with a high degree of sensitivity or specificity, which patients who have suicidal thoughts will proceed to have a suicide attempt (Hyman 1994 and Sher 2004) (Uptodate.com Suicidal ideation and behavior in adults, accessed March 2020).

According to the applicant, research in the field of suicidal depression indicates that patients with MDD who have active suicidal ideation with intent represent a particularly ill subpopulation. It can be agreed that compared with MDD patients without suicidal ideation, MDD patients with suicidal ideation have more severe symptoms of depression, higher scores of hopelessness, anhedonia, worthlessness, and lack of optimism, as well as greater psychiatric comorbidity, higher rates of insomnia, alcohol

dependence/abuse, poor social support, worse functioning and quality of life, and more prior suicide

attempts. Some physiological differences [e.g., elevated levels of inflammation (interleukin-6, C-reactive protein)] have also been reported in MDD patients who have high levels of suicidal ideation versus patients whose levels of suicidal ideation were lower. These findings suggest that depression with suicidal ideation is most likely a more severe form of the illness that requires rapid and aggressive treatment to help alleviate the debilitating symptoms these patients are experiencing.

It is postulated that nearly all patients with MDD who attempt or die by suicide have suicidal ideation prior to the event, and individuals with more severe ideation, defined as intent or intent with plan, are at a greater risk of suicide or suicide attempt than those without suicidal intent. Importantly, the interval between the onset of suicidal ideation and suicide attempt is often very short (minutes to hours), highlighting the need for urgent treatment.

## *Disease or condition*

Depression is the leading cause of disability worldwide and a major contributor to the overall global burden of disease. Major Depressive Disorder is a serious, disabling psychiatric illness that can have a devastating impact on the lives of patients. Moreover, MDD is the psychiatric condition most commonly associated with suicide. Suicide-related morbidity and mortality in patients with MDD are a major public health concern. The reported prevalence of suicidal ideation in adult patients with MDD is as high as 60% and the lifetime prevalence of attempted suicide in this population ranges between 10% and 20%. Further, the lifetime risk of completed suicide is estimated to be 3.4% in this population.

## *State the claimed therapeutic indication*

The applicant was initially seeking approval of SPRAVATO for the following indication:

*"Esketamine is indicated, as acute short-term treatment, co-administered with oral antidepressant therapy, for the rapid reduction of depressive symptoms in adult patients with a moderate to severe episode of MDD who have current suicidal ideation with intent."*

## *Epidemiology and risk factors, screening tools/prevention*

Reported rates of suicides probably underestimate the true burden because of misclassification of deaths. Suicides may be misclassified as accidents or unintentional because of uncertainty about the decedent's intent as well as sensitivity about suicide and social stigma; in some countries, suicide is illegal. Misclassification may also occur because of legal and procedural issues related to death registration.

Worldwide, the crude suicide mortality rates dropped between 2000 and 2016, by 16% in men and 20% in women. In 2016, nearly 800 000 deaths were due to suicide, equivalent to an annual global crude suicide mortality rate of 10.6 per 100 000 population or one person every 40 seconds (WHO.int mental health/suicide accessed March 2020).

Suicide is considered the 14$^{th}$ leading cause of global mortality and the causes of death from self-harm can be nearly 250 (Uptodate.com Suicidal ideation and behavior in adults, accessed March 2020).

Suicide is a global phenomenon and occurs throughout the lifespan. In fact, 79% of suicides occurred in low- and middle-income countries in 2016. Effective and evidence-based interventions can be implemented at population, sub-population and individual levels to prevent suicide and suicide attempts.

There are indications that for each adult who died by suicide there may have been more than 20 others attempting suicide. This ratio differs widely by country, region, sex, age and method (WHO.int mental health/suicide accessed March 2020).

According to the applicant, the population of patients with MDD who have active suicidal ideation with intent is identifiable by treating clinicians. Monitoring and assessment of suicidality could be a routine part of psychiatric practice, and this evaluation typically includes an assessment of the frequency and severity of suicidal thoughts, intent to act on thoughts, plans and methods, past suicidal behavior, risk and protective factors and impulsivity. The WHO and European MDD guidelines recommend all patients with depression should be assessed for suicidality. The collection of suicidality information is part of the standard mental status examination and there are a number of tools that can be used to identify suicidality in the primary care or emergency room setting [e.g. Columbia Suicide Severity Scale (C-SSRS), Columbia Classification Algorithm of Suicide Assessment (C-CASA), Beck Scale for Suicidal Ideation (BSS), InterSePT Scale for Suicidal Thinking, SAD PERSONS Scale, Manchester Self-Harm Rule (MSHR) , ReACT, which is a modification of MSHR, Sodersjukhuset Self Harm Rule, Beck Hopelessness Scale (Posner, Oquendo et al., 2007; Runeson et al 2017; Turecki and Brent 2016)].

However, despite the number of standardized scales, which have been proposed to evaluate suicide risk, none is associated with a high predictive value. Scales for the suicide risk are mostly used for safety evaluation and not for efficacy. Depression rating scales are commonly used, but these are better measures of the severity of depression than of the suicide risk (Runeson et al 2017).

## *Aetiology and pathogenesis*

Psychiatric illness is a strong predictor of suicide. More than 90 percent of patients who attempt suicide have a psychiatric disorder, and 95 percent of patients who successfully commit suicide have a psychiatric diagnosis.

Severity of psychiatric illness is associated with risk of suicide. As an example, a meta-analysis found that the lifetime risk of suicide is 8.6% in patients who have had a psychiatric inpatient admission involving suicidal ideation, 4% in patients who have had a psychiatric admission for an affective disorder without suicidality, 2.2% in psychiatric outpatients, and less than 0.5% in the general population. Patients who have multiple psychiatric comorbidities appear to be at higher risk than those with uncomplicated depression or an anxiety disorder.

The psychiatric disorders most commonly associated with suicide include depression, bipolar disorder, alcoholism or other substance abuse, schizophrenia, personality disorders, anxiety disorders including panic disorder, posttraumatic stress disorders, and delirium. Among patients with depression, a history of suicide attempts correlated most strongly with feelings of worthlessness. Concurrent personality disorder was also strongly correlated with suicide attempts in depressed patients.

Anxiety disorders more than double the risk of suicide attempts (odds ratio 2.2), and a combination of depression and anxiety greatly increases the risk (odds ratio 17). Symptoms of psychosis (delusions, command auditory hallucinations, paranoia) may increase the risk regardless of the specific diagnosis (Uptodate.com Suicidal ideation and behavior in adults, accessed March 2020).

Alterations in the glutamate signalling may have a role in depression pathogenesis. It has also been suggested that there are differences in the glutamate system between patients with MDD with or without suicidal ideation (Zhao et al. 2016).

In addition, emergence of suicidal ideation and behaviour (SIB) has been reported as an adverse drug reaction following administration of a pharmacological treatment; this is referred to as treatment-emergent SIB. Treatment emergent SIB has been associated with a number of medicines used to treat psychiatric conditions (e.g. antidepressants and some antiepileptics), with other products targeting the CNS (e.g. products for smoking cessation and weight loss) and also with products for non-CNS conditions (e.g. tretinoins, beta blockers and reserpine).

## *Clinical presentation, diagnosis and stage/prognosis*

While the link between suicide and mental disorders (in particular, depression and alcohol use disorders) is well established in high-income countries, many suicides happen impulsively in moments of crisis with a breakdown in the ability to deal with life stresses, such as financial problems, relationship break-up or chronic pain and illness (WHO.int mental health/suicide accessed March 2020).

Patients with expressed suicidal ideation should be queried on the nature of the ideation, plans and methods and intent to act. Risk factors, prior history of suicide attempts, comorbid disorders and family history of suicidality should be assessed (Wasserman et al 2012). Whether a patient will undertake their intent of suicide is difficult to predict, as there are no identified factors which would determine the course of suicidal ideation and behaviour (Pirkis et al. 2002, Kapur et al 2005).

Suicidal behaviours are complex. Research and evidence indicate that no single cause or stressor alone can explain a suicidal act. The foundation of prevention is to understand what puts a person at risk (WHO.int mental health/suicide accessed March 2020).

Depression is the most common psychiatric disorder in people who die by suicide (Hawton et al 2013).

## *Management*

Patients with MDD who have a current suicidal ideation reflect an acutely ill population that requires immediate intervention. Management of the suicidal individual should include:

- Hospitalisation
- Medical stabilization
- Reducing immediate risk and treatment planning
- Managing underlying factors and psychiatric disorders
- Monitoring and follow-up (Uptodate.com Suicidal ideation and behavior in adults, accessed March 2020).

However, there are no approved pharmacological treatments for the rapid reduction of the symptoms of depression and suicidality in such patients. Furthermore, only limited information is available to guide clinical decisions, since this population has typically been excluded from antidepressant drug trials in the past. Current standard practice includes initiation or optimization of oral antidepressants and, frequently, hospitalization. Standard antidepressants may take several weeks to exert their full effect, limiting their

utility in crisis situations. Additionally, hospitalizations are temporary and not completely effective, and the risks for attempted and completed suicide remain high in the weeks immediately after discharge.

Some studies in the literature suggest that patients with MDD who have suicidal ideation show a worse response to antidepressant treatment than MDD patients without suicidal ideation. In one study evaluating the response to a new antidepressant after 6 weeks of treatment in 4,041 depressed outpatients, suicidal patients were less likely to improve or attain remission than non-suicidal patients. In the multivariate analyses, active suicidal ideation (odds ratio] = 1.40; 95% confidence interval [CI]: 1.18-1.65) and a history of suicide attempt (odds ratio = 1.39; 95% CI: 1.16-1.66) were the best predictors of non-remission, independent of the class of antidepressant treatment.

There is a clear unmet medical need for the treatment of patients who suffer from suicidal ideation and/or behaviour. There are options such as structured and protective environment for the management of the suicidality of these patients. If the patients can be identified most important rapid management would still be hospitalization and oral antidepressants. Clear benefit would have been if outpatient pharmacological treatment became possible.

According to the applicant esketamine is expected to address this unmet need due to its novel mechanism of action and demonstrated ability to act quickly (within hours to days) to relieve symptoms of depression in this severely ill population.

### 2.1.2. About the product

There is increasing evidence that the glutamate system and molecular mechanisms related to synaptic and neuronal plasticity may play a role in the pathology of depression, and alterations in glutamate signaling have also been implicated in the pathophysiology of suicide.

Esketamine, the S-enantiomer of racemic ketamine, is a non-selective, noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor. The mechanism by which esketamine exerts its antidepressant effect is unknown, but evidence within the literature suggests that, through NMDA receptor antagonism, esketamine produces a transient increase in glutamate release leading to increases in α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) stimulation and subsequently to increases in neurotrophic signaling that restore synaptic function. Unlike other antidepressant therapies, esketamine's primary antidepressant action does not directly involve monoamine, γ-amino butyric acid-ergic (GABA), or opioid receptors. Thus, esketamine offers a novel mechanism of action compared with other antidepressants.. A summary of pharmacologic evidence supporting the presumed mechanism of action for esketamine in depression has been previously presented in the Marketing Authorisation Application (MAA) submitted for the TRD indication.

Spravato is a nasal spray formulation of esketamine. The esketamine drug product is a clear and colourless solution of esketamine HCl in Water for Injection at a concentration of 161.4 mg/mL and an esketamine base equivalent concentration of 140 mg/mL. The pharmaceutical form approved for marketing is a nasal spray solution with one presentation: a 28-mg single-use nasal spray device.

## 2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The efficacy and safety of esketamine in the proposed indication are primarily supported by the results of two identically designed Phase 3 studies (54135419SUI3001 and 54135419SUI3002) and one Phase 2 proof-of-concept study (ESKETINSUI2001). These studies evaluated the efficacy, safety, and tolerability of esketamine nasal spray (84 mg, given twice weekly over 4 weeks) in addition to comprehensive standard of care (SOC), including antidepressant therapy and initial hospitalization, in adults with MDSI.

In addition, the Council for International Organization of Medical Sciences (CIOMS) reports for deaths, other serious adverse events (SAEs), and pregnancies are provided for an ongoing open-label extension study in adult and elderly subjects with TRD (54135419TRD3008), an ongoing blinded study in pediatric subjects with MDSI (ESKETINSUI2002), and two ongoing blinded studies in adults with TRD (ESKETINTRD2005 and ESKETINTRD3006) (see Table 4 from the Clinical Overview). No new or additional Phase 1 clinical pharmacology or biopharmaceutic studies were conducted for the target indication.

Of note, the short-term and long-term safety data generated in the TRD program are considered supportive for the Type II Variation for patients with moderate to severe MDD who have active suicidal ideation with intent. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnosis of MDD encompasses patients with TRD as well as patients who have active suicidal ideation with intent. Within the DSM-5 there is no diagnostic distinction for these subgroups. In the absence of a fully elucidated etiology of depression, a shared pathophysiology of the primary condition, MDD, can be assumed for these populations. The safety profile of esketamine has been thoroughly characterized within the TRD program, which includes extensive exposure to esketamine. Across the completed and ongoing Phase 3 TRD studies as of 31 December 2018, exposure to esketamine nasal spray was 611 patient-years at the 56-mg dose level and 1,151 patient-years at the 84-mg dose level.

A pre-submission meeting was held with the Rapporteur (BfArM) and Co-Rapporteur (MEB) on 25 October 2019. The CHMP indicated that the clinical package in principle appeared adequate to support the submission of a Type II new indication variation. The adopted meeting minutes have been provided.

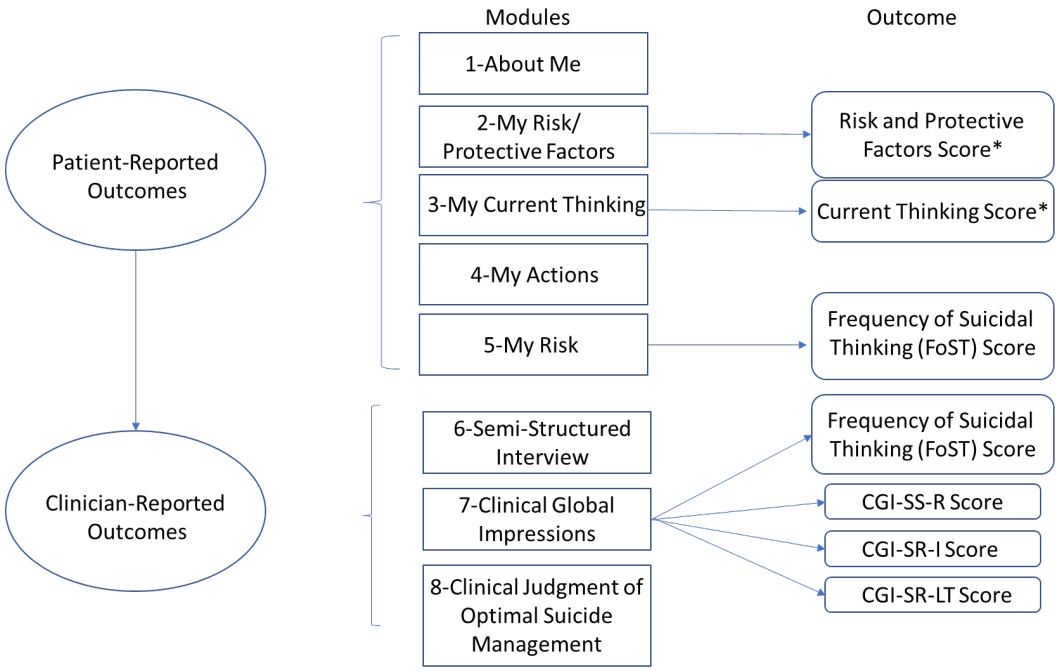
The applicant received scientific advice on the MDSI program from the CHMP on 19 December 2013 (EMEA/H/SA/2406/1/FU/1/2013/II), with follow-up scientific advice received on 10 November 2016 (EMEA/H/SA/2406/1/FU/4/2016/II). The applicant also received qualification advice for the Suicide Ideation and Behavior Assessment Tool (SIBAT) on 24 July 2014 (EMEA/H/SAB/051/1/QA/2014) and on 13 December 2018 (EMEA/H/SAB/051/1/FU/1/2018). The applicant has also received separate scientific advice from the CHMP on quality (EMEA/H/SA/2406/1/FU/3/2015/I) and clinical pharmacology (EMEA/H/SA/2406/1/FU/5/ 2017/I) aspects of the development program for esketamine.

In the provided scientific advices, the appropriateness of the sought indication was discussed. The CHMP highlighted that the wording of the indication depends largely on whether correlation of depressive symptoms and suicidality is shown. Design of the Phase 2 and Phase 3 studies were also discussed, and the applicant's strategy with respect to clinical data package and filing of the application. The CHMP considered in principle the proposed patient population acceptable, however it was emphasized that the included patient population should reflect the real-life patients admitted to emergency care due to suicidality. With respect to endpoints, it was emphasized that the SIBAT should be validated before the commencement of Phase 3, should the applicant wish to use it as a key secondary endpoint to measure suicidality. Other relevant endpoints to address suicidality were also mentioned (e.g. MADRS-SI sub-item).

With respect to endpoints, it was emphasized that the SIBAT should be validated before the commencement of Phase 3, should the applicant wish to use it as a key secondary endpoint to measure suicidality. Other relevant endpoints to address suicidality were also mentioned (e.g. MADRS-SI sub-item).

Overview of the SIBAT tool is provided in **Figure 1**and **Table 2**

**Figure 1 Overview of the SIBAT**




* Risk and Protective Factors Score and Current Thinking Score are exploratory outcomes
CGI-SS-R Clinical Global Impression of Severity of Suicidality (Revised)
CGI-SR-I Clinical Global Impression immediate suicide risk
CGI-SR-LT Clinical Global Impression long-term suicide risk

**Table 2 Overview of SIBAT PRO and ClinRO Modules.**

| Module | Objective | Number of Items | Recall Period |
|---|---|---|---|
| Introduction | Determines if the patient is present for visit or the reason for a missed visit | 1 item | Current |
| Patient Modules | | | |
| About Me (Module 1) | Patient demographic information and relevant lifetime risk factors for suicide, including personal and family history | 29 items | Lifetime |
| My Risk/ Protective Factors (Module 2) | Patient risk and protective factors experienced during the previous 7 days | 25 items | Past 7 days |
| My Current Thinking (Module 3) | Current patient suicidal thinking, relevant risk, and protective factors | 48 items | Current |
| My Actions (Module 4) | Patient self-report of suicide behaviors since previous visit. Includes characterization of suicidal behavior including method, plan, and intent | 14 items | Since last visit |
| My Risk (Module 5) | Patient self-assessment of suicide risk | 5 items | Past 7 days; Current |
| Clinician Modules | | | |
| Clinician Semi-Structured Interview (Module 6) | Questioning related to amplification and clarification of patient-reported information, including areas of reported risk and inconsistencies of the report | Approximately 19 items | Current |
| Clinical Global Impressions (Module 7) | Based on the patient-reported material and the semi-structured interview and any other information available to the clinician, provide the best understanding of the patient's suicidality and suicide risk | 4 items | Current |
| Clinical Judgment of Optimal Suicide Management (Module 8) | Based on the patient-reported material and the semi-structured interview and any other information available to the clinician, provide the best understanding of the patient's optimal management in an ideal setting | 1 item | Current |

Abbreviations: ClinRO: Clinician-reported outcome; PRO: Patient-reported outcome; SIBAT: Suicidal Ideation and Behavior Assessment Tool

The CGI-SS-R summarizes the clinician's overall impression of severity of suicidality on a 7-point scale from 0 (normal, not at all suicidal) to 6 (among the most extremely suicidal patients), based on the totality of information available to the clinician, including information from the completed modules of the SIBAT. In the qualification advice for SIBAT, the CHMP concluded that although the SIBAT derived CGI-SS-R has face validity, a confirmation that it can be used as key secondary efficacy endpoint cannot be given. It was considered that further research is needed to evaluate the responsiveness of the SIBAT global clinical ratings to changes in clinical status. As such the planned phase 3 studies with intranasal esketamine in patients with MDD at imminent risk of suicide were considered to be an important step.

The applicant is developing esketamine nasal spray for the treatment of major depressive disorder with imminent risk for suicide (MDSI) in adolescents (12 to <18 years). The Paediatric Investigation Plan (PIP) was agreed with the Paediatric Committee (PDCO) in December 2016. The applicant is planning to conduct 3 paediatric clinical studies in adolescents with MDSI, including 2 double-blind (DB) and psychoactive placebo-controlled clinical studies and 1 open-label (OL) safety study. Approximately half of the planned 145 subjects have been randomized in the ongoing Phase 2 proof-of-concept study. The entire paediatric program is expected to take approximately 8 years to complete.

### 2.1.4. General comments on compliance with GCP

There is a statement from the applicant that all studies included in this submission were conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, applicable regulatory requirements, and in compliance with the respective protocols.

This was considered sufficient by the CHMP.

## *2.2. Non-clinical aspects*

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

### 2.2.1. Ecotoxicity/environmental risk assessment

The applicant submitted a justification for absence of an environmental risk assessment for the esketamine MDSI indication variation application.

The patient population related to the current submission is adults with Major Depressive Disorder (MDD) assessed to be at imminent risk for suicide (hereafter referred to as MDSI). MDSI is a subgroup of the patient population of depressive disorders (i.e. MDD) as defined in the initial submission for the TRD indication. As such, the MDSI indication does not extend the depressive disorder population, and therefore there is no increase in environmental exposure versus the exposure calculated for the current approved TRD indication. Consequently, the conclusions of the initial ERA are still valid and no updated ERA for esketamine is required to support this MDSI variation application submission.

A complete ERA for the active ingredient esketamine was provided within procedure EMEA/H/C/4535. Esketamine was not expected to pose a risk to the surface water, groundwater and sediment compartment as all risk quotients are below 1. Assessment of the risk to the terrestrial compartment was considered not necessary. Esketamine was not a potential PBT substance. However, the active substance has to be classified as very persistent in sediments due to the half-life (DT50) of 738.4 days (normalised to 12 °C, the average outdoor temperature in the EU).

The new indication does not lead to a significant increase in environmental exposure of esketamine and therefore the CHMP agreed with the applicant, an update of the existing ERA is not required.

### 2.2.2. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of esketamine.

Any changes in the dosage and duration of treatment will require an updated ERA.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

The clinical pharmacology, efficacy, and safety of esketamine is supported by a large global clinical development program, including 19 Phase 1 studies, two Phase 2a studies with existing IV formulations

of esketamine or ketamine, six completed Phase 2 and 3 studies with esketamine nasal spray in patients with TRD (a Phase 2 dose-ranging study, three short-term Phase 3 studies, and two long-term Phase 3 studies), and one ongoing Phase 3 open-label (OL) safety extension study. Over 1,700 adults were exposed to esketamine nasal spray in the completed Phase 2 and 3 studies in adults with TRD. The newly proposed indication is supported by two phase pivotal and one phase 2 studies (Table 3).

For ease of review, in the document, Studies ESKETINSUIxxxx and 54135419SUIxxxx are abbreviated as Studies SUIxxxx, and studies ESKETINTRDxxxx and 54135419TRDxxxx are abbreviated as Studies TRDxxxx.

## GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

- Tabular overview of clinical studies

**Table 3 (Summary of Clinical Efficacy): Table of Completed Studies in the Esketamine MDSI Development Program**

| Study | Study Description<br>Primary Efficacy Endpoint<br>Key Secondary Efficacy Endpoint (If Applicable) | Study Treatments<br>Duration of Treatment | Number of Subjects Evaluated for Efficacy |
|---|---|---|---|
| **Phase 3 Studies** | | | |
| SUI3001 and SUI3002 | Randomized, double-blind, placebo-controlled, multi-center study that evaluated the efficacy and safety of esketamine nasal spray in addition to comprehensive SOC[a] for the rapid reduction of symptoms of MDD, including suicidal ideation, in adult subjects with MDD assessed to be at imminent risk for suicide<br><br>Primary Endpoint: Change in MADRS total score from baseline (Day 1, predose) to 24 hours after the first dose<br><br>Key Secondary Efficacy Endpoint: Change in CGI-SS-R score from baseline (Day 1, predose) to 24 hours after the first dose | Esketamine nasal spray 84 mg/ twice weekly + SOC<br><br>Placebo nasal spray/ twice weekly + SOC<br><br>Duration of treatment: 25 days | SUI3001:<br>Esketamine + SOC: n=112<br>Placebo + SOC: n=112<br><br>SUI3002:<br>Esketamine + SOC: n=114<br>Placebo + SOC: n=113 |
| **Phase 2 Study** | | | |
| SUI2001 | Randomized, double-blind, placebo-controlled, multi-center study that evaluated the efficacy and safety of esketamine nasal spray in addition to comprehensive SOC[a] for the rapid reduction of symptoms of MDD, including suicidal ideation, in adult subjects assessed to be at imminent risk of suicide<br><br>Primary Endpoint: Change in MADRS total score from baseline (Day 1, predose) to 4 hours after the first dose | Esketamine nasal spray 84 mg/ twice weekly + SOC<br><br>Placebo nasal spray/ twice weekly + SOC<br><br>Duration of treatment: 25 days | Esketamine + SOC: n=35<br>Placebo + SOC: n=31 |

CGI-SS-R = Clinical Global Impression – Severity of Suicidality - Revised; MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = major depressive disorder; MDSI = MDD in patients assessed to be at imminent risk for suicide;
SOC = standard of care

[a] Comprehensive SOC included initial hospitalization (5 days recommended) and the initiation or optimization of antidepressant therapy (antidepressant monotherapy or antidepressant plus augmentation therapy), enhanced by twice-weekly study visits as well as permitted concomitant medications and psychotherapy. In Study SUI3001 and most countries in Study SUI3002, the recommended duration of hospitalization was 5 days; in some countries in Study SUI3002, the recommended duration was 14 days to be consistent with local practice.

Cross-reference: TRD/Mod5.3.5.1/SUI2001/CSR, Mod5.3.5.1/SUI3001/CSR, and Mod5.3.5.1/SUI3002/CSR.

**Table 4 Modified (Clinical Obverview): Ongoing Studies of Esketamine Included in the Type II Variation Application for MDSI**

| Study ID | Study Design | Enrolled/ Treated w/esketamine |
|---|---|---|
| **Ongoing Studies in Subjects with TRD and in Subjects with MDSI** | | |
| Open-Label Long-term Extension Safety Study[b] | | |
| TRD3008 | Multicenter, OL long-term extension safety study of esketamine in subjects with TRD<br>Study treatment: esketamine (flexible dose: 28[c], 56, or 84 mg) + oral AD<br>Duration of treatment: Variable (median exposure as of 31 Dec 2018: 15.4 months) | 1,140 ESK (as of 31 Dec 2018) |
| Ongoing, Blinded Efficacy and Safety Studies[d] | | |
| SUI2002 | Randomized, DB, psychoactive placebo[e]-controlled study of esketamine for the rapid reduction of the symptoms of major depressive disorder, including suicidal ideation, in pediatric subjects assessed to be at imminent risk for suicide<br>Study treatment: esketamine (28, 56 or 84 mg) + SOC versus psychoactive placebo + SOC<br>Duration of DB treatment: 25 days | 145 planned |
| TRD3006[f] | Randomized, DB, active-controlled study to evaluate the efficacy, pharmacokinetics, safety and tolerability of flexible doses of esketamine plus an oral AD in Chinese and non-Chinese adult subjects with TRD<br>Study treatment: esketamine (flexible dose: 56 or 84 mg) + oral AD versus placebo + oral AD<br>Duration of DB treatment: 28 days | 234 planned |
| TRD2005[f] | Randomized, DB, placebo-controlled study to evaluate the efficacy, safety and tolerability of fixed doses of esketamine in Japanese adult subjects with TRD<br>Study treatment: esketamine (28, 56 or 84 mg) + oral AD versus placebo + oral AD<br>Duration of DB treatment: 28 days | 202 enrolled |

[b] The population of this ongoing extension study includes adult and elderly subjects who previously participated in one of the Phase 3 TRD studies. An interim abbreviated clinical study report was submitted and assessed with the Day 120 responses during the initial MAA (Sequence 0002/Mod5.3.5.2/TRD3008 Interim CSR) and provided safety data for 1,140 subjects through the cutoff date of 31 December 2018. CIOMS reports from 31 December 2018 up to a cutoff date of 20 April 2019 are also provided with this application.
[c] 28 mg dose is only applicable for elderly subjects (≥65 years).
[d] For these studies, CIOMS reports up to a cutoff of 20 April 2019 are provided.
[e] Psychoactive placebo (oral midazolam 0.125 mg/kg).
[f] Study TRD3006 will support the registration of esketamine in China, and Study TRD2005 will support the registration of esketamine in Japan.

AD=antidepressant; CIOMS=Council for International Organization of Medical Sciences; DB=double-blind; ESK=treated with esketamine; FU=follow-up phase; MAA=Marketing Authorisation Application; MDD=major depressive disorder; MDSI=MDD at imminent risk for suicide; OL=open-label; SOC=standard of care; TRD=treatment-resistant depression

## 2.3.2. Pharmacokinetics

No new biopharmaceutical or pharmacokinetic studies were performed to support the so-called MDSI indication. The Phase 3 MDSI clinical studies used the same esketamine formulation and nasal spray device that was used in the Phase 3 TRD studies.

Additional analyses were performed to support the claimed indication, namely a population pharmacokinetic analysis and exposure-response analyses for both efficacy (MADRS) and safety (systolic blood pressure, diastolic blood pressure, CADSS). The provided pharmacokinetic analyses are considered not to have an impact on the benefit-risk assessment in the proposed indication. Other concerns on the population pharmacokinetic model were made and resolved during the assessment.

***Analytical methods***

Non-chiral LC-MS/MS assays for the quantification of esketamine and noresketamine in human heparin plasma were developed and validated at Contract Research Organization Frontage Laboratories, Exton, USA.

The methods consist of a solid phase extraction sample preparation after addition of stable isotope labelled internal standards (ketamine-D4 and norketamine-D4). The resulting extracts were evaporated to dryness, reconstituted and then injected on a reversed phase high performance liquid chromatography (HPLC) column using a gradient method. Detection was done by tandem mass spectrometry in the multiple reaction monitoring (MRM) mode with TurboIonSprayTM ionization in the positive ion mode.

Initially, in 2012 a manual solid phase extraction (SPE) method using individual SPE cartridges was developed and validated (method BTM-1487). Later, in 2016, a more automated SPE method was developed and validated using equivalent 96 well SPE plates (method BTM-2246). Both methods produce equivalent results as demonstrated by a cross validation with quality control samples.

The validation of the analytical methods (BTM-1487 and BTM-2246) has been assessed and approved previously. Studies **SUI3001** and **SUI3002** used BTM-2246. Methods are also validated within study and bioanalytical reports have been provided (JNJ-R7964 and JNJ-R7870).

***Dose proportionality and time dependencies***

The dosing regimen used in the double-blind phase of the MDSI Phase 2 proof-of-concept study SUI2001 included 4-week treatment with esketamine 84 mg + SOC. The esketamine dose could be reduced at any time after the first dose to 56 mg for subsequent doses if a subject was unable to tolerate 84 mg. This regimen was agreed upon based on results from Phase 2 studies conducted in patients with TRD and with input from health authorities.

The esketamine dose (84 mg) was selected for this program based on efficacy, safety, tolerability, and pharmacokinetic data obtained with the esketamine nasal spray formulation and intravenous esketamine in the Phase 2 studies conducted in subjects with TRD. The aim was to yield the mean maximum concentration (Cmax) achieved with intravenous esketamine 0.4 mg/kg (corresponding to absolute doses of ~ 26 to 36 mg) that demonstrated efficacy in Study ESKETIVTRD2001 (135 ng/mL). While a lower intravenous esketamine dose (0.2 mg/kg) was also efficacious in ESKETIVTRD2001, given that the Phase 2 and Phase 3 MDSI studies were being conducted in the context of an acute illness, the 84 mg dose was selected to provide the greatest opportunity for rapid onset of efficacy, with acceptable tolerability.

The relationship between the change from baseline in MADRS total score (ΔMADRS) at 24 hours after the first dose in the Phase 3 MDSI studies and esketamine exposure was investigated as the primary endpoint. Results of the analysis support selection of the 84-mg dose of esketamine to achieve rapid and robust improvement in depressive symptoms since a linear relationship between placebo-corrected ΔMADRS and esketamine area under the plasma concentration-time curve (AUC) has been submitted with this application (please see also below).

Dose Reductions in the Phase 3 Studies

The majority of subjects in the Phase 3 studies were able to tolerate the assigned 84 mg dose of esketamine per protocol. Dose reductions in the pooled studies during the double-blind treatment phase were as follows:

- 45 of 226 subjects (19.9%) treated with esketamine + SOC in the full efficacy analysis set received a reduced dose of esketamine on at least 1 dosing day.
- 35 subjects (15.5%) in the esketamine + SOC group had a protocol-permitted, one-time dose reduction (and received the 56-mg dose during all subsequent dosing sessions) due to adverse

events or tolerability issues (33 subjects), investigator discretion based on expected side effects (1 subject), and Interactive Web Response System user error (1 subject).

- The change in MADRS total score over time was also evaluated for the 35 subjects who required a dose reduction during the double-blind treatment phase. The findings in these subjects were consistent with the results of the primary analysis
- 5 subjects did not administer all 3 devices (and did not receive an 84-mg dose) during at least 1 dosing session due to adverse events or tolerability issues that occurred during dose administration. A dose reduction was not entered in the Interactive Web Response System for these subjects.
- 5 subjects received partial doses of esketamine during at least 1 dosing session (and an 84-mg dose during the other dosing sessions) for reasons other than adverse events or tolerability (ie, issues with device administration, site or user error, refusal to administer third device).

***Pharmacokinetics using human biomaterials***

**Population Pharmacokinetics and Exposure Response (Efficacy and Safety) Report JNJ-54135419 Date: 10 December 2019**

Objective

a) characterise the PK of esketamine and noresketamine for subjects randomized to receive esketamine in studies SUI3001 and SUI3002

b) explore the relationship between exposure to esketamine and the change from baseline to 24 h post first dose in MADRS Total Score and in CGI-SS-R

c) confirm the relationship between exposure to esketamine and selected safety measurements i.e. diastolic and systolic BP and probability of having a CADSS score >4 (i.e., the threshold for experiencing clinically meaningful dissociative symptoms) at 40 minutes pot-dose

Software

Non-linear mixed effect modelling of concentration-time data and the exposure-efficacy data were performed using NONMEM (Version 7.2 or higher, ICON plc)

**Table 5: Data**

| Study | PK sampling | Timing of response assessment |
|---|---|---|
| ESKETINSUI3001<br>Dose 84 mg IN<br>n = 225<br>A Double-blind, Randomized, Placebo-controlled Study to<br>Evaluate the Efficacy and Safety of Intranasal Esketamine in Addition to Comprehensive<br>Standard of Care for the Rapid Reduction of the Symptoms of Major | Sparse PK at two occasions<br>Day 1 and Day 4 at the following time windows: 30-50 min,<br>1.5 to 2.5 h and<br>4-12 h post-dose | MADRS:<br>Baseline and on Day 1<br>(4h), Days 2, 4, 8, 11, 15, 18, 22, 25 and 25 (4h)<br>SIBAT:<br>Baseline and on Day 1<br>(4h), Days 2, 4, 8, 11, 15, 18, 22 and 25<br>BP: |

| | | |
|---|---|---|
| Depressive Disorder,<br>Including Suicidal Ideation, in Adult Subjects Assessed to be at Imminent Risk for Suicide. | | Pre-dose, 0.67h, 1h and 1.5h Post-dose on day of nasal dosing<br>CADSS:<br>Pre-dose, 0.67h and<br>1.5h post-dose on day of nasal dosing |
| ESKETINSUI3002<br>Dose 84 mg IN<br>n = 227<br>A Double-blind, Randomized, Placebo-controlled Study to<br>Evaluate the Efficacy and Safety of Intranasal Esketamine in Addition to Comprehensive<br>Standard of Care for the Rapid Reduction of the Symptoms of Major Depressive Disorder,<br>Including Suicidal Ideation, in Adult Subjects Assessed to be at Imminent Risk for Suicide. | | |

**Population PK analysis**

The previously developed population PK model was used (Population Pharmacokinetics Report JNJ-54135419 (Esketamine). Department of Global Clinical Pharmacology. Janssen Research & Development, 20 July 2018.). It was an open, linear, three-compartment disposition model for esketamine and an open, linear two-compartment disposition model for noresketamine in combination with a separate hepato-portal-compartment ("first-pass model"). Age, Japanese and Asian subjects, were statistically associated with esketamine or noresketamine pharmacokinetic parameters. Relative to non-Asians, the Asian population showed a 64.0% and 19.4% decrease in the esketamine metabolism rate constant (kel) and the apparent clearance of noresketamine (CLn/F), respectively. The Japanese subjects exhibited a 34% increase in FRn, relative to other subjects. The hepatic blood flow (Qh) decreased at a rate 21.9 L/h×10 years from 60 years onwards.

1) Exploratory analysis

The SUI3001 and SUI3002 were graphically explored for concentration and/or time effects and assist in identifying potential aberrant data. In addition, the exploratory graphical analysis of every quantitative covariate consisted of a histogram, box plots and plots of quartiles of covariate distributions and quantiles of standard normal distribution (QQ plot).

2) External model evaluation

was performed to verify the predictive performance of the previously developed population model for the current analysis dataset.

VPC and pcVPC the $5^{th}$, $50^{th}$, and $95^{th}$ percentiles of the observed esketamine and noresketamine data were compared with the model-based predicted percentiles for each bin across time and replicates. A total of 100 replicates of the analysis dataset were generated and used for each analysis.

A maximum a posteriori (MAP) estimation using the previously developed population model as prior information was used to estimate the Empirical Bayes Estimates (EBE's) of the random effect for subjects included in the studies SUI3001 and SUI3002. This analysis was conducted using the MAXEVAL=0 option in NONMEM. The GOF plots were graphically assessed by the examination of scatterplots of observed data versus population/individual predictions.

The NPC was performed on the mean and the standard deviation (SD) of the exposure metrics (AUCinf and Cmax), since these reflect the central tendency and the variability of the esketamine exposure metrics. The model-based distribution of the mean and SD of the esketamine exposure metrics across replicates was obtained and its 2.5th and 97.5th percentile was used to calculate the lower and upper limit of the 95% confidence interval (CI) of the model-based predicted mean and SD of the exposure metrics, which were then compared to the actual metric of exposure obtained from the SUI3001 and SUI3002 studies.

3) Since the sparse sampling implemented in the SUI3001 and SUI3002 studies to characterise the esketamine and noresketamine PK, does not allow to directly estimate the parameter values by fitting the model directly to the data, the MAP estimation using the previously developed population model as prior information was used to derive the individual PK parameters. The accuracy and precision of the structural model previously developed was verified17 by showing similar parameter estimates obtained using intensively sampled PK data of study TRD1009 including 3 different routes of administration (oral, IV and intranasal) and the updated PK parameter estimates after a pooled PK analysis of TRD data.

Results

Overall, 1225 esketamine and 1225 noresketamine samples from 220 subjects were available in the analysis dataset.

A total of 104 (7.8%) esketamine and 104 (7.8%) noresketamine plasma concentration were excluded. There were 7 subjects with no measurable PK concentrations. For these subjects, the typical model based PK concentrations were derived from the typical PK parameters taking into account the individual demographic values. In this way, these subjects were included in the efficacy and safety analysis.

Graphical exploration:

Asian subjects (12.7%) have a similar exposure for esketamine and a tendency of increased exposure for noresketamine (Figure 5 of the POPPK report). Due to the limited sample size, a similar exploratory analysis exercise could not be performed for subjects older than 60 years (5.3%) or Japanese subjects (0%).

External evaluation:

The central tendency and variability in the observed plasma concentrations of esketamine and noresketamine in the SUI3001 and SUI3002 studies were similar to the model-predicted central tendency and variability for esketamine as well as noresketamine plasma concentrations (VPC Figure 8 of the POPK report). These results indicated the model is able to describe the time course of esketamine and noresketamine plasma concentrations and its associated variability well.

The GOF plots (Figure 9 of the POPK report) show the previously developed PK model adequately describes the central tendency in the PK of esketamine well; however, noresketamine shows a minor underprediction at high plasma concentrations, not confirmed in the VPC. Therefore, the previously developed PopPK model adequately described the esketamine and noresketamine PK in subjects enrolled in the SUI3001 and SUI3002 studies and no model updates were required.

The NPC demonstrated that the model was appropriate to describe the mean esketamine AUCinf and Cmax as the observed means were contained within the 95%CI of the model predictions (Figure 10 of the report). However, the SD of esketamine Cmax was slightly (<10%) below the 95%CI of predictions, which could be related to the shrinkage (Figure 11 of the POPK report) due to the sparse sampling scheme used in studies SUI3001 and SUI3002.

The model-based distribution of the mean and SD of the esketamine exposure metrics across replicates was obtained and its 2.5th and 97.5th percentile was used to calculate the lower and upper limit of the 95% confidence interval (CI) of the model-based predicted mean and SD of the exposure metrics, which were then compared to the actual metric of exposure obtained from the **SUI3001** and **SUI3002** studies.

**Table 6: PopPK-1 (Table 6 of the PopPK report): Summary of subjects' relevant demographic baseline characteristics of included subjects in the popPK analysis (SUI3001 and SUI3002) versus all subjects included in development dataset (TRD)**

| Subject Characteristics | ESKETIN SUI3001[b] (N=111) | ESKETIN SUI3002[b] (N=109) | ESKETIN SUI3001[b] & SUI3002[b] (N=220) | TRD (N=820) |
|---|---|---|---|---|
| Body weight (kg) | 75 [47 - 207] | 77 [48 - 127] | 75 [47 - 207] | 74 [39 - 170] |
| Age (years) | 39 [19 - 62] | 41 [18 - 61] | 40 [18 - 62] | 45 [18 - 86] |
| Race[a] | | | | |
| White | 75 (67.6) | 86 (78.9) | 161 (73.2) | 594 (72.4) |
| Caucasian (=not Hispanic or Latino) | 65 (58.6) | 68 (62.4) | 133 (60.5) | 529 (89.1) |
| Hispanic or Latino | 10 (9) | 18 (16.5) | 28 (12.7) | 65 (10.9) |
| Black (African heritage or African American) | 5 (4.5) | 7 (6.4) | 12 (5.5) | 56 (6.82) |
| Asian | 28 (25.2) | 0 (0) | 28 (12.7) | 112 (13.7) |
| Japanese | 0 (0) | 0 (0) | 0 (0) | 72 (64.3) |
| Non-Japanese | 28 (25.2) | 0 (0) | 28 (12.7) | 40 (35.7) |
| Native Hawaiian, Pacific Islander, other | 1 (0.9) | 0 (0) | 1 (0.5) | 58 (7.07) |
| Unknown/not reported | 2 (1.8) | 16 (14.7) | 18 (8.2) | / |

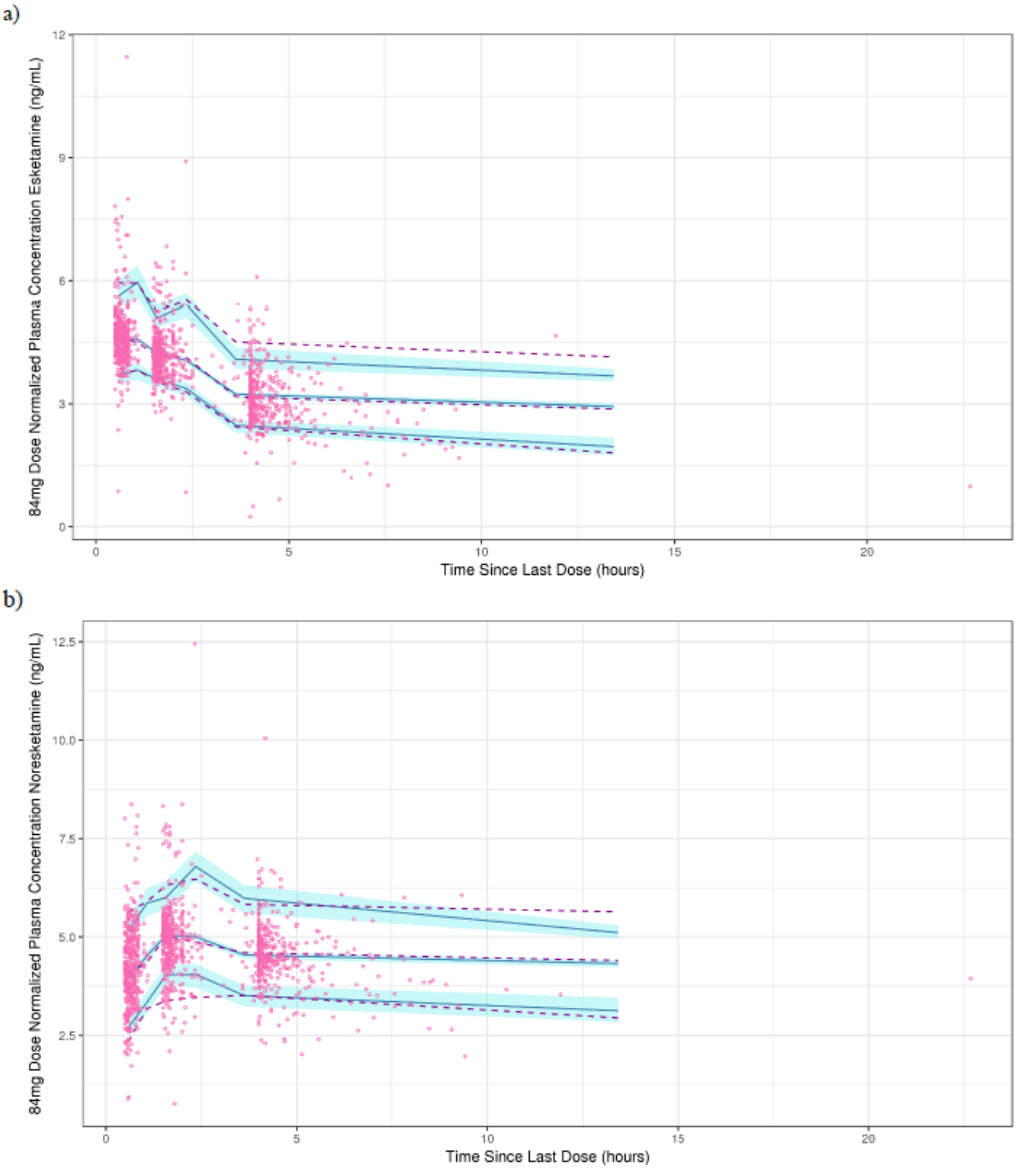
Continuous variables are expressed as median [range], whereas categorical variables are expressed as counts (%).

[a] Ethnicity (Caucasian, Hispanic, Chinese, Japanese, etc.) is expressed as percentage of race classification (White, Asian).

[b] Subjects of active treatment arm.

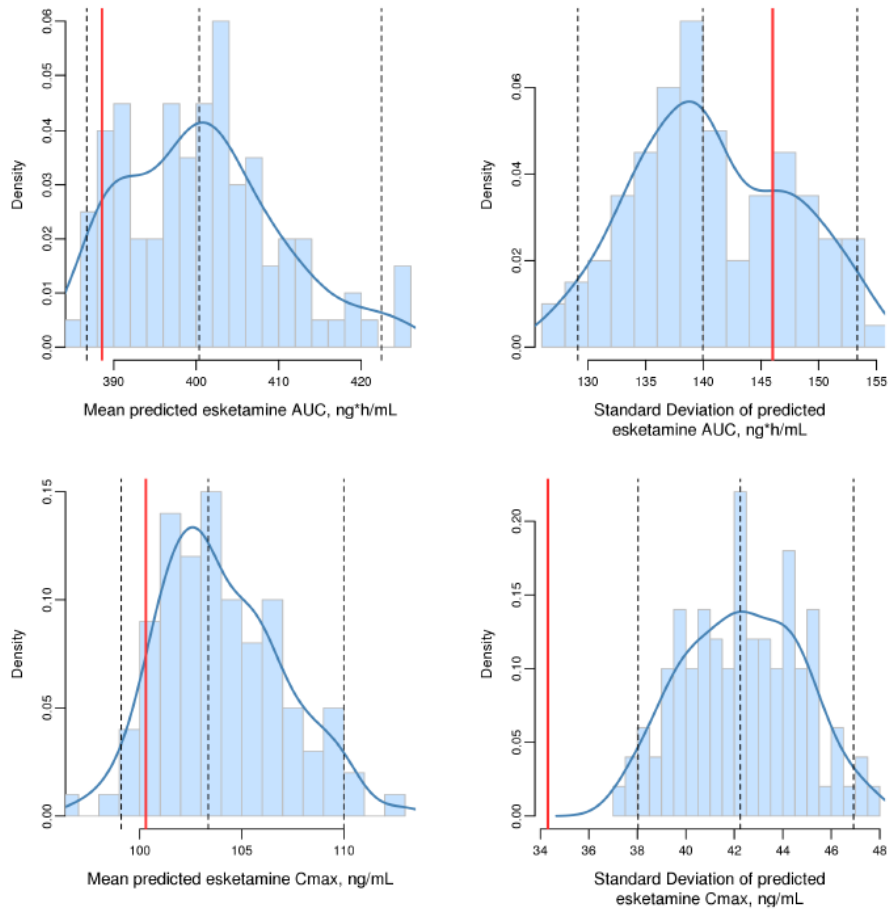
The PK analysis dataset of studies **SUI3001** and **SUI3002** comprised of 1,329 esketamine and 1,329 noresketamine plasma concentrations from 227 subjects receiving nasal esketamine and SOC. However, a total of 104 (7.8%) esketamine and 104 (7.8%) noresketamine plasma concentration were excluded. Main reason for exclusion was the lack of sampling times (n = 94 for both esketamine and noresketamine) and sample BQL (n = 9 for both esketamine and noresketamine).

**Figure 2: PopPK-1 (Figure ES 1 of the PopPK report): Visual Predictive Check Applying the Previously Developed PopPK Model to SUI3001 and SUI3002 data for esketamine (a) and noresketamine (b).**




The open circles represent the log transformed observed concentrations of esketamine (panel a) and noresketamine (panel b). The median and 5th and 95th percentiles of the observations are indicated as the dashed line in the same color as the observations. The simulation-derived median and 90% prediction intervals (PI) are accompanied by their 95% confidence intervals and are indicated as blue lines and shaded blue area, respectively.

**Figure 3: PopPK-2 (Figure 9 of the PopPK report): Numerical Predictive Check showing the predictive performance of the previously developed popPK model for the central tendency and variability at steady-state for esketamine AUCinf (upper) and Cmax (lower).**




The applicant conducted a pre-specified external validation of a previously developed popPK model (see also EMEA/H/C/004535/0000) based on phase 2 and 3 data obtained mainly for patients with treatment-resistant major depressive disorder, but also one study in major depressive disorder to be at imminent risk for suicide (**SUI2001**). The external validation was performed on data of **SUI3001** and **SUI3002**. In general, the pcVPC indicates that the central tendency for both esketamine and noresketamine is adequately reflected. For esketamine, there is a slight underestimation around 5 hours in the 95$^{th}$ percentile and, for noresketamine, there is an overestimation around 2 hours in the 5$^{th}$ percentile. The influence on the estimates of AUC and $C_{max}$ is expected to be minimal. However, from the structural model, it is clear that the elimination rate constant from the compartment representing the hepato-portal system, causes parameter identifiability issues. As a consequence, multiple parameter solutions are available that result in a similar model fit, which could have affected the estimates of $AUC_{inf}$ and $C_{max}$ . Therefore, the current estimates of AUC and Cmax cannot be trusted yet. The applicant was requested to provide a condition number of the population pharmacokinetic model. Furthermore, the applicant was requested to test for input–output reachability of the structural model. Several methods are described by Bonate (*Bonate PL. 2012. Pharmacokinetic-pharmacodynamic modeling and simulation. Springer)*, of which the easiest approach is simulation-based. Finally, the applicant was also asked to evaluate and discuss the potential impact on $AUC_{inf}$ and $C_{max}$.

Individual estimates of exposure of esketamine and noresketamine:

The reference model was further used to generate the individual PopPK Empirical Bayes parameter estimates to derive the individual predicted esketamine plasma concentrations at timepoints of blood pressure measurements used for the exposure safety analysis and to allow prediction of individual exposure parameters Cmax and AUCinf used for the exposure efficacy analysis (Table PopPK-2, i.e. Table 7 of the report).

A contingency table (Table 8 of the POPK report) was constructed to investigate whether any potential confounding bias may exist between the exposure metrics (i.e., quartile of exposures) and the stratification factors in the studies SUI3001 and SUI3002. The counts and percentages of the number of subjects within each stratification factor category were well balanced by treatment arm (placebo + SOC vs esketamine + SOC) as well as by the quartiles of the esketamine exposure.

**Table 7: PopPK-2 (Table 7 of the report): Summary Statistics of Model Predicted Esketamine and Noresketamine AUCinf and Cmax**

| Parameter Estimate: mean (sd) | Analyte | ESKETINSUI3001 | | ESKETINSUI3002 | | ESKETINSUI3001 + ESKETINSUI3002 | |
|---|---|---|---|---|---|---|---|
| | | 56mg | 84mg | 56mg | 84mg | 56mg | 84mg |
| Cmax (ng/mL) | Esketamine | 85.4 (31.4) | 98.6 (33.3) | 82.7 (29.9) | 105 (35.7) | 84.1 (30.1) | 101.7 (34.6) |
| $AUC_{inf}$ (ng.h/mL) | Esketamine | 290.2 (97) | 372.4 (125.5) | 298 (108.8) | 417 (163.8) | 293.9 (100.9) | 394.3 (146.9) |
| Cmax (ng/mL) | Nor-esketamine | 117.6 (42.9) | 159.6 (67.8) | 106.1 (31.3) | 151.1 (54.5) | 112.1 (37.5) | 155.5 (61.7) |
| $AUC_{inf}$ (ng.h/mL) | Nor-esketamine | 965.9 (356.8) | 1318.8 (580.2) | 847.8 (240.7) | 1263.1 (427.5) | 909.1 (306.6) | 1291.5 (510.6) |

Note: some subjects will be accounted twice in this table if a dose reduction from 84 to 56mg occurred.

Questions were raised on the Population PK model, such as why is the y-axis dose normalised to 84 mg, if the participants of studies SUI3001 and SUI3002 have all been treated with 84 mg? Have some participants received other doses? Additionally in this context, if the participants of studies SUI3001 and SUI3002 have all been treated with 84 mg, it is not clear why exposure for the 56 mg dosage is given.

Data on VPCs and GOF plots reveal that the previously developed population PK model seems to be applicable to the data obtained from studies SUI3001 and E SUI3002. Thus, it is anticipated that dose recommendations will be the same for patients with MDSI as for patients with TRD.

## 2.3.3. Pharmacodynamics

No new pharmacodynamic studies have been submitted with this type II variation application.

Esketamine hydrochloride (HCl) is currently assigned to two Anatomical Therapeutic Chemical (ATC) classification codes: Psychoanaleptics/Other antidepressants (N06AX27) and Anaesthetics/Other general anaesthetics (N01AX14). The applicant petitioned the World Health Organization (WHO) Collaborative Center for Drug Statistics Methodology to assign the additional ATC code for esketamine under the N06AX group of "Other Antidepressants" to clearly differentiate between the utilization of esketamine nasal spray in the treatment of depression-related indications and the use of IM or IV esketamine in anesthesia. The new ATC code (N06AX27) was published as "Final" by WHO in May 2019 for esketamine nasal formulations indicated for MDD.

### *Mechanism of action*

Esketamine, the S-enantiomer of racemic ketamine, is a non-selective, non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor.

The mechanism by which esketamine exerts its antidepressant effect is unknown, but evidence within the literature suggests that, through NMDA receptor antagonism, esketamine produces a transient increase in glutamate release leading to increases in α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) stimulation and subsequently to increases in neurotrophic signalling that restore synaptic function. Unlike other antidepressant therapies, esketamine's primary antidepressant action does not directly involve monoamine, γ-amino butyric acid-ergic (GABA), or opioid receptors.

A summary of pharmacologic evidence supporting the presumed mechanism of action for esketamine in depression was presented previously in the Marketing Authorisation Application (MAA) submitted for the TRD indication.

There may be evidence that the glutamate system and molecular mechanisms related to synaptic and neuronal plasticity could play a role in the pathology of depression, and alterations in glutamate signalling have also been implicated in the pathophysiology of suicide. The latter condition has not been established yet.

### *Primary and secondary pharmacology*

The applicant has not performed any primary pharmacodynamic *in vivo* studies in humans, because direct measurement of NMDAR inhibition in humans is hardly applicable (Spravato EPAR, EMA website accessed March 2020).

The primary and secondary pharmacological properties of esketamine are being investigated and these have been already described (Spravato Product Information). Esketamine is the S-enantiomer of racemic ketamine. Through NMDA receptor antagonism, esketamine causes increases in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) stimulation and subsequently to increases in neurotrophic signalling which may contribute to the restoration of synaptic function in these brain regions involved with the regulation of mood and emotional behaviour. Restoration of dopaminergic neurotransmission in brain regions involved in the reward and motivation, and decreased stimulation of brain regions involved in anhedonia, may contribute to the rapid response.

## 2.3.4. PK/PD modelling

**Population Pharmacokinetics and Exposure Response (Efficacy and Safety) Report JNJ-54135419 Date: 10 December 2019**

**Exposure- Response analyses**

The analyses assume that for model comparisons, p-values lower than 0.05 is statistically significant. No correction for multiple statistical testing was implemented.

**Exposure metrics for esketamine**

As only one dose was tested previously, where the average dose had the strongest statistical association with the efficacy endpoint was not suitable to analyse the current dataset.

The exposure metrics AUCinf and Cmax for esketamine were computed after single-dose, as no accumulation of esketamine was seen in the twice-weekly dosing regimen used in the phase 3 studies. These exposure metrics were calculated for the dose that is related to the time-point when the MADRS

Total Score was measured, so that the exposure metrics within a subject will change if the dose changed during the treatment duration. The exposure metrics were derived based on the maximum a posteriori estimates of the individual PK model parameters for esketamine, which were obtained from the plasma concentrations collected in the studies SUI3001 and SUI3002 and the previously developed PopPK model.

For the safety analyses, the ER analysis was performed by using the predicted concentrations in plasma at the time of safety endpoint measurement.

**Efficacy endpoints**

1) ΔMADRS
2) CGI-SS-R

Severity of suicidality as measured by the CGI-SS-R at 24 h post first dose. The CGI-SS-R scale is module 8 of suicide ideation and behaviour assessment tool (SIBAT), consisting of 6 categories. Those six categories were dichotomized into a group with a CGI-SS-R score <2 and a CGI-SS-R score ≥2. We explored the probability of having a CGI-SS-R < 2 at 24 hours post first dose.

Covariates explored: age, race, gender, prior suicide attempt status, baseline MADRS Total Score (MADRS0), type of SOC and class of oral antidepressant (Serotonin and Norepinephrine Reuptake Inhibitors (SSRI) or Selective Serotonin Reuptake Inhibitors (SNRI)).

No dose-response was assessed as only one dose (i.e. 84 mg) was given per protocol. However, the predictability of esketamine exposure (AUCinf and Cmax) on the MADRS and CGI-SS-R was explored.

1) An exploratory data analysis was conducted to present change from baseline MADRS and CGI-SS-R, to assist in identifying aberrant data and potential outliers, and to explore the relationships (correlations) between covariates, which may have helped in building a covariate model and avoid the confounding bias.
2) The purpose of the exposure-efficacy analysis was to assess the longitudinal relationship between esketamine systemic exposure and change from baseline in MADRS Total Score in studies SUI3001 and SUI3002. The analysis was based on a general exposure-efficacy model for the MADRS change from baseline (ΔMADRS(t)), also applied for the ER modelling of ΔMADRS(t) for the TRD indication.
3) The probability of having a CGI-SS-R score below 2 (P(CGI-SS-R<2)) was assessed by evaluating the proportion of subjects who achieved a CGI-SS-R score below 2, in the double-blind phase of the studies SUI3001 and SUI3002.

The proportion of subjects at the scheduled assessment time points (Days 1(4h), 2, 8, 11, 15, 18, 22, and 25), who had a CGI-SS-R score below 2 in the double-blind phase of the study, for different treatment groups and prior suicide attempt status were calculated from the data. The proportion was calculated as the number of subjects achieving a CGI-SS-R < 2 divided by the total number of subjects who had CGI-SS-R measurements at that time-point. No imputation was performed for missing data. In addition, a possible relationship between esketamine exposure and P(CGI-SS-R<2) at 24 hours post first dose was explored.

The correlation between both endpoints CGI-SS-R and MADRS Total Score was investigated by regression analysis.

**Safety endpoints**

1) Blood pressure measurement

2) The probability of having a CADSS >4 at 40 minutes post-dose

The purpose of the exploratory data analysis was to present diastolic and systolic BP data graphically, to assist in identifying aberrant data and potential outliers, and to explore the relationships (correlations) between covariates, which may help in building a covariate model and avoid the confounding bias. Previously, a PKPD model for diastolic and systolic blood pressure was developed using data from the three phase 3 studies conducted for the TRD indication. For the systolic blood pressure, the covariate age was statistically associated with systolic blood pressure at baseline.

Previously, a PKPD model for the probability of having CADSS > 4 at 40 minutes post-dose was developed using data from the three phase 3 studies conducted for the TRD indication. A power model, with esketamine dose as predictor, on the logit scale was shown to be the best model to describe the incidence of CADSS > 4.

An external model evaluation was performed to verify the predictive performance of the previously developed PKPD models for the current analysis datasets. GOF plots were generated for blood pressure, VPCs for blood pressure and CADSS. A total of 100 and 1000 replicates (blood pressure and CADSS, respectively) of the analysis dataset were generated and used for each analysis.

**Results**

**Longitudinal Exposure-Efficacy Analysis**

From the Full Analysis Dataset containing 452 subjects, data from 450 subjects (226 receiving nasal esketamine and SOC and 224 receiving nasal placebo and SOC) enrolled in SUI3001 and SUI3002 were included in the ER analysis. The unstructured placebo model was applied to the placebo + SOC data and an exploratory graphical analysis of the different covariates was performed. In order to account for the effect of MADRS0 as in the primary statistical analysis, and be consistent with the model developed for TRD population, the MADRS0 was incorporated in the model (ΔOFV = -75.75; df=1; p<0.001). A drug effect, linearly related to the esketamine AUCinf, performed better compared to a constant drug effect (i.e. esketamine exposure independent effect - reference model) (ΔOFV = -13.75) and the slope of the relationship between drug effect and AUCinf was -0.00914 (RSE: 19.4%) (Figure 17 of the PK report). The trend of having a higher slope of the relationship between drug effect and AUCinf in subjects with prior suicidal attempt, -0.0121 (RSE: 19%) mL/ng.h, than in subject with not prior suicidal attempt, -0.00356 (RSE: 73%), was not statistically significant. However, it does suggest that for a median esketamine AUCinf for a 84 mg dose (390 ng.h/mL), the esketamine effect might be larger in subjects with a prior suicide attempt, 4.72 (95%CI: 2.96; 6.48) points, compared to subjects with no prior suicide attempt, 1.39 (95%CI -0.60; 3.38). The linear drug effect with 95%CI is displayed in Figure 18 of the PK report stratified by prior suicidal attempt status. Gender, age, weight, race, type of SOC therapy and class of oral antidepressant (SSRI vs. SNRI vs. other) were not associated with placebo or drug effects on ΔMADRS. A doubling of the MADRS0 was associated with a 2.8-fold (95%CI: 2.18; 3.57) higher decrease in ΔMADRS, but had no influence on the drug effect. The parameter estimates of the final model are presented in Table 12 of the report. GOF plots and VPCs are presented in Figure 21(Appendix 6) of the PK report and Figure 22. The predicted drug effect on placebo-corrected ΔMADRS (±95CI) for the mean of every quartile esketamine AUCinf depending on a subjects prior suicide attempt status and a baseline MADRS of 41is summarised in Table 13 of the PK report.

**Descriptive Analyses to Evaluate the Probability of CGI-SS-R < 2**

The data used for this analysis included 450 subjects with a total of 4,479 CGI-SS-R score evaluations (2234 for placebo + SOC and 2245 for esketamine + SOC) during the double-blind period from studies SUI3001 and SUI3002.

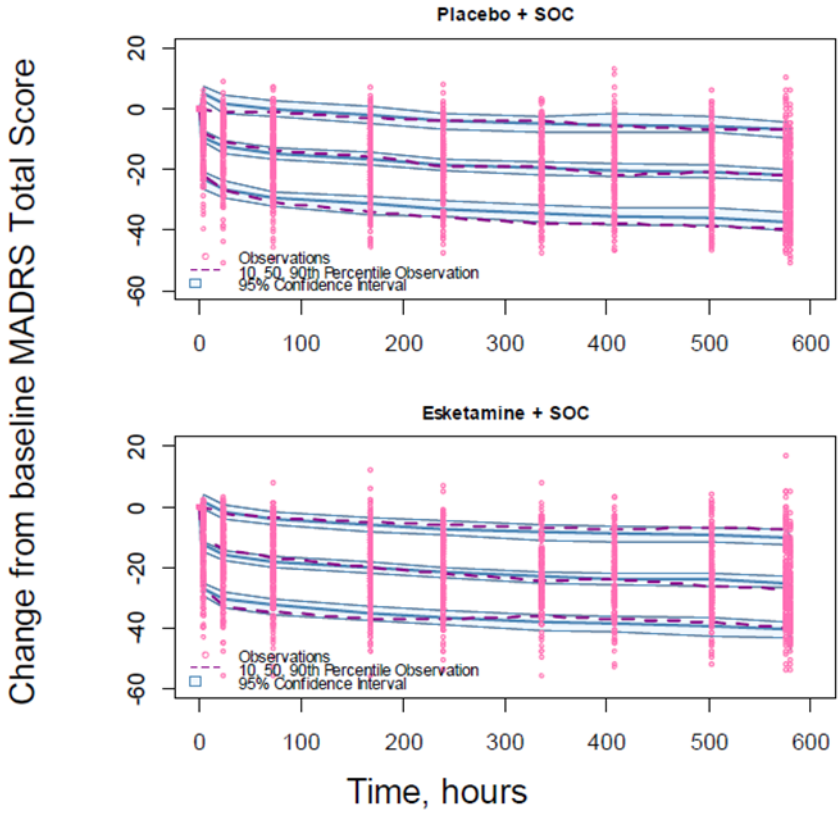
As the exploration of the possible relationship between esketamine exposure and P(CGI-SSR<2) at 24 hours post first dose was not statistically significant (p>0.05), a descriptive analysis was performed. The P(CGI-SSR<2) increased sharply after the subjects received the initial esketamine/placebo dose on Day 1 with the highest difference between both treatment groups at 4 hours post first dose (13%) (Figure 25 of the PK report). Although the 95%CI between both treatment groups were largely overlapping, esketamine treatment resulted in numerically higher number of subjects having a P(CGI-SS-R<2) compared to placebo. Subjects who had a previous suicide attempt showed a lower placebo + SOC response compared to those who had no previous suicide attempt. For subjects who had a previous suicide attempt, the proportion of subjects who achieved a P(CGI-SS-R<2) was consistently higher in the esketamine + SOC treatment group which was not the case for subjects without a previous suicide attempt. Results are presented in Figure 26 and Table 15 of the PK report.

Additionally, the correlation between the MADRS Total Score and CGI-SS-R was explored for baseline and 24 hours post first dose by linear regression. The linear regression at baseline for the placebo + SOC group and esketamine + SOC group showed no difference in slope and intercept while at 24 hours post first dose, the slope was the same but the intercept was different (Figure 27 of the PK report).

**MADRS**

The drug effect on placebo-corrected ΔMADRS (ΔΔMADRS), linearly related to the esketamine AUCinf, performed better compared to an exposure independent additive drug effect (i.e. treated vs. non-treated) (ΔOFV = -13.75). When stratifying the analysis by prior suicide attempt status, the esketamine effect on ΔΔMADRS was estimated to be 4.72 (95%CI: 2.96; 6.48) points for a median esketamine AUCinf at 84 mg dose (i.e. 390 ng.h/mL) for subjects with prior suicidal attempt. For subjects without a prior suicide attempt, the decrease in ΔΔMADRS for a median esketamine AUCinf at 84 mg dose (i.e. 390 ng.h/mL) was smaller 1.39 (95%CI: -0.60; 3.38). The parameter estimates of the exposure-efficacy model are presented and a VPC is presented.

**Figure 4: Change from baseline MADRS Total Score**




All parameters could be estimated with adequate precision, as measured by relative standard error (RSE) of < 20% for the fixed and random effects), except for the drug effect of subjects without prior suicide attempt (i.e. RSE=73%).

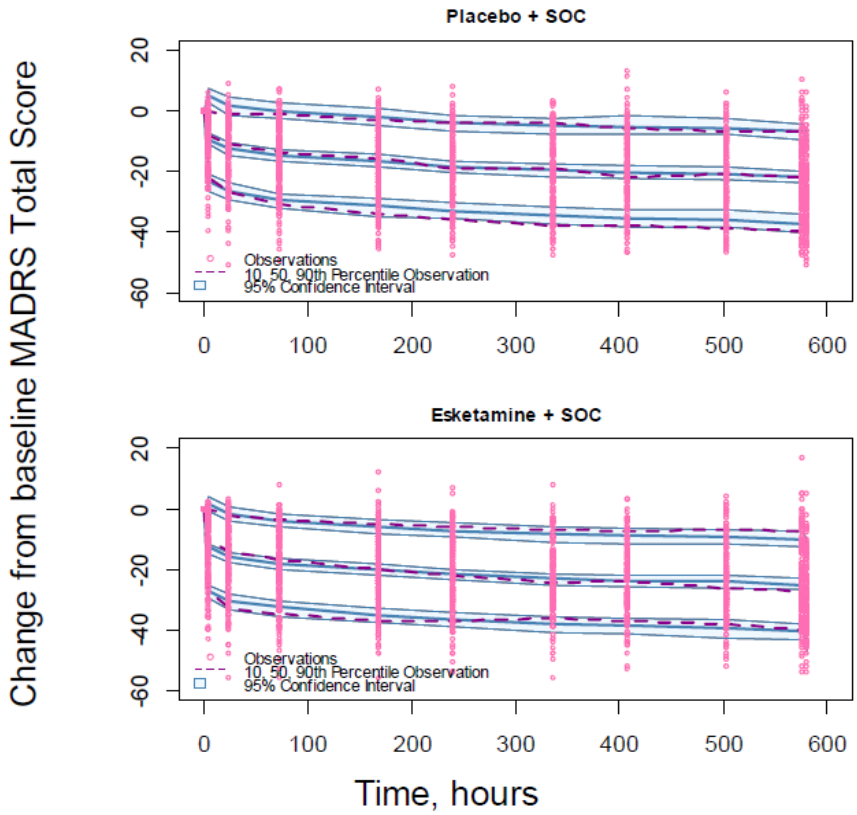
**Table 8: Table 12 of the PopPK report: Final Parameter Estimates (%RSE) for the Longitudinal Exposure-efficacy Model (MADRS_2004.mod)**

| | *Structural model parameters* | | *Inter-individual variability* | |
|---|---|---|---|---|
| | **Parameter** | **Estimate (%RSE)** | **Parameter** | **Estimate (%RSE)** |
| **Typical Response (subjects with no prior suicide attempt)** | *Day 1, 4h* | -11.1 (9.00) | *IIV on response (SD)* | 8.55 (5.91) |
| | *Day 2* | -14.6 (7.67) | | |
| | *Day 4* | -16.8 (6.90) | | |
| | *Day 8* | -19.3 (5.70) | | |
| | *Day11* | -20.0 (5.30) | | |
| | *Day 15* | -22.3 (4.89) | | |
| | *Day 18* | -23.3 (4.55) | | |
| | *Day 22* | -23.4 (4.62) | | |
| | *Day 25* | -25.0 (4.20) | | |
| | *Day 25, 4h* | -27.6 (3.50) | | |
| **Typical Response (subjects with prior suicide attempt)** | *Day 1, 4h* | -8.67 (8.15) | | |
| | *Day 2* | -11.7 (6.70) | | |
| | *Day 4* | -14.1 (5.75) | | |
| | *Day 8* | -16.0 (5.18) | | |
| | *Day 11* | -18.2 (4.51) | | |
| | *Day 15* | -18.9 (4.32) | | |
| | *Day 18* | -19.5 (4.26) | | |
| | *Day 22* | -20.2 (4.13) | | |
| | *Day 25* | -20.9 (4.05) | | |
| | *Day 25, 4h* | -24.6 (3.42) | | |
| **Covariates** | *Baseline MADRS*[a] | 1.48 (12.3) | | |
| | *Drug Effect for subjects with prior suicide attempt*[b] *(mL/ng.h)* | -0.0121 (19.0) | | |
| | *Drug Effect for subjects without prior suicide attempt*[b] *(mL/ng.h)* | -0.00356 (73.0) | | |
| | ***Objective function value*** 20448.21 | | ***Residual variability (SD)*** | |
| | | | $\sigma_1$ | 6.76 (2.25) |

RSE, relative standard error; SD, standard deviation; IIV, inter-individual subject variability (additive)
[a] Power function on typical response: $(\text{Baseline MADRS}/41)^{1.48}$
[b] Slope x esketamine $AUC_{inf}$

Gender, age, weight, race, type of SOC therapy and class of oral antidepressant (Selective Serotonin Reuptake Inhibitors (SSRI) vs. Serotonin and Norepinephrine Reuptake Inhibitors (SNRI) vs. other) were not associated with placebo effect on ΔMADRS.

**Figure 5: Figure 22 of the PopPK report: Visual Predictive Check of the final exposure-efficacy model for the time course of ΔMADRS after dosing of esketamine, stratified by treatment.**




**CGI-SS-R**

**Table 9: Table 7 of the PopPK report: Fraction of Subjects with a P(CGI-SS-R<2) by Treatment Group and Prior Suicide Attempt**

| | | | No prior suicide attempt | | | Prior suicide attempt | | | |
|---|---|---|---|---|---|---|---|---|---|
| Treatment Group | Day | n of samples | Fraction | Lower of 95% CI | Upper of 95% CI | n of samples | Fraction | Lower of 95% CI | Upper of 95% CI |
| Placebo + SOC | 1 | 83 | 0.02 | 0.00 | 0.08 | 140 | 0.03 | 0.01 | 0.07 |
| | 1(4h) | 83 | 0.22 | 0.14 | 0.32 | 140 | 0.19 | 0.13 | 0.26 |
| | 2 | 82 | 0.40 | 0.30 | 0.51 | 140 | 0.29 | 0.22 | 0.37 |
| | 4 | 81 | 0.49 | 0.38 | 0.60 | 139 | 0.40 | 0.32 | 0.48 |
| | 8 | 77 | 0.52 | 0.41 | 0.63 | 135 | 0.44 | 0.36 | 0.52 |
| | 11 | 74 | 0.55 | 0.44 | 0.66 | 129 | 0.49 | 0.41 | 0.58 |
| | 15 | 70 | 0.59 | 0.47 | 0.70 | 124 | 0.54 | 0.45 | 0.63 |
| | 18 | 66 | 0.70 | 0.58 | 0.80 | 122 | 0.58 | 0.49 | 0.66 |
| | 21 | 67 | 0.72 | 0.60 | 0.81 | 110 | 0.64 | 0.55 | 0.72 |
| | 25 | 67 | 0.75 | 0.63 | 0.84 | 113 | 0.65 | 0.56 | 0.73 |
| Esketamine + SOC | 1 | 76 | 0.05 | 0.02 | 0.12 | 148 | 0.01 | 0.00 | 0.04 |
| | 1(4h) | 77 | 0.42 | 0.32 | 0.53 | 144 | 0.29 | 0.22 | 0.37 |
| | 2 | 75 | 0.39 | 0.29 | 0.50 | 145 | 0.34 | 0.27 | 0.42 |
| | 4 | 72 | 0.49 | 0.38 | 0.60 | 142 | 0.44 | 0.36 | 0.52 |
| | 8 | 68 | 0.56 | 0.44 | 0.67 | 133 | 0.50 | 0.42 | 0.58 |
| | 11 | 67 | 0.69 | 0.57 | 0.79 | 133 | 0.59 | 0.51 | 0.67 |
| | 15 | 66 | 0.76 | 0.64 | 0.85 | 127 | 0.63 | 0.54 | 0.71 |
| | 18 | 64 | 0.72 | 0.60 | 0.82 | 128 | 0.69 | 0.61 | 0.76 |
| | 21 | 65 | 0.78 | 0.67 | 0.86 | 120 | 0.68 | 0.59 | 0.76 |
| | 25 | 63 | 0.81 | 0.70 | 0.89 | 121 | 0.74 | 0.66 | 0.81 |

Data of study **SUI3001** and **SUI3002** was used for this analysis. The results of the exposure-efficacy analysis should be interpreted with caution as only one dose-level was included in the phase 3 studies. In addition, further information on the estimates of $AUC_{inf}$ were requested.

Longitudinal Exposure-Efficacy Analysis

A linear relationship between ΔΔMADRS and AUCinf seems to adequately describe the data from studies SUI3001 and SUI3002. The median esketamine AUCinf for a 84 mg dose was 390 ng.h/mL. In participants with a prior suicide attempt, the effect was about 4.72 (95%CI: 2.96; 6.48) points. In participants with no prior suicide attempt, the effect was 1.39 (95%CI -0.60; 3.38) (**Table 8**).

The analysis indicates that the influence of $AUC_{inf}$ on the placebo corrected change from baseline in MADRS is larger in patients with a prior suicide attempt compared to patients without a suicide attempt. For patients without a suicide attempt, the drug-effect was non-significant. A non-parametric structure was used to describe the placebo-effect, which was estimated separately for patients with and without a prior suicide attempt. The provided data indicates that the placebo-effect is different between the two patient groups, which could potentially be explained by differences in the MADRS at baseline. It was unclear whether the different drug effects identified in the two different patient populations can be explained by the differences in placebo-effects.

No clear differences for CGI-SS-R can be observed between placebo and esketamine. It seems that the probability of achieving the CGI-SS-R<2 was numerically higher in participants receiving intranasal esketamine + SOC compared to treatment with placebo + SOC. The highest difference was observed 4 h post-dose (Figure 25).

The applicant has performed post-hoc subgroup analyses based on prior suicide attempt, however no conclusions on differential effect could be made.

**Exposure-safety analysis**

**Blood pressure**

The previously developed PKPD model for diastolic and systolic BP described the central tendency and associated variability in blood pressure in subjects receiving placebo + SOC and esketamine + SOC. GOF plots and VPCs are depict in Figure 32, 33, and 34 of the report, Final parameter estimates are listed in Table 3 of the PK report. Diastolic and systolic blood pressure in subjects with MDSI is similar to that in subjects with TRD included in the dataset used to develop the exposure-blood pressure models.

**Clinician-Administered Dissociative States Scale (CADSS)**

An external validation of the previously developed model (i.e. VPC) for CADSS focusing on the incidence of CADSS score > 4 at 40 min post-dose after every nasal esketamine/placebo dosing (i.e. maximum of 8 events per subject) showed that the previously developed model could describe the CADSS data from the two phase 3 studies (Figure 36 of the PK report).

Exposure-safety analysis

Regarding the VPCs and GOF plots presented in this report, the previously developed model for blood pressure seem to be applicable for the data obtained from studies SUI3001 and SUI3002.

Regarding the logistic regression model for the CADSS (as developed previously for the TRD indication) it is not clear on what the results for the 56 mg does in Figure 36 of the PK report are based, since in studies SUI3001 and SUI3002 only 84 mg were given. However, as shown in Figure 36 of the PK report, the probability of experiencing CADSS > 4 (40 min post-dose) is mostly lower for the 84 mg compared to a 56 mg dose. This required further explanation and justification which was provided satisfactorily by the company. The company was also requested to provide results for the probability of experiencing CADSS > 4 (40 min post-dose) by concentrations, dose, age and gender over time, as presented in Figure 48 for TRD in the Exposure response (efficacy and safety) Report EDMS-ERI-166762698, 07 August 2018.

## 2.3.5. Discussion on clinical pharmacology

For the extension of the indication in the context of this type II variation no further pharmacodynamic data are needed, since esketamine is proposed to be used in a subgroup of depressed patients.

There were however, as mentioned above, a few concerns on the population pharmacokinetic and exposure response (PK/PD) model that were resolved during the assessment.

No new bioavailability, pharmacokinetic or pharmacodynamic studies have been submitted. A population PK model has been further developed using pharmacokinetic data from the two phase 3 studies (SUI3001 and SUI3002). However, certain issues with respect to the results for the 56mg and the probability of experiencing CADSS>4 and further analysis of it had to be clarified.

Despite the fact that the mechanism of action of esketamine in depression has not been fully elucidated, it is known that esketamine is a non-selective, non-competitive, antagonist of the N-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor.

In accordance with the protocol, subjects in Studies SUI3001 and SUI3002 could have a one-time dose reduction any time after the first dose (and for all subsequent doses) to 56 mg if the subject was unable to tolerate the 84 mg dose. In addition, some subjects administered two devices (a 56 mg dose) instead of three devices (an 84 mg dose) on Day 1 of the double-blind treatment period due to adverse events (AEs)/tolerability during study drug administration. Therefore, the esketamine plasma concentrations in **Figure 8** of the population pharmacokinetic (PopPK) report were dose-normalized, and for those subjects who received a 56 mg dose, the exposure and Clinician Administered Dissociative States Scale (CADSS) scores for the 56 mg dose level were provided.

The y-axis was normalized to 84 mg because not all patients were treated with 84 mg. Dose reduction to 56 mg was permitted if a 84 mg dose was not tolerated. Then the issue was considered as resolved.

Patients allocated in the 56 mg group had received a dose reduction due to tolerability problems. Because patients were not randomly allocated to this dosing group, it could be that these patients showed a higher sensitivity to esketamine and therefore had a higher probability to suffer from a CADSS>4.

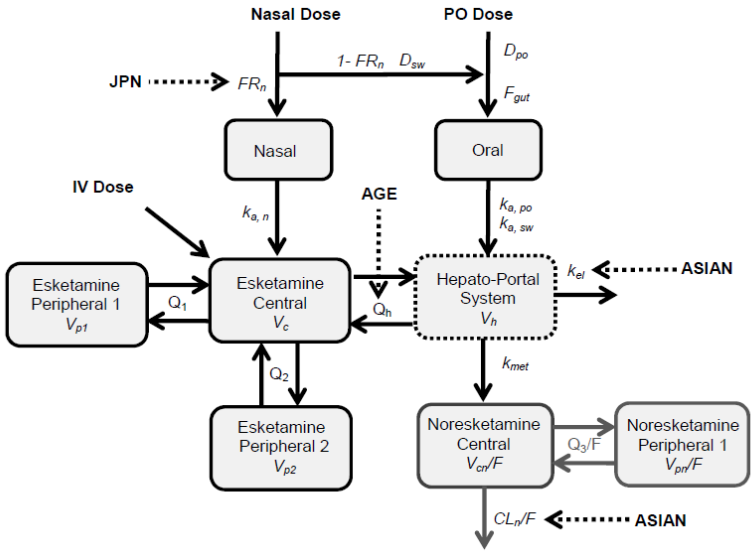
The company provided figures plotting the proportion of subjects experiencing CADSS >4 (40 minutes postdose) by concentrations, dose, age, and gender as a function of time (ie, with increase of the number of nasal esketamine administrations).

Similar to what was seen in the TRD studies, an increased probability of having CADSS >4 at 40 minutes postdose was observed in the SUI3001 and SUI3002 studies in subjects who were treated with esketamine compared to placebo. In addition, the proportion of subjects having a CADSS score >4

showed a decrease as a function of time suggesting development of tolerance, which was also observed in the analysis in the TRD population and implemented in the logistic regression model. A similar profile was observed for subjects who received 56 mg or 84 mg, which may be explained by the relatively small number of subjects who received the lower dose and that subjects were not randomly assigned to the 56 mg and 84 mg doses. However, subjects in Tercile 3 (ie, highest esketamine concentrations) exhibited the highest probability of having a CADSS >4 at 40 minutes postdose relative to subjects in Terciles 1 and 2. The covariates age and gender had no influence on the probability of having a CADSS >4 at 40 minutes postdose.

From the structural model in the popPK analyses, it was clear that the elimination rate constant from the compartment representing the hepato-portal system, causes parameter identifiability issues. As a consequence, multiple parameter solutions are available that result in a similar model fit, which could have affected the estimates of $AUC_{inf}$ and $C_{max}$ . Therefore, the current estimates of AUC and Cmax could not be trusted. The population pharmacokinetic analysis aimed to characterise the pharmacokinetics of esketamine and noresketamine for subjects randomised to receive esketamine in studies SUI3001 and SUI3002 (patients with treatment resistant depression). The identifiability issues refer to the model structure of the population pharmacokinetic model and therefore apply to both analyses. Also, the concern is referring to structural identifiability of the model and not necessarily the numerical identifiability of the model parameter estimates. The structural model used in this application is displayed below.

**Figure 6: Structural Model**




The inclusion of an elimination pathway (parameterized with $k_{el}$) from the hepato-portal system results in irreversible loss of drug (esketamine) from the system, but no observations are taken from this compartment. Therefore, even though it is acknowledged that the model could be mechanistically plausible, the parameter estimates could be influenced by this parameterization and multiple solutions can be identified. It is acknowledged that the model parameters are estimated with accurate precision, but if a model is numerically identifiable, this does not necessarily mean that the model is also structurally identifiable. It was reassuring to note however that the condition number of the model is low, indicating that the model is stable.

The applicant has tested input-output reachability by using stochastic simulation and estimation. However, in order to test input-output reachability, simulations should be conducted without between-subject and residual error to identify whether model parameters can be estimated in the absence of random error. The model should converge within a few iterations if the model structure is

identifiable. Other approaches are also suitable, such as suggested by Shivva *et al. 2013 CPT PSP.* As a result, it is still unclear whether the model is structurally identifiable. The consequences despite not deemed major should be considered in future applications.

The provided NPCs also relate to numerical stability of the model. These graphs demonstrate that the model has good predictive performance to estimate AUC and $C_{max}$ parameters. However, the graphs do not demonstrate the influence of possible identifiability issues. Nonetheless, the pharmacokinetic parameters of all populations exposed to esketamine have been estimated using this model structure. Therefore, if the parameter estimates would change substantially due to a different unique solution, this would apply for all populations. No clear differences between populations can be observed. Therefore, this issue was considered as solved.

### 2.3.6. Conclusions on clinical pharmacology

The pharmacokinetic properties of intranasal esketamine have been investigated adequately during the marketing authorisation application for TRD.

The primary and secondary pharmacological properties of esketamine are already described in the approved product information.

## *2.4. Clinical efficacy*

### 2.4.1. Dose response study(ies)

There was no formal dose-response study submitted in support of this type II variation application.

For the development program for the imminent risk of suicide or suicidal ideation in depressed patients, an esketamine dose of 84 mg was chosen for the initial Phase 2 proof-of-concept study (SUI2001) in subjects with the so-called MDSI (major depressive disorder in patients assessed to be at imminent risk for suicide). The rationale for this dose selection was based on the fact that the so-called condition MDSI requires rapid and robust intervention. The 84 mg dose of esketamine (with an option to reduce to the 56 mg dose) was selected to provide the greatest opportunity for rapid onset of efficacy and longer durability of effect, with acceptable tolerability in acutely ill patients. This regimen was implemented based on results from Phase 2 studies conducted in patients with TRD and with input from health authorities. Study treatment was initially administered in a hospital setting where any adverse effects were closely monitored and managed.

Based on the findings of the Phase 2 study SUI2001, which supported a positive benefit-to-risk ratio of acute treatment with esketamine 84 mg in this population, the dose of 84 mg was also used in the subsequent Phase 3 studies of similar design.

Spravato 84 mg twice weekly is the approved recommended dose in the induction phase in patients with TRD, after the starting dose of 56 mg in patients <65 years. Hence, clinical experience with 84mg esketamine is already available.

### 2.4.2. Main studies

For the support of the efficacy of esketamine in the proposed indication two Phase 3 studies in subjects with the so-called MDSI (SUI3001 and SUI3002) have been submitted, with additional supportive information from the Phase 2 study (SUI2001).

The Phase 3 studies (SUI3001 and SUI3002) were global, double-blind, randomized, placebo-controlled studies designed to evaluate the efficacy, safety, and tolerability of esketamine nasal spray 84 mg compared with placebo nasal spray in the treatment of subjects with MDSI and they were conducted across multiple countries worldwide:

- Study SUI3001 enrolled a total of 226 subjects across 10 countries (Bulgaria, Estonia, Germany, Hungary, Malaysia, South Africa, Republic of Korea, Spain, Taiwan, and the United States);
- Study SUI3002 enrolled 230 subjects across 12 countries (Argentina, Austria, Belgium, Brazil, Canada, Czech Republic, France, Lithuania, Poland, Spain, Turkey, and the United States).

In contrast, the Phase 2 study (SUI2001) was a smaller (N=68) proof of concept study conducted at sites in the US only.

Since the Phase 3 efficacy and safety pivotal studies had an identical design, the description of the main characteristics studies will be done in a combined manner in the rest of the document. The information on the Phase 2 proof-of-concept study (SUI2001) will be presented afterwards.

## Title of Studies

| Study Code | Title |
|---|---|
| Study Name: ASPIRE I<br>Protocol No.: 54135419SUI3001<br>EudraCT Number: 2016-003990-17<br>NCT No.: NCT03039192<br>Clinical Registry No.: CR108284 | A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Intranasal Esketamine 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 |
| Study Name: ASPIRE II<br>Protocol No.: 54135419SUI3002<br>EudraCT Number: 2016-003992-23<br>NCT No.: NCT03097133<br>Clinical Registry No.: CR108285 | A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Intranasal Esketamine 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 |

## *Methods*

Two double-blind, randomized, placebo-controlled, multi-center, global Phase 3 studies of identical design (Studies SUI3001 and SUI3002) were conducted in adults with MDD considered as patients, who were at imminent risk for suicide, by responding Yes to two questions [B3 and B10 of the Mini International Neuropsychiatric Interview (MINI)]. The studies investigated the efficacy of esketamine nasal spray (84 mg) plus comprehensive standard of care (SOC) compared with placebo nasal spray plus comprehensive SOC in reducing the symptoms of MDD, including suicidal ideation. Due to the vulnerability of the population, all subjects were treated in the context of comprehensive SOC, consisting of initial inpatient psychiatric hospitalization and the initiation or optimization of antidepressant therapy, enhanced by twice-weekly study visits with extensive clinical contact as well as permitted concomitant medications and psychotherapy. The treatment assignments are referred to as "esketamine + SOC" and "placebo + SOC" in the remainder of this document.

The studies consisted of 3 phases: a screening evaluation performed within 48 hours prior to the Day 1 dose of study medication (if possible, screening should have occurred within 24 hours prior to the Day 1 intranasal dose), immediately followed by a 25-day double-blind treatment phase, and a 65-day follow-up phase.

Multicenter, randomised, double-blind, placebo controlled trials are commonly conducted in depression and thus are considered appropriate for the patient population selected.

## Study participants

Subjects enrolling in the Phase 3 MDSI studies were required to meet the DSM-5 criteria for MDD (without psychosis), based on diagnostic assessment with the Mini International Neuropsychiatric Interview (MINI), and must have had a MADRS total score >28 at baseline, corresponding to moderate to severe depression. It is considered that more severe MDD patients typically have suicidal ideation than patients with less severe MDD and without suicidal ideation.

Depression Characteristics and Psychiatric History

Subjects enrolled in the Phase 3 MDSI studies represented a moderately to severely depressed population. In the pooled Phase 3 studies (SUI3001/3002), the mean (SD) baseline MADRS total score was 40.4 (5.82) (range: 29-58) and the median duration of the current depressive episode, derived from the MADRS euthymic baseline, was 15.8 months (range: 1-445 months).

Most subjects in the pooled Phase 3 studies had a prior history of suicide attempt(s) within their lifetime, and more than one-quarter of subjects reported a recent suicide attempt (ie, within the last month). Overall, subjects presented with evidence of an acute psychiatric illness as measured by multiple suicidality indices (please see Baseline Data section below).

It is noted that all subjects satisfied the enrolment criteria, which required that subjects had current suicidal ideation with intent at screening and within 24 hours of randomization, confirmed by a "Yes" response to the MINI Questions B3 (*Think [even momentarily] about harming or of hurting or of injuring yourself: with at least some intent or awareness that you might die as a result; or think about suicide [ie, about killing yourself]*) and B10 (*Intend to act on thoughts of killing yourself?*) assessed within 24 hours of randomization.

Demographic, baseline and depression characteristics and psychiatric history were generally similar between the treatment groups across the two Phase 3 pivotal studies (for details please see Baseline Data section below).

## Key Eligibility Criteria

Subjects enrolled in studies SUI3001 and SUI3002 were required to meet the following key criteria:

- Subject was a man or woman, 18 to 64 years of age, inclusive.
- Subject met Diagnostic and Statistical Manual of Mental Disorders - 5th edition (DSM-5) diagnostic criteria for MDD, without psychotic features, based upon clinical assessment and confirmed by the Mini International Neuropsychiatric Interview (MINI).
- Subject had current suicidal ideation with intent, confirmed by a "Yes" response to MINI Question B3 (Think [even momentarily] about harming or of hurting or of injuring yourself: with at least some intent or awareness that you might die as a result; or think about suicide [ie, about killing yourself]?) and Question B10 (Intend to act on thoughts of killing yourself?) within 24 hours prior to randomization. If the screening period was more than 24 hours prior to randomization, Question B3 and B10 assessments were repeated to confirm eligibility.
- In the physician's opinion, acute psychiatric hospitalization was clinically warranted due to subject's imminent risk of suicide.

- Subject had a Montgomery-Åsberg Depression Rating Scale (MADRS) total score of >28 predose on Day 1.
- Subject agreed to be hospitalized voluntarily for a recommended period of 5 days after randomization and to be administered prescribed non-investigational antidepressant therapy(ies) for at least the duration of the double-blind treatment phase.

Subjects were not enrolled in the studies if it was determined that they:

- Had a current DSM-5 diagnosis of bipolar (or related disorders), antisocial personality disorder, or obsessive compulsive disorder.
- Currently met DSM-5 criteria for borderline personality disorder.
- Had a current clinical diagnosis of autism, dementia, or intellectual disability.
- Had a current or prior DSM-5 diagnosis of a psychotic disorder, or MDD with psychotic features.
- Met the DSM-5 severity criteria for moderate or severe substance or alcohol use disorder (except for nicotine or caffeine) within the 6 months before screening.

All eligibility criteria in studies SUI3001 and SUI3002 are provided in the study protocols.

The key inclusion and exclusion criteria are in general acceptable.

It is noted that only MDD patients participated in the phase 3 studies and patients with other disorders were excluded. As already mentioned the studies focused on a subgroup of MDD patients.

The applicant states that the exclusion of subjects with a recent history of moderate to severe substance or alcohol use disorder was to ensure that subject's depressive symptoms were not due to substance-induced depressive disorder. However the DSM-5 diagnostic criteria already includes this specific criterion. The applicant further states that the use of substances during the study, which might be more likely for patients with previous use, could hamper conclusion on safety and efficacy. In addition, the applicant states that these patients might be more susceptible for the abuse potential of esketamine.

Exclusion of these subjects from the studies is unfortunate. Substance and alcohol abuse is relatively common in severely depressed patients and these patients could be potential candidates for esketamine treatment once brought to the emergency care due to suicidality. The argument on abuse potential is not agreed with, given that esketamine is administered in a controlled setting for short-term and the fact that studies in the TRD population did not show any drug seeking behaviour after discontinuing esketamine treatment. The proposed SmPC included a warning on individuals with a history of drug abuse or dependence. The applicant was requested to discuss whether this warning was.

## Treatments

Eligible subjects were randomized to esketamine nasal spray 84 mg + SOC or placebo nasal spray + SOC, administered 2 times per week for 4 weeks.

**Table 10 (SUI3001/SUI3002 CSR): Intranasal treatment administration during the double-blind phase, 84 mg**

| | Time of Nasal Spray Device Administration | | |
|---|---|---|---|
| Study Treatment | 0 [a] | 5 minutes | 10 minutes |
| Nasal spray device [b] | 1st | 2nd | 3rd |
| Placebo for 84 mg | 1 spray of placebo to each nostril | 1 spray of placebo to each nostril | 1 spray of placebo to each nostril |
| Esketamine 84 mg | 1 spray of esketamine to each nostril | 1 spray of esketamine to each nostril | 1 spray of esketamine to each nostril |

[a] Time 0 was defined as the time of administration of the first spray to one nostril from the first device.
[b] One device was used at each time point. Each individual device contained 2 sprays. The devices containing esketamine delivered 14 mg per spray, for a total of 28 mg per individual device (ie, 2 sprays).

**Table 11 (SUI3001/SUI3002 CSR): Intranasal treatment administration during the double-blind phase, 56 mg**

| | Time of Nasal Spray Device Administration | | |
|---|---|---|---|
| Treatment | 0 [a] | 5 minutes | 10 minutes |
| Nasal spray device [b] | 1st | 2nd | 3rd |
| Placebo for 56 mg | 1 spray of placebo to each nostril | 1 spray of placebo to each nostril | 1 spray of placebo to each nostril |
| Esketamine 56 mg | 1 spray of esketamine to each nostril | 1 spray of esketamine to each nostril | 1 spray of placebo to each nostril |

[a] Time 0 was defined as the time of administration of the first spray to one nostril from the first device.
[b] One device was used at each time point. Each individual device contained 2 sprays. The devices containing esketamine delivered 14 mg per spray, for a total of 28 mg per individual device (ie, 2 sprays).

The applicant chose the 84 mg dose for the MDSI studies in order to provide the patients the best chance of improvement. However, a clear dose-response or a justified choice of one dose above the other could not be concluded in the TRD studies. Therefore a flexible dosing approach was chosen. As such, the 84 mg dose is considered to be acceptable from safety perspective, and the SmPC includes the possibility to reduce the dose to 56 mg in case of intolerance. This is an acceptable approach, as efficacy in terms of MADRS is consistent with the 84 mg dose.

Comprehensive SOC:

This was the first global registration program of patients with MDSI, a population typically excluded from antidepressant treatment trials. To ensure a proper standard of safety and ethical trial conduct in this vulnerable population, the Phase 2 and Phase 3 MDSI studies were implemented in the context of comprehensive SOC, which included:

- Initial inpatient psychiatric hospitalization
- Newly initiated or optimized antidepressant therapy per the clinician's judgement, including antidepressant monotherapy or antidepressant plus augmentation therapy (antidepressant plus an additional antidepressant, antipsychotic, or mood stabilizer)
- Permitted concomitant medications (eg, benzodiazepines) and psychotherapy per standard of care.

Additionally, the comprehensive SOC was enhanced by twice-weekly study visits with extensive clinical contact (during initial hospitalization and after hospital discharge) during the double-blind phase. This aspect of the program is important to consider when interpreting the results.

**Table 12 (Summary of Clinical Efficacy): Standard of Care Received (>5% of Subjects Overall); Double-blind Treatment Phase; Safety Analysis Set**

| | Study SUI3001 | Study SUI3002 | Pooled Studies SUI3001 and SUI3002 |
|---|---|---|---|
| Analysis set: Safety | 225 | 227 | 452 |
| No. of subjects with standard of care received | 224 (99.6%) | 227 (100.0%) | 451 (99.8%) |
| Standardized Medication Name | | | |
| Venlafaxine | 56 (24.9%) | 64 (28.2%) | 120 (26.5%) |
| Quetiapine | 32 (14.2%) | 64 (28.2%) | 96 (21.2%) |
| Escitalopram | 36 (16.0%) | 39 (17.2%) | 75 (16.6%) |
| Duloxetine | 35 (15.6%) | 33 (14.5%) | 68 (15.0%) |
| Mirtazapine | 35 (15.6%) | 29 (12.8%) | 64 (14.2%) |
| Sertraline | 20 (8.9%) | 31 (13.7%) | 51 (11.3%) |
| Bupropion | 24 (10.7%) | 24 (10.6%) | 48 (10.6%) |
| Aripiprazole | 22 (9.8%) | 25 (11.0%) | 47 (10.4%) |
| Desvenlafaxine | 15 (6.7%) | 21 (9.3%) | 36 (8.0%) |
| Trazodone | 10 (4.4%) | 17 (7.5%) | 27 (6.0%) |
| Fluoxetine | 11 (4.9%) | 13 (5.7%) | 24 (5.3%) |
| Lithium | 10 (4.4%) | 14 (6.2%) | 24 (5.3%) |
| Paroxetine | 16 (7.1%) | 8 (3.5%) | 24 (5.3%) |

Source: Adapted from Mod5.3.5.1/SUI3001/AttTSICM04A, Mod5.3.5.1/SUI3002/AttTSICM04A, and Appendix 9

The first dose was administered in the emergency room or other permitted setting, including the inpatient psychiatric unit. Subjects were to remain in the inpatient psychiatry unit for a recommended duration consistent with local SOC [5 or 14 days (in Study SUI3001 and most countries in Study SUI3002, the recommended duration of hospitalization was 5 days; in some countries in Study SUI3002, the recommended duration was 14 days to be consistent with local practice)] with shorter or longer hospitalizations permitted if clinically warranted. Following discharge, subsequent visits for the double-blind treatment phase were conducted twice weekly at an outpatient psychiatric facility through Day 25. During the follow-up phase, subjects were to be monitored twice weekly for the first 2 weeks after study medication treatment, then followed up weekly for the next 2 weeks, and every 2 weeks for the rest of the follow-up period through Day 90.

It is noted that all types of antidepressants were allowed as SOC, which allowed flexibility and minimum treatment restrictions. This is required for such a depressed population with thoughts of committing suicide.

## Objectives

The two Phase 3 studies (ASPIRE I, 54135419SUI3001 and ASPIRE II, 54135419SUI3002) had the same primary objective:

- to evaluate the efficacy of intranasal esketamine 84 mg compared with intranasal placebo in addition to comprehensive standard of care in reducing the symptoms of MDD, including suicidal ideation, in subjects who were assessed to be at imminent risk for suicide, as measured by the change from baseline on the MADRS total score at 24 hours post first dose.

The key secondary objective for both phase 3 studies was:

- The key secondary objective was to assess the efficacy of intranasal esketamine compared with intranasal placebo in reducing severity of suicidality as measured by the Clinical Global Impression – Severity of Suicidality – Revised (CGI-SS-R) at 24 hours post first dose.

The objectives of the studies are considered appropriate and reduction of suicidality is considered as an essential part of the primary objective.

## Outcomes/endpoints

**Efficacy Endpoints**

The predefined efficacy endpoints for each of the Phase 3 studies are provided below.

Primary Endpoint

The primary efficacy endpoint was change from baseline (Day 1, predose) to 24 hours after the first dose (Day 2) in MADRS total score.

Key Secondary Endpoint

The key secondary efficacy endpoint was change from baseline for CGI-SS-R at 24 hours after the first dose (Day 2).

Other Secondary Efficacy Endpoints

Other secondary efficacy endpoints evaluated over time through the end of the double-blind treatment phase (Day 25) included the following:

Change in MADRS total score from baseline

Number of subjects who achieved remission of MDD (MADRS total score ≤12)

Change in CGI-SS-R from baseline

Number of subjects who achieved resolution of suicidality (CGI-SS-R score of 0 or 1)

Change in CGI-SR-I from baseline

Change in BHS total score from baseline

Changes in EQ-5D-5L dimension scores, health status index, EuroQol Group, Visual Analogue Scale (EQ-VAS), and sum score from baseline

Change in QLDS score from baseline

TSQM-9 domain scores of effectiveness, convenience and global satisfaction

Change in clinician-rated FoST from baseline

Change in patient-reported FoST from baseline

Change in Module 5 Question 1 (Desire to Die in the Past 7 Days), Question 2 (Intent to End Life in the Past 7 Days) and Question 4 (Likelihood to Attempt to End Life in the Near Future); note, these were post-hoc analyses in Study SUI3001 from baseline

Exploratory Efficacy Endpoints

Exploratory efficacy endpoints evaluated over time through the end of the double-blind treatment phase (Day 25) included the following:

Number of subjects who achieved response (at least 50% improvement in MADRS total score from baseline)

Change in MADRS individual item scores from baseline

Change in SIBAT Module 2 (My Risk/Protective Factors) total score from baseline

Change in SIBAT Module 3 (My Current Thinking) total score from baseline

Change in SIBAT Module 7 CGI-SR-LT score assessing long-term suicide risk from baseline

Change in SIBAT Module 8 (Clinical Judgment of Optimal Suicide Management) score from baseline

As additional exploratory endpoints, all efficacy assessments described above were evaluated over time during the post-treatment follow-up phase through Day 90.

With respect to Major Depressive Disorder and depressive symptoms, MADRS is considered the most appropriate scale. Other important MADRS endpoints are the proportion of responders and remitters throughout the study as well as the change in MADRS total score from baseline to the end of the DB treatment phase.

CGI-SS-R, which was used for the assessment of suicidality, is part of the SIBAT. At the time of the qualification advice of SIBAT, it was emphasised that the clinical meaningfulness of changes in the score in CGI-SS-R were unclear and that whether CGI-SS-R can be used as a key secondary endpoint cannot be confirmed. Further research was expected in order to evaluate the responsiveness of the SIBAT global clinical ratings to changes in clinical status. The relationship between changes in CGI-SS-R scores and changes in MADRS total score, suicidal ideation item and the SIBAT FoST was expected to be assessed and finally validated in the Phase 3 program. It was also stated that the underlying assumption that increasing CGI-SS-R risk level is associated with an increased probability of suicide/attempted suicide/self-harm will need to be further substantiated. In addition, sensitivity to change and sensitivity to detect a treatment effect would be required for final validation of the SIBAT. Nevertheless, the applicant has chosen to apply CGI-SS-R as key secondary endpoint, while it is not fully validated.

It should be noted that the Beck Scale for Suicidal Ideation (BSS), which was used in the Phase 2 study, could have been also used in the Phase 3 studies to assess the patient's suicidality and as an anchor to validate the CGI-SS-R within the same study.

It should be also noted that a reliable, validated, commonly used, standard tool/scale, as in the case of depression, does not exist for the complex issue of suicidality. It has been reported that most of the instruments were not developed to detect rapid fluctuations of suicidal ideation or behaviour by the patients or to allow a well-informed clinician's assessment. There is no sensitive and specific algorithm to predict suicide in clinical practice and improve the recognition and understanding of clinical, psychological, sociological, and biological factors, which may facilitate the detection of high-risk individuals and assist in treatment selection.

## Sample size

The two Phase 3 studies had the same sample size determination:

The sample size for this study was calculated assuming an effect size of 0.45 for the MADRS total score at 24 hours after the first dose (Day 2), a two-sided significance level of 0.05, and a drop-out rate at 24 hours of 5%. Approximately 112 subjects were required to be randomly assigned to each treatment group to achieve 90% power. The effect size used in this calculation was based on results of the SUI2001 study where the effect size for the change from baseline to Day 2 was 0.65 (mean difference between treatment groups of -7.2 and a pooled SD of 11.02) for MADRS total score. Given that the SUI2001 study was a Phase 2 study carried out in only one country, the sample size for this Phase 3 study was determined

using a smaller effect size of 0.45 to allow for greater variability that was expected for a study conducted globally.

Sample size calculation was deemed appropriate.

## Randomisation

Randomization was used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes were evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. The randomization was stratified by study center and by the SOC antidepressant therapy (ie, antidepressant monotherapy or an antidepressant plus augmentation therapy, as determined by the investigator). The stratification was aimed at balancing treatment groups within the SOC antidepressant therapy to be initiated or optimized on Day 1, as antidepressant monotherapy and antidepressant plus augmentation therapy may be differentially effective.

Randomisation was required and deemed appropriate.

## Blinding (masking)

Blinded intranasal treatment (esketamine versus placebo) was used to reduce potential bias during data collection and evaluation of clinical endpoints. As esketamine has known characteristic effects that may impact blinding (such as dissociative symptoms, sedation, and elevation of blood pressure), these specific treatment-emergent events potentially could have biased the research staff who observed dose administration. To minimize this bias, the protocols for the Phase 3 studies required that different raters perform efficacy and safety assessments; this was also recommended in the Phase 2 study protocol (SUI2001).

In addition, the esketamine and placebo nasal spray devices used in the Phase 2 and 3 studies were indistinguishable, and a bittering agent (denatonium benzoate) was added to the placebo solution to simulate the taste of the esketamine solution.

The efforts to minimise the risk of a potential effect on blinding were considered sufficient.

## Statistical methods

The same statistical methods were applied for both of the phase 3 studies (SUI3001/SUI3002).

Target of estimation (estimand)

The primary estimand, the main clinical quantity of interest to be estimated in the study, was defined by the following 4 components:

- Population: subjects with MDSI, as defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population;
- Variable: change from baseline to 24 hours after the first dose (Day 2) in the MADRS total score;
- Intervention Effect: the effect of the initially randomized treatment that would have been observed had all subjects remained on their treatment until Day 2 of the double-blind treatment phase;
- Summary Measure: the difference in variable LS means.

The primary analysis was based on the full analysis set and the MADRS total scores collected at Day 2.

The wording suggests that a hypothetical strategy was used for all intercurrent events. Targeting a hypothetical treatment effect is usually not of primary interest from a regulatory point of view because it tends to overestimate the effect that can be expected in clinical practice. However, as remaining on treatment until Day 2 only means taking the initial dose of study medication (as second dose was taken after Day 2), in this case, targeting the hypothetical effect makes a negligible difference to targeting the effect regardless of study medication intake that is usually of primary regulatory interest, as usually almost all patients are treated.

Analysis methods

The efficacy analyses of data in the double-blind treatment phase were based on the full efficacy analysis set. The full efficacy analysis set was defined as all randomized subjects who received at least 1 dose of double-blind study agent and had both a baseline and a post baseline evaluation for the MADRS total score or CGI-SS-R.

The follow-up analysis set was defined as all subjects who completed the double-blind treatment phase and either entered the follow-up phase or provided AE data after the double-blind treatment phase. This analysis set was used for both efficacy and safety analyses during the follow-up phase.

Statistical analysis tests were conducted at a 2-sided 0.050 level of significance unless specified otherwise. Multiplicity, with regard to testing multiple endpoints (the primary and the key secondary), was controlled by a fixed sequence testing procedure, ie, the key secondary hypothesis was to be tested only after the null hypothesis for the primary endpoint was rejected. Two-sided p-values were only presented for the primary and key secondary endpoint. Point estimates of the treatment differences and 95% confidence interval (CIs) were presented for all other endpoints.

For endpoints using ANCOVA, the last observation carried forward (LOCF) method was applied to the MADRS, CGI-SS-R, CGI-SR-I, BHS, and QLDS score for the double-blind and follow-up phases. Double-blind observations were not carried forward into the follow-up phase. The last post baseline observation during the double-blind treatment phase was carried forward as the endpoint for that phase. The last post baseline observation during the follow-up phase was carried forward as the endpoint for that phase. In addition to the observed cases and the endpoint assessment, the LOCF values were created for intermediate post baseline time points as well.

The primary efficacy endpoint of change from baseline (Day 1, predose) to 24 hours after the first dose (Day 2) in MADRS total score, was analyzed using an ANCOVA (LOCF) model, with factors for treatment (placebo or esketamine 84 mg), analysis center, SOC antidepressant treatment as randomized (antidepressant monotherapy or antidepressant plus augmentation therapy), and baseline MADRS total score as a continuous covariate.

If over 5% of the primary endpoint data at 24 hours was missing, then additional sensitivity analyses that rely on Missing Not at Random assumptions were to be performed to assess the robustness of the primary analysis. To assess the sensitivity of the results of the ANCOVA (LOCF) model for the primary efficacy endpoint, a baseline observation carried forward (BOCF) imputation was applied.

For subgroup analysis, forest plots were provided displaying analysis results for each subgroup. The point estimate of the treatment difference and its 95% confidence interval for each subgroup was based on an ANCOVA for the primary endpoint using the appropriate contrast based on the same model as for primary analysis but including subgroup and treatment-by-subgroup as additional factors.

The analysis of the key secondary efficacy endpoint, change from baseline for CGI-SS-R at 24 hours after the first dose (Day 2), was performed for LOCF data using an ANCOVA model on the ranks of change with

factors for treatment, analysis center, SOC antidepressant treatment as randomized (ie, antidepressant monotherapy or an antidepressant plus augmentation therapy) and baseline CGI-SS-R (unranked) as a covariate. The treatment difference was estimated using the Hodges-Lehmann estimate, which is the median of all possible paired differences for the change from baseline for CGI-SS-R at 24 hours. The treatment difference was also estimated using LS means based on an ANCOVA model on the actual change with factors for treatment, analysis center, SOC antidepressant treatment as randomized (ie, antidepressant monotherapy or antidepressant plus augmentation therapy) and baseline CGI-SS-R (unranked) as a covariate. The cumulative distribution function for any improvement and percent improvement from baseline to 24 hours in CGI-SS-R were graphically presented. Item response modeling was used to estimate treatment difference using an odds ratio by transforming the ordinal data to a hidden continuous scale via the logit model. The estimated treatment effect was transferred back to the original scale by exponentiation and was then interpreted as an odds ratio.

To assess the sensitivity of the results of models for the key secondary endpoint (change from baseline for CGI-SS-R at 24 hours post first dose), a BOCF imputation was applied.

Forest plots were provided displaying analysis results for each subgroup. The median estimate of the treatment difference in terms of odds ratio and its 95% credible interval for each subgroup were based on item response modeling for the key secondary endpoint using the appropriate contrast.

The above-mentioned analyses were also performed for the pooled Phase 3 studies (SUI3001/3002), with study number (SUI3001 or SUI3002) added as an additional factor to the statistical models.

The ANCOVA as described above for the change in MADRS total score was also used to analyze all other post baseline timepoints for both observed case and LOCF data. To assess the sensitivity of the results of the ANCOVA at the double-blind and follow-up endpoints, an MMRM analysis based on observed case data was performed comparing treatments for the change from baseline (Day 1, predose) to Day 25 (double-blind treatment phase) and Day 90 (follow-up phase) in MADRS total score. The model included baseline MADRS total score as a continuous covariate, and day, treatment, analysis center, SOC antidepressant treatment as randomized (antidepressant monotherapy or antidepressant plus augmentation therapy), and day-by-treatment interaction as fixed effects, and a random subject effect.

At each time-point during the double-blind and follow-up phases, a frequency distribution of the CGI-SS-R score and changes from baseline were provided for both the observed case and LOCF data. In addition, descriptive statistics for these scores and the changes from baseline were provided for both the observed case and LOCF data. Hodges-Lehmann estimates and the corresponding 95% CI for the treatment differences were provided for each time-point. An ANCOVA model on the change from baseline for both LOCF and observed case data was performed for each time-point as an additional exploratory analysis.

Frequency distributions of subjects who achieved response (≥50% improvement in MADRS total score from baseline), remission (MADRS total score ≤12) and resolution of suicidality were provided at each time point during the double-blind treatment and follow-up phases. The estimates of the treatment difference in proportions and the 95% CIs were reported at each time point.

Additional analyses for the change in CGI-SS-R score and other suicidality indices (ie, MADRS suicidal thoughts item, CGI-SR-I, clinician-rated FoST, patient-reported FoST) over time were added post-hoc, including item response modelling with LOCF and BOCF, ANCOVA (LOCF) and MMRM with observed case data.

The statistical methods are generally considered acceptable.

The primary analysis should usually be based on all randomised patients not excluding non-treated patients or patients without baseline or post-baseline data. However, the number of excluded patients

was negligible. A per protocol analysis set was not defined and a per protocol analysis, with exclusion of major protocol deviations was requested and provided.

The significance level was specified as 2-sided 0.05 and multiplicity was controlled by a fixed sequence testing procedure for the primary and key secondary endpoint, which is acceptable.

The primary analysis was performed using ANCOVA, including stratification factors and baseline values. As sensitivity analysis, MMRM on observed cases was performed. These analyses are considered acceptable.

The method for handling missing values should be aligned to the target of estimation (estimand). It appears questionable whether it can be assumed that the last observed value corresponds to the value that could be expected to be observed if a patient had remained on treatment. However, as missing values at Day 2 were negligible, this is not considered an issue for the primary analysis or key secondary analysis.

For the key secondary endpoint, several different analyses were pre-defined. It is assumed that the ANCOVA model on the ranks of changes in CGI-SS-R was the main analysis for deciding on efficacy of treatment for this endpoint, and the Hodges-Lehmann estimate is the main effect measure. During scientific advice, an alternative such as an ANCOVA based on original data, an ordered logistic regression or an analysis based on a responder definition for the CGI-SS-R were suggested. Here item response modelling and ANCOVA of original data were performed as sensitivity analyses. It is acknowledged that describing the treatment effect for an ordinal-scaled endpoint is not straightforward because distances between categories of the scale cannot be interpreted. Therefore, it is not clear whether the ANCOVA analysis based on the actual values is valid. The item response analysis resulting in an odds ratio for achieving a lower score is an interesting explorative analysis but also difficult to interpret. Firstly, the application of the Bayesian framework is not standard in the regulatory context. It is not clear why no alternative frequentist likelihood-based methods were applied for the item response model; a proportional odds model would also have been an alternative allowing a similar interpretation as the item response analysis. Secondly, the interpretation of odds ratios in terms of clinical relevance is generally difficult and not intuitive, particularly for ordinal scales.

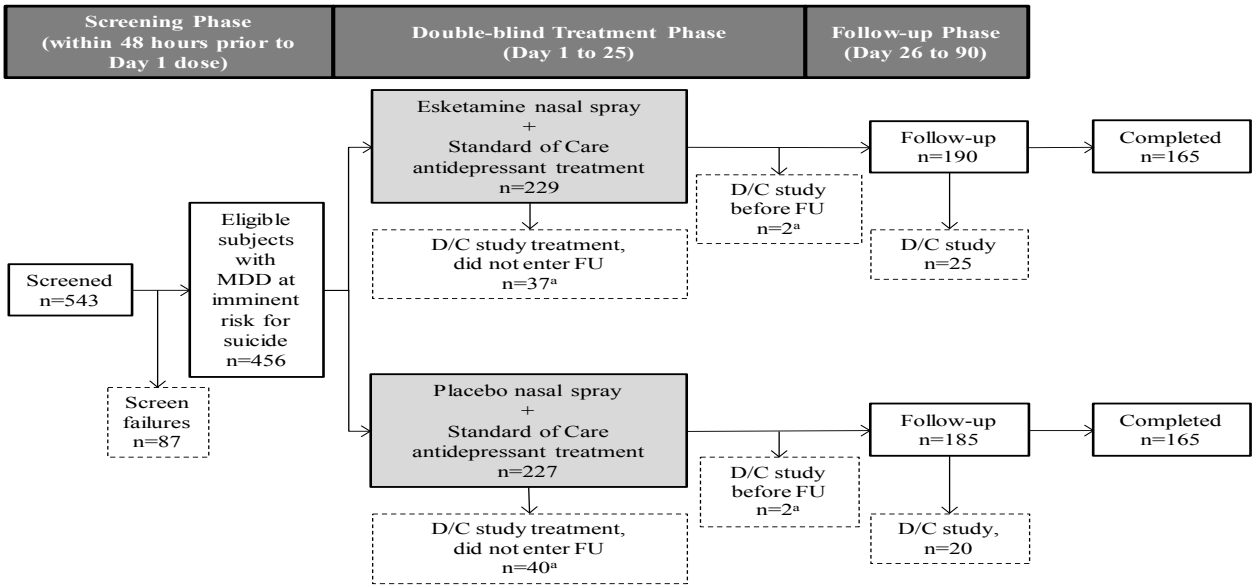
For the change in MADRS total score over time, it is not clear what treatment effect (estimand) was actually intended to be addressed by the ANCOVA (LOCF) analysis. It can neither be considered to be aligned to the hypothetical effect if a patient had remained on treatment (for which an improvement compared to last observed value may be expected), nor to the effect regardless of treatment discontinuation (under which worsening of condition might be expected because of loss of effect after discontinuation). A BOCF analysis may be expected to be a conservative analysis for targeting the effect regardless of treatment discontinuation that is of primary regulatory interest. This analysis was provided for the pooled studies and is reported in the SmPC, which is acceptable.

Similar considerations apply for the additional endpoints that were analyzed by ANCOVA(LOCF).

## *Results*

## Participant flow

**Figure 7 (Summary of Clinical Efficacy): Participant Flow Diagram Through Studies SUI3001 and SUI3002**




Abbreviations: CSR = Clinical Study Report; D/C=discontinued; FU=follow-up phase; MDD=major depressive disorder

[a] Itemized reasons for withdrawal are described in **Table 16** (for the double-blind treatment phase) and in the CSRs (for all phases).Source: Mod5.3.5.1/SUI3001/Sec4.1 and Mod5.3.5.1/SUI3002/Sec4.1

The design of the study together with the duration of the double-blind and follow-up phases are considered appropriate for the specific subgroup of patients. ≥80% of subjects completed the double-blind treatment phase, which is a similar completion rate to the TRD studies. A rapid action on depression was expected since this has already been indicated by the studies performed with esketamine in TRD and the available information up to now. A rapid acting antidepressant effect can be demonstrated within at Day 2 and sustained at 4 weeks time. A subsequent follow-up period of 10 weeks is considered sufficient in such a case.

## Recruitment

| Study Code | Study period |
|---|---|
| ASPIRE I<br>54135419SUI3001 | 29 June 2017 (Date first subject signed informed consent) to 18 December 2018 (Date of last observation for last subject recorded as part of the database) |
| ASPIRE II<br>54135419SUI3002 | 22 June 2017 (Date first subject signed informed consent) to 11 April 2019 (Date of last observation for last subject recorded as part of the database) |

## Conduct of the study

| Study Code | Study centres |
|---|---|
| Study Name: ASPIRE I<br>Protocol No.: 54135419SUI3001<br>EudraCT Number: 2016-003990-17<br>NCT No.: NCT03039192<br>Clinical Registry No.: CR108284 | Subjects were enrolled in Bulgaria (5 sites), Estonia (2 sites), Germany (3 sites), Hungary (5 sites), Malaysia (3 sites), South Africa (2 sites), Republic of Korea (5 sites), Spain (7 sites), Taiwan (4 sites), and the United States (13 sites) |
| Study Name: ASPIRE II<br>Protocol No.: 54135419SUI3002<br>EudraCT Number: 2016-003992-23<br>NCT No.: NCT03097133<br>Clinical Registry No.: CR108285 | Subjects were enrolled in Argentina (4 sites), Austria (2 sites), Belgium (2 sites), Brazil (5 sites), Canada (1 site), Czech Republic (2 sites), France (5 sites), Lithuania (2 sites), Poland (4 sites), Spain (3 sites), Turkey (4 sites), and the United States (13 sites) |

Protocol amendments

*SUI3001*

Three substantial protocol amendments occurred during the study.

In the first protocol amendment on 7 April 2017, the main protocol amendments concerned clarifications on the inclusion and exclusion criteria.

In the second protocol amendment on 20 April 2017, the main protocol amendments concerned clarifications on the inclusion and exclusion criteria as well as texts regarding drug discontinuation and study withdrawal, revision of the Time and Events Schedule for the follow-up phase, further specifications on the statistical methods

In the third amendment on 8 February 2018 the previously planned interim analysis was removed from the study to ensure that the study has sufficient numbers of subjects from key global regions/countries. Other main amendments considered clarifications on endpoints and exclusion criteria and modifying screening procedures with respect to timing.

*SUI3002*

Two substantial protocol amendments occurred during the study, which were identical to amendments two and three in study SUI3001.

The protocol amendments are not considered such that they could have a major impact on overall study results.

Protocol deviations

*SUI3001*

Of 226 subjects randomly assigned to treatment, there were 29 (12.8%) patients with 1 or more major protocol deviations. In total, 32 major protocol deviations were reported. The most common protocol deviation was entering incorrect stratification factor in SOC antidepressant therapy (monotherapy/augmentation). This occurred in 18 patients. No patients were withdrawn from the study due to protocol deviation.

*SUI3002*

Of 230 subjects randomly assigned to treatment, there were 34 (14.8%) with 1 or more major protocol deviations. In total, 36 major protocol deviations were reported. As in study SUI3001, The most common protocol deviation was entering incorrect stratification factor in SOC antidepressant therapy, which occurred in 11 patients. One patient (in the SOC + placebo group) was withdrawn from the study due to protocol violation, which was positive urine test for cocaine use.

Major protocol deviations concerned entering the wrong stratification factor in terms of SOC antidepressant therapy. The number of patients where this occurred is notable, 38 in the pooled Phase 3 study population. Efficacy of esketamine on top of SOC seemed to be only slightly more pronounced in patients on augmentation therapy as compared to patients on AD monotherapy. It was considered that these protocol deviations did not impact the overall conclusions of the studies.

## Baseline data

The demographic and baseline characteristics for subjects in the full efficacy analysis set are summarized in **Table 13** of the Summary of Clinical Efficacy. Additional details are provided in the CSRs, and in Appendices 5 and 6 of the Summary of Clinical Efficacy.

Demographics were generally similar across treatment groups and across studies, as follows:

- Overall, the mean (SD) age was 40.1 (13.00) years, ranging from 18 to 64 years.
- The majority of subjects were female (60.8%).
- Nearly three-quarters of subjects (73.2%) were White, 13.1% were Asian, and 5.8% were Black or African American.
- Enrollment in the Phase 3 studies by geographic region was 49.4% in Europe, 27.3% in North America, 11.8% in Asia, and 11.5% in South America; more than one-quarter (27.1%) of subjects were enrolled in the United States. The two phase 3 studies included patients from Europe: pooled studies placebo + SOC n=106 and Esketamine 84 plus SOC n=117 (SUI3001: Bulgaria, Estonia, Germany, Hungary and Spain; SUI3002: Austria, Belgium, Czech Republic, France, Lithuania, Poland and Spain). The rest of the patients from the pooled studies were 65 and 58 from North America, 27 and 26 from Asia and 27 and 25 from South America for placebo + SOC and Esketamine + SOC, respectively.
- Prior to entering the study, 92.0% of the patients were receiving antidepressant therapy (including antidepressants, mood stabilizers, atypical antipsychotics and typical antipsychotics); see Appendix 5 (TSICM07_SCE).

- As recorded at randomization, 47.0% of subjects (55.4% in Study SUI3001 and 38.8% in Study SUI3002) were to receive antidepressant monotherapy as SOC treatment, and 53.0% of subjects (44.6% in Study SUI3001 and 61.2% in Study SUI3002) were to receive antidepressant plus augmentation therapy.

Depression Characteristics and Psychiatric History at Baseline

Subjects enrolled in the Phase 3 MDSI studies represented a moderately to severely depressed population. Depression characteristics and psychiatric history at baseline for subjects in the Phase 3 MDSI studies included in the full efficacy analysis set are summarized in **Table 14** of the Summary of Clinical Efficacy. Additional details can be found in the CSRs.

The eligibility criteria in each study were similar, resulting in depression characteristics and psychiatric history that were generally similar across studies and across treatment groups, with the following results in the pooled analysis:

- The mean (SD) baseline MADRS total score was 40.4 (5.82) overall, ranging from 29 to 58, which corresponds to moderate to severe depression.
- The median (range) duration of the current depressive episode, derived from the MADRS euthymic baseline, was 15.8 (1; 445) months overall.
- The majority of subjects (90.0%) were rated by the clinician to be moderately to extremely suicidal, as measured by the CGI-SS-R scale.
- All subjects (100.0%) responded "Yes" to MINI Questions B3 and B10 Current Status within 24 hours prior to randomization (ie, confirming active suicidal ideation and intent).
- Based on responses to MINI Question B3 Current Status – Frequency at baseline, 87% of subjects were thinking about suicide often or very often, and 94% were thinking about suicide with moderate or severe intensity
- The majority of subjects (63.1%) reported any prior suicide attempt and 27.3% reported a suicide attempt within the last month.
- 86% of subjects were considered by the clinician to have moderate to extreme imminent risk for suicide within the next 7 days, as measured by the Clinical Global Impression – Imminent Suicide Risk (CGI-SR-I).
- The mean (SD) baseline Beck Hopelessness Scale (BHS) total score was 15.6 (4.26), indicating a severe sense of hopelessness.

Depression characteristics and psychiatric history were generally similar between the treatment groups, and between the 2 studies. There was however a higher proportion of subjects in the esketamine + SOC group than in the placebo + SOC group who had a recent suicide attempt (ie, within the last month) in Study SUI3002 (31.6% versus 21.2%, respectively); the corresponding proportions were 28.6% versus 27.7%, respectively, in SUI3001, and 30.1% versus 24.4%, respectively, in the pooled Phase 3 studies.

**Table 13 (Summary of Clinical Efficacy modified): Summary of Demographics and Baseline Characteristics of the Phase 3 Studies; Full Efficacy Analysis Set**

| | Study SUI3001 | | | Study SUI3002 | | | Pooled Studies SUI3001 and SUI3002 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Placebo + SOC | Esk 84 mg + SOC | Total | Placebo + SOC | Esk 84 mg + SOC | Total | Placebo + SOC | Esk 84 mg + SOC | Total |
| Analysis set: Full Efficacy | 112 | 112 | 224 | 113 | 114 | 227 | 225 | 226 | 451 |
| Sex | | | | | | | | | |
| N | 112 | 112 | 224 | 113 | 114 | 227 | 225 | 226 | 451 |
| Female | 73 (65.2%) | 65 (58.0%) | 138 (61.6%) | 67 (59.3%) | 69 (60.5%) | 136 (59.9%) | 140 (62.2%) | 134 (59.3%) | 274 (60.8%) |
| Male | 39 (34.8%) | 47 (42.0%) | 86 (38.4%) | 46 (40.7%) | 45 (39.5%) | 91 (40.1%) | 85 (37.8%) | 92 (40.7%) | 177 (39.2%) |
| Standard of Care Antidepressant Treatment as Randomized | | | | | | | | | |
| N | 112 | 112 | 224 | 113 | 114 | 227 | 225 | 226 | 451 |
| Antidepressant Monotherapy | 65 (58.0%) | 59 (52.7%) | 124 (55.4%) | 43 (38.1%) | 45 (39.5%) | 88 (38.8%) | 108 (48.0%) | 104 (46.0%) | 212 (47.0%) |
| Antidepressant Plus Augmentation Therapy | 47 (42.0%) | 53 (47.3%) | 100 (44.6%) | 70 (61.9%) | 69 (60.5%) | 139 (61.2%) | 117 (52.0%) | 122 (54.0%) | 239 (53.0%) |
| Standard of Care Antidepressant Treatment as Actually Received | | | | | | | | | |
| N | 111 | 112 | 223 | 113 | 114 | 227 | 224 | 226 | 450 |
| Antidepressant Monotherapy | 51 (45.9%) | 52 (46.4%) | 103 (46.2%) | 36 (31.9%) | 43 (37.7%) | 79 (34.8%) | 87 (38.8%) | 95 (42.0%) | 182 (40.4%) |
| Antidepressant Plus Augmentation Therapy | 50 (45.0%) | 56 (50.0%) | 106 (47.5%) | 68 (60.2%) | 67 (58.8%) | 135 (59.5%) | 118 (52.7%) | 123 (54.4%) | 241 (53.6%) |
| AD Monotherapy/AD Plus Augmentation Therapy[a] | 10 (9.0%) | 4 (3.6%) | 14 (6.3%) | 9 (8.0%) | 4 (3.5%) | 13 (5.7%) | 19 (8.5%) | 8 (3.5%) | 27 (6.0%) |

AD = antidepressant; Esk = esketamine; N/A = not applicable; SD = standard deviation; SOC = standard of care

[a] Subjects received both antidepressant monotherapy and antidepressant augmentation therapy.

Source: Adapted from Mod5.3.5.1/SUI3001/Tab7, Mod5.3.5.1/SUI3002/Tab7, Appendix 5 (TSIDEM01B_SCE), and Appendix 6

The included patient population is as expected, middle aged and females as majority. The percentage of patients in which antidepressant treatment was amended between monotherapy and augmentation therapy is small, ~6%. With respect to demographics and baseline characteristics, it is noted that the treatment groups are quite well balanced and there were no differences, which could impact the results, between the treatment groups. A slightly higher proportion of patients in the SOC + placebo arm received antidepressant plus augmentation therapy as compared to the SOC + esketamine group.

**Table 14 (Summary of Clinical Efficacy): Depression History and Baseline Psychiatric History in Phase 3 Studies; Full Efficacy Analysis Set**

| | Study SUI3001 | | | Study SUI3002 | | | Pooled Studies SUI3001 and SUI3002 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Placebo + SOC | Esk 84 mg + SOC | Total | Placebo + SOC | Esk 84 mg + SOC | Total | Placebo + SOC | Esk 84 mg + SOC | Total |
| Analysis set: Full Efficacy | 112 | 112 | 224 | 113 | 114 | 227 | 225 | 226 | 451 |
| MADRS Total Score | | | | | | | | | |
| N | 112 | 111 | 223 | 113 | 114 | 227 | 225 | 225 | 450 |
| Mean (SD) | 41.0 (6.29) | 41.3 (5.87) | 41.1 (6.07) | 39.9 (5.76) | 39.5 (5.19) | 39.7 (5.48) | 40.4 (6.04) | 40.3 (5.60) | 40.4 (5.82) |
| Median | 42.0 | 41.0 | 42.0 | 40.0 | 39.0 | 39.0 | 41.0 | 40.0 | 41.0 |
| Range | (29; 58) | (29; 56) | (29; 58) | (29; 54) | (29; 54) | (29; 54) | (29; 58) | (29; 56) | (29; 58) |
| MADRS Item 10 - Suicidal Thoughts | | | | | | | | | |
| N | 112 | 111 | 223 | 113 | 114 | 227 | 225 | 225 | 450 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 1 (0.9%) | 0 | 1 (0.4%) | 1 (0.9%) | 1 (0.9%) | 2 (0.9%) | 2 (0.9%) | 1 (0.4%) | 3 (0.7%) |
| 3 | 8 (7.1%) | 4 (3.6%) | 12 (5.4%) | 6 (5.3%) | 12 (10.5%) | 18 (7.9%) | 14 (6.2%) | 16 (7.1%) | 30 (6.7%) |
| 4 | 27 (24.1%) | 31 (27.9%) | 58 (26.0%) | 25 (22.1%) | 30 (26.3%) | 55 (24.2%) | 52 (23.1%) | 61 (27.1%) | 113 (25.1%) |
| 5 | 43 (38.4%) | 49 (44.1%) | 92 (41.3%) | 56 (49.6%) | 53 (46.5%) | 109 (48.0%) | 99 (44.0%) | 102 (45.3%) | 201 (44.7%) |
| 6 | 33 (29.5%) | 27 (24.3%) | 60 (26.9%) | 25 (22.1%) | 18 (15.8%) | 43 (18.9%) | 58 (25.8%) | 45 (20.0%) | 103 (22.9%) |
| Duration of Current Depressive Episode, months | | | | | | | | | |
| N | 106 | 99 | 205 | 106 | 100 | 206 | 212 | 199 | 411 |
| Mean (SD) | 33.8 (54.43) | 36.1 (49.34) | 34.9 (51.92) | 49.9 (79.36) | 45.4 (71.07) | 47.7 (75.30) | 41.8 (68.37) | 40.7 (61.25) | 41.3 (64.94) |
| Median | 13.3 | 15.9 | 13.7 | 21.2 | 16.5 | 17.1 | 15.2 | 16.3 | 15.8 |
| Range | (2; 339) | (1; 249) | (1; 339) | (2; 445) | (2; 341) | (2; 445) | (2; 445) | (1; 341) | (1; 445) |
| CGI-SS-R | | | | | | | | | |
| N | 112 | 111 | 223 | 113 | 114 | 227 | 225 | 225 | 450 |
| Normal, not at all suicidal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Questionably suicidal | 3 (2.7%) | 5 (4.5%) | 8 (3.6%) | 3 (2.7%) | 1 (0.9%) | 4 (1.8%) | 6 (2.7%) | 6 (2.7%) | 12 (2.7%) |
| Mildly suicidal | 11 (9.8%) | 6 (5.4%) | 17 (7.6%) | 6 (5.3%) | 10 (8.8%) | 16 (7.0%) | 17 (7.6%) | 16 (7.1%) | 33 (7.3%) |
| Moderately suicidal | 28 (25.0%) | 29 (26.1%) | 57 (25.6%) | 33 (29.2%) | 35 (30.7%) | 68 (30.0%) | 61 (27.1%) | 64 (28.4%) | 125 (27.8%) |
| Markedly suicidal | 42 (37.5%) | 38 (34.2%) | 80 (35.9%) | 42 (37.2%) | 48 (42.1%) | 90 (39.6%) | 84 (37.3%) | 86 (38.2%) | 170 (37.8%) |
| Severely suicidal | 27 (24.1%) | 29 (26.1%) | 56 (25.1%) | 28 (24.8%) | 17 (14.9%) | 45 (19.8%) | 55 (24.4%) | 46 (20.4%) | 101 (22.4%) |
| Among the most extremely suicidal patients | 1 (0.9%) | 4 (3.6%) | 5 (2.2%) | 1 (0.9%) | 3 (2.6%) | 4 (1.8%) | 2 (0.9%) | 7 (3.1%) | 9 (2.0%) |

**Table 14 (Summary of Clinical Efficacy): Depression History and Baseline Psychiatric History in Phase 3 Studies; Full Efficacy Analysis Set**

| | Study SUI3001 | | | Study SUI3002 | | | Pooled Studies SUI3001 and SUI3002 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Placebo + SOC | Esk 84 mg + SOC | Total | Placebo + SOC | Esk 84 mg + SOC | Total | Placebo + SOC | Esk 84 mg + SOC | Total |
| MINI Current Status: Think about suicide | | | | | | | | | |
| N | 112 | 112 | 224 | 113 | 114 | 227 | 225 | 226 | 451 |
| Yes | 112 (100.0%) | 112 (100.0%) | 224 (100.0%) | 113 (100.0%) | 114 (100.0%) | 227 (100.0%) | 225 (100.0%) | 226 (100.0%) | 451 (100.0%) |
| No | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| MINI Current Status: Intend to act on thoughts of killing yourself | | | | | | | | | |
| N | 112 | 112 | 224 | 113 | 114 | 227 | 225 | 226 | 451 |
| Yes | 112 (100.0%) | 112 (100.0%) | 224 (100.0%) | 113 (100.0%) | 114 (100.0%) | 227 (100.0%) | 225 (100.0%) | 226 (100.0%) | 451 (100.0%) |
| No | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| SIBAT: Prior Suicide Attempt | | | | | | | | | |
| N | 112 | 111 | 223 | 113 | 114 | 227 | 225 | 225 | 450 |
| Yes | 68 (60.7%) | 66 (59.5%) | 134 (60.1%) | 72 (63.7%) | 78 (68.4%) | 150 (66.1%) | 140 (62.2%) | 144 (64.0%) | 284 (63.1%) |
| No | 44 (39.3%) | 45 (40.5%) | 89 (39.9%) | 41 (36.3%) | 36 (31.6%) | 77 (33.9%) | 85 (37.8%) | 81 (36.0%) | 166 (36.9%) |
| Suicide attempt within the last month | | | | | | | | | |
| N | 112 | 112 | 224 | 113 | 114 | 227 | 225 | 226 | 451 |
| Yes | 31 (27.7%) | 32 (28.6%) | 63 (28.1%) | 24 (21.2%) | 36 (31.6%) | 60 (26.4%) | 55 (24.4%) | 68 (30.1%) | 123 (27.3%) |
| No | 81 (72.3%) | 80 (71.4%) | 161 (71.9%) | 89 (78.8%) | 78 (68.4%) | 167 (73.6%) | 170 (75.6%) | 158 (69.9%) | 328 (72.7%) |

CGI-SS-R = Clinical Global Impression – Severity of Suicidality – Revised; Esk = esketamine; MADRS = Montgomery-Åsberg Depression Rating Scale; MINI = Mini International Neuropsychiatric Interview; SD = standard deviation; SIBAT = Suicide Ideation and Behavior Assessment Tool; SOC = standard of care
Note: MADRS total score ranges from 0 to 60; a higher score indicates a more severe condition.
MADRS item 10 - suicide score ranges from 0 to 6; a higher score indicates a more severe condition.
Duration of current depressive episode is derived from MADRS euthymic baseline.
CGI-SS-R (score ranges from 0-6; a higher score indicates a more severe condition): "Considering your total clinical experience with suicidal patients and all information now available to you, how suicidal is this patient at this time?"
SIBAT Prior Suicide Attempt from Module 1: "I have made one or more attempts to end my life"
Source: Adapted from Mod5.3.5.1/SUI3001/Tab8, Mod5.3.5.1/SUI3002/Tab8, and Appendix 7

Patients clearly suffered from moderate to severe depression, since the lower range of the MADRS score is 29 which is the upper range of moderate depression according to the scale.

The mean duration of the current depressive episode was long, approximately 3 years, however there was a large variation with median duration of 15.8 months.

In terms of MADRS item 10, most patients were clearly severely suicidal.

With respect to baseline psychiatric history it is noted that the main criterion for entering the study was by answering "Yes" to MINI Questions B3 and B10 Current Status within 24 hours prior to randomization (i.e., potentially confirming active suicidal ideation and intent). It is also noted that there was a minor imbalance between groups in the individual studies for those who were questionably suicidal (SUI3001: 2.7% vs 4.5% and in SUI3002: 2.7% vs 0.9% for the placebo + SOC vs esketamine 84mg+SOC, respectively). However, when the studies were pooled together this imbalance was "cancelled out" 2.7% vs 2.7% for the placebo + SOC vs esketamine84mg+SOC, respectively).

The CGI-SS-R and CGI-SR-I scores do not seem to correlate with the outcomes of the MINI. As per MINI interview, 100% of patients confirmed to think about suicide and intended to act, as was required per inclusion criteria. Majority of patients also thought of suicide often or frequently, and with severe intensity. However, there were quite some patients that according to the CGI-SS-R and CGI-SR-I were moderately or mildly suicidal (35.1%), or were considered to be at most in moderate imminent suicide risk (40.8% in study SUI3001 and 40.5% in study SUI3002). This may reflect the incapability of SIBAT to fully capture suicidal ideation.

The majority of patients had not been hospitalized due to depression or suicidality in the past 12 months. However, from those who had, a large proportion were free of symptoms only for a short period of time, before admitted to the emergency medical care again.

The treatment groups were fairly well balanced, patients in the SOC + esketamine group had a slightly longer duration of current depressive episode and more depressive episodes, and more patients in this group had extreme suicidal ideation and suicide risk as assessed with the SIBAT, as compared to the SOC + placebo group.

To better characterise the included patient population, the applicant was requested to provide details on previous treatments i.e. number of antidepressant treatments, including augmentation therapy, psychotherapy and possible ECT.

*Prior and concomitant therapies*

Of the 225 subjects in the safety analysis set, most (96.9%) received one or more medications of special interest (antidepressants, antipsychotics, benzodiazepines, non-benzodiazepine hypnotics and anxiolytics, and mood stabilizers/antiepileptics) *prior to enrolment* in the study.

The 5 most frequently reported SOC antidepressant medications during the DB treatment phase were venlafaxine (24.9%), escitalopram (16.0%), duloxetine (15.6%), mirtazapine (15.6%), and quetiapine (14.2%).

During the double-blind treatment phase, all 225 subjects in the safety analysis set reported use of one or more concomitant medications. The 5 most frequently used concomitant medications were lorazepam (38.2%), clonazepam (30.7%), quetiapine (25.8%), venlafaxine (25.8%), and paracetamol (19.1%).

The applicant was requested to provide an overview of the most common combinations of drugs in augmentation therapy.

*Duration of hospitalization*

Study SUI3001

The median (range) duration of initial hospitalization was 11.0 days (range: 2 to 69) in the SOC + placebo group and 12.0 days (range: 1 to 84) for subjects in the SOC + esketamine group. Mean duration of hospitalization was 16.3 days in the SOC + placebo group and 16.4 days for subjects in the SOC + esketamine group.

The median duration of hospitalization was similar between regions, however there were rather large differences within Europe. The median duration of hospitalization varied from 8.0 days in the SOC + esketamine group is Spain, to median duration of 23.5 days in the SOC + esketamine group in Bulgaria.

Study SUI3002

The median (range) duration of initial hospitalization was 10.0 days (range: 2 to 85 days) for those in the SOC + placebo treatment group and 14.0 days (range: 1 to 89 days) for subjects in the SOC + esketamine treatment group. The mean duration of initial hospitalization was 19.1 in the SOC + placebo group and 21.6 in the SOC + esketamine group.

Duration of hospitalization was considerably different between regions, as presented in **Table 15**. There were also large differences between countries within Europe, ranging from a median duration of 6 days in the SOC + placebo group in Spain, to 48.5 days in the SOC + placebo group in Austria.

**Table 15: THEHRUQ02C1 (CSR SUI3002): Duration (in Days) of the Initial Hospitalization by Region; Safety Analysis Set (Study SUI3002)**

| Duration of Initial Hospitalization (days) | N | Mean | SD | Median | Min | Max |
|---|---|---|---|---|---|---|
| Region: North America | | | | | | |
| Placebo + SOC | 34 | 7.3 | 3.36 | 6.0 | 3 | 15 |
| Esk 84 mg + SOC | 29 | 8.0 | 4.57 | 8.0 | 2 | 22 |
| Region: Europe | | | | | | |
| Placebo + SOC | 43 | 27.7 | 23.29 | 24.0 | 2 | 85 |
| Esk 84 mg + SOC | 49 | 25.0 | 19.63 | 20.0 | 1 | 89 |
| Region: South America | | | | | | |
| Placebo + SOC | 27 | 20.2 | 18.10 | 12.0 | 2 | 71 |
| Esk 84 mg + SOC | 24 | 31.0 | 26.03 | 24.5 | 4 | 84 |

The differences in duration of hospitalization within Europe illustrate the differences in clinical practises between countries. The applicant was requested to discuss the large difference in duration of hospitalization in North America and Europe. This difference was not observed in study SUI3001, where the duration of hospitalization was similar between the regions. This was clarified during the assessment.

*Prior and concomitant therapies*

Of the 227 subjects in the safety analysis set, most (95.6%) subjects received one or more medications of special interest (antidepressants, typical antipsychotics, benzodiazepines, non-benzodiazepine hypnotics and anxiolytics, atypical antipsychotics, and mood stabilizers and antiepileptics) *prior to enrolment* in the study.

During the double-blind treatment phase, all 227 subjects in the safety analysis set reported use of one or more concomitant medications. The 5 most frequently reported SOC antidepressant medications were venlafaxine and quetiapine (28.2% subjects each), escitalopram (17.2% subjects), duloxetine (14.5% subjects), and sertraline (13.7% subjects).re concomitant medications.

The applicant was requested to provide an overview of the most common combinations of drugs in augmentation therapy.

## Numbers analysed

Datasets Analyzed

Subjects were classified into the following analysis sets for the pooled efficacy analyses: all randomized, full efficacy, safety and follow-up analysis sets:

- The all randomized analysis set included all subjects in pooled studies SUI3001 and SUI3002 who were randomized (ie, subjects who reported a randomization date, or were assigned a randomization number) regardless of whether or not treatment was received.
- The full efficacy analysis set included all randomized subjects in pooled studies SUI3001 and SUI3002 who received at least 1 dose of study medication during the double-blind treatment phase and had both a baseline and a post-baseline evaluation for the MADRS total score or CGI-SS-R.
- The safety analysis set included all randomized subjects in pooled studies SUI3001 and SUI3002 who received at least 1 dose of study medication in the double-blind treatment phase.
- The follow-up analysis set included all subjects in pooled studies SUI3001 and SUI3002 who completed the double-blind treatment phase and entered the follow-up phase or provided adverse event data after the double-blind phase.

The populations for analysis of efficacy (ie, the full analysis sets) in each study were as follows: 224 subjects in Study SUI3001 (112 esketamine 84 mg + SOC; 112 placebo + SOC) and 227 subjects in Study SUI3002 (114 esketamine 84 mg + SOC; 113 placebo + SOC).

**Table 16: (Summary of Clinical Efficacy) Treatment Disposition for the Double-blind Treatment Phase of the Phase 3 Studies; All Randomized Analysis Set**

| | Study SUI3001 | | | Study SUI3002 | | | Pooled Studies SUI3001 and SUI3002 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Placebo + SOC | Esk 84 mg + SOC | Total | Placebo + SOC | Esk 84 mg + SOC | Total | Placebo + SOC | Esk 84 mg + SOC | Total |
| Analysis set: All randomized | 112 | 114 | 226 | 115 | 115 | 230 | 227 | 229 | 456 |
| Completed study treatment | 93 (83.0%) | 102 (89.5%) | 195 (86.3%) | 94 (81.7%) | 90 (78.3%) | 184 (80.0%) | 187 (82.4%) | 192 (83.8%) | 379 (83.1%) |
| Discontinued study treatment | 19 (17.0%) | 12 (10.5%) | 31 (13.7%) | 21 (18.3%) | 25 (21.7%) | 46 (20.0%) | 40 (17.6%) | 37 (16.2%) | 77 (16.9%) |
| Reason for discontinuation | | | | | | | | | |
| Withdrawal by subject | 6 (5.4%) | 2 (1.8%) | 8 (3.5%) | 5 (4.3%) | 10 (8.7%) | 15 (6.5%) | 11 (4.8%) | 12 (5.2%) | 23 (5.0%) |
| Adverse event | 5 (4.5%) | 5 (4.4%) | 10 (4.4%) | 3 (2.6%) | 9 (7.8%) | 12 (5.2%) | 8 (3.5%) | 14 (6.1%) | 22 (4.8%) |
| Lack of efficacy | 6 (5.4%) | 1 (0.9%) | 7 (3.1%) | 6 (5.2%) | 2 (1.7%) | 8 (3.5%) | 12 (5.3%) | 3 (1.3%) | 15 (3.3%) |
| Other | 1 (0.9%) | 3 (2.6%) | 4 (1.8%) | 4 (3.5%) | 3 (2.6%) | 7 (3.0%) | 5 (2.2%) | 6 (2.6%) | 11 (2.4%) |
| Lost to follow-up | 1 (0.9%) | 0 | 1 (0.4%) | 1 (0.9%) | 1 (0.9%) | 2 (0.9%) | 2 (0.9%) | 1 (0.4%) | 3 (0.7%) |
| Change from voluntary to involuntary hospitalization | 0 | 1 (0.9%) | 1 (0.4%) | 1 (0.9%) | 0 | 1 (0.4%) | 1 (0.4%) | 1 (0.4%) | 2 (0.4%) |
| Protocol violation | 0 | 0 | 0 | 1 (0.9%) | 0 | 1 (0.4%) | 1 (0.4%) | 0 | 1 (0.2%) |

Esk = esketamine; SOC = standard of care
Note: 2 subjects in placebo + SOC and 3 subjects in esketamine 84 mg + SOC who were randomized but did not receive any study medication are included in this summary.
Source: Mod5.3.5.1/SUI3001/Tab6, Mod5.3.5.1/SUI3002/Tab6, and Appendix 3

Only a small number of patients discontinued study treatment and approximately 83% of the patient population completed the study, which is considered acceptable.

## Outcomes and estimation

Primary Efficacy Endpoint

For the individual studies SUI3001 and SUI3002, the primary efficacy analysis was performed on the full efficacy analysis set with LOCF data using an ANCOVA model. Results for the primary efficacy endpoint, change in MADRS total score from baseline to 24 hours after the first dose (Day 2), demonstrated statistically significant improvement of esketamine + SOC versus placebo + SOC in both studies (**Table 17**).

- In Study SUI3001, the LS mean treatment difference (SE) was -3.8 (1.39); the 2-sided p-value was 0.006.
- In Study SUI3002, the LS mean treatment difference (SE) was -3.9 (1.39); the 2-sided p-value was 0.006.

For the pooled studies, the LS mean treatment difference (95% CI) at 24 hours after the first dose was -3.8 (-5.75; -1.89); see Table 17).

**Table 17 (Summary of Clinical Efficacy): MADRS Total Score: Change from Baseline to 24 Hours After the First Dose (Day 2) by ANCOVA LOCF for the Double-blind Treatment Phases in Studies SUI3001 and SUI3002 (Full Efficacy Analysis Sets)**

| | Study SUI3001 | | Study SUI3002 | | Pooled Studies SUI3001 and SUI3002 | |
|---|---|---|---|---|---|---|
| | Placebo + SOC (N=112) | Esk 84 mg + SOC (N=112) | Placebo + SOC (N=113) | Esk 84 mg + SOC (N=114) | Placebo + SOC (N=225) | Esk 84 mg + SOC (N=226) |
| **Baseline** | | | | | | |
| N | 112 | 111 | 113 | 114 | 225 | 225 |
| Mean | 41.0 | 41.3 | 39.9 | 39.5 | 40.4 | 40.3 |
| SD | 6.29 | 5.87 | 5.76 | 5.19 | 6.04 | 5.60 |
| **24 Hours (Day 2) LOCF** [a] | | | | | | |
| N | 112 | 112 | 113 | 113 | 225 | 225 |
| Mean | 28.2 | 24.7 | 27.5 | 23.7 | 27.8 | 24.2 |
| SD | 11.97 | 12.12 | 11.13 | 11.75 | 11.54 | 11.92 |
| **Change, baseline to 24 Hours (Day 2)** | | | | | | |
| N | 112 | 111 | 113 | 113 | 225 | 224 |
| Mean | -12.8 | -16.4 | -12.4 | -15.7 | -12.6 | -16.1 |
| SD | 10.73 | 11.95 | 10.43 | 11.56 | 10.56 | 11.73 |
| **Statistical analysis** [b] | | | | | | |
| Difference of LS Means (SE) | -3.8 (1.39) | | -3.9 (1.39) | | -3.8 (0.98) | |
| 95% CI | (-6.56; -1.09) | | (-6.60; -1.11) | | (-5.75; -1.89) | |
| 2-sided p-value | 0.006 | | 0.006 | | | |

ANCOVA = analysis of covariance; CI = confidence interval; Esk = esketamine; LOCF = last observation carried forward; MADRS = Montgomery-Åsberg Depression Rating Scale; SD = standard deviation; SE = standard error; SOC = standard of care

[a] One subject in Study SUI3001 (placebo + SOC group) and 5 subjects in SUI3002 (3 in the esketamine + SOC group and 2 in the placebo + SOC group) did not have the Day 2 MADRS total score, and the MADRS total score was carried forward from 4 hours after the first dose. In Study SUI3002, 1 additional subject was missing both the Day 1, 4 hour and Day 2 values; however, all other post-baseline assessments were performed.

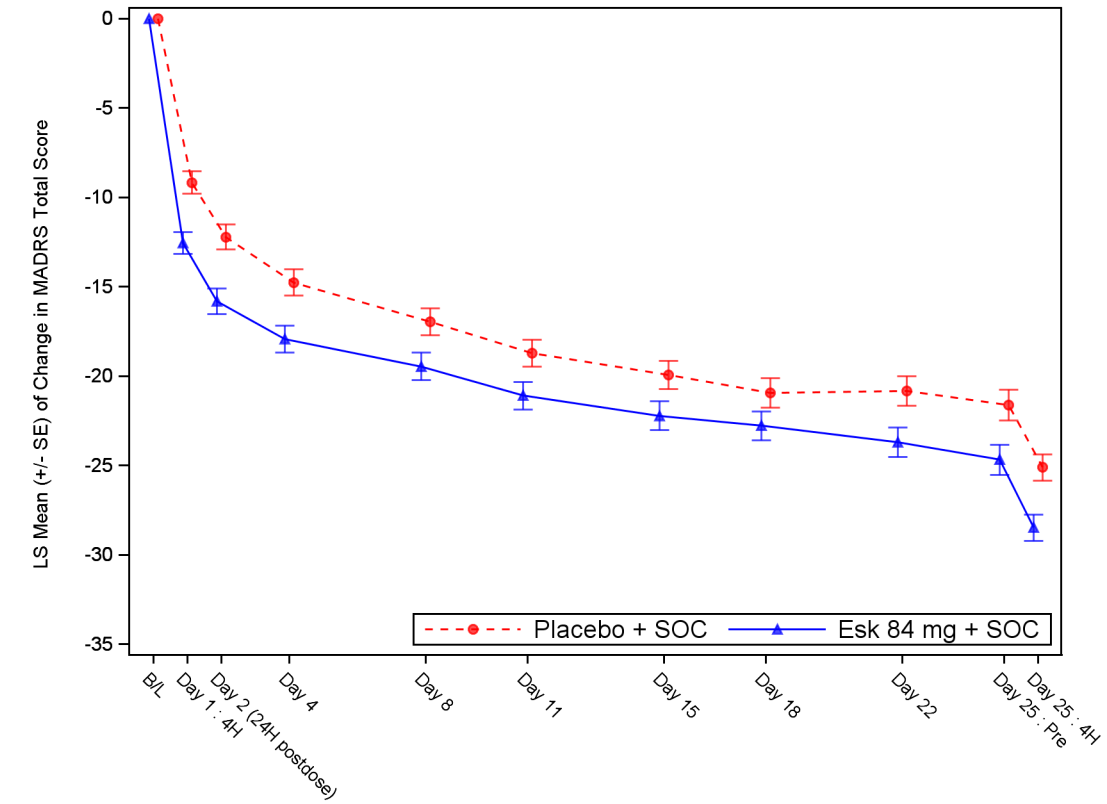
[b] Based on ANCOVA model with study number (for analysis of pooled studies only), treatment (placebo, esketamine 84 mg), analysis center within study number, SOC antidepressant treatment as randomized (antidepressant monotherapy, antidepressant plus augmentation therapy) as factors and baseline value as a covariate.

Notes: The MADRS total score ranges from 0 to 60 points; a higher score indicates a more severe condition, and a negative change in score indicates improvement.

Sources: Mod5.3.5.1/SUI3001/Tab16, Mod5.3.5.1/SUI3002/Tab16, and Appendix 14

The LS mean changes (±SE) in MADRS total score from baseline over time during the double-blind treatment phase are plotted in **Figure 8**(Summary of Clinical Efficacy).

**Figure 8 (Summary of Clinical Efficacy): Montgomery-Åsberg Depression Rating Scale (MADRS) Total Score: LS Mean (+/- SE) of Changes Over Time – MMRM Observed Case; Double-blind Treatment Phase; Full Efficacy Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**




No. of Subjects:

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo + SOC | 225 | 224 | 222 | 221 | 213 | 202 | 198 | 184 | 186 | 180 | 175 |
| Esk 84 mg + SOC | 225 | 222 | 221 | 216 | 203 | 195 | 195 | 186 | 193 | 181 | 177 |

Note: LS mean and SE were based on MMRM analysis with study number, treatment (placebo, esketamine 84 mg), time, analysis center within study number, standard of care antidepressant treatment as randomized (antidepressant monotherapy, antidepressant plus augmentation therapy), time by treatment interaction as factors and baseline value as a covariate.
Negative change in score indicates improvement.

[GEFMAD03C_SCE.RTF] [JNJ-54135419\Z_SCE\DBR_MDSI_2019\RE_MDSI_2019\PROD\GEFMAD03C.SAS] 24JUN2019, 16:06

The primary endpoint, change in MADRS total score from baseline to 24 hours after the first dose (Day 2), showed a significant and clinically relevant difference between the treatment groups placebo + SOC and esketamine + SOC. A rapid reduction of depressive symptoms was observed in both studies [SUI3001: -3.8 (SE=1.39); p=0.006 and SUI3002: -3.9 (SE=1.39); p=0.006]. For the pooled studies, the LS mean treatment difference (95% CI) at 24 hours after the first dose was -3.8 (-5.75; -1.89). A BOCF sensitivity analysis corroborated these results.

The observed improvement in the SOC + placebo arm is striking, considering that the patients were severely depressed as reflected in the mean MADRS baseline total score of ~40, and the fact that the primary endpoint was at 24 hours after the first dose of treatment. However as patients could have been hospitalized for 48 hours before the first dosing (the screening period), a patient could have been under intensive medical attention for up to 4 days at the time of the primary endpoint measurement. The large improvement in the control arm may be explained by this.

The provided MMRM and BOCF analysis demonstrated similar results as the primary analysis, however the applicant was requested to provide the p values from these analyses.

Key Secondary Efficacy Endpoint

In both studies SUI3001 and SUI3002, the key secondary analysis was performed on the full efficacy analysis set with LOCF data using an ANCOVA model on ranks of change. Results for the key secondary endpoint, the change in CGI-SS-R score from baseline to 24 hours after the first dose, are shown in Table 18. The median changes in CGI-SS-R from baseline (range) at 24 hours after the first dose (Day 2) were -1.0 (-6; 2) in the esketamine + SOC groups in both studies, and -1.0 (-5; 1) and -1.0 (-5; 2) in the placebo + SOC groups in Study SUI3001 and Study SUI3002. The Hodges-Lehmann estimates of the treatment difference were 0.0 (-1.00; 0.00) and 0.0 (0.00; 0.00) in Study SUI3001 and Study SUI3002, respectively. Using an ANCOVA model on ranks with LOCF data, the estimated treatment differences were not statistically significant (2-sided p-value = 0.107 in Study SUI3001 and 0.379 in Study SUI3002).

For the pooled studies, the Hodges-Lehmann estimate of the treatment difference (95% CI) was 0.0 (0.00; 0.00).

**Table 18 (Summary of Clinical Efficacy): Clinical Global Impression – Severity of Suicidality - Revised (CGI-SS-R) Score: Change from Baseline to 24 Hours After the First Dose (Day 2) by ANCOVA LOCF on Ranks for the Double-blind Treatment Phases in Studies SUI3001 and SUI3002 (Full Efficacy Analysis Sets)**

| | Study SUI3001 | | Study SUI3002 | | Pooled Studies SUI3001 and SUI3002 | |
|---|---|---|---|---|---|---|
| | Placebo + SOC (N=112) | Esk 84 mg + SOC (N=112) | Placebo + SOC (N=113) | Esk 84 mg + SOC (N=114) | Placebo + SOC (N=225) | Esk 84 mg + SOC (N=226) |
| **Baseline** | | | | | | |
| N | 112 | 111 | 113 | 114 | 225 | 225 |
| Median | 4.0 | 4.0 | 4.0 | 4.0 | 4.0 | 4.0 |
| Range | 1; 6 | 1; 6 | 1; 6 | 1; 6 | 1; 6 | 1; 6 |
| **24 Hours (Day 2) LOCF** [b] | | | | | | |
| N | 112 | 112 | 113 | 113 | 225 | 225 |
| Median | 2.5 | 2.0 | 3.0 | 2.0 | 3.0 | 2.0 |
| Range | 0; 5 | 0; 6 | 0; 6 | 0; 5 | 0; 6 | 0; 6 |
| **Change, baseline to 24 Hours (Day 2)** | | | | | | |
| N | 112 | 111 | 113 | 113 | 225 | 224 |
| Median | -1.0 | -1.0 | -1.0 | -1.0 | -1.0 | -1.0 |
| Range | -5; 1 | -6; 2 | -5; 2 | -6; 2 | -5; 2 | -6; 2 |
| **Statistical analysis** [a] | | | | | | |
| Hodges-Lehmann Estimate of Treatment Difference | 0.0 | | 0.0 | | 0.0 | |
| 95% CI | -1.00; 0.00 | | 0.00; 0.00 | | 0.00; 0.00 | |
| 2-sided p-value | 0.107 | | 0.379 | | | |

ANCOVA = analysis of covariance; CGI-SS-R = Clinical Global Impression – Severity of Suicidality – Revised; CI = confidence interval; Esk = esketamine; LOCF = last observation carried forward; SOC = standard of care

[a] Based on ANCOVA model on ranks with study number (for analysis of pooled studies only), treatment (placebo, esketamine 84 mg), analysis center within study number and standard of care antidepressant treatment as randomized (antidepressant monotherapy, antidepressant plus augmentation therapy) as factors, and baseline value (unranked) as a covariate.

[b] In Study SUI3001, although the analysis considered LOCF data if data was not available at the 24-hour timepoint, all subjects in the full efficacy analysis set had data available at this timepoint. In Study SUI3002, of the 8 subjects who did not have data available at the 24-hour timepoint, 7 subjects (2 in the placebo + SOC group and 5 in the esketamine + SOC group) had the Day 1, 4-hour assessment carried forward for Day 2. One additional subject was missing both the Day 1, 4 hour and Day 2 values.

Notes: The CGI-SS-R score ranges from 0 to 6; a higher score indicates a more severe condition, and a negative change in score indicates improvement.

Sources: Mod5.3.5.1/SUI3001/Tab17, Mod5.3.5.1/SUI3002/Tab17, and Appendix 20

The key secondary endpoint, change in CGI-SS-R score from baseline to 24 hours after the first dose (Day 2), failed to show statistically significant difference in favour of esketamine + SOC vs placebo + SOC in both studies and the pooled studies data. Not even a direction of change or a trend in favour of esketamine can be seen.

The applicant also provided different frequency distribution graphs on CGI-SS-R score at various time points (e.g. **Figure 9**). While the frequency distribution at all time points (4 hrs, 24 hrs and 25 days) shows that a larger percentage of patients in the SOC + esketamine groups had a score of 0 (normal) as compared to the SOC + placebo group, the Hodges-Lehmann estimate of the treatment difference with respect to change from baseline was 0 at all time points.

Based on the results presented, esketamine add on to SOC does not seem to improve the severity of suicidality, throughout the course of 4-week treatment. It should be also noted that the SIBAT, from which the CGI-SS-R is derived from, is not a fully validated assessment tool, and it is therefore unclear whether the CGI-SS-R is sensitive to change and sensitive to detect a treatment effect. As was seen in the baseline data, the CGI-SS-R score does not seem to correlate with the suicidality outcomes of the MINI. As discussed in further results, none of the suicidality endpoints demonstrate significant improvement in suicidality with esketamine add on treatment. The proposed indication including 'suicidal ideation with

intent' is therefore not agreed, as this gives the connotation that esketamine add-on therapy would, next to depressive symptoms in general, target suicidality as a specific entity, while the available clinical data does not demonstrate any added benefit of add-on esketamine over standard of care in reducing suicidality.

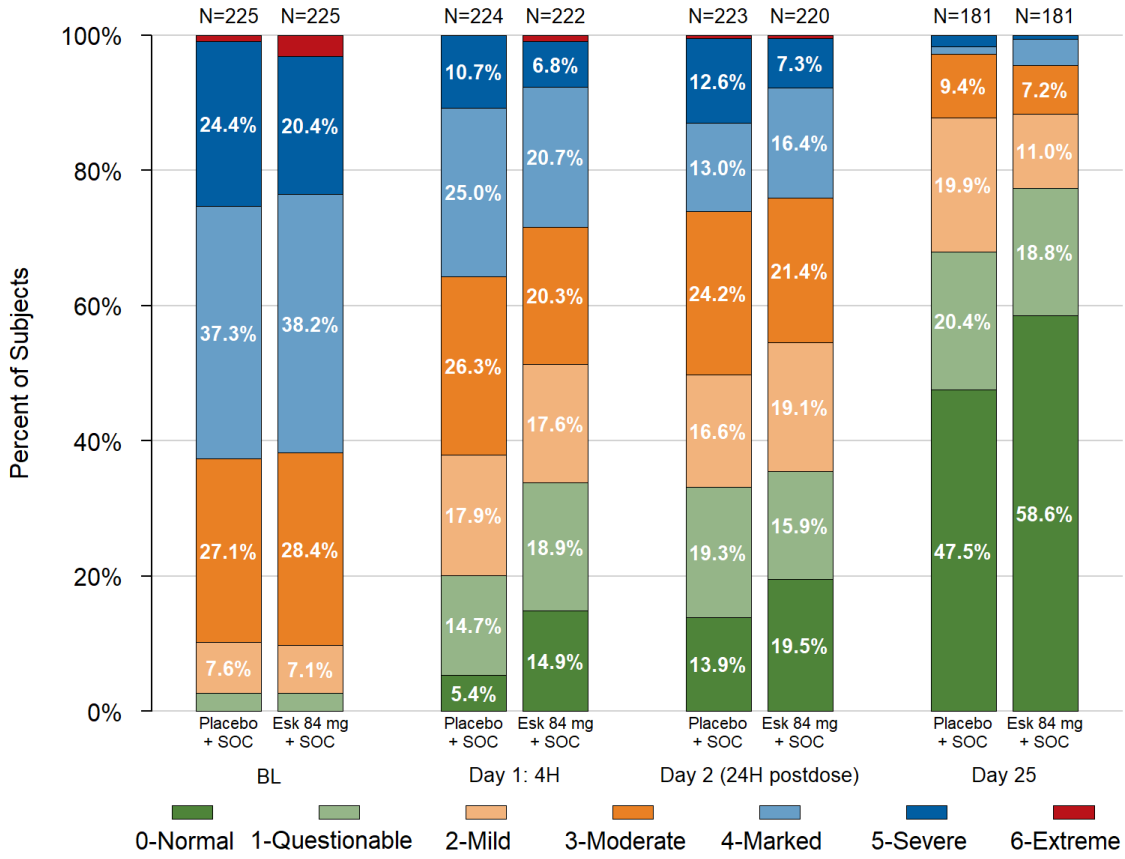
Concerns were raised during the assessment that reduction in depressive symptoms with the MADRS did not translate into a beneficial effect on suicidality.

CGI-SS-R and Other Suicidality Indices Over Time

Frequency Distribution of CGI-SS-R Scores Over Time

Frequency distributions of CGI-SS-R scores at baseline, 4 hours after the first dose, 24 hours after the first dose (Day 2), and Day 25 predose (observed cases) for studies SUI3001 and SUI3002 are included in the CSRs; the frequency distribution for the pooled studies is displayed in **Figure 9** (Summary of Clinical Efficacy). For the individual Phase 3 studies and the pooled studies, CGI-SS-R scores improved from baseline to the end of the double-blind treatment phase (Day 25) in both treatment groups.

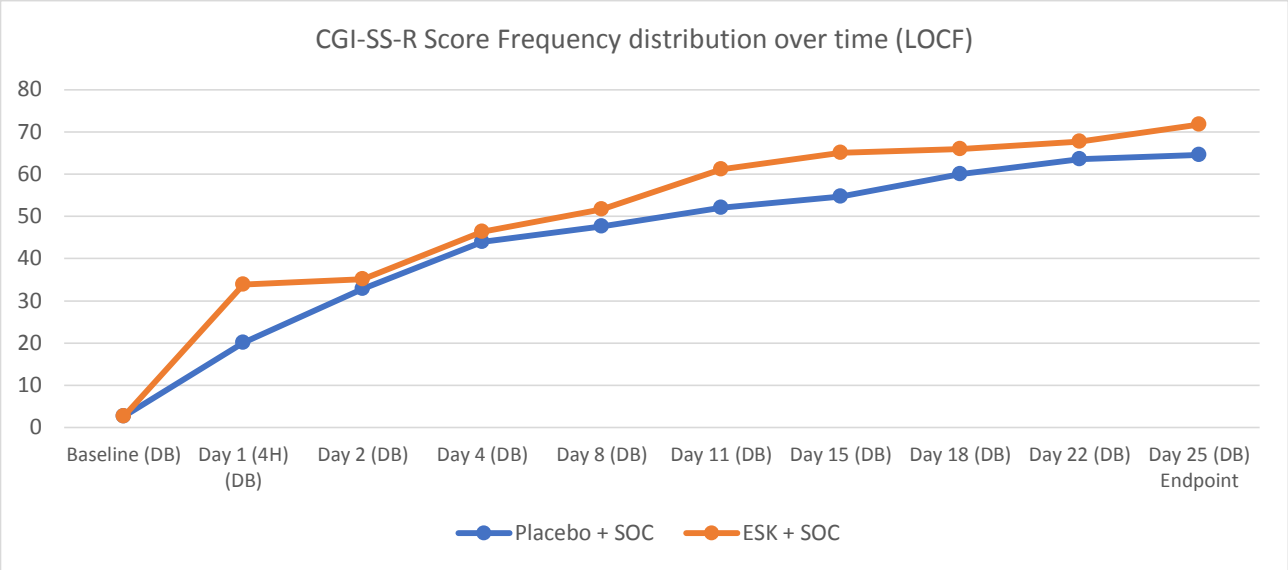
**Figure 9 (summary of Clinical Efficacy): Clinical Global Impression – Severity of Suicidality - Revised (CGI-SS-R) Score: Frequency Distribution at Baseline, 4 Hours Post First Dose, 24 Hours Post First Dose and Day 25; Observed Case; Double-blind Treatment Phase; Full Efficacy Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**




The percentages of patients who responded "Normal, not at all suicidal" plus "Questionably suicidal" for the Placebo + SOC and Esketamine + SOC groups over time are presented in the following Figure (prepared by the assessment teams).

**Figure 10: Clinical Global Impression – Severity of Suicidality - Revised (CGI-SS-R) Score: Frequency Distribution Over Time; Double-blind Treatment Phase Only 0-Normal plus**

**1-Questionable; Full Efficacy Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**




There was improvement over time in the CGI-SS-R translated as increase of the percentages of patients who responded "0-Normal, not at all suicidal" plus "1-Questionably suicidal" in both treatment groups (placebo + SOC and Esketamine + SOC). However, no differences between treatment groups could be observed at any time point.

Remission of MDD Over Time

Remission of MDD during the double-blind treatment phase is presented below using 2 definitions: MADRS total score ≤12 and MADRS total score ≤10. As prespecified in the protocols for the Phase 3 studies, a subject was considered to achieve remission of MDD at a given time point if the MADRS total score was ≤12; the results for the pooled studies are presented below, and results for individual studies are presented in the CSRs.

During the double-blind treatment phase, the percentage of subjects who achieved remission defined as MADRS total score ≤12 was greater in the esketamine + SOC group than the placebo + SOC group at all timepoints in Study SUI3001 and at all timepoints except for Day 18 in Study SUI3002.

**Table 19 (Summary of Clinical Efficacy): Number of Subjects Who Achieved Remission of MDD Defined as MADRS Total Score ≤12 at Days 1, 2 and 25; Double-blind Treatment Phase; Full Efficacy Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**

| • Assessment | • Placebo + SOC • (N = 225) | • Esketamine + SOC • (N = 226) | • Treatment Difference in % (95% CI) |
|---|---|---|---|
| • Day 1: 4 hours after the first dose | • 13 (5.8%) | • 24 (10.6%) | • 4.8 (-0.20; 9.88) |
| • Day 2: 24 hours after the first dose | • 22 (9.8%) | • 46 (20.4%) | • 10.6 (4.05; 17.10) |
| • Day 25: predose | • 69 (30.7%) | • 95 (42.0%) | • 11.4 (2.55; 20.18) |
| • Day 25: 4 hours postdose | • 84 (37.3%) | • 114 (50.4%) | • 13.1 (4.03; 22.19) |

**CI = confidence interval; MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = major depressive disorder;**
**SOC = standard of care**
**Source: Adapted from Appendix 25**

During the double-blind treatment phase, the percentage of subjects who achieved remission, defined as MADRS total score ≤10, was greater in the esketamine + SOC group than the placebo + SOC group at all timepoints except for Day 15 in Study SUI3001 and at all timepoints in Study SUI3002.

**Table 20 (Summary of Clinical Efficacy): Number of Subjects Who Achieved Remission of MDD Defined as MADRS Total Score ≤10 at Days 1, 2 and 25; Double-blind Treatment Phase; Full Efficacy Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**

| Assessment | Placebo + SOC (N = 225) | Esketamine + SOC (N = 226) | Treatment Difference in % (95% CI) |
|---|---|---|---|
| Day 1: 4 hours after the first dose | 10 (4.4%) | 16 (7.1%) | 2.6% (-1.66; 6.93) |
| Day 2: 24 hours after the first dose | 18 (8.0%) | 37 (16.4%) | 8.4% (2.39; 14.36) |
| Day 25: predose | 57 (25.3%) | 82 (36.3%) | 10.9% (2.49; 19.41) |
| Day 25: 4 hours postdose | 73 (32.4%) | 101 (44.7%) | 12.2% (3.33; 21.16) |

CI = confidence interval; MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = major depressive disorder; SOC = standard of care
Source: Adapted from Appendix 28 (TEFMADRM01A1_SCE)

Remission and response rates increase rather steadily throughout the study period in both treatment groups. Large remission and response rates early on in the study are most likely due to the intensive medical care setting of the study.

Other secondary efficacy endpoints:

- Change in MADRS total score over time: In both studies, the LS mean treatment differences based on an MMRM analysis on observed case data numerically favoured the esketamine + SOC group at all timepoints during the double-blind treatment phase: 4 hours and 24 hours after the first dose as well as Days 4, 8, 11, 15, 18, 22, and 25 (predose and 4 hours post dose). The LS mean (95% CI) treatment difference on Day 25, 4 hours postdose, was -4.1 (-6.74; -1.40) in Study SUI3001 and -2.7 (-5.75; 0.28) in Study SUI3002.
- Remission of MDD (MADRS total score ≤12): During the double-blind treatment phase, the percentage of subjects who achieved remission was greater in the esketamine + SOC group than the placebo + SOC group at all timepoints in Study SUI3001 and at all timepoints except for Day 18 in Study SUI3002. At the last MADRS assessment during the double-blind phase on Day 25, 4 hours post dose, the difference (95% CI) between treatment groups in percentage of subjects who achieved remission was 16.1% (3.20; 28.94) in Study SUI3001 and 10.2% (-2.58; 22.98) in Study SUI3002.

  Data summarizing the LS mean change in MADRS over time and the proportion of remitters, treatment with esketamine + SOC in the double-blind phase compared to placebo + SOC resulted in:

  - Slightly more subjects who achieved remission: 4.8 (95% CI: -0.20; 9.88), 10.6 (95% CI: 4.05; 17.10) and 13.1 (95% CI: 4.03; 22.19) more remitters per 100 patients at Day 1:4H, Day 2, and Day 25:4H, respectively, for esketamine + SOC.
- Change in CGI-SS-R over time: CGI-SS-R scores improved from baseline to the end of the double-blind treatment phase in both treatment groups. At the end of the double-blind treatment phase, the changes from baseline in CGI-SS-R score were similar for the 2 treatment groups; the Hodges-Lehmann estimate of the treatment difference (95% CI) for observed case data at Day 25 (predose) was 0.0 (-1.00; 0.00) in Study SUI3001 and 0.0 (0.00; 0.00) in Study SUI3002.
- Resolution of suicidality: The percentage of subjects achieving resolution of suicidality based on CGI-SS-R score was greater in the esketamine + SOC treatment group than the placebo + SOC group at all timepoints in Study SUI3001 and at all timepoints except for Day 8 in Study SUI3002. The difference between treatment groups in percentage of subjects achieving resolution of suicidality at Day 25 (predose) was 12.5% (-0.36; 25.36) in Study SUI3001 and 2.1% (-10.65; 14.89) in Study SUI3002.

**Table 21 (Summary of Clinical Efficacy): Number of Subjects Who Achieved Resolution of Suicidality at Days 1, 2 and 25; Double-blind Treatment Phase; Full Efficacy Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**

| • Assessment | • Placebo + SOC • (N = 225) | • Esketamine + SOC • (N = 226) | • Treatment Difference in % (95% CI) |
|---|---|---|---|
| • Day 1, 4 hours after the first dose | • 45 (20.0%) | • 75 (33.2%) | • 13.2% (5.12; 21.25) |
| • Day 2, 24 hours after the first dose | • 74 (32.9%) | • 78 (34.5%) | • 1.6% (-7.10; 10.35) |
| • Day 25: predose | • 123 (54.7%) | • 140 (61.9%) | • 7.3% (-1.80; 16.36) |

CI = confidence interval; SOC = standard of care, Source: Adapted from Appendix 30

- In both studies, CGI-SR-I scores, clinician-rated FoST, and patient-reported FoST improved from baseline to the end of the double-blind treatment phase in both treatment groups; see the individual CSRs for additional information.

Results for patient-reported EQ-5D-5L scores and TSQM-9 domain scores directionally favoured treatment with esketamine + SOC over placebo + SOC during the double-blind treatment phase in both studies. Further information about all patient-reported outcomes (ie, BHS total score and QLDS score in addition to the outcomes mentioned above) are provided in the CSRs.

An improvement in quality of life in depression was analyzed using a decrease of more than or equal to 4 on the QLDS. Compared to placebo + SOC, treatment with esketamine + SOC from Day 1 through Day 25 resulted in a small percentage:

- 4.6 (95% CI: -4.56; 13.86) more patients who achieved a clinically meaningful improvement in quality of life at Day 25 per 100 patients.

A reduction in hopelessness was analyzed using the BHS cut-off level of <9 among subjects with BHS of at least 9 at baseline. A cut-off level of 9 was selected, as BHS scores ≥9 could be considered predictive of suicide risk. Compared to placebo +SOC, treatment with esketamine + SOC from Day 1 through Day 25 resulted in:

- 6.8 (95% CI: -2.74; 16.37) slightly more patients with a reduction in hopelessness (BHS<9) at Day 25 per 100 patients.

There was improvement in the change in MADRS total score over time and remission of MDD (MADRS total score ≤12) in both studies. The differences, however, in favour of esketamine 84mg plus SOC in the other secondary efficacy endpoints related to suicidality, such as resolution of suicidality (CGI-SS-R≤1), reduction of hopelessness using BHS and quality of life using QLDS, were small and of questionable significance and clinical relevance. The significance and the clinical relevance of the results of these other secondary endpoints were further discussed by the applicant.

A decrease in the percentages for the claimed resolution of suicidality over time is observed, while a constantly increasing trend would have been expected [(CGI-SS-R≤1): 13.2 (95% CI: 5.12; 21.25), 1.6 (95% CI: -7.10; 10.35) and 7.3 (95% CI: -1.80; 16.36) more patients with resolution of suicidality per 100 patients for esketamine + SOC at Day 1:4H, Day 2 and Day 25, respectively].

In addition, there were differences observed between the two phase 3 studies [Change in MADRS total score over time LS mean treatment difference on Day 25, 4 hours postdose, was -4.1 (-6.74; -1.40) in Study SUI3001 and -2.7 (-5.75; 0.28) in Study SUI3002; Remission of MDD (MADRS total score ≤12) difference (95% CI) between treatment groups in percentage of subjects who achieved remission was 16.1% (3.20; 28.94) in Study SUI3001 and 10.2% (-2.58; 22.98) in Study SUI3002; resolution of

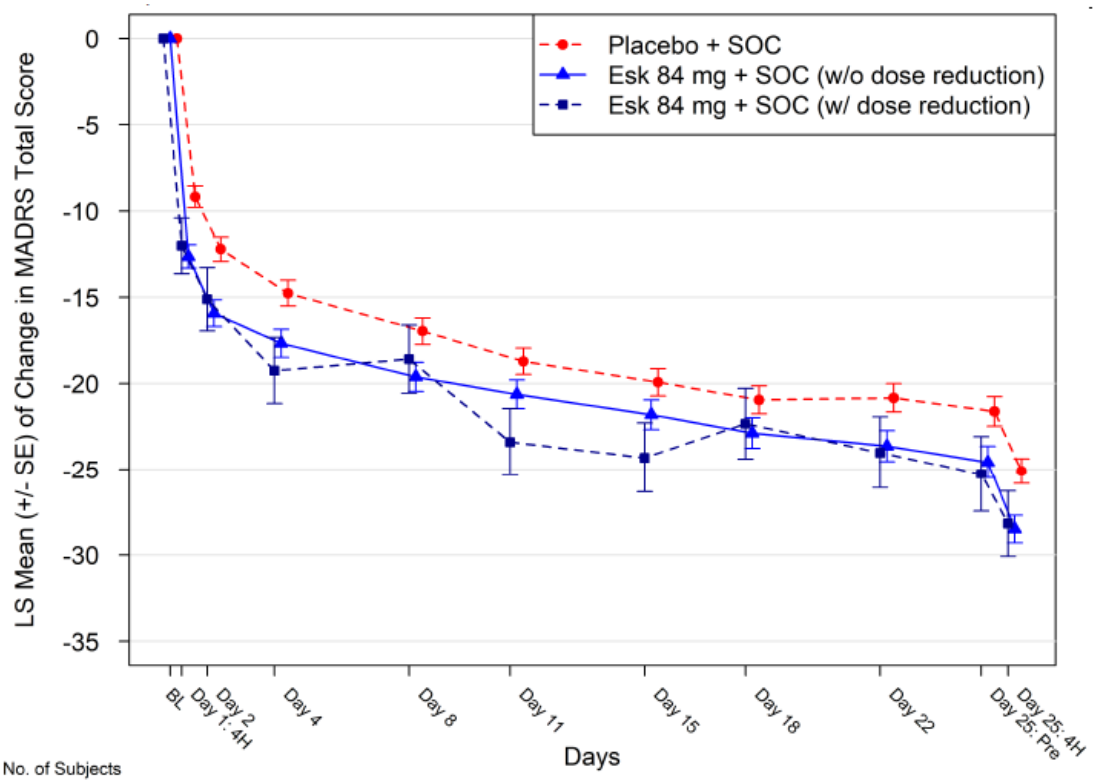
suicidality at Day 25 (predose) was 12.5% ( 0.36; 25.36) in Study SUI3001 and 2.1% (-10.65; 14.89) in Study SUI3002]. The applicant was requested to discuss these together with the potential reasons.

In general, the total MADRS score continues to decrease throughout the studies in both treatment arms. The mean change from baseline to Day 25 (post-dose) was large i.e. >-25 points, however this improvement was seen in both treatment groups. The difference in means has not been tested statistically. However the LS mean difference throughout the DB study period is rather constant approximately 2-4 points.

The applicant was requested to provide an analysis of change in MADRS score over time in subgroups (categories e.g. <5, ≥ 5 - 10, >10) per duration of hospitalisation.

Across the pivotal studies, 35 subjects (15.5%) in the esketamine + SOC group had a protocol-permitted, one-time dose reduction (and received the 56-mg dose during all subsequent dosing sessions). The change in MADRS total score over time was also evaluated for these 35 subjects. The findings in these subjects were consistent with the results of the primary analysis, as presented in the following Figure below.

**Figure 11: Figure from Appendix 45 of the Summary of Clinical Efficacy MADRS Total Score in Subjects With and Without Dose Reduction: LS Mean (+/- SE) of Changes Over Time – MMRM Observed Case; Double-blind Treatment Phase; Full Efficacy Analysis Set (Pooled Studies SUI3001, SUI3002)**




| No. of Subjects | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo + SOC | 225 | 224 | 222 | 221 | 213 | 202 | 198 | 184 | 186 | 180 | 175 |
| Esk 84 + SOC (w/o dose reduction) | 190 | 188 | 187 | 181 | 171 | 162 | 164 | 155 | 162 | 153 | 151 |
| Esk 84 + SOC (w/ dose reduction) | 35 | 34 | 34 | 35 | 32 | 33 | 31 | 31 | 31 | 28 | 26 |

Note: Based on the question 'Was a dose reduction needed?' in eCRF. Dose reductions that occurred for device or dose administration issues are not included.
Negative change in score indicates improvement.

A small number of patients had a protocol-permitted dose reduction to 56 mg. Efficacy in terms on MADRS follows the same pattern as the 84 mg dose. The proposed dose recommendation was therefore considered acceptable.

## Ancillary analyses

Primary efficacy endpoint

Analysis of the change in MADRS total score from baseline to 24 hours after the first dose performed using a MMRM model on the full efficacy analysis set with observed case data was consistent with the primary efficacy analysis. The LS mean (95% CI) treatment difference at 24 hours after the first dose was:

-3.7 (-6.44; -0.98) for Study SUI3001

-3.5 (-6.21; -0.78) for Study SUI3002

-3.6 (-5.51; -1.67) for the pooled studies

Key secondary endpoint

An analysis of change in CGI-SS-R score from baseline to 24 hours after the first dose was also performed with unranked LOCF data using an ANCOVA model. The LS mean treatment difference (95% CI) was:

-0.3 (-0.59; 0.08) for Study SUI3001

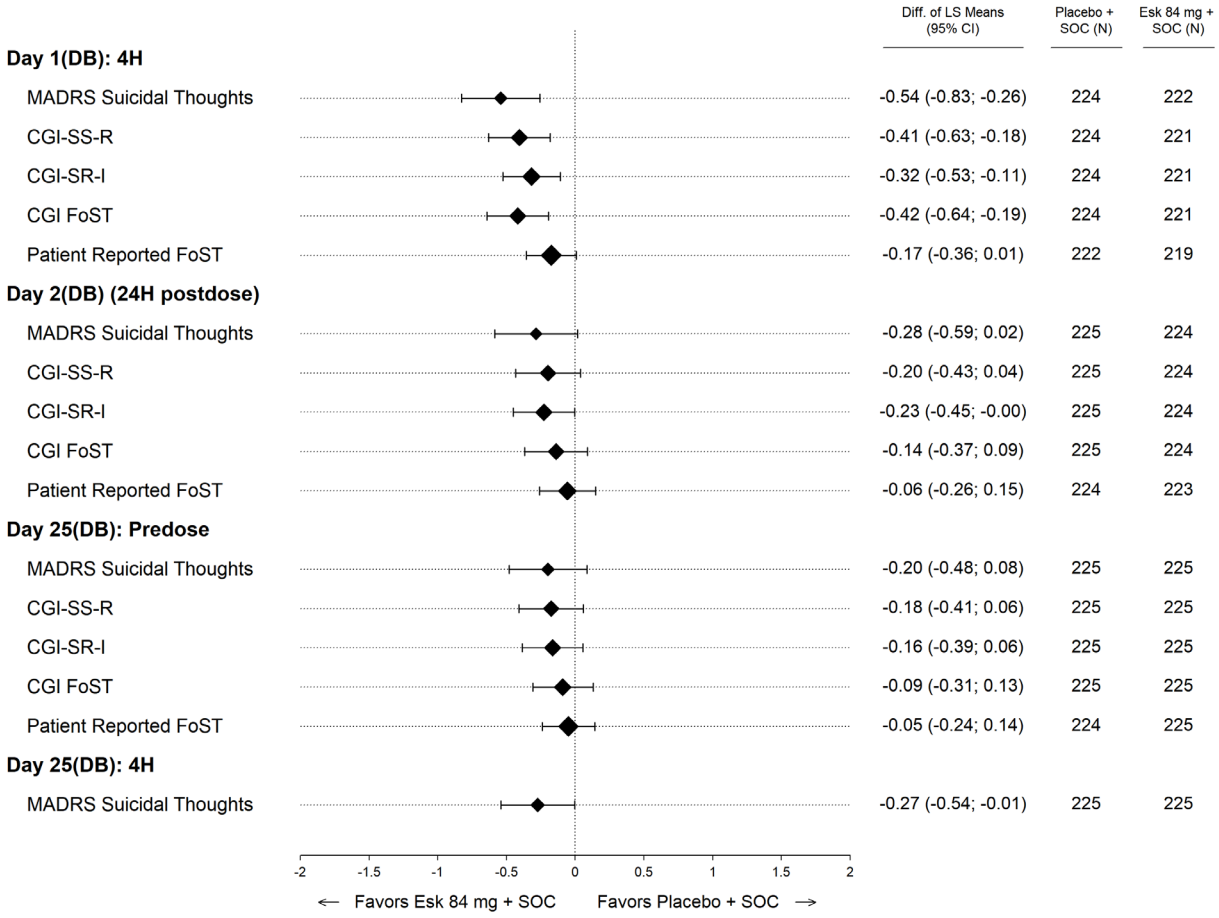
-0.1 (-0.48; 0.19) for Study SUI3002

-0.2 (-0.43; 0.04) for the pooled studies

Analysis of CGI-SS-R Score and Other Suicidality Indices Based on ANCOVA with LOCF Data

The change in CGI-SS-R score and other suicidality indices (ie, the MADRS suicidal thoughts item, CGI-SR-I, clinician-rated FoST [or CGI FoST as noted in figure below], and patient-reported FoST) were evaluated at Day 1, 4 hours after the first dose, Day 2, 24 hours after the first dose and Day 25 during the double-blind treatment phase using ANCOVA with LOCF data. The analyses of change in CGI-SS-R scores from baseline to Day 1, 4 hours after the first dose, and to Day 2, 24 hours after the first dose, were prespecified in the Phase 3 SAP. All of the other analyses described in this section were post-hoc analyses in the individual Phase 3 studies.

**Figure 12 (Summary of Clinical Efficacy): Suicide Items: Change From Baseline to 4 Hours Post First Dose, 24 Hours Post First Dose, Day 25 Predose and Day 25 at 4H Postdose; ANCOVA LOCF; Double-blind Treatment Phase; Full Efficacy Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**




Key: FoST = frequency of suicidal thinking
Note: Based on analysis of covariance (ANCOVA) model with study number, treatment (placebo, esketamine 84 mg), analysis center within study number, standard of care antidepressant treatment as randomized (antidepressant monotherapy, antidepressant plus augmentation therapy) as factors and baseline value as a covariate.
MADRS item 10 - suicide score ranges from 0 to 6; a higher score indicates a more severe condition.
CGI-SS-R (score ranges from 0-6; a higher score indicates a more severe condition): "Considering your total clinical experience with suicidal patients and all information now available to you, how suicidal is this patient at this time?"
CGI-SR-I (score ranges from 0-6; a higher score indicates a more severe condition): "Considering all aspects of this patient's suicidal thinking, behavior and related contributory/protective factors, what is your best clinical judgment of this patient's imminent risk for suicide within the next 7 days?"
CGI FoST ranges from 0-5; a higher score indicates a more severe condition.
Patient reported FoST ranges from 0-4; a higher score indicates a more severe condition.

Subpopulation Analyses for Change in MADRS Total Score from Baseline to 24 Hours After the First Dose

The treatment differences (95% CI) between esketamine + SOC and placebo + SOC were -4.81 (-7.26; -2.36) for the subpopulation that reported a prior suicide attempt (lifetime, based on SIBAT response) and -2.32 (-5.54; 0.91) for the subpopulation that did not report a prior suicide attempt.

Subpopulation Analyses for Change in CGI-SS-R Score from Baseline to 24 Hours After the First Dose

LS mean treatment difference (95% CI) of change in CGI-SS-R score for the pooled studies were -0.31 (-0.61; -0.01 for the subpopulation that reported a prior suicide attempt (lifetime, based on SIBAT response) and -0.03 (-0.42; 0.37) for the subpopulation that did not report a prior suicide attempt.

CGI-SS-R Score and Other Suicidality Indices Over Time by Prior Suicide Attempt

Individual studies

For the individual studies, the odds ratios for improved scores on the CGI-SS-R and other suicidality indices (ie, the MADRS suicidal thoughts item, CGI-SR-I, clinician-rated FoST, and patient-reported FoST) by prior suicide attempt were evaluated at Day 1, 4 hours after the first dose, Day 2, 24 hours after the first dose and Day 25 during the double-blind treatment phase using item response modeling with LOCF data.

Pooled studies

The odds ratios for improved scores on the CGI-SS-R and other suicidality indices by prior suicide attempt were evaluated at Day 1, 4 hours after the first dose, Day 2, 24 hours after the first dose and Day 25 using item response modeling with LOCF data (Appendix 36).

For CGI-SS-R score specifically, the odds ratios (95% CrI) for an improved score were:

Day 1, 4 hours after the first dose:

2.33 (1.24; 4.42) for the subpopulation that reported a prior suicide attempt

2.93 (1.28; 6.98) for the subpopulation that did not report a prior suicide attempt

Day 2, 24 hours after the first dose:

2.09 (1.06; 4.23) for the subpopulation that reported a prior suicide attempt

1.14 (0.46; 2.83) for the subpopulation that did not report a prior suicide attempt

On Day 25 (predose):

3.73 (1.39; 10.65) for the subpopulation that reported a prior suicide attempt

0.70 (0.18; 2.78) for the subpopulation that did not report a prior suicide attempt

Note, point estimates >1 directionally favor the esketamine + SOC group, and those <1 directionally favor the placebo + SOC group.

**Figure 13: Clinical Global Impression – Severity of Suicidality - Revised (CGI-SS-R) Score: change from baseline over time, double-blind period (LOCF) in the subgroup SIBAT prior suicide attempt YES; Full Efficacy Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**

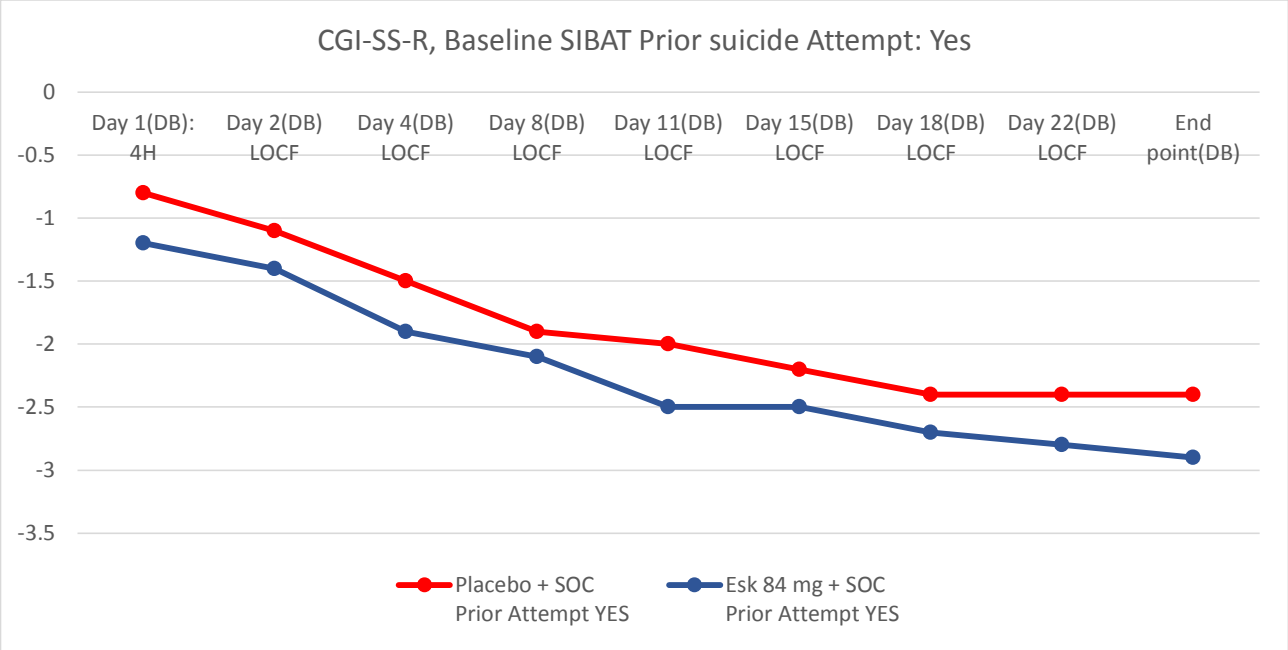
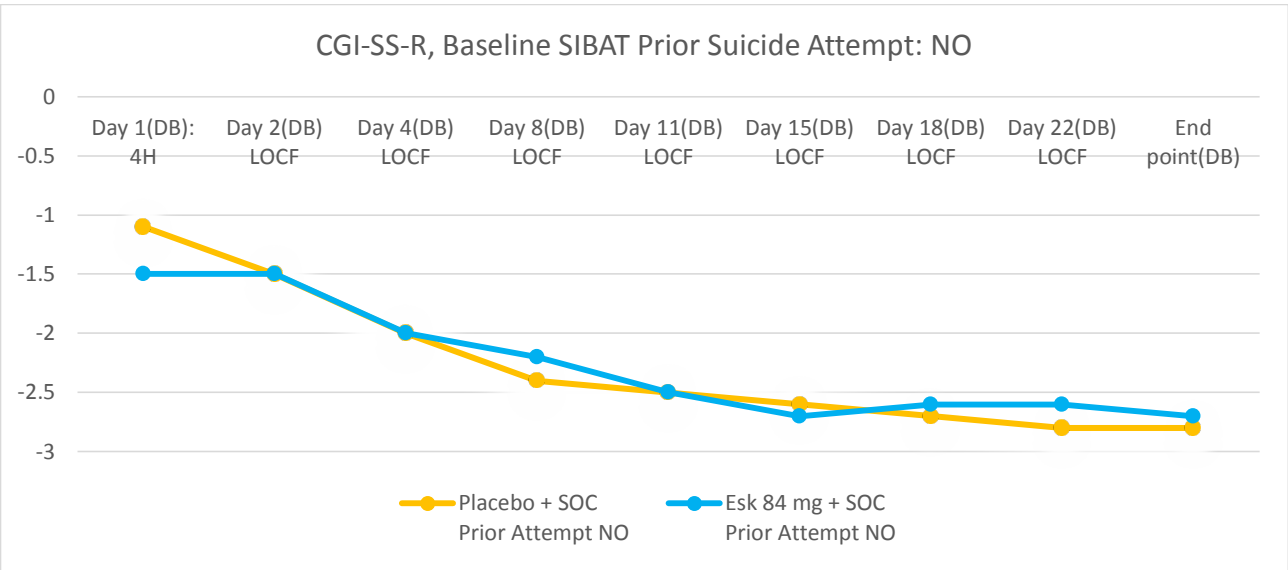



**Figure 14: Clinical Global Impression – Severity of Suicidality - Revised (CGI-SS-R) Score: change from baseline over time, double-blind period (LOCF) in the subgroup SIBAT prior suicide attempt NO; Full Efficacy Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**




As stated earlier, the validity of the CGI-SS-R score was questioned.

The item response analysis revealed some differences between the subpopulations who had reported a prior suicide attempt at baseline and those who had not. However, this is a post-hoc exploratory analysis in subgroups of the clinical trial population that might at best be considered as relevant or supportive for the suicidality indices. As no effect for the suicidality indices was observed in the overall population, such retrospective analyses aiming to present more convincing results in a subpopulation are associated with a high risk of selection bias and could be characterised as a post-hoc identification of only favourable data.

Furthermore, by visual observation of the above graphs, showing the development of LS means of CGI-SS-R over time, it can be seen that the differences between the treatment groups of Placebo + SOC and Esketamine + SOC in absolute terms in the change of CGI-SS-R are very small in the subgroup of patients with prior suicide attempt and non-existent in the subgroup without a prior suicide attempt. (although it is acknowledged that the validity of calculating LS means for an ordinal scale may be questionable). This highlights that interpretation of the effects in terms of the odds ratio is not straightforward; in particular, it is not clear how to interpret the OR in terms of clinical relevance. Especially, it is remarkable that the OR is largest at day 25 in the subgroup of patients with a prior suicide attempt, while the absolute CGI-SS-R decreases with time in both Placebo + SOC and Esketamine + SOC group and the difference between these groups is small; therefore, it appears highly questionable whether the OR, which is a measure on a relative scale, corresponds to a clinically relevant absolute decrease in risk. In conclusion, even using the item response analyses, it is not convincing that a favourable effect of esketamine on the suicidality of patients with a prior suicide attempt exists.

An analysis based on the MADRS severity (for the subgroup with MADRS=>35 at baseline) was requested to investigate whether severely depressed patients who are expected to be more prone to suicidal thoughts are affected by the treatment of esketamine plus SOC.

***CGI-SR-I***

The CGI-SR-I is a scale summarizing the clinician's best assessment of the likelihood that the subject will attempt suicide in the next 7 days. In both studies, the changes from baseline in the CGI-SR-I score were similar for the 2 treatment groups at all time-points during the double-blind treatment phase. The Hodges-Lehmann estimate of the treatment difference for both observed case and LOCF data was 0.0 at all time points.

Concerns were raised that esketamine add-on did not provide additional benefit over standard of care in investigator assessed risk of suicide, as captured by the SIBAT.

***MADRS suicidal thoughts***

SUI3001

The LOCF median change from baseline in the MADRS suicidal thoughts item at 4 hours was -1 (-6;1) in the SOC + placebo group and -2 (-6;1) in the SOC + esketamine group. The Hodges-Lehmann estimate of the treatment difference [95% CI] was -1.0 [-1.00; 0.00]). The estimate was 0.0 (1.00; 0.00) at 25 hrs after the first dose as well as Day 25 (post-dose).

SUI3002

The LOCF median change from baseline in the MADRS suicidal thoughts item at 4 hours was -1 (-6;1) in the SOC + placebo group and -2 (-6;1) in the SOC + esketamine group. The Hodges-Lehmann estimate of the treatment difference [95% CI] with observed case data was 0.0 [-1.00; 0.00]). The same estimate was observed at 25 hrs after the first dose as well as Day 25 (post-dose).

Although the results on MADRS suicidal thoughts item might suggest some numerical benefit of esketamine add-on at 4 hours post-dose, there was no difference between the treatment groups based on the Hodges-Lehmann estimate.

***Beck Hopelessness Scale***

The results on the changes in BHS total score from baseline, based on MMRM analysis, are presented in **Table 22** for both studies.

**Table 22. Beck Hopelessness Scale (BHS) Total Score: Change From Baseline to Day 25: MMRM Observed Case; Double-blind Treatment Phase; Full Efficacy Analysis Set (Studies 3001 and 3002)**

| | **SUI3001** | | **SUI3002** | |
|---|---|---|---|---|
| | **SOC + placebo (N=112)** | **SOC + Esk (N=112)** | **SOC + placebo (N=113)** | **SOC + Esk (N=114)** |
| **Baseline** | | | | |
| N | 112 | 112 | 112 | 112 |
| Mean (SD) | 15.9 (4.60) | 15.2 (4.27) | 15.6 (3.95) | 15.5 (4.22) |
| Median | 18.0 | 17.0 | 16.0 | 16.5 |
| Range | 1; 20 | 1; 20 | 0; 20 | 1; 20 |
| **Day 25** | | | | |
| N | 98 | 105 | 97 | 92 |
| Mean (SD) | 9.4 (6.70) | 8.4 (6.62) | 8.4 (6.40) | 7.9 (6.52) |
| Median | 9.0 | 7.0 | 7.0 | 6.0 |
| Range | 0; 20 | 0; 20 | 0; 20 | 0; 20 |
| **Change from baseline** | | | | |
| N | 98 | 105 | 96 | 91 |
| Mean (SD) | -6.6 (6.63) | -6.9 (6.92 | -7.0 (6.47) | -8.0 (6.31) |
| Median | -4.0 | -7.0 | -6.0 | -8.0 |
| Range | -20;3 | -20; 9 | -20; 11 | -20; 5 |
| **Diff. of LS means (95% CI)** | | -1.1<br>-2.75; 0.61 | | -0.9<br>-2.64; 0.91 |

The results based on ANCOVA were consistent with the MMRM analysis.
Treatment difference between the groups in change in BHS total score from baseline to Day 25 was considered to be very small if not absent.

## Follow-up phase

The pivotal studies included a 9-week follow up phase (up to Day 90).

SUI 3001

192 patients (N=80 SOC + placebo, N=84 SOC + esketamine) entered the follow-up phase, 164 patients (85.4%) completed the entire study. The most common reason for study termination prematurely was withdrawal by subject (N=14, 7.3%).

At the end of the follow-up phase (Day 90), the mean changes in MADRS total score from baseline (SD) were -26.8 (13.30) in the placebo + SOC group and -26.2 (14.32) in the esketamine + SOC group. Using a MMRM model, the LS mean (95% CI) treatment difference was 1.7 (-2.49; 5.86).

At Day 90, the changes from baseline in CGI-SS-R score were similar for the two treatment groups; the Hodges- Lehmann estimate of the treatment difference (95% CI) for observed case data was 0.0 (0.00; 1.00).

SUI3002

183 patients (N=94 SOC + placebo, N=89 SOC + esketamine) entered the follow-up phase, 166 patients (90.7%) completed the entire study. The most common reason for study termination prematurely was withdrawal by subject (N=6, 3.3%).

At the end of the follow-up phase (Day 90), the mean changes in MADRS total score from baseline (SD) were -26.0 (12.03) in the placebo + SOC group and -28.0 (11.75) in the esketamine + SOC group. Using a MMRM model, the LS mean (95% CI) treatment difference was -1.3 (-4.73; 2.06).

At Day 90, the changes from baseline in CGI-SS-R score were similar for the 2 treatment groups; the Hodges- Lehmann estimate of the treatment difference (95% CI) for observed case data was 0.0 (0.00; 0.00).

The results suggest no differences between the treatment groups at Day 90. It is notable that in study SUI3001 the change in MADRS score from baseline to Day 90 is in favour of SOC + placebo group. However the results should be interpreted with caution as they are open-label.

The applicant was requested to provide details on continuation of SOC antidepressant treatment during the follow-up phase.

## *Summary of main studies*

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see also later sections).

**Table 23 : Summary of Efficacy for trial SUI3001**

| **Title: A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Intranasal Esketamine 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 (SUI3001)** | | |
|---|---|---|
| Study identifier | Study Name: ASPIRE I<br>Protocol No.: 54135419SUI3001<br>EudraCT Number: 2016-003990-17<br>NCT No.: NCT03039192<br>Clinical Registry No.: CR108284 | |
| Design | This was a randomized, double-blind, placebo-controlled, multicenter study with subjects enrolled at multiple sites in Bulgaria, Estonia, Germany, Hungary, Malaysia, South Africa, Republic of Korea, Spain, Taiwan, and the United States. The study evaluated the efficacy and safety of esketamine nasal spray in male and female subjects, 18 to 64 years of age, with MDD, presenting to an emergency room (ER) or other permitted setting, and assessed to be at imminent risk for suicide. An Independent Data Monitoring Committee (IDMC) was established to monitor data to ensure the continuing safety of the subjects enrolled in this study. | |
| | Duration of main phase: | Day 1 to 25<br>(Inpatient Psychiatric Unit 5 days) |
| | Duration of Run-in phase: | Screening within 48hrs |
| | Duration of Extension phase: | Day 26 to 90 |

| | | | |
|---|---|---|---|
| Hypothesis | Superiority to placebo | | |
| Treatments groups | ESK + Standard of Care (SOC) | | Esketamine nasal spray was supplied as a solution of esketamine hydrochloride 16.14% weight/volume; equivalent to 14% weight/volume esketamine base) in a nasal spray pump (device), which delivered 16.14 mg esketamine hydrochloride (14 mg esketamine base) per 100-µL spray<br>Twice weekly |
| | Placebo + Standard of Care (SOC) | | Intranasal placebo was supplied as a solution of water for injection with a bittering agent (0.001 mg/mL denatonium benzoate). |
| | | | Comprehensive SOC =<br>- Initial inpatient psychiatric hospitalization<br>- Newly initiated or optimized antidepressant therapy per the clinician's judgement, including antidepressant monotherapy or antidepressant plus augmentation therapy (antidepressant plus an additional antidepressant, antipsychotic, or mood stabilizer)<br>- Permitted concomitant medications (eg, benzodiazepines) and psychotherapy per standard of care.<br>Additionally, the comprehensive SOC was enhanced by twice-weekly study visits with extensive clinical contact (during initial hospitalization and after hospital discharge) during the double-blind phase. |
| Endpoints and definitions | Primary endpoint | MADRS | Change in MADRS total score from baseline to 24 hours after the first dose (Day 2) |
| | Key Secondary endpoint | CGI-SS-R | Change in CGI-SS-R from baseline (range) at 24 hours post first dose (Day 2) |
| | Secondary endpoint | Remission of MDD (MADRS total score $\leqslant$12) | MADRS total score ≤12 over time at 4 hours and 24 hours post first dose, and through the end of the double-blind treatment phase (Day 25). |
| | Secondary endpoint | Change in MADRS total score over time | Change in MADRS total score over time, at 4 hours post first dose on Day 1, and through the end of the double-blind treatment phase (Day 25). |
| | Secondary endpoint | Change in CGI-SS-R over time: | CGI-SS-R at 4 hours post first dose on Day 1, and through the end of the double-blind treatment phase (Day 25). |
| | Secondary endpoint | Resolution of suicidality | the score of 0 (normal, not at all suicidal)or 1 (questionably suicidal) of the CGI-SS-R measured at 4 hours and 24 hours post first dose, and through the end of the double-blind treatment phase (Day 25). |

| | | | |
|---|---|---|---|
| | Secondary endpoint | Clinical Global Impression – Imminent Suicide Risk (CGI-SR-I) | Clinical Global Impression – Imminent Suicide Risk (CGI-SR-I) at 4 hours and 24 hours post first dose, and through the end of the double-blind treatment phase (Day 25). |
| | Secondary endpoint | patient-relevant concepts through the end of the double-blind treatment phase (Day 25) | - Hopelessness as measured by Beck Hopelessness Scale (BHS)<br>- Health related quality of life and health status, using the European Quality of Life (EuroQol) Group, 5-Dimension, 5-Level (EQ-5D-5L) questionnaire<br>- Health related quality of life using the Quality of Life in Depression Scale (QLDS)<br>- Treatment satisfaction using the Treatment Satisfaction Questionnaire for Medication (TSQM-9)<br>- Patient-reported suicidality using the Suicide Ideation and Behavior Assessment Tool (SIBAT), including Module 5 My Risk, Question 3 (patient-reported frequency of suicidal thinking) |
| | Secondary endpoint | safety and tolerability of intranasal esketamine during the double-blind treatment phase and the follow-up phase | -Potential effects on suicidal ideation and behavior using the SIBAT<br>-On dosing days:<br>- Effect on heart rate, blood pressure, respiratory rate, and blood oxygen saturation<br>- Effect on alertness and sedation using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale<br>- Treatment-emergent dissociative symptoms using the Clinician Administered Dissociative States Scale (CADSS) |
| Database lock | 31 January 2019. The database was re-locked on 03 May 2019 | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** |
|---|---|
| Analysis population and time point description | The planned total sample size was approximately 224 subjects (n=112 subjects per treatment group); 226 subjects were randomized |

| | Placebo + SOC | Esk 84 mg + SOC | Total |
|---|---|---|---|
| All randomized | 112 | 114 | 226 |
| Safety analysis set | 112 (100.0%) | 113 (99.1%) | 225 (99.6%) |
| Full efficacy analysis set | 112 (100.0%) | 112 (98.2%) | 224 (99.1%) |
| Follow-up analysis set | 91 (81.3%) | 101 (88.6%) | 192 (85.0%) |

One subject was excluded from the safety analysis set and the full efficacy analysis set because the subject was randomized to the esketamine + SOC group, but discontinued the double-blind treatment phase before receiving the first dose of study agent. Another subject in the esketamine + SOC group was excluded from the full efficacy analysis set because the subject discontinued due to an adverse event after the first dose of study agent on Day 1 and did not provide efficacy data after baseline (Day 1, predose).

| | | | | |
|---|---|---|---|---|
| Descriptive statistics and estimate variability | Treatment group | ESK 84mg + SOC | Placebo + SOC | |
| | Number of subject | 111 | 112 | |

| | | | | |
|---|---|---|---|---|
| | Mean MADRS 24 Hours (Day 2) LOCF | 24.7 | 28.2 | |
| | SD | 12.12 | 11.97 | |
| | Mean Change MADRS, baseline to 24 Hours (Day 2) | -16.4 | -12.8 | |
| | SD | 11.95 | 10.73 | |
| | | | | |
| | | | | |

| | | | |
|---|---|---|---|
| Effect estimate per comparison | Primary endpoint: MADRS Total Score: Change from Baseline to 24 Hours After the First Dose (Day 2) by ANCOVA LOCF | Comparison groups | Esk + SOC vs Placebo + SOC |
| | | Difference of LS Means (SE) | -3.8 (1.39) |
| | | 95% CI | (-6.56; -1.09) |
| | | P-value | 0.006 |
| | Secondary endpoint: Clinical Global Impression – Severity of Suicidality - Revised (CGI-SS-R) Score: Change from Baseline to 24 Hours After the First Dose (Day 2) by ANCOVA LOCF | Comparison groups | Esk + SOC vs Placebo + SOC |
| | | Hodges-Lehmann Estimate of Treatment Difference | 0.0 |
| | | 95% CI | -1.00; 0.00 |
| | | P-value | 0.107 |
| | Secondary endpoint: CGI-SR-I scores | Comparison groups | Esk + SOC (n=109) vs Placebo + SOC (n=112) |
| | | Hodges-Lehmann estimate of the treatment difference | 0.00 |
| | | 95% CI | -1.00; 0.00 |
| | | P-value | |
| Notes | **Table 6: Treatment Disposition; Double-blind Phase; All Randomized Analysis Set (Study 54135419SUI3001)** | | |

| | Placebo + SOC | Esk 84 mg + SOC | Total |
|---|---|---|---|
| Analysis set: All Randomized | 112 | 114 | 226 |
| Completed study treatment | 93 (83.0%) | 102 (89.5%) | 195 (86.3%) |
| Discontinued study treatment | 19 (17.0%) | 12 (10.5%) | 31 (13.7%) |
| Reason for discontinuation | | | |
| Adverse event | 5 (4.5%) | 5 (4.4%) | 10 (4.4%) |
| Withdrawal by subject | 6 (5.4%) | 2 (1.8%) | 8 (3.5%) |
| Lack of efficacy | 6 (5.4%) | 1 (0.9%) | 7 (3.1%) |
| Other | 1 (0.9%) | 3 (2.6%) | 4 (1.8%) |
| Change from voluntary to involuntary hospitalization | 0 | 1 (0.9%) | 1 (0.4%) |
| Lost to follow-up | 1 (0.9%) | 0 | 1 (0.4%) |

Note: 1 subject in Esk 84 mg + SOC who was randomized but did not receive any study medication is included in this summary.
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| | |
|---|---|
| **Analysis description** | For the individual studies SUI3001 and SUI3002, the primary efficacy analysis was performed on the full efficacy analysis set with LOCF data using an ANCOVA model. Results for the primary efficacy endpoint, change in MADRS total score from baseline to 24 hours after the first dose (Day 2), demonstrated statistically significant improvement of esketamine + SOC versus placebo + SOC in both studies |

| | |
|---|---|
| | To assess the robustness of the conclusions from the primary efficacy analysis, sensitivity analyses were performed using an ANCOVA model with BOCF data; this was a post-hoc analysis in Study SUI3001 and a prespecified analysis in Study SUI3002. For Study SUI3001, Study SUI3002, and the pooled studies, results of these sensitivity analyses were consistent with the ANCOVA using LOCF data. The LS mean (95% CI) treatment difference at 24 hours after the first dose was:<br>• -3.7 (-6.41; -0.92) for Study SUI3001<br>• -3.8 (-5.69; -1.82) for the pooled studies |

**Table 24: Summary of Efficacy for trial SUI3002**

| **Title: A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Intranasal Esketamine 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 (SUI3002)** | | |
|---|---|---|
| Study identifier | Study Name: ASPIRE II<br><br>Protocol No.: 54135419SUI3002<br><br>EudraCT Number: 2016-003992-23<br><br>NCT No.: NCT03097133<br><br>Clinical Registry No.: CR108285 | |
| Design | This was a randomized, double-blind, placebo-controlled, multicenter study with subjects enrolled at multiple sites in Argentina, Austria, Belgium, Brazil, Canada, Czech Republic, France, Lithuania, Poland, Spain, Turkey, and the United States. The study evaluated the efficacy and safety of esketamine nasal spray in male and female subjects, 18 to 64 years of age, with MDD, presenting to an emergency room (ER) or other permitted setting, and assessed to be at imminent risk for suicide. An Independent Data Monitoring Committee (IDMC) was established to monitor data to ensure the continuing safety of the subjects enrolled in this study. | |
| | Duration of main phase: | Day 1 to 25<br>(Inpatient Psychiatric Unit 5 days) |
| | Duration of Run-in phase: | Screening within 48hrs |
| | Duration of Extension phase: | Day 26 to 90 |
| Hypothesis | Superiority to placebo | |
| Treatments groups | ESK + Standard of Care (SOC) | Esketamine nasal spray was supplied as a solution of esketamine hydrochloride 16.14% weight/volume; equivalent to 14% weight/volume esketamine base) in a nasal spray pump (device), which delivered 16.14 mg esketamine hydrochloride (14 mg esketamine base) per 100-µL spray<br>Twice weekly |
| | Placebo + Standard of Care (SOC) | Intranasal placebo was supplied as a solution of water for injection with a bittering agent (0.001 mg/mL denatonium benzoate). |

| | | | |
|---|---|---|---|
| | | | Comprehensive SOC =<br>- Initial inpatient psychiatric hospitalization<br>- Newly initiated or optimized antidepressant therapy per the clinician's judgement, including antidepressant monotherapy or antidepressant plus augmentation therapy (antidepressant plus an additional antidepressant, antipsychotic, or mood stabilizer)<br>- Permitted concomitant medications (eg, benzodiazepines) and psychotherapy per standard of care.<br>Additionally, the comprehensive SOC was enhanced by twice-weekly study visits with extensive clinical contact (during initial hospitalization and after hospital discharge) during the double-blind phase. |
| Endpoints and definitions | Primary endpoint | MADRS | Change in MADRS total score from baseline to 24 hours after the first dose (Day 2) |
| | Key Secondary endpoint | CGI-SS-R | Change in CGI-SS-R from baseline (range) at 24 hours post first dose (Day 2) |
| | Secondary endpoint | Remission of MDD (MADRS total score $\leqslant$12) | MADRS total score ≤12 over time at 4 hours and 24 hours post first dose, and through the end of the double-blind treatment phase (Day 25). |
| | Secondary endpoint | Change in MADRS total score over time | Change in MADRS total score over time, at 4 hours post first dose on Day 1, and through the end of the double-blind treatment phase (Day 25). |
| | Secondary endpoint | Change in CGI-SS-R over time: | CGI-SS-R at 4 hours post first dose on Day 1, and through the end of the double-blind treatment phase (Day 25). |
| | Secondary endpoint | Resolution of suicidality | the score of 0 (normal, not at all suicidal)or 1 (questionably suicidal) of the CGI-SS-R measured at 4 hours and 24 hours post first dose, and through the end of the double-blind treatment phase (Day 25). |
| | Secondary endpoint | Clinical Global Impression – Imminent Suicide Risk (CGI-SR-I) | Clinical Global Impression – Imminent Suicide Risk (CGI-SR-I) at 4 hours and 24 hours post first dose, and through the end of the double-blind treatment phase (Day 25). |

| | | | |
|---|---|---|---|
| | Secondary endpoint | patient-relevant concepts through the end of the double-blind treatment phase (Day 25) | - Hopelessness as measured by Beck Hopelessness Scale (BHS)<br>- Health related quality of life and health status, using the European Quality of Life (EuroQol) Group, 5-Dimension, 5-Level (EQ-5D-5L) questionnaire<br>- Health related quality of life using the Quality of Life in Depression Scale (QLDS)<br>- Treatment satisfaction using the Treatment Satisfaction Questionnaire for Medication (TSQM-9)<br>- Patient-reported suicidality using the Suicide Ideation and Behavior Assessment Tool (SIBAT), including Module 5 My Risk, Question 3 (patient-reported frequency of suicidal thinking) |
| | Secondary endpoint | safety and tolerability of intranasal esketamine during the double-blind treatment phase and the follow-up phase | -Potential effects on suicidal ideation and behavior using the SIBAT<br>-On dosing days:<br>- Effect on heart rate, blood pressure, respiratory rate, and blood oxygen saturation<br>- Effect on alertness and sedation using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale<br>- Treatment-emergent dissociative symptoms using the Clinician Administered Dissociative States Scale (CADSS) |
| Database lock | 07 May 2019 | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** |
|---|---|
| Analysis population and time point description | The planned total sample size was approximately 224 subjects (n=112 subjects per treatment group); 230 subjects were randomized. |

| | Placebo + SOC | Esk 84 mg + SOC | Total |
|---|---|---|---|
| All randomized | 115 | 115 | 230 |
| Safety analysis set | 113 (98.3%) | 114 (99.1%) | 227 (98.7%) |
| Full efficacy analysis set | 113 (98.3%) | 114 (99.1%) | 227 (98.7%) |
| Follow-up analysis set | 94 (81.7%) | 89 (77.4%) | 183 (79.6%) |

Descriptive statistics and estimate variability

| Treatment group | Placebo + SOC | Esk 84mg + SOC | |
|---|---|---|---|
| Number of subject | 113 | 114 | |
| Mean MADRS 24 Hours (Day 2) LOCF | 27.5 | 23.7 | |
| SD | 11.13 | 11.75 | |
| Mean Change MADRS, baseline to 24 Hours (Day 2) | -12.4 | -15.7 | |
| SD | 10.43 | 11.56 | |
| | | | |

<table>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td rowspan="7">Effect estimate per comparison</td><td rowspan="4">Primary endpoint: MADRS Total Score: Change from Baseline to 24 Hours After the First Dose (Day 2) by ANCOVA LOCF</td><td>Comparison groups</td><td>Esk + SOC vs Placebo + SOC</td></tr>
<tr><td>Difference of LS Means (SE)</td><td>-3.9 (1.39)</td></tr>
<tr><td>95% CI</td><td>(-6.60; -1.11)</td></tr>
<tr><td>P-value</td><td>0.006</td></tr>
<tr><td rowspan="4">Secondary endpoint: Clinical Global Impression – Severity of Suicidality - Revised (CGI-SS-R) Score: Change from Baseline to 24 Hours After the First Dose (Day 2) by ANCOVA LOCF</td><td>Comparison groups</td><td>Esk + SOC vs Placebo + SOC</td></tr>
<tr><td>Hodges-Lehmann Estimate of Treatment Difference</td><td>0.0</td></tr>
<tr><td>95% CI</td><td>0.00; 0.00</td></tr>
<tr><td>P-value</td><td>0.379</td></tr>
<tr><td rowspan="4">Secondary endpoint: CGI-SR-I scores</td><td>Comparison groups</td><td>Esk + SOC (n=113) vs Placebo + SOC (n=113)</td></tr>
<tr><td>Hodges-Lehmann estimate of the treatment difference</td><td>0.00</td></tr>
<tr><td>95% CI</td><td>-1.00; 0.00</td></tr>
<tr><td>P-value</td><td></td></tr>
<tr><td>Notes</td><td colspan="3">
Table 6: Treatment Disposition; Double-blind Treatment Phase; All Randomized Analysis Set (Study 54135419SUI3002)
<table>
<tr><th></th><th>Placebo + SOC</th><th>Esk 84 mg + SOC</th><th>Total</th></tr>
<tr><td>Analysis set: All Randomized</td><td>115</td><td>115</td><td>230</td></tr>
<tr><td>Completed study treatment</td><td>94 (81.7%)</td><td>90 (78.3%)</td><td>184 (80.0%)</td></tr>
<tr><td>Discontinued study treatment</td><td>21 (18.3%)</td><td>25 (21.7%)</td><td>46 (20.0%)</td></tr>
<tr><td>Reason for discontinuation</td><td></td><td></td><td></td></tr>
<tr><td>Withdrawal by subject</td><td>5 (4.3%)</td><td>10 (8.7%)</td><td>15 (6.5%)</td></tr>
<tr><td>Adverse event</td><td>3 (2.6%)</td><td>9 (7.8%)</td><td>12 (5.2%)</td></tr>
<tr><td>Lack of efficacy</td><td>6 (5.2%)</td><td>2 (1.7%)</td><td>8 (3.5%)</td></tr>
<tr><td>Other</td><td>4 (3.5%)</td><td>3 (2.6%)</td><td>7 (3.0%)</td></tr>
<tr><td>Lost to follow-up</td><td>1 (0.9%)</td><td>1 (0.9%)</td><td>2 (0.9%)</td></tr>
<tr><td>Change from voluntary to involuntary hospitalization</td><td>1 (0.9%)</td><td>0</td><td>1 (0.4%)</td></tr>
<tr><td>Protocol violation</td><td>1 (0.9%)</td><td>0</td><td>1 (0.4%)</td></tr>
</table>
Note: 2 subjects in placebo + SOC and 1 subject in esketamine 84 mg + SOC who were randomized but did not receive any study medication is included in this summary.<br>
[TSIDS01A.RTF] [JNJ-54135419\SUI3002\DBR_FINAL\RE_CSR\PROD\TSIDS01A.SAS] 09MAY2019, 11:59
</td></tr>
<tr><td>Analysis description</td><td colspan="3">For the individual studies SUI3001 and SUI3002, the primary efficacy analysis was performed on the full efficacy analysis set with LOCF data using an ANCOVA model. Results for the primary efficacy endpoint, change in MADRS total score from baseline to 24 hours after the first dose (Day 2), demonstrated statistically significant improvement of esketamine + SOC versus placebo + SOC in both studies</td></tr>
<tr><td></td><td colspan="3">To assess the robustness of the conclusions from the primary efficacy analysis, sensitivity analyses were performed using an ANCOVA model with BOCF data; this was a post-hoc analysis in Study SUI3001 and a prespecified analysis in Study SUI3002. For Study SUI3001, Study SUI3002, and the pooled studies, results of these sensitivity analyses were consistent with the ANCOVA using LOCF data. The LS mean (95% CI) treatment difference at 24 hours after the first dose was:<br>
• -3.9 (-6.65; -1.12) for Study SUI3002<br>
• -3.8 (-5.69; -1.82) for the pooled studies</td></tr>
</table>

## *Analysis performed across trials (pooled analyses and meta-analysis)*

Since the Phase 3 pivotal studies had an identical design, pooled analyses were performed (please see the relevant sections above).

Response across subgroups is consistent with the overall effect In terms of MADRS. Response seems to be somewhat higher in patients with higher median MADRS score at baseline.

CGI-SS-R response across subgroups is consistent with the overall effect. As with MADRS, response seems to be somewhat higher in patients with higher median MADRS score at baseline.

Post-hoc subpopulation analyses of MADRS total score, remission (MADRS total score ≤12), CGI-SS-R score and other suicidality indices, and resolution of suicidality (CGI-SS-R of 0 or 1) over time were performed by prior suicide attempt. The results suggested that response is higher across the endpoints in patients with prior suicide attempt.

Concerns were raised that these post-hoc analyses were data driven and should be therefore handled with caution. The differential effect was almost completely driven by results of study SUI3001, the results could not be replicated in study SUI3002.

## *Clinical studies in special populations*

The applicant has not studied the efficacy and safety of esketamine add-on treatment in MDSI in elderly. The TRD clinical program included a study in elderly, however it is considered that the TRD elderly patient population differs considerably from the MDSI patient population, for example with respect to concomitant medications. The proposed SmPC includes a statement in section 4.2 that esketamine has not been studied in elderly patients with MDD who have current suicidal ideation with intent. The applicant has not provided a discussion, while efficacy and safety in elderly MDSI patient population was brought under discussion in the provided CHMP scientific advices. Therefore, the applicant is requested to discuss in particular safety in the elderly MDSI patient population, taking into consideration the differences to TRD elderly population which is considered to largely preclude extrapolation from TRD studies to elderly patients with MDSI. (**OC**)

***Supportive study SUI2001***

In Study SUI2001, subjects were enrolled in the United States: 68 subjects were randomly assigned to receive double-blind treatment (36 subjects with esketamine + SOC and 32 with placebo + SOC), and 49 (72.1%) subjects completed study treatment (27 subjects [75.0%] in the esketamine + SOC group and 22 [68.8%] in the placebo + SOC group).

The demographic and baseline characteristics were generally similar in the esketamine and placebo groups. Approximately two-thirds (65.2%) of subjects were female and 53.0% were white. The median age was 31.5 years, and the majority (54.5%) of subjects were aged 18 to 34 years.

The key eligibility criteria for Study SUI2001 were consistent with the Phase 3 studies with the exception of the criterion for MADRS total score on Day 1. In Study SUI2001, subjects were required to have a MADRS total score of ≥22 predose on Day 1 of the double-blind treatment phase. The mean (SD) MADRS total score at baseline was 38.6 (6.53). All subjects had current suicidal ideation with intent based on the current status of MINI Questions B5 and B9 (MINI for DSM-IV), and 62.1% of subjects had a prior history of suicide attempt (57.1% in the esketamine + SOC group and 67.7% in the placebo + SOC group).

Efficacy Results

Primary efficacy endpoint:

Results for the change in MADRS total score from baseline to 4 hours after the first dose demonstrated statistically significant improvement with esketamine + SOC versus placebo + SOC. Using an ANCOVA model, the LS mean (±SE) treatment difference was -5.3 (2.10) at Day 1, 4 hours after the first dose (2-sided p = 0.015).

Other efficacy endpoints:

- Change in MADRS total score over time: The treatment difference based on MMRM analysis with observed case data numerically favored the esketamine + SOC group at all timepoints during the double-blind treatment phase. The LS mean treatment difference (95% CI) was -7.7 (-13.29; -2.06) at 24 hours after the first dose and -4.8 (-10.65; 1.01) at the endpoint of the double-blind phase (Day 25, 4 hours postdose).
- Change in CGJ-SR score: The differences between treatment groups based on ANCOVA of the ranks of change from baseline over time in the CGJ-SR score suggested a potential therapeutic effect of esketamine + SOC compared with placebo + SOC at Day 1, 4 hours after the first dose, and at Day 2, approximately 24 hours after the first dose. Further details are provided in the CSR (TRD/Mod5.3.5.1/SUI2001/Sec6.3.7).

Response (≥50% improvement from baseline) based on MADRS total score, remission of MDD (MADRS total score ≤12), sustained response (≥50% reduction from baseline in MADRS total score from 4 hours after the first dose through the end of the double-blind treatment phase), MADRS suicidal thoughts item score, patient-reported global assessment of suicide risk, BHS total score, and BSS total score have also been investigated.

Study SUI2001 was a supportive proof-of-concept study. It could be agreed that in this study, esketamine nasal spray 84 mg, compared to placebo, demonstrated a clinically meaningful and statistically significant rapid reduction of depressive symptoms in subjects with MDD who were assessed to be at imminent risk for suicide, as demonstrated by change from baseline in the MADRS total score at both, 4 hours postdose and on Day 2 (approximately 24 hours postdose)

## 2.4.3. Discussion on clinical efficacy

There were concerns raised on the design and conduct of clinical studies. The proof-of-concept study SUI2001 evaluated the efficacy of safety of 84 mg intranasal esketamine, administered twice weekly for 4 weeks, in adult hospitalized subjects with major depression assessed to be in imminent risk for suicide. The double-blind treatment period was 25 days, followed by an 8-week follow-up phase. Patients were randomized to receive either placebo of esketamine on top of SOC, including newly initiated of optimized antidepressant therapy (monotherapy or augmentation therapy). Patients were hospitalized at treatment initiation, and were recommended to remain in hospital for a minimum of 5 days. As per inclusion criteria, the baseline MADRS score had to be ≥22. Current suicidal ideation with intent was addressed with two questions from the MINI interview. The primary endpoint was the change in MADRS total score from Baseline (Day 1, pre-dose) to Day 1, 4 hours post-dose of the double-blind phase. Suicidality was assessed on SIBAT-Clinical Global Judgment of Suicide Risk (CGJ-SR).

The design of the two main phase 3 pivotal studies SUI3301 and 3002 was identical: double-blind, randomized, placebo-controlled, multi-center, international studies in adults with MDD, who have responded that they think about harming or of hurting or of injuring themselves and who intend to act on

thoughts of killing themselves (questions B3 and B10 of MINI). These type of studies are common in depression and the design is in principle considered appropriate.

As per inclusion criteria, the baseline MADRS score had to be >28. Current suicidal ideation with intent was addressed with two questions from the MINI interview. The key inclusion and exclusion criteria are in general acceptable. The mean baseline MADRS total scores in the subjects who entered the Phase 2 and 3 MDSI studies corresponded to moderate to severe depression (mean scores: 40.4 in the pooled Phase 3 studies and 38.6 in the Phase 2 study).

Substance and alcohol abuse are relatively common in severely depressed patients and these patients could be potential candidates for esketamine treatment once brought to the emergency care due to suicidality. The proposed SmPC included a warning on individuals with a history of drug abuse or dependence, it was unclear whether this was sufficient in the patient population as described in the indication. This was further clarified when the final indication was agreed upon with the applicant.

Sample size calculation was appropriate based on an effect size for the MADRS total score and a number of 451 patients in total (with 226 patients receiving Esketamine + SOC and 225 on placebo + SOC) can be considered sufficient. Randomisation was also implemented. Blinding was maintained by adding a bittering agent to the placebo nasal spray (as in the studies for TRD) and by using different raters to perform efficacy and safety assessments.

With respect to demographics and baseline characteristics, it is noted that there were no differences, which could have impacted the results, between the treatment groups.

The primary endpoint was considered appropriate to investigate the depressive symptoms (MADRS). With respect to the suicidality issue (key secondary endpoint CGI-SS-R and other indices such as MADRS Suicidal thoughts, CGI-SR-I, CGI-FoST, Patient reported FoST) it is unclear whether the scales/instruments used were appropriate. It has already been mentioned that there are reports in the literature suggesting that no diagnostic tool has demonstrated clinical value for the assessment of short-term suicide risk among high-risk individuals. CGI-SS-R, as part of the SIBAT, has undergone through a qualification advice and it was expected to be validated with the phase 3 clinical studies.

The key secondary endpoint was the SIBAT derived Clinical Global Impression – Severity of Suicidality – Revised (CGI-SS-R). SIBAT is a tool developed by the applicant for assessing suicidality in patients with MDD. The CHMP has given qualification advice twice for this tool, it was also addressed in the given CHMP scientific advices. In these advices it was stated that the underlying assumption that increasing CGI-SS-R risk level is associated with an increased probability of suicide/attempted suicide/self-harm will need to be further substantiated. In addition, sensitivity to change and sensitivity to detect a treatment effect would be required for final validation of the SIBAT. Nevertheless, the applicant has chosen to apply CGI-SS-R as key secondary endpoint, while it is not fully validated.

Unfortunately, the Beck Scale for Suicidal Ideation (BSS) was not included in the pivotal phase 3 studies, as this was done in the Phase 2 study, to further assess the patient's suicidality and to use this as anchor to validate the CGI-SS-R within the same study. Therefore, the CGI-SS-R is considered an exploratory outcome.

There were also concerns raised on the efficacy data and additional analysis. In the proof-of-concept study SUI2001, the reduction in MADRS total score from baseline to 4 hrs was large. Difference of LS means of -5.3 is statistically significant and considered clinically relevant. A significantly greater improvement in MADRS score was also observed in the esketamine group compared with the placebo group at ~24 hours, however concerns were raised that esketamine did not separate from placebo at 4 weeks endpoint.

There was no effect in the investigator-assessed suicide risk at 4 hours post-dose as well as 24 hrs post-dose.

In the main phase 3 Studies SUI3301 and 3002, ≥80% of subjects completed the double-blind treatment phase, which is a similar completion rate to the TRD studies. The mean duration of the current depressive episode was long. The applicant did not provide data on previous treatments (number of antidepressant treatments, including augmentation therapy, psychotherapy and possible ECT), which was then requested during the assessment to better characterise the included patient population.

The treatment groups were fairly well balanced in terms of demographics and psychiatric history.
In study SUI3002, the mean duration of hospitalisation during the study was considerably different between regions. The same difference was not observed in study SUI3001. The applicant was requested to discuss the large difference between North America and Europe in study SUI3002.

A few questions were raised on concomitant treatments, for example the most common combinations of drugs in augmentation therapy.

The primary endpoint change in MADRS total score from baseline to 24 hours after the first dose (day 2) was achieved. A rapid reduction of depressive symptoms in patients suffering from MDD with esketamine 84mg twice weekly can be acknowledged. For the primary endpoint LS mean treatment difference in the change of MADRS total score from baseline to 24 hours after the first dose (Day 2) was observed in both studies [SUI3001: -3.8 (SE=1.39); p=0.006 and SUI3002: -3.9 (SE=1.39); p=0.006]. For the pooled studies, the LS mean treatment difference (95% CI) at 24 hours after the first dose was -3.8 (-5.75; -1.89).

The observed improvement in the SOC + placebo arm is striking, considering that the patients were moderately to severely depressed as reflected in the mean MADRS baseline total score of ~40, and the fact that the primary endpoint was at 24 hours after the first dose of treatment. However, as patients could have been hospitalized for 48 hours before the first dosing (the screening period), a patient could have been under intensive medical attention for up to 4 days at the time of the primary endpoint measurement. Nevertheless, esketamine demonstrated an improvement in depressive symptoms versus placebo which is statistically significant and clinically relevant. The applicant was also requested to provide an analysis of change in MADRS score over time in subgroups (categories e.g. <5, ≥ 5 - 10, >10) per duration of hospitalisation, to examine the impact of time spent under intensive medical attention.

For the 4 hours postdose on Day 25, the results were -4.1 (-6.74; -1.40) in Study SUI3001 and -2.7 (-5.75; 0.28) in Study SUI3002. The results are in favour of the rapid antidepressant action of esketamine. However, the reasons for observing differences between the two identical phase 3 studies were unclear.

Overall, these results are reassuring of the rapid reduction of depressive symptoms in a subgroup of MDD patients. This can be considered confirmatory and underpins the consistent antidepressant effect of esketamine, which was initially demonstrated in the Marketing Authorisation procedure for Treatment Resistant Depression.

However, the results with suicide indices and endpoints related to the suicidality (suicidal ideation and/or behaviour) of the patients cannot be considered convincing since no difference could be observed between placebo + SOC and Esketamine + SOC groups.

The key secondary endpoint, change in CGI-SS-R score from baseline to 24 hours after the first dose (Day 2) failed to show a difference greater than 1 between the treatment groups [SUI3001 -0.3; SUI3002 -0.1 and pooled studies -0.2]. Subjects in both treatment groups experienced improvement in the severity of their suicidality as measured by the CGI-SS-R scale at 24 hours postdose, although there was no

statistically significant difference between treatment groups. Not even a direction of change in favour of esketamine can be seen. In study SUI3001, the median changes from baseline (range) at 24 hours were -1.0 (-5; 1) in the SOC + placebo group and -1.0 (-6; 2) in the SOC + esketamine group. The Hodges-Lehmann estimate of the treatment difference (95% CI) was 0.0 (-1.00; 0.00). (2-sided p=0.107). In study SUI3002, the median changes from baseline (range) at 24 hours were -1.0 (-6; 2) in the SOC + esketamine group and -1.0 (-5; 2) in the SOC + placebo. The Hodges-Lehmann estimate of the treatment difference (95% CI) was 0.0 (0.00; 0.00). (2-sided p=0.379). Even the use of complex, post-hoc analyses in subgroups could not reveal a substantial difference between the treatment groups. It is unclear whether a small effect favouring Esketamine + SOC can be attributed only to the effect of esketamine in reducing suicidal ideation and/or suicide risk. This effect could also be due to the overall management of patients during the double-blind treatment phase, since an improvement was observed for both treatment groups. As stated by the applicant, the beneficial effects of inpatient psychiatric hospitalization in diffusing the acute suicidal crisis in subjects in both treatment groups together with the effect of comprehensive SOC enhanced by twice-weekly study visits with extensive clinical contact, during the double-blind treatment phase, might have obscured a potential treatment difference on the CGI-SS-R score.

The CGI-SS-R and CGI-SR-I scores do not seem to correlate well with the outcomes of the MINI, which further shadows the validity of CGI-SS-R as a measure to examine suicidality. As per MINI interview, 100% of patients confirmed to think about suicide and intended to act, as was required per inclusion criteria. Majority of patients also thought of suicide often or frequently, and with severe intensity. However, there were quite some patients that according to the CGI-SS-R and CGI-SR-I were only moderately or mildly suicidal (36.8%), or were considered to be *at most* in moderate imminent suicide risk (40.8%). Furthermore, all of the suicide indices such as MADRS suicidal thoughts, CGI-SS-R scores, CGI-SR-I scores, clinician-rated FoST, and patient-reported FoST showed improvement from baseline to the end of the double-blind treatment phase for both treatment groups. There were only small differences (much lower than 1.0) observed between placebo + SOC and Esketamine + SOC [MADRS suicidal thoughts-0.20; CGI-SS-R -0.18; CGI-SR-I -0.16; CGI-FoST -0.09 and Patient reported FoST -0.05]. It is questionable whether these small potential beneficial effects may or may not be due to a reducing effect of suicidal ideation/behaviour by esketamine treatment.

A larger proportion of patients in the esketamine group (compared to placebo) achieved remission of depressive symptoms (MADRS total score ≤12). At the double-blind endpoint (Day 25, 4 hours postdose), 50% of subjects in the esketamine + SOC group and 37% in placebo + SOC group had a MADRS total score ≤12. The corresponding treatment difference (95% CI) was 13.1% (4.03; 22.19). A percentage as high as 37% of patients who achieved remission of depressive symptoms (MADRS total score ≤12) for the placebo group cannot be unnoticed. However, the beneficial effects of esketamine treatment on depressive symptoms could not be translated into a reduction of suicidal behaviour.

Results in other secondary endpoints related to suicidality, such as resolution of suicidality (CGI-SS-R≤1), reduction of hopelessness using BHS and quality of life using QLDS, were small and of questionable significance. The differences observed per 100 patients in favour of esketamine 84mg plus SOC were in line with the results observed for the key secondary endpoint and other important suicidality indices, which could not demonstrate a statistical significant and clinically relevant difference in favour of esketamine + SOC treatment.

Reducing suicidality was an essential part of the primary objective, as suicidal ideation is specifically mentioned in the context of reduction of depressive symptoms. As no improvement in suicidality was observed in the studies, the primary objective of the study was not fully met.

The results of the open-label follow-up phase suggest minimal to absent differences between the treatment groups at Day 90, in terms of MADRS and CGI-SS-R. It is notable that in study SUI3001 the

change in MADRS score from baseline to Day 90 is in favour of SOC + placebo group. However, the results should be interpreted with caution as they are open-label. SOC antidepressant treatment was to be continued as per clinical judgement during the follow-up phase, details on continuation of SOC antidepressant treatment were requested.

Efficacy and safety in elderly patient population in the target indication has not been discussed, while this was brought under discussion in the provided CHMP scientific advices. The TRD clinical program included a study in elderly, however it was considered that the TRD elderly patient population differs considerably from the MDSI patient population, for example with respect to concomitant medications, which was considered to largely preclude extrapolation from TRD studies to elderly patients with MDSI.

Although, the population who participated in the two identical phase 3 clinical trials were those who responded positively to specific questions of MINI related to suicidal ideation/thoughts, it is highly unlikely (questionable) that it can reflect a true identifiable population in the clinical practice with actual suicidality issues (suicidal ideation/suicidal thoughts/prone to suicide).

Esketamine + SOC showed a rapid reduction of depressive symptoms, as it was anticipated from the TRD program. However, there were no measurable (via suicidal indices) beneficial effects in managing suicidality in a specific subgroup of MDD patients. This renders the reliable identification of such a patient population in the clinical practice difficult.

The key secondary endpoint and other important suicidality indices could not demonstrate a statistical significant difference in favour of esketamine 84mg plus SOC treatment. Other secondary endpoints did not provide supportive evidence.

Due to the above concerns, the applicant was requested to justify the patient population of the proposed indication and to provide sound evidence how this patient population can be reliably identified in clinical practice. The Applicant acknowledged the CHMP's concern that it would be difficult for prescribers to detect suicidal intent or to predict future suicidal behavior, and that currently available scales have limited utility in accurately identifying those patients who will go on to attempt or complete suicide. Taking this into consideration, the Applicant is proposing to revise the description of the patient population in the indication statement. Instead of "adult patients with a moderate to severe depressive episode of MDD who have current suicidal ideation **with intent**", the proposed population is now described as "adult patients with a moderate to severe episode of MDD **and** current suicidal ideation **or behaviour**". The intention of this rewording is to remove any connotation that prescribers are expected to assess and/or predict the patient's "intent" or "risk" for future suicide. Instead, the assessment is based on the patient's directly identifiable current symptoms.

The Applicant presented a modified indication based on the below argumentation (please note key differences shown below in bold font and discussed hereafter in this response):

> *Spravato, co-administered with oral antidepressant therapy, is indicated as acute short-term treatment for the rapid reduction of depressive symptoms* ***when this is urgently required*** *in adult patients with a moderate to severe episode of MDD* ***and*** *current suicidal* ***ideation or behaviour****.*
>
> ***Note: The effectiveness of Spravato in preventing suicide or in reducing suicidal ideation or behaviour has not been demonstrated. Use of Spravato does not preclude the need for hospitalisation if clinically warranted, even if patients experience improvement after an initial dose of Spravato.***

Suicidal ideation and suicidal behavior are common and discernible symptoms in patients with MDD. This population is therefore expected to be readily identifiable by treating clinicians, since assessment of suicidal ideation and behavior is part of the core competency for a psychiatry specialty. For patients with

MDD, monitoring and assessment of suicidality is a routine part of suicidal thoughts, intent to act on thoughts, plans and methods, past suicidal behavior, risk and protective factors and impulsivity. The company argued that there is no single test or assessment method that is proven to be an adequate predictor of suicide on an individual basis. The goal of suicidality assessment is, therefore, to identify, characterize, quantify, and manage those factors that contribute to clinical risk. Mental health professionals are well trained in identifying suicidal ideation and behavior. Although some patients may feel ambivalent and deny or conceal these thoughts and behaviours, they are usually able to be detected by way of psychiatric interview, collateral information from family, friends, and medical records. In addition, the target population includes patients who are actively seeking treatment or already undergoing treatment, and therefore may be more willing to share their concerns and symptoms with the clinician.

Findings of a survey conducted on behalf of the Applicant by a third-party research organization, Cello Health Insight, suggest that prescribers are proficient at recognizing and identifying suicidal ideation and behavior in patients with MDD and do so regularly as part of routine evaluation. The survey included 671 European psychiatrists and physicians actively treating patients with MDD across different healthcare settings in the UK (n=121), France (n=127), Germany (n=112), Italy (n=115), Spain (n=128), Belgium (n=38) and the Netherlands (n=30). The survey participants were asked to respond to the following question: "Thinking about your MDD patients, how do you normally assess and determine if there is an imminent risk for suicide?" Based on the verbatim responses, most respondents (91%) indicated that they assessed acute suicidality based on clinical evaluation and interview, including such elements as clinical/medical history, clinical assessment of suicidal ideation/intent and history of suicidality, psychological evaluation, discussion with the patient and family/caregivers. The majority of respondents indicated they performed a regular assessment of suicidality in MDD patients, with 57% of non-office based psychiatrists (n=426), 42% of primary care physicians/office-based psychiatrists (n=170), and 40% of emergency room physicians (n=75) performing an assessment at least once a month. The findings in this report are in agreement with the knowledge that the CHMP team has accumulated up to now.

The primary objective of these studies was to evaluate efficacy of esketamine + SOC compared with placebo + SOC for the rapid reduction of the symptoms of MDD. Therefore, the primary and key secondary efficacy endpoints were assessed on Day 2 (24 hours after the first dose). Results of the primary efficacy analysis showed a statistically significant difference in favour of esketamine + SOC versus placebo + SOC for the change in MADRS total score on Day 2, with very similar LS mean treatment differences observed in both studies (-3.8 in SUI3001 and -3.9 in SUI3002).

Clear undisputed beneficial effects on suicidality indices have not been demonstrated, given that the key secondary objective of the Phase 3 studies [statistical difference between esketamine + SOC and placebo +SOC in the change in CGI SS-R score from baseline (Day 1, predose) to 24 hours after the first dose (Day 2)] was not achieved.
The rapid reduction of depressive symptoms with the results from two pivotal studies (SUI2001 and SUI3002) has been recognised by CHMP [statistically significant difference between esketamine +SOC and placebo + SOC in the change in MADRS total score from baseline (Day 1, predose) to 24 hours after the first dose]. Despite the comprehensive SOC, which included initial hospitalization and initiation/optimization of antidepressant therapy, permitted benzodiazepine, and permitted psychotherapy, enhanced by twice-weekly study visits with extensive clinical contact, esketamine + SOC managed to demonstrate a statistically significant and clinically relevant difference from placebo + SOC.

The wording "when urgently required" was proposed by the company to further define the intended population. Per the NICE CG90 guideline, actively suicidal ideas or plans are amongst those factors listed as favouring urgent referral to specialist mental health services. Severity of depression and "danger to

self" have been identified among key clinical variables important in disposition decisions in the psychiatric emergency room. In one Dutch study evaluating patients who were assessed by outreach psychiatric emergency services during the period of 2009 to 2014, suicidal behavior was identified in 66% of assessed patients with depressive disorder.

The intended target population of "adult patients with a moderate to severe episode of MDD and current suicidal ideation or behavior" accurately reflects the population studied in the Phase 3 SUI3001 and SUI3002 studies. Subjects enrolled in these studies were required to present with current suicidal ideation with intent within 24 hours of randomization. Additionally, patients had moderate to severe depression (Montgomery-Asberg Depression Rating Scale [MADRS] baseline score >28) and in the physician's opinion, acute psychiatric hospitalization of the subject was clinically warranted due to the subject's imminent risk for suicide. Subjects presented with consistent evidence of an acute psychiatric illness as measured by multiple suicidality indices: clinicians considered 90% of subjects as moderately to extremely suicidal at baseline (as measured by the Clinical Global Impression – Severity of Suicidality - Revised [CGI-SS-r]), and 86% as having moderate to extreme imminent risk for suicide within the next 7 days (as measured by the Clinical Global Impression – Imminent Suicide Risk [CGI-SR-I] scale). In addition, a large proportion of subjects had current or recent evidence of suicidal behavior: 63.1% reported any prior suicide attempt; 27.3% (30.1% in the esketamine + standard of care [SOC] group and 24.4% in the placebo + SOC group) reported a suicide attempt within the last month (Seq0006/Mod2.5/Sec4.2); and 19.1% (19.9% in the esketamine + SOC group and 18.2% in the placebo + SOC group) reported a suicide attempt within the week prior to screening.

The intention of this rewording is to remove any connotation that prescribers are expected to assess and/or predict the patient's "intent" or "risk" for future suicide. Instead, the assessment is based on the patient's directly identifiable current symptoms.

Finally, the company proposed to add a new clarification to make it clear to the prescriber that Spravato has not demonstrated a direct, beneficial effect on suicidality. Given that the Phase 3 studies did not meet the key secondary endpoint, the Applicant has proposed to add a clarification note within the indication statement stating that the "effectiveness of Spravato in preventing suicide or in reducing suicidal ideation or behaviour has not been demonstrated ". This statement, and other related statements elsewhere in the SmPC, is intended to very clearly communicate to prescribers that they should not expect an improvement in patients' suicidality beyond the rapid reduction of depressive symptoms.

The CHMP reviewed the proposed indication and could concur on the following:

- in the clinical practice psychiatrists monitor patients for suicidal ideation or behaviour (since these patients belong to an increased risk group of depressed patients).
- that the patients included in the studies suffered from a moderate to severe episode of MDD [in the pooled Phase 3 dataset (full efficacy analysis set), 181 (80%) subjects in the placebo + SOC group and 189 (84%) subjects in the esketamine + SOC group had a baseline MADRS total score of score of $\geq$35 (i.e., severe depression].
- That these patients a) were thinking about suicide and b) intended to act on thoughts of killing themselves (MINI current Status) (Yes, in both questions, 100%)

It is also considered that urgency should be maintained in the indication. Inclusion of urgency narrows the target population to those most in need of rapid reduction of symptoms.

The phrase "when this is urgently required" could be justified by the rapid reduction of depressive symptoms (already acknowledged from the TRD program and also seen in the MDSI clinical trials). However, this wording was considered to be expected to lead to misinterpretation by prescribing

physicians. The phrase "when this is urgently required" would only add unnecessary complexity to the indication or might increase the expectation that esketamine can relevantly reduce suicidality. Esketamine is currently thought to bridge the efficacy gap, providing urgent relief of depressive symptoms until the background Standard of Care (SOC) antidepressant therapy can exert its full effect. The "urgently required" term does not accurately reflect the expected esketamine use in the specific population.

The CHMP preferred to emphasize the urgent need for rapid reduction of depressive symptoms in the indication but not to specifically mention patients with suicidal ideation or behaviour since this may be perceived as esketamine having shown an effect on suicidality.

There were also concerns that the proposed indication mentioning suicidal ideation would give the connotation that Spravato is effective in the treatment of suicidality, while this was not demonstrated in the pivotal studies. Additional safety data provided by the Applicant regarding suicidal behaviour also did not allow for definitive conclusions to be drawn. Though a clear signal (i.e. statistical significance) cannot be established due to the low numbers, the data still indicate that there is a numerical difference in the occurrence of suicidal behaviour at the expense of esketamine, and thus a relationship can therefore not be excluded either.

The company then suggested the following indication:

"Spravato, co-administered with oral antidepressant therapy, is indicated as acute short-term treatment for the rapid reduction of depressive symptoms in a psychiatric emergency, as per clinical judgement, in adult patients with a moderate to severe episode of MDD (see section 5.1 for a description of the population studied)"

Following further discussions within the CHMP, it was agreed that the latest indication as worded above was broad and implied that Spravato could be given in any psychiatric emergency which could be driven by complex psycho-social events and not necessarily acute relapse of depression. Thereby the CHMP proposed the following indication which was agreed upon by the company:

"Spravato, co-administered with oral antidepressant therapy, is indicated in adults with a moderate to severe episode of major depressive disorder, as acute short term treatment, for the rapid reduction of depressive symptoms, **which according to clinical judgement constitute a psychiatric emergency** (see section 5.1 for a description of the population studied)".

With respect to the proposed note highlighting that effectiveness of Spravato in preventing suicide or in reducing suicidal ideation or behaviour has not been demonstrated, section 4.1 after the indications could be a possible place for such a note. However, several concerns exist with the lack of confirmatory and robust data for an effect on suicidal ideation and/or behaviour of patients. Furthermore, misuse has been associated with esketamine and specific measures are already in place to avoid or minimise that. Last, but not least, there is a possibility that patients, who have stopped receiving esketamine after 4 weeks of treatment, return or engage again to suicidal thoughts or thoughts of harming themselves in the post-marketing setting. An increase in suicidality could then be observed, since the numbers of patients in the post-marketing setting are expected be higher than those in clinical trials and would lead to the detection of such cases.
With regard to having a boxed note/warning, this should be used for safety in exceptional cases, not lack of efficacy.

As a compromise, instead of a boxed warning, the information that the effectiveness of SPRAVATO in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated was included in the SmPC.

It was also agreed that the need of hospitalization, if clinically warranted, as well as monitoring for suicidality, is included in the SmPC.

It has been agreed that there is a concern that it would be difficult for prescribers to detect suicidal intent or to predict future suicidal behavior, and that currently available scales have limited utility in accurately identifying those patients who will go on to attempt or complete suicide. It is also agreed that physicians will require some form of education and training. However, general recommendations and general treatment guidelines for monitoring suicidal ideation or behaviour in depressed patients may not be the most optimal approach and a more practical way should be proposed by the Applicant e.g. use of MINI together with medical history of patients (e.g. prior suicide attempts). The Applicant proposes to carefully educate and communicate with healthcare professionals to ensure that the appropriate population receives esketamine and what effects should and should not be expected. This educational approach however, is not described in detail in the responses submitted. The educational material for the prescribers was requested and provided satisfactorily prior to the finalisation of the procedure.

A significant benefit for this uniquely vulnerable population, as characterised by the Applicant, could justify an additional 1 year market protection period. It was indeed shown that administration of esketamine led to rapid reduction of depressive symptoms in a subset of patients with MDD who have current suicidal ideation or behaviour and probably reflect an acutely ill population that requires quick intervention. It has to be taken into account that these increased risk patients have been excluded from previous antidepressant treatment trials and current standard of care for their management includes initiation or optimization of oral antidepressants and, frequently, hospitalization. An unmet medical need for approved pharmacological treatments exists for such patients. It is expected that esketamine will probably bridge the efficacy gap due to the delayed onset of action of standard antidepressants, which may take several weeks to exert their full effect.

The Applicant has revised the wording of the indication, taking into consideration the concern that there is no direct beneficial effect on suicidality and an improvement in patients' suicidality beyond the rapid reduction of depressive symptoms should not be expected. So related efficacy issues on suicidality were resolved.

There were differences observed for some efficacy endpoints between the two phase 3 studies.

It is acknowledged that results of the primary efficacy analysis showed a statistically significant and clinically meaningful difference in favour of esketamine + SOC versus placebo + SOC for the change in MADRS total score on Day 2 (24 hours after the first dose), with very similar LS mean treatment differences observed in both studies (-3.8 in SUI3001 and -3.9 in SUI3002, pooled studies -3.8). Likewise, the results of the key secondary endpoint (change from baseline in CGI-SS-r score on Day 2, 24 hours after the first dose) were also very similar between the 2 studies. This was well clarified by the company during the assessment. The factors causing differences between study the two Phase 3 studies include: higher proportion of randomized subjects who received an antidepressant + augmentation therapy, longer mean duration of illness, higher proportion of patients who had a recent suicide attempt, higher number of discontinuations and longer duration with hospitalisation and "increased care" for the patients in study SUI3002 compared to SUI3001.
The explanations for the differences observed between study SUI3002 and SUI3001 are plausible and the potential factors influencing the results are factual and part of the clinical practice.

Also an analysis based on the MADRS severity (for the subgroup with MADRS =>35 at baseline) was requested to investigate whether severely depressed patients who are expected to be more prone to suicidal thoughts are affected by the treatment of esketamine plus SOC.

The Applicant performed all the requested analyses. Baseline characteristics from the group of patients who had a MADRS score at baseline =>35 (N=370) were similar to those of the total clinical trial population (N=451). The results for the primary and important secondary endpoints using various analysis methods (MMRM and BOCF) were more pronounced in this more severely ill population, however

comparable and consistent with the results in the overall trial population. The group of patients that had a MADRS score at baseline =>35 corresponds to the majority of the trial population 82%. It should be also noted that in this population with severe depression, effects on suicidality were not very different i.e. for the subgroup with baseline MADRS =>35 the between group differences in the percentage of subjects who achieved resolution of suicidality at Days 1, 2 and 25 were 16.2%, 4.6% and 5.6%, respectively. In the case of the overall population the respective between group differences in the percentage at Days 1, 2 and 25 were 13.2%, 1.6% and 7.3%, respectively. Taken the data into consideration, it could be concluded that there is no sound scientific reason for the "isolation" or the "separation" of this subgroup from the overall trial population or specifically include this population in the wording of the indication.

The proposed SmPC included a warning on individuals with a history of drug abuse or dependence, these patients were excluded from the studies while substance and alcohol abuse is relatively common in severely depressed patients and these patients could be potential candidates for esketamine treatment once brought to the emergency care due to suicidality. The applicant was requested to discuss whether the current warning in the SmPC is sufficient on other patient populations outside of TRD.

The Applicant's proposal for the warning in the SmPC regarding these patients is meant to convey the need to evaluate and recognize those patients at risk for abuse and dependence and manage them adequately during the treatment. Given the limited postmarketing authorization experience available to date, the Applicant preferred to take a conservative and consistent approach across indications. Specifically, the Applicant recommended that the risk for abuse should be assessed prior to prescribing esketamine, and that patients should be monitored for the development of behaviours or conditions of abuse or misuse, including drug seeking behaviour. The Applicant's position is that the same text regarding the warning on drug abuse or dependence is therefore appropriate for both the TRD indication and this new indication.

The applicant approach was endorsed by the CHMP. It is considered that patients with a history of substance abuse or dependence can be treated with Spravato also in patients with severe depression, after careful consideration and in the context of close monitoring. As the intended treatment period for rapid reduction of depressive symptoms is short, the risk of abuse could be considered even lower than in the treatment of patients with TRD.

The proposed warning in the SmPC was considered to be sufficient.

The primary analysis set for efficacy analysis, i.e. full analysis set was acceptable and during the assessment the company provided a per protocol analysis, with exclusion of major protocol deviations. The conclusions based on the full and per-protocol analysis were alike.

To better characterise the included patient population in the pivotal studies, the applicant provided details on previous treatments i.e. number of antidepressant treatments, including augmentation therapy, psychotherapy and possible ECT.

The available data concerning previous treatments does not allow a full characterisation of the patients population as history of previous antidepressant treatments did not extend beyond 30 days prior to study entry. Based on these data, one might conclude the patients included in the study have not received optimal treatment for their severe depression, as for example only 4 patients have received psychotherapy. It is unclear which proportion of patients has received augmentation therapy as prior antidepressant use includes both treatment with single antidepressant and augmentation. Nevertheless, the included patient population was clearly in need of rapid reduction of their depressive symptoms, which most likely could have not been reached with optimizing their current treatment. The proposed SmPC included the following statements in section 4.2:

*After 4 weeks of treatment with Spravato, the oral antidepressant (AD) therapy should be continued, per clinical judgement.*

*In these patients, treatment with Spravato should be part of the comprehensive clinical care plan.*

This advice is considered adequate to cover treatment optimization after the patients depressive symptoms are improved with treatment with SOC + esketamine.

The applicant has provided the requested data, which does not allow a full characterisation of patients' treatment history. It is considered important that the patient's treatment is optimized after initial treatment period with esketamine, this is covered in the agreed SmPC.

The applicant was requested to discuss the large difference in duration of hospitalization during the study in North America and Europe in study SUI3002. This difference was not observed in study SUI3001, where the duration of hospitalization was similar between the regions.

The applicant has adequately discussed the possible causes of the observed duration of hospitalization between geographic regions in study SUI3002. Due to a regional protocol amendments in a number of European countries, the duration of hospitalization was extended to 14 days in some European countries, which in turn affected the average hospitalization duration in the EU region. Some European countries stand out with very long duration of hospitalization, which is likely related to local treatment practises. This is also observed in study SUI3001. It is noted that there is also a difference in duration of hospitalization between in study In the United States, in study SUI3001 longer duration of hospitalization is observed in comparison to study SUI3002. This is likely due to inclusion of different study centres, as also mentioned by the applicant

The applicant provided an overview of the most common combinations of drugs in augmentation therapy showing that those patients using augmentation therapy received many different combinations, a few also with 3 or more concomitant drugs. This reflects the patient population in clinical practise. As the number of patients per a specific combination is low, no analysis on differential response to SOC + esketamine treatment per concomitant treatment could be performed. Many different combinations of drugs were used in augmentation therapy, which reflects the patient population in clinical practise.

The provided MMRM and BOCF analysis on the primary endpoint demonstrated similar results as the primary analysis, however the applicant was requested to provide the p values from these analyses. The MMRM and BOCF analyses of primary endpoint show a statistically significant difference between SOC + placebo and SOC + esketamine, in line with the primary analysis using LOCF. The conclusions on statistical significance based on the MMRM and BOCF analysis are alike to the primary analysis with LOCF.

The applicant provided an analysis of change in MADRS score over time in subgroups per duration of hospitalisation (categories e.g. <5, ≥ 5 - 10, >10).31 subjects in total were excluded from the analysis as the duration of hospitalization was missing for these patients. The results seem to suggest that the treatment effects would be largest in patients with a hospitalization duration of <5 days. However this subgroup is rather small (39 patients) as compared to the other subgroups, and the confidence interval is wide. The results do not suggest differences in treatment effect between patients hospitalized for 5-10 days and >10 days. The current SmPC does not address hospitalization or inpatient setting at the treatment initiation. Specific advice on hospitalization cannot be given. Based on the provided data, no recommendations on hospitalization can be given. The current statements in the proposed SmPC are considered adequate.

The results suggest minimal to absent differences between the treatment groups at Day 90. It is notable that in study SUI3001 the change in MADRS score from baseline to Day 90 is in favour of SOC + placebo group. The applicant was requested to provide details on whether and how SOC antidepressant treatment was continued during the follow-up phase.

During the follow-up phase, all patients but one continued to receive SOC antidepressant therapy. The majority of patients received two concomitant ADs. The pattern of number of SOC antidepressant therapies in the double-blind treatment phase and follow-up phase is similar in both treatment groups. Therefore the observed difference between the treatment groups in favour of SOC + placebo at Day 90 in study SUI3001 is in any case not driven by difference in SOC between the groups. The available data suggests that the added benefit of esketamine on top of SOC is gained in the first few weeks of treatment without any further benefit beyond this period. However any conclusions regarding efficacy beyond 4 weeks of treatment cannot be made as the follow-up phase was open label.

In overall no major changes occurred in the SOC AD therapy after the double-blind phase, albeit a higher number of patients received ≥3 AD therapies in the follow-up phase as compared to the double-blind phase, in both treatment groups. This might reflect optimizing AD therapy after initial treatment with esketamine.

The applicant provided the requested data, which shows similar pattern of SOC for both treatment groups in the follow-up phase. A larger proportion of patients received ≥3 SOC antidepressant therapies in the follow-up phase as compared to the double-blind phase, perhaps reflecting optimizing SOC. The SmPC section 4.2 addresses continuation of AD therapy adequately.

The applicant was requested to discuss the efficacy and safety of esketamine in elderly patient population in the target indication. The TRD clinical program included a study in elderly, however it is considered that the TRD elderly patient population differs considerably from the so-called "MDSI patient population", for example with respect to concomitant medications, which is considered to largely preclude extrapolation from TRD studies to elderly patients with MDSI.

The applicant agreed that extrapolation from the elderly population in the TRD studies to elderly population which could be considered candidates for treatment with esketamine for rapid reduction of depressive symptoms, cannot be made. The proposed indication specifies adults as target population and lack of evidence in elderly is adequately addressed in the proposed SmPC.

## Additional expert consultation

An additional expert consultation has not been requested.

## Assessment of paediatric data on clinical efficacy

The applicant is currently performing a study in adolescents, data are not available yet.

## 2.4.4. Conclusions on the clinical efficacy

Based on the data provided, the CHMP considered that the clinical efficacy was demonstrated.

## *2.5. Clinical safety*

**Introduction**

Spravato is currently approved as add-on treatment for adults with treatment-resistant Major Depressive Disorder, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode. The most commonly observed adverse reactions in

treatment-resistant depression patients treated with Spravato were dizziness (30%), nausea (27%), dissociation (26%), headache (24%), somnolence (18%), vertigo (18%), dysgeusia (17%), hypoaesthesia (11%), and vomiting (10%).

Because of the possibility of sedation, dissociative symptoms and increased blood pressure, patients must be monitored by a healthcare professional at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting.

***Safety of esketamine in MDSI***

The primary safety assessment for the Major Depression with Suicidal Ideation (MDSI) program is based on data from the 2 completed Phase 3 studies (SUI3001 and SUI3002) and 1 completed Phase 2 study (SUI2001) in subjects with MDSI.

In addition, CIOMS reports (for deaths, serious AEs, and pregnancies) are provided for 3 ongoing studies in adults with Treatment Resistant Depression (TRD) (TRD3008, TRD2005, TRD3006) and 1 ongoing study in pediatric subjects with MDSI (SUI2002). The Sponsor previously submitted an interim CSR for Study TRD3008 that included safety data up to a clinical cutoff date of 31 December 2018 and now has provided an updated report for the period of 31 December 2018 through 20 April 2019. For the other ongoing studies (TRD2005, TRD3006, SUI2002) cumulative CIOMS reports are provided through 20 April 2019.

The safety and tolerability data collected during the TRD clinical program are also considered supportive for the MDSI indication.

In the Phase 2 and 3 MDSI studies, safety was evaluated through AE monitoring, clinical laboratory tests, vital sign measurements, pulse oximetry, electrocardiograms (ECGs), nasal examination, nasal symptom questionnaire (SUI2001 only), and physical examinations including body weight. Specific scales were also used to evaluate symptoms of interest, including the CADSS, the Modified Observer's Assessment of Alertness/Sedation (MOAA/S). In addition, for Phase 3 studies (SUI3001/3002), responses from patient-reported modules of the SIBAT were mapped to corresponding categories of the Columbia Classification Algorithm for Suicide Assessment (C-CASA) 2012 Plus to assess suicidal ideation/behavior.

Rigorous evaluation of events of special interest was performed as part of the MDSI program for esketamine, and involved analysis of all relevant safety information, including AEs as well as analysis of validated rating scales (eg, CADSS) and quantitative assessments (eg, ECG, vital sign data).

The safety sets are defined by the applicant as follows:

- **Studies SUI3001 and SUI3002**

In each of these studies, the all randomized analysis set included all subjects who were randomized regardless of whether treatment was received. The safety analysis set included all randomized subjects who received at least 1 dose of study medication in the double-blind treatment phase. The follow-up analysis set was defined as all subjects who completed the double-blind treatment phase and either entered the follow-up phase or provided AE data after the double-blind treatment phase. This analysis set was used for the safety analyses during the follow-up phase.

- **Phase 2 Study SUI2001**

The all randomized analysis set included all subjects who were randomized regardless of whether treatment was received. The safety analysis set included all randomized subjects who received at least 1 dose of study medication in the double-blind treatment phase. Safety analyses for the follow-up phase were performed on the safety (follow-up) analysis set which included all subjects who had at least 1 visit during the follow-up phase.

**Patient exposure**

Across the completed Phase 3 studies (SUI3001, SUI3002) and the Phase 2 study (SUI2001) in MDSI, a total of 262 subjects received at least 1 dose of esketamine and 256 received at least 1 dose of placebo. The combined cumulative exposure to esketamine in the 3 completed MDSI studies was 15.8 patient-years (13.8 patient-years in the Phase 3 studies), and the combined cumulative exposure to placebo nasal spray was 15.7 patient-years (13.9 patient-years in the Phase 3 studies).

Exposure in Subjects with MDSI

In the MDSI studies, all subjects were to receive esketamine 84 mg on Day 1, with a protocol permitted one-time dose reduction to 56 mg allowed after the first dose if a subject was unable to tolerate the higher dose. Subjects who had protocol-permitted dose reduction then received 56 mg for the remainder of the double-blind phase.

In the pooled Phase 3 studies (SUI3001/3002), the mean (SD) duration of exposure to study medication was 22.2 (7.20) days in the esketamine + SOC group and 22.5 (6.42) days in the placebo + SOC group. During the double-blind treatment phase, all 227 subjects in the esketamine + SOC group received at least one esketamine dose of 84 mg. At least one esketamine dose of 56 mg or less was administered to 45 subjects (19.8%); of those, 35 subjects (15.4%) required a protocol permitted one time dose reduction to 56 mg for tolerability reasons, and the remaining 10 subjects received a lower dose due to an administration/device error.

In the Phase 2 study (SUI2001), the mean (SD) duration of exposure to study medication during the double-blind phase was 20.7 (8.49) days in the esketamine + SOC group and 21.5 (7.22) days for the placebo + SOC group. Of the 35 subjects in the esketamine + SOC group, all subjects received the dose of 84 mg on Day 1; 3 subjects had their dose reduced to 56 mg due to adverse events and 2 subjects had their dose reduced in error.

In the Phase 3 studies, the median duration of initial hospitalization during the double-blind treatment phase was between 10 and 14 days.

**Table 25: Treatment Disposition; Double-blind Treatment Phase; Safety Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**

| | Placebo + SOC | Esk 84 mg + SOC | Total |
|---|---|---|---|
| Analysis set: Safety | 225 | 227 | 452 |
| Completed study treatment | 187 (83.1%) | 192 (84.6%) | 379 (83.8%) |
| Discontinued study treatment | 38 (16.9%) | 35 (15.4%) | 73 (16.2%) |
| Reason for discontinuation | | | |
| Adverse event | 8 (3.6%) | 14 (6.2%) | 22 (4.9%) |
| Withdrawal by subject | 11 (4.9%) | 11 (4.8%) | 22 (4.9%) |

**Table 25: Treatment Disposition; Double-blind Treatment Phase; Safety Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**

| | Placebo + SOC | Esk 84 mg + SOC | Total |
|---|---|---|---|
| Lack of efficacy | 12 (5.3%) | 3 (1.3%) | 15 (3.3%) |
| Other | 4 (1.8%) | 5 (2.2%) | 9 (2.0%) |
| Lost to follow-up | 2 (0.9%) | 1 (0.4%) | 3 (0.7%) |
| Change from voluntary to involuntary hospitalization | 1 (0.4%) | 1 (0.4%) | 2 (0.4%) |

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**Table 26: Summary of Exposure to Study Agent; Double-blind Treatment Phase; Safety Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**

| | Placebo + SOC | Esk 84 mg + SOC |
|---|---|---|
| Analysis set: Safety | 225 | 227 |
| | | |
| Total duration of exposure (days) [a] | | |
| N | 225 | 227 |
| Mean (SD) | 22.5 (6.42) | 22.2 (7.20) |
| Median | 25.0 | 25.0 |
| Range | (1; 32) | (1; 34) |
| | | |
| Total duration of exposure (days) [a] | | |
| <=7 | 12 (5.3%) | 23 (10.1%) |
| 8-14 | 16 (7.1%) | 7 (3.1%) |
| 15-21 | 9 (4.0%) | 4 (1.8%) |
| 22-25 | 127 (56.4%) | 132 (58.1%) |
| >25 | 61 (27.1%) | 61 (26.9%) |
| | | |
| Total number of days dosed | | |
| N | 225 | 227 |
| Mean (SD) | 7.2 (1.81) | 7.1 (2.05) |

**Table 26: Summary of Exposure to Study Agent; Double-blind Treatment Phase; Safety Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**

| | Placebo + SOC | Esk 84 mg + SOC |
|---|---|---|
| Median | 8.0 | 8.0 |
| Range | (1; 8) | (1; 8) |
| | | |
| Total number of days dosed | | |
| 1 | 6 (2.7%) | 13 (5.7%) |
| 2 | 4 (1.8%) | 7 (3.1%) |
| 3 | 9 (4.0%) | 5 (2.2%) |
| 4 | 10 (4.4%) | 3 (1.3%) |
| 5 | 2 (0.9%) | 4 (1.8%) |
| 6 | 6 (2.7%) | 2 (0.9%) |
| 7 | 3 (1.3%) | 9 (4.0%) |
| 8 | 185 (82.2%) | 184 (81.1%) |
| | | |
| Total exposure (subject [years]) | 13.9 | 13.8 |

[a] Total duration of exposure is defined as time between the first and the last day of study agent in the double-blind phase.

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Safety data is derived from two completed Phase 3 studies and one supportive Phase 2 study. The Phase 3 studies provide short term exposure data for 262 patients in the esketamine group and 256 patients in the placebo group. The exposure is considered sufficient for a general safety assessment.

Rate of discontinuation was low across the pooled phase 3 studies. The most common reason for discontinuation in the esketamine group was adverse event, whereas for the placebo group this was lack of efficacy.

In the pooled phase 3 studies most subjects received all 8 doses of 84 mg esketamine/placebo in the double blind phase. Around 20% of subjects had a dose reduction to 56 mg and continued on the 56 mg esketamine dose. Of note, 10 out of 45 patients who received a reduced dose in the Phase 3 studies and 2 of 5 in the Phase 2 did so due to an administration/device error. This means that 22% of all dose reductions in the Phase 3 studies as well as 40% of the dose reductions in the Phase 2 study were in error. This is somewhat puzzling, since the medication is not given out to patients but has to be administered under supervision at the study sites. The applicant is asked to provide more data about the medication errors and what measures could be undertaken in a clinical routine use to avoid this unusually high number of wrongly reduced doses. (**OC**)

Exposure in Subjects with TRD

The safety profile of esketamine in the MDSI indication is also supported by data from the TRD clinical development program. This program includes 6 completed Phase 2 and 3 studies (1,708 subjects who received esketamine [611 patient-years of exposure] and 486 subjects who received placebo [107 patient-years of exposure]) and the ongoing OL extension safety study TRD3008 (1,140 adult and elderly subjects who previously participated in the Phase 3 TRD studies [1,198 patient-years exposure]). The median duration of exposure in TRD3008 as of 31 December 2018 was 15.4 months (range: 0 to 31 months).

Across TRD studies, subjects received either fixed or flexible dosing with esketamine at a dose of 56 or 84 mg (or 28, 56, or 84 mg in elderly subjects). As of 31 December 2018, across completed and ongoing Phase 3 TRD studies, 1,739 subjects had received at least one dose of esketamine 56 mg for 611 patient years of exposure, and 1,279 subjects had received at least one dose of esketamine 84 mg for 1,151 patient-years of exposure.

**Table 27: Extent of Cumulative Exposure to Intranasal Study Medication by Dose Across All Studies and Treatment Phases: Safety/Full Analysis Sets: (Studies ESKETINTRD3001 ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, ESKETINTRD3005, ESKETINTRD3008)**

| | Intranasal Esk 28 mg + Oral AD (N=254) | Intranasal Esk 56 mg + Oral AD (N=1739) | Intranasal Esk 84 mg + Oral AD (N=1279) |
|---|---|---|---|
| Duration, months | | | |
| ≤Month 1 (≤Day 28) | 212 (83.5%) | 1089 (62.6%) | 310 (24.2%) |
| ≥ 6 months (180 days) exposure | 26 (10.2%) | 410 (23.6%) | 756 (59.1%) |
| ≥ 12 months (365 days) exposure | 15 (5.9%) | 239 (13.7%) | 595 (46.5%) |
| Mean (SD) | 2.1 (5.51) | 4.6 (7.73) | 11.7 (10.05) |
| Median | 0.3 | 0.5 | 11.0 |
| Range | (0; 33) | (0; 39) | (0; 37) |
| Total exposure (subject years) | 40 | 611 | 1151 |

Note: The duration of exposure to each dose is defined as exposure stop date-exposure start date+1. For subjects who received a flexible dose, the duration was calculated as the date before the dose increase/decrease-date start at that dose+1. If a subject received a dose multiple times during the course of treatment the durations were summed to obtain the final duration.
Note: Some of the study designs included flexible dosing and/or allowed dose modifications during the course of treatment. Subject who received at least one dose of esketamine at more than one dose level, would be counted in multiple dose categories (28 mg, 56 mg, or 84 mg). Thus, the number of subjects added across dose categories exceeds the total number of subjects in the TRD studies.
Adapted from Appendix Q150_EX_POOL_T257

Long term exposure data is only available from the development program in treatment resistant depression (TRD). No biological differences between TRD and subjects with major depressive disorder having current suicidal ideation with intent (MDSI) are to be expected, therefore the extrapolation of long term exposure safety data from TRD to MDSI is acceptable. However, since the applied use is for immediate symptom relief, long term treatment in subjects with MDSI is currently not intended.

**Adverse events**

Summary of findings

Overall, esketamine nasal spray 84 mg was safe and tolerated in the Phase 2 and 3 MDSI studies. The adverse events reported were generally consistent with the safety profile of esketamine observed in

previous studies in subjects with TRD. There were no new or unexpected safety concerns noted with the administration of esketamine in the MDSI clinical program. As observed in the TRD program, most TEAEs reported during esketamine treatment, including those that were most common, were mild or moderate in severity, were observed postdose on the day of dosing, and resolved the same day.

Incidence

In the pooled Phase 3 studies (SUI3001/3002), 89.9% of the subjects in the esketamine + SOC group (n=227) and 75.6% in the placebo + SOC group (n=225) experienced at least 1 TEAE during the 4-week double-blind phase. The most common TEAEs (reported by ≥10% subjects) observed more frequently in the esketamine + SOC group versus placebo + SOC group during the double-blind phase were: dizziness (38.3% versus 13.8%), dissociation (33.9% versus 5.8%), nausea (26.9% versus 13.8%), somnolence (20.7% versus 10.2%), dysgeusia (19.8% versus 12.9%), vision blurred (11.9% versus 4.9%), paresthesia (11.5% versus 3.1%), vomiting (11.5% versus 5.3%), blood pressure increased (11.5% versus 4.0%), sedation (10.1% versus 2.2%), and anxiety (10.1% versus 7.6%). Headache was observed in similar proportion of subjects in both groups (20.3% vs. 20.4%).

**Table 28**: **Overall Summary of Treatment-emergent Adverse Events; Double-blind Treatment Phase; Safety Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**

| | Placebo + SOC | Esk 84 mg + SOC |
|---|---|---|
| Analysis set: Safety | 225 | 227 |
| Subjects with 1 or more: | | |
| TEAEs | 170 (75.6%) | 204 (89.9%) |
| TEAEs leading to death [a] | 0 | 0 |
| Serious TEAEs | 12 (5.3%) | 9 (4.0%) |
| Severe TEAEs | 13 (5.8%) | 31 (13.7%) |
| TEAEs leading to discontinuation of study agent | 8 (3.6%) | 14 (6.2%) |

Key: TEAE = treatment-emergent adverse event

[a] TEAEs leading to death are based on TEAE outcome of Fatal.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

Adapted from Appendix TSFAE01A_SCS

**Table 29: Number of Subjects with Treatment-emergent Adverse Events with Frequency of at Least 5% in Any Treatment Group by System Organ Class and Preferred Term; Double-blind Treatment Phase; Safety Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002**)

| | Placebo + SOC | Esk 84 mg + SOC |
|---|---|---|
| Analysis set: Safety | 225 | 227 |
| Subjects with 1 or more TEAEs | 170 (75.6%) | 204 (89.9%) |
| System organ class | | |
| Preferred term | | |
| Nervous system disorders | 101 (44.9%) | 163 (71.8%) |
| Dizziness | 31 (13.8%) | 87 (38.3%) |
| Somnolence | 23 (10.2%) | 47 (20.7%) |
| Headache | 46 (20.4%) | 46 (20.3%) |
| Dysgeusia | 29 (12.9%) | 45 (19.8%) |
| Paraesthesia | 7 (3.1%) | 26 (11.5%) |
| Sedation | 5 (2.2%) | 23 (10.1%) |
| Hypoaesthesia | 3 (1.3%) | 20 (8.8%) |
| Dizziness postural | 3 (1.3%) | 15 (6.6%) |
| Psychiatric disorders | 63 (28.0%) | 125 (55.1%) |
| Dissociation | 13 (5.8%) | 77 (33.9%) |
| Anxiety | 17 (7.6%) | 23 (10.1%) |
| Euphoric mood | 1 (0.4%) | 17 (7.5%) |
| Insomnia | 18 (8.0%) | 16 (7.0%) |
| Depersonalisation/derealisation disorder | 0 | 14 (6.2%) |
| Gastrointestinal disorders | 66 (29.3%) | 102 (44.9%) |
| Nausea | 31 (13.8%) | 61 (26.9%) |
| Vomiting | 12 (5.3%) | 26 (11.5%) |
| Constipation | 14 (6.2%) | 22 (9.7%) |

**Table 29: Number of Subjects with Treatment-emergent Adverse Events with Frequency of at Least 5% in Any Treatment Group by System Organ Class and Preferred Term; Double-blind Treatment Phase; Safety Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002**)

| | Placebo + SOC | Esk 84 mg + SOC |
|---|---|---|
| Paraesthesia oral | 3 (1.3%) | 16 (7.0%) |
| Hypoaesthesia oral | 2 (0.9%) | 12 (5.3%) |
| Respiratory, thoracic and mediastinal disorders | 34 (15.1%) | 48 (21.1%) |
| Nasal discomfort | 13 (5.8%) | 12 (5.3%) |
| Investigations | 21 (9.3%) | 40 (17.6%) |
| Blood pressure increased | 9 (4.0%) | 26 (11.5%) |
| Eye disorders | 13 (5.8%) | 34 (15.0%) |
| Vision blurred | 11 (4.9%) | 27 (11.9%) |
| Ear and labyrinth disorders | 6 (2.7%) | 20 (8.8%) |
| Vertigo | 1 (0.4%) | 14 (6.2%) |

Key: TEAE = treatment-emergent adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.
Adverse events are coded using MedDRA Version 21.1.

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During the follow-up phase, AEs were observed in 53.7% of the subjects in the esketamine + SOC group and 50.8% of those in the placebo + SOC group. The most common AEs (reported by ≥5% subjects) observed more frequently in the esketamine + SOC group than the placebo + SOC group were: depression (6.8% versus 3.2%) and insomnia (6.3% versus 5.9%). Adverse events observed more frequently in the placebo + SOC group than the esketamine + SOC group during the follow-up phase were: anxiety (9.7% versus 5.8%), suicidal ideation (6.5% versus 5.3%), and headache (9.2% versus 6.8%).

A similar pattern of results was observed in the Phase 2 study (SUI2001).

**Table 30: Overall Summary of Adverse Events; Follow-up Phase; Follow-up Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**

| | Placebo + SOC | Esk 84 mg + SOC |
|---|---|---|
| Analysis set: Follow-up | 185 | 190 |
| Subjects with 1 or more: | | |
| AEs | 94 (50.8%) | 102 (53.7%) |
| AEs leading to death [a] | 0 | 1 (0.5%) |
| Serious AEs | 22 (11.9%) | 22 (11.6%) |
| Severe AEs | 16 (8.6%) | 12 (6.3%) |

Key: AE = adverse event
[a] AEs leading to death are based on AE outcome of Fatal.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

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**Table 31: Number of Subjects with Adverse Events with Frequency of at Least 5% in Any Treatment Group by System Organ Class and Preferred Term; Follow-up Phase; Follow-up Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**

| | Placebo + SOC | Esk 84 mg + SOC |
|---|---|---|
| Analysis set: Follow-up | 185 | 190 |
| Subjects with 1 or more AEs | 94 (50.8%) | 102 (53.7%) |
| System organ class | | |
| Preferred term | | |
| Psychiatric disorders | 48 (25.9%) | 58 (30.5%) |
| Depression | 6 (3.2%) | 13 (6.8%) |
| Insomnia | 11 (5.9%) | 12 (6.3%) |
| Anxiety | 18 (9.7%) | 11 (5.8%) |
| Suicidal ideation | 12 (6.5%) | 10 (5.3%) |

**Table 31: Number of Subjects with Adverse Events with Frequency of at Least 5% in Any Treatment Group by System Organ Class and Preferred Term; Follow-up Phase; Follow-up Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**

| | Placebo + SOC | Esk 84 mg + SOC |
|---|---|---|
| Nervous system disorders | 31 (16.8%) | 27 (14.2%) |
| Headache | 17 (9.2%) | 13 (6.8%) |

Key: AE = adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.
Adverse events are coded using MedDRA Version 21.1.

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As expected, the adverse events observed in subjects with MDSI are comparable to those with TRD. The incidence rate during the double-blind phase was higher in the esketamine than in the placebo group. The most common adverse events reported were dizziness, dissociation, nausea, somnolence, headache and dysgeusia. For the placebo group these were headache, dizziness, nausea and dysgeusia. Reporting of dysgeusia in both groups is likely the result of the intranasal route of administration, due to the added flavouring in both active and placebo device. The events were primarily in the area of expected CNS effects and can be expected to be either related to the known safety profile of esketamine or the underlying disease.

The difference between treatment groups was less pronounced during the follow-up phase. During this phase, subjects did not receive esketamine or placebo, which is reflected by the lack of device or esketamine specific adverse events. Adverse events reported by subjects in the follow up phase either appear to be related to the underlying disease (e.g. depression, suicidal ideation) or a comorbid disorder (e.g. anxiety, insomnia).

TEAE occurrence and resolution

Most TEAEs in Phase 3 studies, including those most commonly occurring in esketamine-treated subjects, were reported on the day of nasal spray dosing. Of those TEAEs occurring on a dosing day, the proportion that resolved on the same day was 94.9% for the esketamine + SOC group and 85.2% for the placebo + SOC group in the pooled Phase 3 studies.

The TEAEs with at least 50 total occurrences in the esketamine + SOC group were similar to the most commonly occurring TEAEs (≥10% of subjects reporting the event): dizziness, dysgeusia, somnolence, nausea, headache, paresthesia, hypoesthesia, sedation, dissociation, and blood pressure increased. Of these TEAEs, all except headache had at least 50 occurrences on a dosing day and ≥94.4% of those events resolved the same day.

**Table 32: Occurrence and Resolution of Treatment-emergent Adverse Events on Intranasal Dosing Days; Double-blind Treatment Phase; Safety Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**

| Study Phase | Treatment (+ Oral AD) | N | Subjects with Any TEAE[a] | Proportion of TEAEs Occurring on Dosing Days[b] | Proportion of TEAEs Which Occur on Dosing Days with Same Day Resolution |
|---|---|---|---|---|---|
| Pooled SUI3001/3002 | Placebo + SOC | 225 | 170 (75.6%) | 656/952 (68.9%) | 559/656 (85.2%) |
| | Esk 84 mg + SOC | 227 | 204 (89.9%) | 2383/2650 (89.9%) | 2261/2383 (94.9%) |

[a] Incidence in this column is based on the number of subjects experiencing at least one AE, not the number of events.
[b] Numerator is the number of AEs occurring post-dose on a dosing day. Denominator is the total number of occurences of an AE. A subject may be counted more than once if they had multiple occurrences of an AE.

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Adverse events were closely correlated with administration of the study drug and usually of short duration and resolved in the majority of cases on the same day. For subjects receiving placebo, the percentage of adverse events occurring on the dosing day is lower, also for events resolving on the same day, probably as these are related to the underlying disease. These findings are consistent with what has been previously observed in the TRD studies.

No information has been provided on the occurrence/resolution of adverse events on dosing days for Study SUI2001. The applicant provided this to allow for interpretation.

Severity

Across the Phase 2 and 3 MDSI studies, most TEAEs were assessed by the investigator as mild or moderate in severity. During the double-blind phase of the pooled Phase 3 studies, severe TEAEs were observed in 13.7% of subjects in the esketamine + SOC group and 5.8% in the placebo + SOC group. The most common severe TEAEs among esketamine-treated subjects were associated with the known transient effects of intranasal esketamine administration and included dissociation (4.0% in the esketamine + SOC group vs. 0% in the placebo + SOC group), nausea (2.2% vs. 0%), and increased blood pressure (1.8% vs. 0%). Other severe TEAEs included those related to the underlying disease state (eg, depression, suicidal ideation), which were reported at low rates (<2%) in the esketamine + SOC group and occurred at similar rates in the placebo + SOC group.

In the pooled Phase 3 studies, the pattern of occurrence and resolution for severe TEAEs was consistent with the observations noted for TEAEs of all severity categories. Most of the severe TEAEs had a median duration of ≤2.5 hours until resolution. The only severe TEAEs that were reported on a dosing day and not reported as resolved the same day were depression (2 events) and suicide attempt (1 event) in the

esketamine + SOC group and depression (1 event), depression suicidal (1 event), suicide attempt (1 event), and erectile dysfunction (1 event) in the placebo + SOC group.

In the Phase 2 study SUI2001, severe TEAEs were reported in 5 (14.3%) subjects in the esketamine + SOC group and 1 (3.2%) of subjects in the placebo + SOC group during the double-blind phase, with dysgeusia (n=3 [8.6%]) being the only severe event reported in >1 subject exposed to esketamine.

**Table 33: Treatment-emergent Severe Adverse Events in at Least 1% of Subjects in Any Treatment Group; Double-blind Treatment Phase; Safety Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**

| | Placebo + SOC | Esk 84 mg + SOC |
|---|---|---|
| Analysis set: Safety | 225 | 227 |
| Subjects with 1 or more TEAEs | 13 (5.8%) | 31 (13.7%) |
| System organ class | | |
| Preferred term | | |
| Psychiatric disorders | 9 (4.0%) | 20 (8.8%) |
| Dissociation | 0 | 9 (4.0%) |
| Anxiety | 1 (0.4%) | 4 (1.8%) |
| Suicide attempt | 2 (0.9%) | 3 (1.3%) |
| Depression | 3 (1.3%) | 2 (0.9%) |
| Suicidal ideation | 3 (1.3%) | 1 (0.4%) |
| Gastrointestinal disorders | 0 | 7 (3.1%) |
| Nausea | 0 | 5 (2.2%) |
| Investigations | 0 | 5 (2.2%) |
| Blood pressure increased | 0 | 4 (1.8%) |

Key: TEAE = treatment-emergent adverse event
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Adverse events are coded using MedDRA version 21.1.

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The pattern of severe adverse events was similar to those of mild and moderate severity. Severe dissociation, nausea and blood pressure increases were only found in the esketamine arm and not under placebo. Severe adverse event found in both arms (anxiety, suicide attempt, depression, suicidal ideation) were considered as probably related to the underlying disease.

Supportive Ongoing Long-term OL Extension Study TRD3008

As of the clinical cut-off date for the TRD3008 interim CSR (31 December 2018), 1,140 subjects with TRD were enrolled in this ongoing, long-term OL Phase 3 extension safety study. Overall, the TEAE data in TRD3008 were consistent with the findings of the completed Phase 2 and 3 studies in subjects with MDSI and in the previously completed TRD clinical studies.

Adverse Drug Reactions

Adverse drug reactions (ADRs) are AEs that were considered to be reasonably associated with the use of esketamine based on a comprehensive assessment of available AE information. An analysis of ADRs was conducted based on AEs reported in 3 completed Phase 2 and 3 MDSI studies, with support from the 5 completed TRD Phase 3 studies (TRD3001, TRD3002, TRD3003, TRD3004 and TRD3005) and 1 completed Phase 2 TRD study (TRD2003). A total of 1,971 subjects received esketamine and were evaluable for safety in these studies.

A total of 47 individual preferred terms were identified as ADRs for esketamine across indications. To provide a meaningful estimate of the proportion of subjects experiencing ADRs, some preferred terms belonging to the same medical concept were grouped together.

The new terms determined to be ADRs for esketamine following the MDSI ADR assessment are similar to those previously identified in the TRD data. Overall, this evaluation demonstrated that esketamine had a consistent risk profile in the TRD and the MDSI clinical development programs. The ADRs identified for esketamine are not indication specific.

**Adverse Events by Organ System or Syndrome**

Anticipated Dosing-related Adverse Events

Based on the known pharmacological properties and the well-characterized safety profile of esketamine, a number of events were categorized as anticipated dosing-related AEs determined to be associated with esketamine use. Specifically, this category included the following preferred terms: Anxiety, Anticipatory anxiety, Dissociation, Dizziness, Dizziness postural, Feeling abnormal, Feeling drunk, Nausea, Somnolence, Vertigo, Vomiting.

As expected, in the pooled Phase 3 studies SUI3001/3002, anticipated dosing-related AEs were reported by 73.1% of subjects in the esketamine + SOC group compared to 38.2% of subjects in the placebo + SOC group in the double-blind treatment phase. In both treatment groups, most anticipated dosing-related AEs occurred on dosing days and most of these resolved on the same day. For both treatment groups, the events of dissociation, dizziness, nausea, and vomiting, the number of events reported on a dosing day decreased from Day 1 to Day 8 with similar numbers of events reported from Day 8 to Day 25.

Psychiatric and nervous system related events of interest

- Dissociative/perceptual changes captured using the Clinician-administered Dissociative States Scale (CADSS) rating scale peaked by 40 minutes postdose and typically resolved within 1.5 hours.

Reported adverse events associated with these symptoms were primarily mild or moderate in severity, occurred on the day of dosing and resolved the same day.

- Treatment-emergent AEs related to anxiety were reported more frequently in the esketamine + SOC group compared to the placebo + SOC group (13.2% vs 8.9% in pooled Phase 3 studies and 25.7% vs 12.9% in the Phase 2 study SUI2001) and approximately half of all events had onset on a dosing day. Anxiety was reported as severe in intensity in esketamine-treated subjects in isolated cases. One subject in the esketamine + SOC group in the Phase 2 study SUI2001 discontinued due to a TEAE of agitation.
- Dizziness was reported as one of the most common side effects of esketamine. Treatment emergent AEs in the category of dizziness/vertigo primarily (>90%) occurred on the day of dosing and resolved spontaneously the same day. Discontinuations due to TEAEs in the category of dizziness/vertigo were reported in isolated cases (2 esketamine-treated subjects in the pooled Phase 3 studies and 1 esketamine-treated subject in the Phase 2 study SUI2001). No SAEs of or discontinuations due to dizziness or vertigo were reported in esketamine-treated subjects in the Phase 2 and Phase 3 MDSI studies.
- Sedative effects based on the MOAA/S scale and reported TEAEs of somnolence and sedation were generally mild, had an onset shortly after the start of the dose and typically resolved 1 to 1.5 hours postdose. None of the subjects who had MOAA/S score ≤2 had respiratory depression. In the cases of sedation, no symptoms of respiratory distress were observed and hemodynamic parameters (including vital signs and oxygen saturation) remained within normal ranges. There were no cases of respiratory depression reported in any of the MDSI studies and no clinically significant decreases in respiratory rate were observed.
- Across the Phase 2 and 3 studies in MDSI, psychotic-like symptoms were observed in isolated cases. No TEAEs of mania or hypomania were reported.
- A history of one or more prior suicide attempts was reported for approximately 60% of the 518 subjects in the safety analysis set of the Phase 2 and 3 MDSI studies. Prior suicide attempt is the single most important predictor of subsequent suicidal behavior. Across completed Phase 2 and Phase 3 MDSI studies, rates of AEs potentially related to suicidality (ie, preferred terms consistent with the Standardised MedDRA Query [SMQ] for suicide/self-injury), including serious events, were similar between treatment groups in the double-blind and follow-up phases. One completed suicide occurred in the follow-up phase in a subject who was treated with esketamine + SOC during the double-blind treatment phase and who had a history of several prior suicide attempts (including one within 30 days of study entry). Based on Kaplan-Meier estimates of first onset of any adverse event (AE) potentially related to suicidality (and for the AEs of suicide attempt or completed suicide) during the follow-up phase, there was no apparent difference between treatment groups for the time to first event after discontinuation of study medication. Assessment of the odds ratios for TEAEs potentially related to suicidality across the Phase 2 and 3 studies suggested a similar risk for suicidality AEs, including suicide attempts and completed suicides, for subjects in both treatment groups in each of the study phases.

<u>Lower Urinary Tract Symptoms</u>

- Treatment-emergent AEs potentially related to cystitis were reported by 3.1% of esketamine treated subjects in the completed pooled Phase 3 studies SUI3001/3002 and no subjects in the Phase 2 study SUI2001. There were no cystitis-related SAEs or TEAEs resulting in withdrawal of study medication.

<u>Post-dose Gastrointestinal Symptoms</u>

- Nausea and vomiting were reported among the most common side effects of esketamine in the Phase 2 and 3 MDSI studies. Most of these events occurred on the day of dosing and resolved spontaneously the same day, with the median duration not exceeding 1 hour in most subjects across dosing sessions. Discontinuation of study medication due to TEAEs of nausea and vomiting was reported in <1% of subjects in the pooled Phase 3 studies SUI3001/3002 and for a single subject in the Phase 2 study SUI2001. Rates of reported nausea and vomiting decreased over time across dosing sessions.

Abuse Potential

- The TEAEs suggestive of abuse potential most commonly associated with esketamine included dizziness, dissociation and somnolence. These symptoms were predominantly reported shortly after dosing on the day of esketamine administration, were transient and self-limiting, and mild or moderate in severity. There were no reported TEAEs with Preferred Terms of drug abuse, drug abuser, drug dependence, drug detoxification, drug rehabilitation, drug tolerance, drug tolerance increased, or drug use disorder.

Cardiovascular Effects

- Transient increases in systolic blood pressure (SBP) and diastolic blood pressure (DBP) were observed in the Phase 2 and 3 MDSI studies shortly after esketamine administration, reaching a maximum within 40 minutes and generally returning to values close to pretreatment within 1.5 hours after administration. The greatest mean maximum blood pressure (BP) increases across all intranasal dosing day compared to predose values in the pooled Phase 3 studies SUI3001/3002 were 14.3 mm Hg (SBP) and 10.0 mm Hg (DBP) for subjects in the esketamine + SOC group compared to the corresponding BP increases of 5.6 mm Hg (SBP) and 4.4 mm Hg (DBP) in subjects in the placebo + SOC group.
- There were no clinically meaningful changes in ECG findings in the completed Phase 2 and 3 MDSI studies, including QTc interval or PR interval.

The adverse events/adverse drug reactions observed in subjects with major depressive disorder (MDD) having current suicidal ideation with intent is comparable to the already established safety profile observed in patients with treatment resistant depression. No significant, unexpected safety signals were found during the two Phase 3 studies or the supporting Phase 2 study. Given that the study population in patients with MD and suicidal ideation is overall similar to those with treatment resistant depression and it is doubtful a biological differentiation between the populations is possible the similarity in safety profiles is to be expected.

Sedation and somnolence were commonly reported with esketamine treatment and usually resolved on the same day as dosing. There was one subject that had an MOAA/S score of 0 and 1 on multiple dosing days, corresponding to severe sedation. Though the subject did not require medical intervention, such deep sedation has not previously been reported in the TRD studies. The applicant provided case report and discuss the relationship between the event and esketamine dosing.

**Serious adverse event/deaths/other significant events**

**Deaths**

Overall, across all completed and ongoing studies with esketamine in the MDSI and TRD indications, 8 deaths have been reported up to 20 April 2019.

**Table 34: Subject Who Died in All Completed and Ongoing Clinical Studies of Esketamine**

| Study | Age Sex | Dictionary-derived Term (Reported Term) | Study Day of Onset | Protocol Phase | Onset Dose (mg)[a]/ Days since Last Dose | Investigator's assessment of Relationship |
|---|---|---|---|---|---|---|
| **COMPLETED AND ONGOING STUDIES IN MDSI** | | | | | | |
| *Double-blind Phase 3 Study (esketamine + SOC), n=262* | | | | | | |
| **SUI3001** | 53 Female | Completed Suicide (Suicide Completed) | 27 | FU | <84> 3 | Not related |
| **COMPLETED AND ONGOING STUDIES IN TRD** | | | | | | |
| COMPLETED STUDIES | | | | | | |
| *Phase 3 TRD Studies (esketamine + newly initiated oral AD), n=1601* | | | | | | |
| **TRD3002**[b] | 41 Male | Multiple injuries (Multiple injuries following a road traffic accident) | 16[b] | DB | <84> 1 | Not related |
| **TRD3004**[b] | 60 Male | Acute Respiratory Failure (Acute Respiratory Failure) | 113 | Optimization/ Maintenance | <56> 5 | Doubtful |
| | | Cardiac Failure Acute (Acute Heart Failure) | 113 | Optimization/ Maintenance | <56> 5 | Doubtful |
| **TRD3004**[b] | 55 Female | Completed Suicide (Completed Suicide) | 188 | Optimization/ Maintenance | <84> 12 | Not related |
| *Phase 2 TRD Study (adjunctive design), n=107* | | | | | | |
| **TRD2003**[b] | 41 Male | Completed suicide (suicide) | 45 | FU | <56> 20 | Not related |
| ONGOING STUDIES | | | | | | |
| *Open-label Phase 3 Long-term Extension TRD Study* | | | | | | |
| **TRD3008**[b] | 48 Male | Completed Suicide (suicide) | 26 | IND | <84> 4 | Not related |
| **TRD3008**[c] | 73 Female | Myocardial Infarction (myocardial infarction) | 321 | Optimization/ Maintenance | <84> 6 | Doubtful |
| **TRD3008**[c] | 59 Male | Multiple Injuries (Polytrauma [Accidental]) | 364 | Optimization /Maintenance | <56> 6 | Not related |

AD: antidepressant; DB: Double-blind; FU: Follow-up; IND: Induction; MDSI= major depressive disorder in patients assessed to be at imminent risk for suicide; SOC=comprehensive standard of care; TRD=treatment-resistant depression
Data are presented through the clinical cutoff date of 20 April 2019
[a] Doses in <> indicate last exposure was with the indicated dose (last dose prior to the event).
[b] This case was reported in TRD/Mod2.7.4/Sec2.1.2
[c] Please refer to TRD3008 interim CSR Seq0002/Mod5.3.5.2/TRD3008/Sec5.1.2.1

- **Completed Phase 2 and 3 MDSI studies:** In the completed Phase 2 and 3 MDSI studies, 1 death was reported in 262 subjects who had been assigned to esketamine + SOC treatment in the double-blind treatment phase (15.8 patient-years of exposure) and 0 deaths were observed in 256 subjects who had been assigned to placebo + SOC (15.7 patient-years of exposure). This death (completed suicide) occurred during the follow-up phase of SUI3001; no deaths were observed during the double-blind treatment phase of the SUI2001, SUI3001, or SUI3002 studies.
    - Subject  was a perimenopausal 53-year-old Asian female with MDD at imminent risk for suicide, in the JNJ54135419 treatment group, who had an SAE of completed suicide on Study Day 27 (in the follow-up phase), that was classified as severe in intensity. The subject's psychiatric history is notable for 5 prior suicide attempts, with the most recent suicide attempt by overdosing on medications occurred in the 30 days prior to screening. The subject has had 4 hospitalizations in the past 12 months due to depression or suicidality. Other notable psychiatric history at study entry includes anxiety and insomnia.

The subject was hospitalized and screened for the study on Day -2. She was randomized on Study Day 1. She received first 6 doses of the study drug in the hospital and was discharged home on Study Day 17. The subject received the last dose of study drug on Study Day 24 and completed the double-blind treatment phase of the study. On the same day, the subject reported having depressed mood and anxiety during the 04 July holiday celebration (on Study Day 22) (Source: CIOMS). According to her husband, she may have been depressed and anxious after spending time with friends and family (feeling like everyone else's life was better than hers).

Relevant assessments on Study Day 24 included: predose MADRS total score of 9 and postdose (after 4 hours) score of 3; predose MADRS-SI score of 1 and postdose (after 4 hours) score of 0; and CGI-SS-R score of 0.

The fatal adverse event of completed suicide was reported on Study Day 27. On the same day, the subject was found dead (suicide attempt). An autopsy was not performed. The investigator considered major depressive disorder, treatment-resistant depression with chronic passive and active suicidal ideation, and three suicide attempts within the last 9 months as the risk factors, and major depressive disorder as the suspected cause for the event of completed suicide. The investigator considered the event of completed suicide to be not related to the study drug.

- **Completed Phase 2 and 3 TRD studies:** As previously reported in the original esketamine MAA, there were 4 deaths reported among the 1,708 subjects who had received treatment with esketamine + oral AD in the completed Phase 2 and 3 studies in TRD (611 patient-years exposure). No deaths were observed among the 486 subjects who had received placebo + oral AD in these studies (108 patient-years exposure). The deaths included 2 completed suicides; 1 of which occurred during the follow-up phase of TRD2003 (20 days after last dose of esketamine) and the other occurred during the OP/MA phase of TRD3004 (last esketamine dose 12 days prior to death). Both subjects were reported to have experienced significant psycho-social stressors in the days prior to the suicide, and both events were considered by the investigator to be of no relationship to study medication. Other causes of death in the completed TRD studies were multiple injuries sustained during a road traffic accident during the double-blind phase of TRD3002 and death as a result of acute cardiac and respiratory failure during the OP/MA phase of TRD3004 in a subject with a history of hypertension, obesity, and vein surgery; these events were assessed by the investigator as not related and doubtfully related to study treatment, respectively.
- **Supportive Ongoing Long-term OL Extension Study TRD3008:** Up to the clinical cutoff date of the interim CSR (31 December 2018), 3 deaths were reported among the 1,140 subjects treated with esketamine in the ongoing extension study TRD3008. These included: 1 death due to completed suicide, which was considered by the investigator as not related to esketamine nasal spray; 1 death due to myocardial infarction, in a subject with a medical history of hypertension and hyperlipidemia, which was considered by the investigator of doubtful relationship to esketamine nasal spray; and 1 death due to multiple injuries (accidental polytrauma) caused by being hit by an automobile while riding a bicycle, which was considered by the investigator as not related to esketamine nasal spray. Note that one of these deaths (completed suicide) was reported in the original TRD MAA. No other deaths were observed in this study (based on CIOMS reports) during the period from 31 December 2018 to 20 April 2019.
- **Ongoing Blinded Studies SUI2002, TRD2005, TRD3006:** No deaths were observed in the ongoing, blinded studies up to 20 April 2019.

So far there have been eight deaths, including four suicides, in clinical studies with esketamine in patients with TRD and MDSI. The non-suicide deaths were either due to cardiac or respiratory failure or due to traffic accidents.

Although the sample size is small and none of the deaths were considered to be related to study drug by the investigators they all occurred in patients either on active treatment with or previously treated with esketamine. The one suicide in the Phase 3 study for MDSI occurred three days after last dose of study drug.

The pattern of deaths does not allow for any clear conclusions. However, although there is no clear safety signal, the imbalance in observed suicides between the esketamine and placebo arm creates at least uncertainty the overall effect on suicidality/suicidal ideation.

For the one completed suicide in the MDSI studies: subject (see above) only limited information is available from the provided narrative. The subject has received all 8 doses of esketamine and appeared to be responsive to treatment in terms of a reduction in MADRS, MADRS SI and CGI-SS-R scores. The final assessments on Day 24 were as follows: Predose MADRS total score of 9 and post dose (after 4 hours) score of 3; predose MADRS-SI score of 1 and post dose (after 4 hours) score of 0; and CGI-SS-R score of 0.

The investigator considered the event unrelated to esketamine and suspected the cause to be the underlying major depressive disorder. Based upon the subjects' MADRS and SIBAT scores, the subject appeared to be in remission. However, there is some uncertainty that subjects treated with esketamine might engage more in suicidal behaviour. Therefore, the possibility that esketamine treatment could have induced brain plasticity leading to an increase in suicidal behaviour cannot be readily excluded. Upon CHMP request, the company provided a discussion on the relationship between pharmacodynamic changes induced by esketamine dosing and suicidality.

**Events Potentially Related to Suicidality**

In the pooled Phase 3 studies SUI3001/3002, the frequency of adverse events potentially related to suicidality (ie, preferred terms consistent with the SMQ for suicide/self-injury) occurring during the double-blind treatment phase was similar in the 2 treatment groups (7.5% in the esketamine + SOC group and 7.6% in the placebo + SOC group). During the double-blind treatment phase, SAEs potentially related to suicidality were experienced by 7 subjects in the esketamine + SOC group vs 8 subjects in the placebo + SOC group: suicide attempt (4 [1.8%]) subjects in each group), suicidal ideation (1 [0.4%] subjects vs 4 [1.8%] subjects), and depression suicidal (2 [0.9%]subjects vs 1 [0.4%] subjects. In the Phase 2 study SUI2001 during the double-blind treatment phase, TEAEs potentially related to suicidality were reported for 3 (8.6%) subjects in the esketamine + SOC group and no subjects in the placebo + SOC group: suicidal ideation (2 subjects) and self-injurious ideation (1 subject). Two subjects in the esketamine + SOC group and no subjects in the placebo + SOC group reported SAEs (preferred term suicidal ideation) in this category.

During the follow-up phase of the pooled Phase 3 studies SUI3001/3002, the incidence of these events was similar in subjects previously exposed to esketamine + SOC (11.1%) or placebo + SOC (10.3%). Seventeen subjects in the esketamine + SOC group experienced SAEs potentially related to suicidality vs 13 subjects in the placebo + SOC group: suicide attempt (7 [3.7%] subjects vs 3 [1.6%] subjects), suicidal ideation (5 [2.6%] subjects vs 6 [3.2%] subjects)-, depression suicidal (5 subjects each), and completed suicide (1 [0.5%] subject vs 0 subjects).

During the follow-up phase of the Phase 2 study SUI2001, the incidence of TEAEs potentially related to suicidality was higher in the placebo + SOC group: 2 (7.4%) of 27 subjects in the esketamine + SOC group: intentional self-injury and suicidal ideation (1 subject each) and 5 (22.7%) of 22 subjects in the

placebo + SOC group: suicide attempt (3 subjects), suicidal ideation, and self-injurious ideation (1 subject each). Serious AEs potentially related to suicidality were reported by 1 subject in the esketamine + SOC group (suicidal ideation) and 4 subjects in the placebo + SOC group (suicide attempt [3 subjects] and suicidal ideation [1 subject]).

The reported frequencies of suicide attempt/completed suicide during the double-blind treatment phase (1.5% in the esketamine + SOC group and 1.6% in the placebo + SOC group) and follow-up phase (3.7% in the esketamine + SOC group and 2.9% in the placebo + SOC group) for the pooled Phase 2 and 3 studies was similar in the 2 treatment groups. In the pooled Phase 2 and 3 studies, there were no completed suicides during the double-blind treatment phase and 1 completed suicide in a subject previously exposed to esketamine during the follow-up phase.

Based on Kaplan-Meier estimates of first onset of any AE potentially related to suicidality (and for the AEs of suicide attempt or completed suicide) during the follow-up phase, there was no apparent difference between treatment groups for the time to first event after discontinuation of study medication. Assessment of the odds ratios for TEAEs potentially related to suicidality across the Phase 2 and 3 studies suggested a similar risk for suicidality AEs, including suicide attempts and completed suicides, for subjects in both treatment groups in each of the study phases.

Across all completed and ongoing studies of esketamine in both indications, 4 completed suicides were reported in subjects who received esketamine during the double-blind or open-label treatment phase (3 subjects in TRD studies and 1 subject in an MDSI study). This corresponds to an incidence of 0.22 completed suicides per 100 patient-years of exposure, ie, a rate comparable to that found per 100 patient-years of exposure in a meta-analysis of studies in MDD patients treated with antidepressants (0.22) and lower than the rate reported in another meta-analysis in TRD patients receiving various treatments (0.47).

**Table 35: Overall Summary of Number of Subjects with Adverse Events Potentially Related to Suicidality; Safety Analysis Set (Pooled Studies ESKETINSUI2001, 54135419SUI3001, 54135419SUI3002)**

| | Placebo + SOC | Esk 84 mg + SOC |
|---|---|---|
| **Double-Blind Treatment Phase** | | |
| Analysis set: Safety | 256 | 262 |
| Subjects with suicidality related AEs in DB Phase (%) | 17 (6.6%) | 20 (7.6%) |
| Odds ratio (95% CI)[a] | | 1.16 (0.59; 2.27) |
| Subjects with suicide attempt/completed suicide[b] in DB Phase (%) | 4 (1.6%) | 4 (1.5%) |
| Odds ratio (95% CI)[a] | | 0.98 (0.25; 3.94) |
| **Follow-up phase[c]** | | |
| Analysis set: Safety | 207 | 217 |

| | | |
|---|---|---|
| Subjects with suicidality related AEs in FU Phase (%) | 24 (11.6%) | 23 (10.6%) |
| Odds ratio (95% CI)[a] | | 0.92 (0.50; 1.68) |
| Subjects with suicide attempt/completed suicide in FU Phase (%) | 6 (2.9%) | 8 (3.7%) |
| Odds ratio (95% CI)[a] | | 1.33 (0.46; 3.85) |

Note: Adverse events potentially related to suicidality include the following MedDRA preferred terms: Completed suicide, Depression suicidal, Intentional overdose, Intentional self-injury, Multiple drug overdose intentional, Poisoning deliberate, Self injurious behavior, Self-injurious behaviour, Self-injurious ideation, Suicidal behaviour, Suicidal behavior, Suicidal ideation, Suicide attempt.

Note: Odds ratios >1 indicate greater risk for Esketamine 84 mg + SOC; Odds ratios < 1 indicate greater risk for Placebo + SOC

Key: AE=adverse event; DB=double-blind; CI=confidence interval; FU=follow-up; SOC=comprehensive standard of care

[a] Mantel-Haenszel estimates of common odd ratios and 95% confidence intervals controlling for study and standard of care.

[b] No completed suicides were reported during the double-blind phase of studies SUI2001, SUI3001, and SUI3002

[c] The follow-up phase was 9 weeks in studies SUI3001 and SUI3002 and 8 weeks in study SUI2001

Modified from Appendix TSFAE62A_SCS and Appendix TSFAE62B_SCS

Safety analysis for Phase 3 studies only:

**Table 36: Treatment-emergent Adverse Events Potentially Related to Suicidality; Double-blind Treatment Phase; Safety Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**

| | Placebo + SOC | Esk 84 mg + SOC |
|---|---|---|
| Analysis set: Safety | 225 | 227 |
| Subjects with 1 or more TEAEs | 17 (7.6%) | 17 (7.5%) |
| System organ class | | |
| Preferred term | | |
| Psychiatric disorders | 17 (7.6%) | 16 (7.0%) |
| Intentional self-injury | 3 (1.3%) | 7 (3.1%) |
| Suicidal ideation | 9 (4.0%) | 7 (3.1%) |

**Table 36: Treatment-emergent Adverse Events Potentially Related to Suicidality; Double-blind Treatment Phase; Safety Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**

| | Placebo + SOC | Esk 84 mg + SOC |
|---|---|---|
| Suicide attempt | 4 (1.8%) | 4 (1.8%) |
| Depression suicidal | 2 (0.9%) | 2 (0.9%) |
| | | |
| Injury, poisoning and procedural complications | 0 | 1 (0.4%) |
| Intentional overdose | 0 | 1 (0.4%) |

Key: TEAE = treatment-emergent adverse event
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Adverse events are coded using MedDRA version 21.1.

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**Table 37: Adverse Events Potentially Related to Suicidality; Follow-up Phase; Follow-up Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**

| | Placebo + SOC | Esk 84 mg + SOC |
|---|---|---|
| Analysis set: Follow-up | 185 | 190 |
| | | |
| Subjects with 1 or more AEs | 19 (10.3%) | 21 (11.1%) |
| | | |
| System organ class | | |
| Preferred term | | |
| | | |
| Psychiatric disorders | 19 (10.3%) | 21 (11.1%) |
| Suicidal ideation | 12 (6.5%) | 10 (5.3%) |
| Suicide attempt | 3 (1.6%) | 7 (3.7%) |
| Depression suicidal | 5 (2.7%) | 5 (2.6%) |
| Intentional self-injury | 2 (1.1%) | 3 (1.6%) |
| Completed suicide | 0 | 1 (0.5%) |

**Table 37: Adverse Events Potentially Related to Suicidality; Follow-up Phase; Follow-up Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**

| | Placebo + SOC | Esk 84 mg + SOC |
|---|---|---|

Key: AE = adverse event
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Adverse events are coded using MedDRA version 21.1.

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Safety analysis for pooled Phase 2 and 3 data:

**Table 38: Treatment-emergent Adverse Events Potentially Related to Suicidality; Double-blind Treatment Phase; Safety Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002, ESKETINSUI2001)**

| | Placebo + SOC | Esk 84 mg + SOC |
|---|---|---|
| Analysis set: Safety | 256 | 262 |
| Subjects with 1 or more TEAEs | 17 (6.6%) | 20 (7.6%) |
| System organ class | | |
| Preferred term | | |
| Psychiatric disorders | 17 (6.6%) | 19 (7.3%) |
| Suicidal ideation | 9 (3.5%) | 9 (3.4%) |
| Intentional self-injury | 3 (1.2%) | 7 (2.7%) |
| Suicide attempt | 4 (1.6%) | 4 (1.5%) |
| Depression suicidal | 2 (0.8%) | 2 (0.8%) |
| Self-injurious ideation | 0 | 1 (0.4%) |
| Injury, poisoning and procedural complications | 0 | 1 (0.4%) |
| Intentional overdose | 0 | 1 (0.4%) |

Key: TEAE = treatment-emergent adverse event
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Adverse events are coded using MedDRA version 21.1.

**Table 38: Treatment-emergent Adverse Events Potentially Related to Suicidality; Double-blind Treatment Phase; Safety Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002, ESKETINSUI2001)**

| | Placebo + SOC | Esk 84 mg + SOC |
|---|---|---|

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**Table 39: Adverse Events Potentially Related to Suicidality; Follow-up Phase; Follow-up Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002, ESKETINSUI2001)**

| | Placebo + SOC | Esk 84 mg + SOC |
|---|---|---|
| Analysis set: Follow-up | 207 | 217 |
| Subjects with 1 or more AEs | 24 (11.6%) | 23 (10.6%) |
| System organ class | | |
| Preferred term | | |
| Psychiatric disorders | 24 (11.6%) | 23 (10.6%) |
| Suicidal ideation | 13 (6.3%) | 11 (5.1%) |
| Suicide attempt | 6 (2.9%) | 7 (3.2%) |
| Depression suicidal | 5 (2.4%) | 5 (2.3%) |
| Intentional self-injury | 2 (1.0%) | 4 (1.8%) |
| Completed suicide | 0 | 1 (0.5%) |
| Self-injurious ideation | 1 (0.5%) | 0 |

- Key: AE = adverse event
  Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
  Adverse events are coded using MedDRA version 21.1.
- [a] The follow-up phase was 9 weeks in studies SUI3001 and SUI3002 and 8 weeks in study SUI2001

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Overall, the frequency of adverse events related to suicidality appears similar in the esketamine and placebo group. Within the pooled Phase 3 data there is a statistically non-significant imbalance with

numerically slightly more events in the esketamine arm for self-injury during the double-blind phase [3 (1.3%) for placebo + SOC group versus 7 (3.1%) for Esk 84mg +SOC] and for suicide attempts in the follow up phase [3 (1.6%) for placebo + SOC group versus 7 (3.7%) for Esk 84mg +SOC]. If the Phase 2 data are also taken into consideration the imbalance for self-injury remains while suicide attempts are now more balanced between treatment groups. Contrastingly, the placebo group experienced more suicidal thoughts (suicidal ideation, depression suicidal) than the esketamine group during active treatment. However, the numbers are too small to allow definite and reliable conclusions.

The sample size is far too small to draw any reliable conclusions from these data. However, there appears to be at least the possibility that subjects treated with esketamine are more involved in self harm in either the form of self injury or a suicidal attempt compared to the placebo group. According to the applicant, none of these events were related to the study drug administered. However, a discussion as to why this is concluded is missing. Currently it cannot be excluded whether the esketamine dose itself, or any of the esketamine-associated side effects such as dissociation leads to increased suicidal behavior. To facilitate the interpretation of the relationship between esketamine and suicidality events, the applicant provided descriptive statistics on when the following suicidality related events occur and their temporal relationship with a study drug dosing day: suicide attempt, intentional self injury, intentional overdose, completed suicide. Case reports for these events were also provided. While so far there is no clear safety signal detected these data do cast further doubt on any positive effect (besides the expected anti-depressive effects) for treatment of patients with suicidality/suicidal ideation.

Several oral anti-depressive drugs are known to increase risk of suicides. If a similar risk might exist for esketamine is unknown at this time. An argument can be made, that in theory the rapid onset of efficacy should reduce risk for patients with suicidal ideation. The observed non-significant imbalances in the treatment arms would however rather point in the opposite direction. Overall, based on the safety data, it can only be concluded that the effect of esketamine on suicidal ideation remains currently unclear.

***C-CASA 2012 Plus***

For the pooled Phase 3 studies SUI3001/3002, responses from patient-reported modules of the SIBAT were mapped to corresponding categories of the C-CASA 2012 Plus (an extended version of C-CASA 2012).10 Using the C-CASA 2012 Plus, suicide assessments were classified using 18 categories:

**Suicidal Ideation (SI-1 to SI-X)**

SI-1: Passive Suicidal ideation

SI-2: Active Suicidal Ideation: Non-specific (no method, intent or plan)

SI-3: Active Suicidal Ideation: method, but no intent or plan

SI-4: Active Suicidal Ideation: method and intent, but no plan

SI-5: Active Suicidal Ideation: method, intent and plan

SI-X: Active Suicidal Ideation: other

**Suicidal Behavior (SB-1 to SB-5)**

SB-1: Completed Suicide

SB-2: Suicide Attempt

SB-3: Interrupted Suicide Attempt

SB-4: Aborted Suicide Attempt

SB-5: Preparatory acts towards imminent suicidal behavior

**Self-Injurious Behavior (SIB-1 to SIB-2)**

SIB-1: Self-Injurious Behavior Without Suicidal Intent

SIB-2: Self-Injurious Behavior, Intent unknown

**No Suicidal Ideation or Behavior / Not Enough Information / Other (13-16)**

13: Not enough information (fatal)

14: Not enough information (non-fatal)

15: Other (accidental, psychiatric medical), no deliberate self-harm

16: No suicidal ideation or behavior

17: Not mapped to categories above

Pooled Phase 3 Studies SUI3001/ SUI3002-Double-blind Treatment Phase

At baseline, the data for most subjects were mapped to the C-CASA 2012 Plus category 'Suicide Attempt', 'Aborted Suicide Attempt', or 'Interrupted Suicide Attempt' (76.1% of subjects in the esketamine + SOC group and 75.1% of subjects in the placebo + SOC group). Based on the C-CASA mapping, all post-baseline 'Suicide Attempts' were cross referenced with AE reporting of 'Suicide Attempts' and queried if an event was not reported as an AE. It is important to note that several self-reported 'Suicide Attempts' from the SIBAT C-CASA mapping were confirmed not to be 'Suicide Attempts' per the investigator.

In both treatment groups, the majority of subjects' most severe postbaseline C-CASA severity category during the double-blind treatment phase was suicidal ideation (66.4% of subjects in the esketamine + SOC group and 69.3% of subjects in the placebo + SOC group).

The most severe postbaseline category versus baseline during the double-blind treatment phase has been presented.

- Of the subjects with a baseline severity category of suicidal ideation, 1 of 21 esketamine + SOC subjects and 1 of 28 placebo + SOC subjects had a most severe postbaseline severity category of 'suicidal behavior'.
- Of the subjects with a baseline severity category of suicidal behavior, the proportion of subjects in the esketamine + SOC group and in the placebo + SOC group with no postbaseline suicidal behavior was similar (81% [153 of 189 subjects]) vs 80% [152 of 190 subjects]).
- Of the subjects with a baseline severity category of suicidal behavior, 36 of 189 (19.0%) subjects in the esketamine + SOC group and 38 of 190 (20.0%) subjects in the placebo + SOC had a most severe postbaseline severity that remained in the suicidal behavior category.

**Table 40: Columbia Classification Algorithm for Suicide Assessment (C-CASA 2012 Plus): Most Severe Postbaseline Category during Double-blind Treatment Phase vs Baseline; Safety Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**

| Most Severe Postbaseline Potentially Suicide-Related Category |
|---|

| | No suicidal ideation or behavior / Not enough information / Other | Self-Injurious Behavior | Suicidal Ideation | Suicidal Behavior | Total |
|---|---|---|---|---|---|
| Placebo + SOC | | | | | |
| Baseline | | | | | |
| No suicidal ideation or behavior / Not enough information / Other | 0 | 0 | 0 | 0 | 0 |
| Self-injurious behavior | 0 | 0 | 0 | 0 | 0 |
| Suicidal ideation | 4 (1.8%) | 0 | 23 (10.6%) | 1 (0.5%) | 28 (12.8%) |
| Suicidal behavior | 24 (11.0%) | 0 | 128 (58.7%) | 38 (17.4%) | 190 (87.2%) |
| Total | 28 (12.8%) | 0 | 151 (69.3%) | 39 (17.9%) | 218 (100.0%) |
| Esk 84 mg + SOC | | | | | |
| Baseline | | | | | |
| No suicidal ideation or behavior / Not enough information / Other | 0 | 0 | 0 | 0 | 0 |
| Self-injurious behavior | 0 | 0 | 0 | 0 | 0 |
| Suicidal ideation | 6 (2.9%) | 0 | 14 (6.7%) | 1 (0.5%) | 21 (10.0%) |
| Suicidal behavior | 26 (12.4%) | 1 (0.5%) | 126 (60.0%) | 36 (17.1%) | 189 (90.0%) |
| Total | 32 (15.2%) | 1 (0.5%) | 140 (66.7%) | 37 (17.6%) | 210 (100.0%) |

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Those with suicidal behavior at baseline more often had suicidal ideation as most severe postbaseline category in the double blind, however a similar proportion of subjects remained within this category for both esketamine (17.1%) as well as placebo group (17.4%).

Intentional self injury did occur during the double blind phase (see discussion above). But this is not reflected in **Table 40** above, where none had self-injurious behavior as worst post baseline category. It is unclear where intentional self injury fits into the C-CASA 2012 plus categories, as this behavior appears to be missing from the table. The applicant clarified this.

*Subjects 18 to 24 Years Old During the Double-blind Treatment Phase*

In the 18 to 24 years old subgroup, there were 39 subjects in the esketamine + SOC group and 40 subjects in the placebo + SOC group. Assessment of C-CASA 2012 Plus mapping for subjects 18 to 24 years old was similar to the overall population. At baseline, the data for most subjects were mapped to the C-CASA 2012 Plus categories of 'Suicide Attempt', 'Aborted Suicide Attempt', or Interrupted Suicide Attempt' (79.5% of subjects in the esketamine + SOC group and 77.5% of subjects in the placebo + SOC group). In both treatment groups, the majority of subjects' most severe postbaseline C-CASA severity category during the double-blind treatment phase was suicidal ideation (60.0% of subjects in the esketamine + SOC group and 62.5% of subjects in the placebo + SOC group).

- Of the subjects with a baseline severity category of suicidal ideation (1 subject in the esketamine + SOC group and 3 subjects in the placebo + SOC group), none had a most severe post baseline category of suicidal behavior.
- Of the subjects with a baseline severity category of suicidal behavior, the proportion of subjects in the esketamine + SOC group and in the placebo + SOC group with no postbaseline suicidal behavior was similar (78.8% [26 of 33 subjects] vs 70.3% [26 of 37 subjects). Seven of 33 (21.2%) subjects in the esketamine + SOC group and 11 of 37 (29.7%) subjects in the placebo + SOC group with a baseline category of suicidal behavior had a most severe postbaseline severity that remained in the suicidal behavior category.

A separate subgroup analysis on suicidality in 18 to 24 year old subjects was discussed by applicant. The proportion of subjects who remained in the suicidal behavior category as most severe post baseline category is somewhat higher than what is observed in older adults (21.2% for esketamine and 29.7% for placebo respectively).

<u>Follow-up phase</u>

According to the applicant, the proportion of subjects whose data were mapped to individual C-CASA 2012 Plus categories was generally similar between the treatment groups throughout the follow-up phase. One subject, with a baseline category of suicide attempt, in the esketamine + SOC group had a completed suicide in the Day 32 (follow-up) analysis visit window which occurred on Study Day 27. In both treatment groups, the majority of subjects' most severe postbaseline C CASA severity category during the follow-up phase was suicidal ideation (50.8% of subjects in the esketamine + SOC group and 56.2% of subjects in the placebo + SOC group). Forty-one (21.7%) subjects in the esketamine + SOC group and 33 (17.8%) subjects in the placebo + SOC group had a most severe postbaseline C-CASA severity category of suicidal behavior in the follow-up phase.

- In the esketamine + SOC group, none of 20 subjects with a baseline severity category of suicidal ideation had a most severe postbaseline severity category of suicidal behavior.
- In the placebo + SOC group, 3 (14%) of 22 subjects with a baseline severity category of suicidal ideation had a most severe postbaseline severity category of suicidal behavior.

*Subjects 18 to 24 Years Old During the Follow-up Phase*

There were 32 follow-up analysis set subjects in each treatment group in the 18 to 24 years old subgroup. The proportion of subjects 18 to 24 years old whose data were mapped to individual C-CASA 2012 Plus categories during the follow-up phase was generally similar between the treatment groups throughout the follow-up phase and similar to the overall follow-up analysis set. In both treatment groups, the most severe postbaseline severity category for most subjects 18 to 24 years old during the follow-up phase was suicidal ideation (41.9% of subjects in the esketamine + SOC group vs 46.9% of subjects in the placebo + SOC group) or suicidal behavior (35.5% of subjects in the esketamine + SOC group vs 34.4% of subjects in the placebo + SOC group).

- Of the subjects with a baseline severity category of suicidal ideation (1 subject in the esketamine + SOC group and 3 subjects in the placebo + SOC group), 1 subject in the placebo + SOC group had a most severe post baseline category of suicidal behavior.
- Of the subjects with a baseline severity category of suicidal behavior, 41.3% (12 of 29) of subjects in the esketamine + SOC group and 48.3% (14 of 29) of subjects in the placebo + SOC group had a most severe post baseline severity category of suicidal ideation. Ten of 29 subjects (34.5%) in the esketamine + SOC group and 10 of 29 subjects in the placebo + SOC group (34.5%) with a baseline category of suicidal behavior had a most severe postbaseline severity that remained in the suicidal behavior category.

In the follow up phase, it appears that suicidal behavior as most severe postbaseline category is reported with a higher frequency in the young adults (18 – 24 years) compared to the adults. For the esketamine groups these are 35.5% and 21.7% for the young adults and adults respectively. For the placebo group this was 34.4% and 17.8% for the young adults and adults respectively. However, the data is difficult to interpret as subjects are not treated with the study drug during this period.

Suicidality in young adults

Thus, it appears that young adults engage more in suicidal behavior compared to the older adults. It is unclear whether this group contributes more to the suicidality related adverse events observed across the MDSI studies than the adults. The applicant was requested to display the suicidality related adverse events observed in the completed MDSI studies per age group (18 – 24 years, > 24 years) to allow for further interpretation. In addition, a discussion was warranted why suicidal behavior occurred more frequently in the younger population compared to the adults.

Overall discussion/conclusion on suicidality

The incidences of suicidality related events are similar between the placebo and esketamine groups across studies SUI3001 and 3002. However, when evaluating the type of events, there is a suggestion that esketamine treated subjects engage more in self-harm/suicidal behavior. Subjects treated with placebo, in contrast, experience more suicidal ideation. This occurs both in the double blind and the follow up phase. Moreover, there was one completed suicide in the esketamine group (see section on "deaths" above).

In the TRD studies discussed in the original MAA, suicidality did not appear to be increased during the initial weeks of treatment. Events were reported in the esketamine groups with an incidence of around < 4% for the induction and maintenance phases of the studies. In the MDSI studies an incidence of 7.5% is reported in the esketamine group during initial treatment (double blind).

It is acknowledged that the study population in the MDSI studies is more severe than the population that was studied in the TRD trials. However, the finding that subjects treated with esketamine engage more in suicidal behavior compared to the placebo group required further discussed.

In addition, it also appears that young adults (aged 18 – 24 years) experience more suicidal behavior than the older adults. This was also requested to be further addressed.

**Serious Adverse Events**

In the Phase 2 and 3 MDSI studies, SAEs were reported in subjects receiving esketamine + SOC at rates that were low and generally similar to those in subjects receiving placebo + SOC.

In the double-blind phase of the pooled Phase 3 studies SUI3001/3002, SAEs were reported for 9 (4.0%) subjects in the esketamine + SOC group (suicide attempt, depression suicidal, depersonalization/derealization disorder, depression, suicidal ideation, and diabetic ketoacidosis) and 12 (5.3%) subjects in the placebo + SOC group (suicide attempt, depression suicidal, depression, suicidal ideation, aggression, arrhythmia, pericardial effusion, hypertransaminasemia, and pneumothorax). After discontinuation from the double-blind phase, 3 (1.3%) subjects in the esketamine + SOC group experienced SAEs (suicidal ideation and acute psychosis) versus 2 (0.9%) subjects in the placebo + SOC group (depression suicidal, major depression, and suicide attempt).

**Table 41: Number of Subjects with Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term; Double-blind Treatment Phase; Safety Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**

| | Placebo + SOC | Esk 84 mg + SOC |
|---|---|---|
| Analysis set: Safety | 225 | 227 |
| Subjects with 1 or more serious TEAEs | 12 (5.3%) | 9 (4.0%) |
| System organ class | | |
| Preferred term | | |
| Psychiatric disorders | 9 (4.0%) | 8 (3.5%) |
| Suicide attempt | 4 (1.8%) | 4 (1.8%) |
| Depression suicidal | 1 (0.4%) | 2 (0.9%) |
| Depersonalisation/derealisation disorder | 0 | 1 (0.4%) |
| Depression | 2 (0.9%) | 1 (0.4%) |
| Suicidal ideation | 4 (1.8%) | 1 (0.4%) |
| Aggression | 1 (0.4%) | 0 |

**Table 41: Number of Subjects with Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term; Double-blind Treatment Phase; Safety Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**

| | Placebo + SOC | Esk 84 mg + SOC |
|---|---|---|
| Metabolism and nutrition disorders | 0 | 1 (0.4%) |
| Diabetic ketoacidosis | 0 | 1 (0.4%) |
| Cardiac disorders | 2 (0.9%) | 0 |
| Arrhythmia | 1 (0.4%) | 0 |
| Pericardial effusion | 1 (0.4%) | 0 |
| Hepatobiliary disorders | 1 (0.4%) | 0 |
| Hypertransaminasaemia | 1 (0.4%) | 0 |
| Respiratory, thoracic and mediastinal disorders | 1 (0.4%) | 0 |
| Pneumothorax | 1 (0.4%) | 0 |

Key: TEAE = treatment-emergent adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.
Adverse events are coded using MedDRA Version 21.1.

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During the follow-up phase, SAEs were observed at similar rates in subjects who were treated with esketamine + SOC during the double-blind phase and subjects who were treated with placebo + SOC during the double-blind phase (11.6% and 11.9%, respectively).

**Table 42: Number of Subjects with Serious Adverse Events by System Organ Class and Preferred Term; Follow-up Phase; Follow-up Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**

| | Placebo + SOC | Esk 84 mg + SOC |
|---|---|---|
| Analysis set: Follow-up | 185 | 190 |
| Subjects with 1 or more SAEs | 22 (11.9%) | 22 (11.6%) |

**Table 42: Number of Subjects with Serious Adverse Events by System Organ Class and Preferred Term; Follow-up Phase; Follow-up Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**

| | Placebo + SOC | Esk 84 mg + SOC |
|---|---|---|
| System organ class | | |
| Preferred term | | |
| Psychiatric disorders | 15 (8.1%) | 22 (11.6%) |
| Suicide attempt | 3 (1.6%) | 7 (3.7%) |
| Depression suicidal | 5 (2.7%) | 5 (2.6%) |
| Suicidal ideation | 6 (3.2%) | 5 (2.6%) |
| Depression | 1 (0.5%) | 2 (1.1%) |
| Major depression | 0 | 2 (1.1%) |
| Acute stress disorder | 0 | 1 (0.5%) |
| Completed suicide | 0 | 1 (0.5%) |
| Homicidal ideation | 1 (0.5%) | 0 |
| Respiratory, thoracic and mediastinal disorders | 0 | 1 (0.5%) |
| Haemothorax | 0 | 1 (0.5%) |
| Infections and infestations | 3 (1.6%) | 0 |
| Erysipelas | 1 (0.5%) | 0 |
| Pyelonephritis | 1 (0.5%) | 0 |
| Staphylococcal bacteraemia | 1 (0.5%) | 0 |
| Injury, poisoning and procedural complications | 1 (0.5%) | 0 |
| Overdose | 1 (0.5%) | 0 |
| Musculoskeletal and connective tissue disorders | 1 (0.5%) | 0 |
| Rhabdomyolysis | 1 (0.5%) | 0 |

**Table 42: Number of Subjects with Serious Adverse Events by System Organ Class and Preferred Term; Follow-up Phase; Follow-up Analysis Set (Pooled Studies 54135419SUI3001, 54135419SUI3002)**

| | Placebo + SOC | Esk 84 mg + SOC |
|---|---|---|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 1 (0.5%) | 0 |
| Papillary thyroid cancer | 1 (0.5%) | 0 |
| Nervous system disorders | 1 (0.5%) | 0 |
| Encephalopathy | 1 (0.5%) | 0 |

Key: SAE = serious adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.
Adverse events are coded using MedDRA Version 21.1.

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In the Phase 2 study SUI2001, SAEs were observed in 4 (11.4%) subjects in the esketamine + SOC group and 0 subjects in the placebo + SOC group during the double-blind phase, and in 1 (3.7%) subject and 5 (22.7%) subjects, respectively, during the follow-up phase.

Supportive Ongoing Long-term OL Extension Study TRD3008: Up to the clinical cutoff date of the TRD3008 interim CSR (31 December 2018) (median duration of exposure: 15.4 months), a total of 91 of 1,140 (8.0%) subjects exposed to esketamine + oral AD had experienced at least 1 SAE. Based on the review of CIOMS data between the period of 31 December 2018 and 20 April 2019, 17 subjects reported a SAE. Overall, the SAEs reported in this ongoing extension study were consistent with those observed in the completed clinical studies in subjects with MDSI or TRD. No new safety signals were identified.

Ongoing Blinded Studies SUI2002, TRD2005, TRD3006: Based on review of CIOMS data up to the clinical cutoff date of 20 April 2019, a total of 23 subjects in these ongoing, blinded studies had reported at least 1 SAE. Overall, no new safety signals were identified.

The frequency of serious adverse events was slightly higher in the placebo arm during the double-blind treatment phase and comparable in both arms during the follow-up phase. The overall frequency of reported adverse events in the follow up phase was higher compared to the double blind phase. This might be due to some serious adverse events actually being related to the underlying disease. For example, the number of suicidal ideations that were rated as serious in the placebo arm was four compared with just one in the esketamine arm. In contrast when looking at all adverse events related to suicidality (see above) the rate of suicidal ideation during the double-blind period was comparable in both arms.

Most of the serious adverse events reported in the double blind phase are related to suicidality. According to the applicant, the only serious events possibly related to esketamine treatment were a suicide attempt and one case of depersonalisation. No discussion of the relationship between esketamine and these events was provided by the applicant. This was requested to be provided.

There is no clear pattern of any serious adverse events that seem to be related to esketamine treatment. Overall, the frequency is low and comparable to previous experience in patients with treatment resistant depression.

**Laboratory findings**

The overall clinical laboratory test results with esketamine in the completed Phase 2 and 3 MDSI studies did not suggest any safety concerns associated with the use of this drug in patients with MDSI. No clinically meaningful changes in mean laboratory analytes (hematology, chemistry, urinalysis parameters) from baseline were observed in the completed Phase 2 and 3 studies in MDSI.

Findings Relevant to Hepatic Safety

There was no evidence of treatment-emergent hepatotoxicity associated with esketamine nasal spray in the MDSI studies. Across the completed Phase 2 and 3 MDSI studies, increases in alanine aminotransferase (ALT) of greater than 3× the upper limit of normal (ULN) occurred at low rates in both the esketamine + SOC and placebo + SOC groups (pooled SUI3001/3002: 3 [1.5%] vs. 3 [1.6%] subjects, respectively; SUI2001: 1 [3.2%] vs. 0 subjects, respectively). No increases in aspartate aminotransferase (AST) >3×ULN or total serum bilirubin levels >2×ULN were observed in any study; no subject met the criteria for severe drug-induced hepatocellular injury as defined by Hy's law. No TEAEs in the hepatobiliary disorders system organ class were observed in the esketamine + SOC group in the Phase 2 or 3 studies (compared with 1 subject in the placebo + SOC group [study SUI3001] who had a TEAE of hypertransaminasemia).

There were no safety concerns based on the clinical laboratory findings.

**Safety in special populations**

Adverse Events by Subgroup

Although sex, race, and age-associated differences in AE rates were observed for some preferred terms in the pooled Phase 3 studies, the results did not suggest that administration of esketamine was associated with a clinically meaningful increased risk in any of the subgroups evaluated. Furthermore, there were no consistent, meaningful differences in the TEAE rates in the pooled Phase 3 studies based on geographic region, SOC antidepressant therapy as randomized (antidepressant monotherapy or antidepressant + augmentation), baseline SIBAT: prior suicide attempt (yes, no), or baseline suicide attempt within the last month (yes, no).

Pregnancy and Lactation

The risks of esketamine during pregnancy or breast-feeding have not been studied. All Sponsor conducted clinical studies with esketamine in TRD and MDSI specifically excluded women who were pregnant, or lactating, as well as women who planned to get pregnant and men who planned to father a child within 3 months after the last dose of study drug. Subjects who became pregnant were to have been discontinued from the study.

Across all completed and ongoing studies in the MDSI and TRD indications, 11 pregnancies have been reported in subjects who were exposed to esketamine or placebo as of the clinical cutoff date of 20 April 2019 (8 cases in Phase 3 studies, 2 cases in Phase 2 studies, and 1 case in a Phase 1 study). Eight of these cases were previously reported.

The 3 new cases included 2 pregnancies in TRD3008 (outcome: spontaneous abortion and elective abortion, respectively), and 1 pregnancy in SUI3001 (placebo + SOC group) (outcome: spontaneous abortion). Three pregnancies were previously reported in partners of male subjects who received esketamine in Phase 3 TRD studies. The outcome for Subject /TRD3008 indicated that the female partner delivered a healthy baby in 2018 and 'everything was normal'). As of the 20 April 2019, 1 additional pregnancy was reported in a partner of male subject who received esketamine (84 mg) in the Phase 3 study TRD3008 (outcome: unknown).

Per the agreed EU SmPC,71 esketamine nasal spray is not recommended during pregnancy and in women of childbearing potential not using contraception. There are no or limited data on the use of esketamine in pregnant women.

No safety signals were detected for specific subgroups.

**Safety related to drug-drug interactions and other interactions**

Not Applicable

**Discontinuation due to adverse events**

In the pooled Phase 3 studies SUI3001/3002, 14 (6.2%) subjects in the esketamine + SOC group and 8 (3.6%) subjects in the placebo + SOC group experienced TEAEs leading to discontinuation of intranasal study medication. TEAEs that led to discontinuation in >1 subject in the esketamine + SOC group were: dissociation (3 subjects), depersonalization/derealisation disorder, nausea, and blood pressure increased (2 subjects each).

In the Phase 2 study SUI2001, 5 (14.3%) subjects in the esketamine + SOC group had a TEAE leading to discontinuation of study medication (dizziness, dysgeusia, aggression, agitation, ventricular extrasystoles, nausea, and dyspnea) versus 1 (3.2%) subject in the placebo + SOC group (dissociative disorder and panic attack).

Adverse Events Leading to Dose Reduction or Interruption

In the pooled Phase 3 studies SUI3001/3002, 15.4% of subjects in the esketamine + SOC group and 1.8% in the placebo + SOC group had a TEAE that led to a dose reduction or dose interruption during the double-blind phase. The most common TEAEs leading to dose reduction or dose interruption in the esketamine + SOC group were: dissociation (5.7%), nausea (4.8%), dizziness (3.1%), somnolence (2.6%), vomiting (2.2%), and blood pressure increased (1.3%).

In the Phase 2 study SUI2001, 3 subjects in the esketamine + SOC group had a dose reduction due to TEAEs (dizziness [2 subjects], and anxiety, chest discomfort, feeling abnormal, and hyperacusis [1 subject]).

Adverse events that lead to study drug discontinuation are in line with the known safety profile. AEs that lead to discontinuation are also comparable to AEs that lead to dose reductions.

**Post marketing experience**

Esketamine nasal spray was approved for marketing in the US under the tradename SPRAVATO on 5 March 2019 for the treatment of TRD in adults and launched in the US on 14 March 2019. The first patient received esketamine nasal spray post-launch on 29 March 2019. Esketamine nasal spray has also received marketing authorizations in the EU and other markets but had not been launched in those regions as of the cutoff date for this this Clinical Overview.

Since launch to 31 October 2019, the estimated cumulative exposure to SPRAVATO in the US was 105,408 devices or 2,951,424 mg distributed by the Sponsor. The Sponsor performed a review of the

Global Medical Sciences global safety database using MedDRA (version 22.0) for all cases of adverse events reported with the use of esketamine during postmarketing use for this period. These cases include both medically confirmed and non-medically confirmed events.

In addition, as agreed with the Rapporteurs at the 25 October 2019 pre-submission meeting, the Sponsor has included two Periodic Adverse Drug Experience Reports (PADERs) for esketamine summarizing the safety data obtained from expedited solicited reports (reported as part of the US patient registry) and non-solicited post-marketing spontaneous reports.

This review of post-marketing data for esketamine did not identify a new signal or safety concern, and as such, the postmarketing experience is consistent with the safety profile of esketamine established from the clinical studies and is reflected in the proposed product labelling.

Post marketing data in patients with treatment resistant depression is in line with the known safety profile and also comparable to the safety profile in the clinical studies with patients with major depression with suicidal ideation.

## 2.5.1. Discussion on clinical safety

The safety profile of esketamine in patients with major depression with suicidal ideation (MDSI) has been investigated in two Phase 3 studies and one supportive Phase 2 study. Additional safety data are provided from the clinical development program for patients with treatment resistant depression as well as post-marketing safety data in the same indication.

262 subjects received at least 1 dose of esketamine and 256 received at least 1 dose of placebo across the combined Phase 2 and 3 studies in MDSI leading to a combined cumulative exposure to esketamine of 15.8 patient-years (13.8 patient-years in the Phase 3 studies) and a combined cumulative exposure to placebo nasal spray of 15.7 patient-years (13.9 patient-years in the Phase 3 studies).

In the pooled Phase 3 studies (SUI3001/3002), the mean (SD) duration of exposure to study medication was 22.2 (7.20) days in the esketamine + SOC group (227 subjects) and 22.5 (6.42) days in the placebo + SOC group (225 subjects). All 227 subjects received at least one esketamine dose of 84 mg. 45 subjects later received a reduced dose of 56 mg during the double-blind treatment phase. 35 dose reductions were due to tolerability reasons, 10 subjects had dose reductions due to an administration/device error.

In the Phase 2 study (SUI2001), the mean (SD) duration of exposure to study medication during the double-blind phase was 20.7 (8.49) days in the esketamine + SOC group and 21.5 (7.22) days for the placebo + SOC group. All of the 35 subjects in the esketamine arm received the dose of 84 mg on Day 1; 3 subjects had their dose reduced to 56 mg due to adverse events and 2 subjects had their dose reduced in error.

The exact nature of these errors that lead to dose reductions in both the Phase 2 and Phase 3 studies is unclear and should be explained in more detail by the applicant **(OC)**. This is especially concerning because the drug is not given out to patients and applied only under supervision by the study sites staff.

Long term exposure data are available from the clinical studies in treatment resistant depression. In the long-term open-label extension study TRD3008 patients were treated up to 31 months with a median duration of exposure as of 31 December 2018 of 15.4 months. No long term treatment is intended in patients with suicidal ideation.

Overall, esketamine nasal spray 84 mg was safe and tolerated in the Phase 2 and 3 MDSI studies. The observed safety profile was consistent with established data in patients with TRD. No new or unexpected safety concerns were noted in the MDSI clinical program. Most AEs reported during esketamine

treatment, including those that were most common, were mild or moderate in severity, were observed postdose on the day of dosing, and resolved the same day. The AEs were primarily in the area of expected CNS effects and either related to the known safety profile of esketamine or the underlying disease.

In the pooled Phase 3 studies there was a high rate of at least one adverse event during the double-blind treatment period in both the esketamine (89.9%) as well as the placebo arms (75.6%). The most common AEs esketamine vs. placebo were: dizziness (38.3% versus 13.8%), dissociation (33.9% versus 5.8%), nausea (26.9% versus 13.8%), somnolence (20.7% versus 10.2%), dysgeusia (19.8% versus 12.9%), vision blurred (11.9% versus 4.9%), paresthesia (11.5% versus 3.1%), vomiting (11.5% versus 5.3%), blood pressure increased (11.5% versus 4.0%), sedation (10.1% versus 2.2%), and anxiety (10.1% versus 7.6%). Headache was observed in similar proportion of subjects in both groups (20.3% vs. 20.4%). In the follow-up phase frequency of observed AEs was similar between the treatment arms with 53.7% of the subjects in the esketamine + SOC group and 50.8% of those in the placebo + SOC group. The most common AEs reported more frequently for the esketamine arm were depression (6.8% versus 3.2%) and insomnia (6.3% versus 5.9%). AEs reported more frequently in the placebo arm were anxiety (9.7% versus 5.8%), suicidal ideation (6.5% versus 5.3%), and headache (9.2% versus 6.8%).

Sedation and somnolence were commonly reported with esketamine treatment. Sedative effects were usually resolved on the same day as dosing. There was one subject that had an MOAA/S score of 0 and 1 on multiple dosing days, corresponding to severe sedation. Though the subject did not require any medical intervention, such deep sedation was not previously seen in the TRD studies. Therefore, the case report and a discussion on the relationship between the event and esketamine dosing was requested.

During the double-blind phase of the pooled Phase 3 studies, severe TEAEs were observed in 13.7% of subjects in the esketamine + SOC group and 5.8% in the placebo + SOC group. The most common severe AEs observed in the esketamine arm included dissociation (4.0% vs. 0%), nausea (2.2% vs. 0%), and increased blood pressure (1.8% vs. 0%). Severe AEs that were reported at low and similar rates for the esketamine and placebo arm were related to the underlying disease. The pattern of occurrence and resolution of severe adverse events was similar and consistent with the observations for all severity categories. Severe AEs that were reported on dosing days and did not resolve on the same day were depression (2 events) and suicide attempt (1 event) in the esketamine arm and depression (1 event), depression suicidal (1 event), suicide attempt (1 event), and erectile dysfunction (1 event) in the placebo arm. According to the applicant, the only serious events possibly related to esketamine treatment were a suicide attempt and one case of depersonalisation. No discussion of the relationship between esketamine and these events was provided by the applicant. This was requested. In the follow up phase, reporting of serious adverse events was higher compared to the double blind phase. As was observed in the double blind phase, most events are related to suicidality.

Across all completed and ongoing studies with esketamine in the MDSI and TRD indications, 8 deaths have been reported up to 20 April 2019 including one suicide in the MDSI studies in a subject assigned to the esketamine arm. This suicide occurred in the follow-up phase three days after the last administration of study drug. Based upon the subjects' MADRS and SIBAT scores, the subject appeared to be in remission. However, there is a possibility that subjects treated with esketamine engage more in suicidal behaviour and that esketamine treatment could have induced pharmacodynamic changes in the brain leading to an increase in suicidal behaviour. A discussion was warranted on the relationship between pharmacodynamic changes induced by (repeat) esketamine dosing and suicidality. The remaining seven deaths included three suicides in the TRD studies. The four non-suicide deaths were either due to cardiac or respiratory failure or due to traffic accidents. Although the sample size is small and none of the deaths were considered to be related to study drug by the investigators they all occurred in patients either on active treatment with or previously treated with esketamine.

In the pooled safety data for the Phase 3 studies the overall frequency of adverse events during the double-blind treatment period potentially related to suicidality was comparable for esketamine (7.5%) and placebo (7.6  The frequency for self-injury was higher in the esketamine arm vs placebo [7(3.1%) vs 3(1.3%)], this was however statistically non-significant. In the follow-up phase the overall frequency of events was also comparable between esketamine vs placebo (11.1% vs 10.3%). There were  7(3.7%) suicide attempts in the esketamine arm compared to 3 (1.6%) in the placebo group. When also pooled with the Phase 2 data the imbalance for self-injury remains the same (7 for esketamine vs 3 for placebo) while the number of suicide attempts in the follow-up phase becomes more balanced between treatment arms (7 for esketamine vs 6 for placebo). The numbers are too small to allow definite conclusions.

Thus there appears to be a suggestion that subjects treated with esketamine might be more involved in self harm in either the form of self injury or a suicidal attempt compared to the placebo group. Currently it cannot be excluded whether the esketamine dose itself, or any of the esketamine-associated side effects such as dissociation would lead to increased suicidal behavior. To facilitate the interpretation of the relationship between esketamine and suicidality events, the applicant is requested to provide descriptive statistics on when the following suicidality related events occur and their temporal relationship with a study drug dosing day: suicide attempt, intentional self injury, intentional overdose, completed suicide (**OC**). Case reports for these events are also requested (**OC**).

In addition, it also appears that young adults (aged 18 – 24 years) experience more suicidal behavior than the older adults. It is unclear whether this group contributes more to the suicidality related adverse events observed across the MDSI studies than the adults. The applicant is requested to display the suicidality related adverse events observed in the completed MDSI studies per age group (18 – 24 years, > 24 years) to allow for further interpretation (OC). In addition, a discussion was warranted why suicidal behavior occurred more frequently in the younger population compared to the adults.

The sample size of deaths and events potentially related to suicidality is far too small to draw any reliable conclusions from these data. While there is no clear safety signal these data also do not point to any positive effect (besides the expected anti-depressive effects) for treatment of suicidality/suicidal ideation or prevention of suicides. For several oral anti-depressive drugs an increase in risk of suicide is actually known. Whether a similar effect could exist for esketamine remains currently unknown. While at least in theory the rapid onset of effect for esketamine should rather prevent suicidal behaviour this assumption is clearly not supported by the observed safety data and the observed imbalances would rather point in the opposite direction. In conclusion, possible effects of esketamine on suicidal ideation/suicidal behaviour, whether positive or negative, remain unclear at this time.

Overall, the safety profiles of esketamine in treatment resistant depression and major depression with suicidal ideation (MDSI) appear comparable. No unexpected, new safety findings were made in the Phase 2 and Phase 3 studies investigating patients with MDSI, but significant uncertainties exist regarding suicidal behaviour.

Ten out of 45 patients who received a reduced dose in the Phase 3 studies and 2 of 5 in the Phase 2 did so due to an administration/device error. This means that 22% of all dose reductions in the Phase 3 studies as well as 40% of the dose reductions in the Phase 2 study were in error. This was somewhat puzzling, since the medication is not given out to patients but has to be administered under supervision at the study sites. The applicant was asked to comment on this and provided a detailed answer and explained that most error were due to a defective device. The device has been redesigned for commercial use and device errors have become unlikely in clinical routine.

The applicant was requested to provide information on the occurrence/resolution of adverse events on dosing days for Study SUI2001this to allow for interpretation. This was provided. The occurrence and resolution of AEs in Study SUI2001 is consistent with those observed in the Phase III studies.

The only serious adverse events in the completed MDSI studies that were considered possible related to esketamine by the applicant were a suicide attempt and a case of depersonalization. The applicant was requested to provide case reports of these events and discuss the relationship between esketamine dosing and the occurrence of these events. The Applicant provided the narratives as requested. The event of attempted suicide occurred approximately one hour after the subject received the final dose of esketamine during the double blind phase. The event was accompanied by severe anxiety, dissociative symptoms and suicidal ideas. The event was resolved on the same day, and subject was discharged 4 hours after the event on his own accord. The anxiety attack secondary to dissociative symptoms was reported as the triggering factor for the event of suicide attempt according to the CIOMS report.

The causality of the event is based on the temporal relationship with the dosing of esketamine. The subject did not have a documented history of prior suicide attempt- it appears that this was the subjects' first attempt. The event is confounded by concurrent events of severe anxiety and dissociation which are known side-effects of esketamine. It may be that there was an interplay between these events that triggered the suicide attempt, as was concluded by the CIOMS. It cannot be excluded that dissociation and anxiety played a role in the subjects' suicide attempt. However, these events are covered in the postdose monitoring as described in the SmPC. The event of depersonalization/derealization occurred 40 minutes after esketamine dosing on Day 21. The CADSS score at 40 minutes postdose was 6, followed by 0 at 1.5 hours post dose. The Applicant's assessment that the event is possible related to esketamine due to the temporal relationship and that depersonalization is a known side-effect of esketamine was agreed. The issue was considered as solved.

There was one completed suicide in SUI3001 that occurred 3 days after the last dose of esketamine. Based upon the subjects' MADRS and SIBAT scores, the subject appeared to be in remission. The possibility that esketamine treatment could have induced pharmacodynamic changes in the brain leading to an increase in suicidal behaviour cannot be readily excluded. A discussion was warranted on the relationship between pharmacodynamic changes induced by esketamine dosing and suicidality. The Applicant provided a detailed discussion. Although MADRS and SIBAT scores showed a remission in week 2 the clinical narrative points towards an overall chronic disease pattern and also a possible relapse close to the completed suicide. Although an increased risk of suicidal behaviour might not be completely excluded at this time the overall data from the esketamine trials as well a clinical use provided no clear signal for a PD effect that might increase suicidal behaviour. Based on the provided discussion, no conclusions can neither be drawn regarding the relationship between esketamine dosing and pharmacodynamic changes in the brain related to suicidality.

In pooled studies SUI3001/3002 there was one subject that had an MOAA/S score of 0 and 1 on multiple dosing days, corresponding to severe sedation, but did not require medical intervention. The applicant is requested to provide case report and discuss the relationship between the event and esketamine dosing. The Applicant provided the case report and the requested discussion. Subject had a MOAA/S score of 0 or 1 during multiple dosing sessions. On some dosing days, the subject was too sedated to administer the final dose of study drug. During the time period that a MOAA/S score of 0 or 1 was reported the subject's vital signs (including respiratory rate and oxygen saturation) remained normal. Though the subject was considered severely sedated, this was not reflected in their vital signs, thus not requiring medical intervention. A relationship between deep sedation and administration of study drug in subject appears likely. However, without meaningful changes in vital signs no intervention was required. Although this is a single case only it clearly provides justification for intake of the drug under supervision.

Given the temporal relationship between the MOAA/S score and esketamine administration, it is agreed with the Applicant that this is due to the pharmacological effect of esketamine. This effect is already covered in the information on the post dose monitoring in the SmPC of Spravato. The issue was considered as solved.

There was a suggestion that suicidal behaviour occurs more frequently in esketamine treated subjects compared to placebo in pooled studies SUI3001/3002. To facilitate the interpretation of the relationship between esketamine and suicidality events, the applicant is requested to provide descriptive statistics on when the following suicidality related events occur and their temporal relationship with a study drug dosing day: suicide attempt, intentional self-injury, intentional overdose, completed suicide. Case reports for these events were also requested. The Applicant provided the requested analyses and five additional narratives that were not submitted preciously as they did not meet the criteria for narrative preparation. In the previous round it was noted that adverse events related to suicidal behavior (e.g. intentional self-injury, suicide attempt and intentional overdose) occurred more frequent in the esketamine group compared to the placebo group. During the double blind phase of pooled studies SUI3001/3002 this was 4.4% for the esketamine group and 3.1% for the placebo group. In the follow-up phase this was 5.3% for the esketamine group and 1.6% for the placebo group.

According to the Applicant, this numerical difference was due to a higher percentage of subjects in the esketamine group reporting a prior history of suicide attempt in study 3002.

In phase 2 study SUI2001 no events related to suicidal behaviour were reported during the double blind phase. In the follow-up phase one event was reported in the esketamine group (intentional self-injury) and 3 events in the placebo group (suicide attempt).

In the double-blind phase of pooled studies SUI2001/3001/3002, the mean time from last study drug dose to first event was 2.5 days (range 1 - 5 days) in the esketamine group and 2.9 days (range 1 – 4 days) in the placebo group. The median time was 3 days for both groups. Thus, there appears to be no difference between the placebo and esketamine groups with regard to time to event from last study dose.

No conclusions can be drawn regarding the follow-up phase of the pooled studies, due to the low number of events in the placebo group. Taken together, no definitive conclusions can be drawn with regard to a possible relationship between esketamine dosing and suicidal behaviour. The numbers are too low to conclude on a clear signal but the numerical difference at the expense of esketamine also does not allow a to conclude that there is no potential risk.

As suicidality including suicidal behaviour is already covered in the SmPC of esketamine, this issue was not pursued further.

Across the completed MDSI studies, on the C-CASA 2012 Plus, it appears suicidal behaviour as most severe post-baseline category is reported with a higher frequency in the young adults (18 – 24 years) compared to the adults. It is unclear whether this group contributes more to the suicidality related adverse events observed across the MDSI studies than the adults. The applicant was requested to display the suicidality related adverse events observed in the completed MDSI studies per age group (18 – 24 years, > 24 years) to allow for further interpretation. In addition, a discussion was warranted why suicidal behaviour occurred more frequently in the younger population compared to the adults.

**R**esults provided suggest there was a higher rate of AEs potentially related to suicidality in the younger age group (18 to 24 years) compared with the older age group (>24 years), regardless of treatment assignment. Of note, the proportion of subjects in the 18 to 24-year-old age group that experienced one of these AEs was lower in the esketamine + SOC group than in the placebo + SOC group during the double-blind phase and follow-up phase. However, these results should be interpreted with caution due to the small number of subjects aged 18 to 24 years.

The risk of suicidal behavior in young adults is well documented in the literature. Several population-based surveys show a higher rate of suicidal ideation, suicide attempts, and selfharming behaviors in the younger population when compared with older individuals.[4,15,26,27,29,32,38] An increased risk of suicidal thoughts and behaviors has also been reported for young patients (<25 years) treated with

antidepressant medications compared with those treated with placebo in clinical studies. This was originally identified for children and adolescents[37] and more recently in young adults (18-24 years),18 resulting in the addition of warnings regarding suicidality in patients aged <25 years in the EU and US labels for selective serotonin reuptake inhibitor (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). This was the reason why the Applicant originally performed the C-CASA analysis in the subgroup of subjects aged 18- to 24-years old.

In summary, consistent with the literature, the observation of a higher rate of AEs potentially related to suicidality in the younger subgroup (18-24 years) compared with the older subgroup (>24 years) in studies SUI3001 and SUI3002, regardless of treatment assignment, was not unexpected. In view of this finding, the Applicant believes it is appropriate to add a general warning about the increased risk of suicidality in patients aged <25 years in the EUPI, consistent with the warning that is included for SSRIs and SNRIs. This is considered particularly important as treatment with Spravato will always be in conjunction with an oral antidepressant medication for which such a warning would be appropriate anyway. The wording proposed for the SmPC (section 4.4) reads as follows:

"A meta-analysis of placebo-controlled clinical studies of oral antidepressants in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo, in patients less than 25 years old".

The Applicant has provided an overview over suicidality in the age range from 18 to 24 years. Based on the provided data a higher rate of AEs related to suicidality is apparent, especially in the esketamine plus placebo group. These results might be simply a characteristic of this specific demographic group and could also be confounded by known risks associated with oral antidepressants in children and young adults. The interpretation of the data a further complicated by the overall small sample size.

The CHMP did not agree with including information on oral antidepressants in the SmPC of Spravato. In addition,there is no clearly identified safety signal for esketamine in young adults and an increased risk when using concomitant oral antidepressants would also be covered by the respective SmPCs. Pointing to potential risk of concomitant medication might also lead to an underreporting of those events after marketing authorization by deemphasizing a possible relation to esketamine itself.

In the C-CASA 2012 Plus analysis on most severe post-baseline category, no cases of self injurious behaviour was reported. However, adverse events of intentional self-injury were reported in the studies. It is unclear where intentional self-injury fits into the C-CASA 2012 plus categories, or whether these events were not reported as the most severe post-baseline category. The applicant provided satisfactorily clarification.

Interactions with benzodiazepines should be further addressed by the Applicant as they are often used in acute mental health disorders, including patients with suicidal ideation/behaviour/thoughts. The additional analysis identified no additional risk that are not already covered in the SmPC.

## 2.5.2. Conclusions on clinical safety

The CHMP reviewed all available data and concluded that clinical safety was demonstrated.

## 2.5.3. PSUR cycle

Based on the different indication, dosing, route of administration, administration setting and target patient population as highlighted by the new ATC code as an antidepressant instead of general anaesthetics, the PRAC was of the opinion that a separate entry in the EURD list for Spravato was needed, as it cannot follow the already existing entry for esketamine. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP

Opinion. The EURD list entry will use the IBD to determine the forthcoming Data Lock Points.

## *2.6. Risk management plan*

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted RMP:

- The PRAC considered that the RMP version 2.5 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the RMP version 2.5 with the following content:

### *Safety concerns*

**Table 43: *Summary table of the Safety Concerns***

| | |
|---|---|
| **Important Identified Risks** | • Drug abuse<br>• Transient dissociative states and perception disorders<br>• Disturbances in consciousness<br>• Blood pressure increased |
| **Important Potential Risks** | • Cognitive disorders and memory impairment (long-term use)<br>• Interstitial cystitis (long-term use) |
| **Missing Information** | • Use during pregnancy |

No changes were proposed to the existing list of safety concerns within this extension of indication.

### *Pharmacovigilance plan*

The current additional pharmacovigilance activities in the RMP for Spravato include three category 3 studies:

- 54135419TRD3008: An open-label longterm extension safety study of intranasal esketamine in TRD treatment-resistant depression
- National Pregnancy Registry for Antidepressants (part of the National Pregnancy Registry for Psychiatric Medications) such as antidepressants including esketamine (in the US)
- Survey to assess effectiveness of the additional risk minimization measures (educational materials).

No changes to the existing additional pharmacovigilance activities were proposed within this extension of indication. Please refer below for further details on the studies above mentioned.

**Table 44: *Summary table of Ongoing and Planned Additional Pharmacovigilance Activities***

| Study Status | Summary of Objectives | Safety Concerns Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| **Category 3** - Required additional pharmacovigilance activities | | | | |
| 54135419TRD3008:<br>An open-label long-term extension safety study of intranasal esketamine in treatment-resistant depression<br>***Ongoing*** | To assess the long-term safety (>1 year) of esketamine nasal spray in subjects with TRD, with special attention to the following: potential long-term effects on cognitive function; TEAEs, including TEAEs of special interest; post–dose effects on heart rate, blood pressure, respiratory rate, and blood oxygen saturation; and potential effects on suicidal ideation/behavior. | • Cognitive disorders and memory impairment (long-term use)<br>• Interstitial cystitis (long-term use) | Protocol submission (initial) | National submissions beginning in 2Q 2016 |
| | | | Trial start date (first patient in) | 21 Jun 2016 |
| | | | Interim report | 2Q 2019 |
| | | | Final report | 1Q 2023<br>Annual analyses of safety results to be provided until the final study report becomes available in 2023. |
| National Pregnancy Registry for Antidepressants (part of the National Pregnancy Registry for Psychiatric Medications)<br>***Planned*** | To the safety profile of SPRAVATO during pregnancy. Periodic safety assessments of data will be conducted from a US pregnancy registry for psychiatric medications, including antidepressants. | • Use during pregnancy | Protocol submission (initial) | Within 6 months after approval of MAA[a]<br>(30 June 2020) |
| | | | Trial start date (first patient in) | Relevant data is being captured since US approval date of 05 March 2019 |
| | | | | Periodic updates will be reported in the PBRER/PSUR. |
| | | | Final report | 4Q 2024 |
| Survey to assess effectiveness of the additional risk minimization materials.<br>***Planned*** | To assess the effectiveness of additional risk minimization materials (ie, Healthcare Professional Guide, Patient Guide, Healthcare Professional Checklist) related to the understanding of the important identified risks ŧ of SPRAVATO. | • Drug abuse<br>• Transient dissociative states and perception disorders<br>• Disturbances in consciousness<br>• Blood pressure increased | Protocol submission (initial) | Within 6 months of MAA[a]<br>(30 June 2020) |
| | | | Trial start date (first patient in) | Initiation of survey (wave 1): within 18 months of availability of the approved educational materials in selected countries.<br><br>Initiation of survey (wave 2): after 2.5-3 years of availability of the approved educational materials in selected countries |

| Study Status | Summary of Objectives | Safety Concerns Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| | | | Final report | 4Q 2022<br>A report on the educational activities undertaken and the results of the survey will be submitted at 18 months and 3 years after launch. Updates will also be reported in the PBRER/PSUR. |

[a] The protocol will be developed within 6 months after approval of the marketing authorization for SPRAVATO. Once developed, this protocol will be included in Annex 3.

Key: MAA = Marketing Authorization Application; PBRER = Periodic Benefit-Risk Evaluation Report; PSUR = Periodic Safety Update Report; Q = quarter; TEAE = treatment-emergent adverse event; TRD = treatment-resistant major depressive disorder US = United States.

## *Risk minimisation measures*

The current additional risk minimisation measures (RMMs) consist of a Healthcare professional guide, Patient Guide, Healthcare Professional Checklist and a Controlled Access Program.

No changes to the existing additional RMMs were proposed within this extension of indication.

**Table 45: *Summary Table of PV Activities and Risk Minimization Activities by Safety Concern***

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| Drug abuse | **Routine risk minimization measures:**<br>• SmPC Section 4.4;<br>• PL Section 2.<br>• Administration under the direct supervision of a healthcare professional (SmPC Sections 4.2 and 4.4, PL Section 3, and Instructions for Use);<br>• Limited pack sizes;<br>• Legal status: Special and restricted medical prescription with categorization at the Member State level.<br>**Additional risk minimization measures:**<br>• Healthcare Professional Guide;<br>• Patient Guide;<br>• Controlled Access Program. | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>• Cumulative review of adverse events of interest including presentation and analysis of abuse-related serious adverse reactions in PBRER/PSUR.<br>**Additional pharmacovigilance activities:**<br>• Survey to assess the effectiveness of the additional risk minimization materials. |
| Transient dissociative states and perception disorders | **Routine risk minimization measures:**<br>• SmPC Sections 4.4, 4.7, and 4.8;<br>• PL Sections 2 and 4.<br>• Recommendations for dose adjustment are included in SmPC Section 4.2;<br>• Recommendation regarding driving a | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>• Cumulative review of adverse events of transient dissociative states and perception disorders at an aggregate level; presentation and analysis of serious adverse reactions in |

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| | motor vehicle or operating machinery is included in SmPC Section 4.7 and PL Section 2;<br>• Recommendation for post–administration observation is included in SmPC Section 4.2;<br>• As described in SmPC Sections 4.2 and 4.4 and PL Section 3, administration and post–administration monitoring take place under the supervision of a healthcare professional.<br>• Legal status: Special and restricted medical prescription with categorization at the Member State level.<br>**Additional risk minimization measures:**<br>• Healthcare Professional Guide;<br>• Patient Guide;<br>• Healthcare Professional Checklist | PBRER/PSUR.<br>**Additional pharmacovigilance activities:**<br>• Survey to assess the effectiveness of the additional risk minimization materials. |
| Disturbances in consciousness | **Routine risk minimization measures:**<br>• SmPC Sections 4.4, 4.7, and 4.8;<br>• PL Sections 2 and 4.<br>• Recommendations for dose adjustment are included in SmPC Section 4.2;<br>• Recommendation regarding driving a motor vehicle or operating machinery is included in SmPC Section 4.7 and PL Section 2;<br>• Recommendation for post–administration observation is included in SmPC Section 4.2;<br>• As described in SmPC Sections 4.2 and 4.4 and PL Section 2, administration and post–administration monitoring take place under the supervision of a healthcare professional.<br>• Recommendation that administration and post–administration observation of SPRAVATO should be carried out in an appropriate clinical setting (SmPC Section 4.2).<br>• Legal status: Special and restricted medical prescription with categorization at the Member State level.<br>**Additional risk minimization measures:**<br>• Healthcare Professional Guide;<br>• Patient Guide;<br>• Healthcare Professional Checklist | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>• Cumulative review of adverse events of disturbances in consciousness at an aggregate level; presentation and analysis of serious adverse reactions in PBRER/PSUR.<br>**Additional pharmacovigilance activities:**<br>• Survey to assess the effectiveness of the additional risk minimization materials. |
| Blood pressure increased | **Routine risk minimization measures:** | **Routine pharmacovigilance activities beyond adverse reactions reporting** |

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| | • SmPC Sections 4.2, 4.3, 4.4 and 4.8;<br>• PL Sections 2 and 4.<br>• Recommendations regarding blood pressure assessment (before and after treatment), monitoring, and actions to manage blood pressure elevation are provided in SmPC Sections 4.2 and 4.4;<br>• Recommendation regarding treatment in patients whose blood pressure is elevated prior to administration is provided in SmPC Section 4.4;<br>• Recommendation not to administer SPRAVATO to patients in whom an elevation of blood pressure would present a serious risk is provided in SmPC Sections 4.2 and 4.3 and PL Section 2.<br>• As described in SmPC Section 4.2, administration and post–administration monitoring take place under the supervision of healthcare professionals with training in blood pressure monitoring.<br>• Legal status: Special and restricted medical prescription with categorization at the Member State level.<br>**Additional risk minimization measures:**<br>• Healthcare Professional Guide;<br>• Patient Guide;<br>• Healthcare Professional Checklist | **and signal detection:**<br>• Cumulative review of adverse events of Blood pressure increased at an aggregate level; presentation and analysis of serious adverse reactions in PBRER/PSUR.<br>**Additional pharmacovigilance activities:**<br>• Survey to assess the effectiveness of the additional risk minimization materials. |
| Cognitive disorders and memory impairment (long-term use) | **Routine risk minimization measures:**<br>• SmPC Section 4.8;<br>• PL Section 2.<br>• Legal status: Special and restricted medical prescription with categorization at the Member State level.<br>**Additional risk minimization measures:**<br>• None. | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>• Cumulative review of adverse events suggestive of impaired cognition (long-term use) at an aggregate level; presentation and analysis of serious adverse reactions in PBRER/PSUR.<br>**Additional pharmacovigilance activities:**<br>• Long-term safety study 54135419TRD3008 (ongoing) |

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| Interstitial cystitis (long-term use) | **Routine risk minimization measures:**<br>• SmPC Sections 4.4 and 4.8;<br>• PL Section 2.<br>• Legal status: Special and restricted medical prescription with categorization at the Member State level.<br>**Additional risk minimization measures:**<br>• None. | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>• None.<br>**Additional pharmacovigilance activities:**<br>• Long-term safety study 54135419TRD3008 (ongoing). |
| Use during pregnancy | **Routine risk minimization measures:**<br>• SmPC Sections 4.6 and 5.3;<br>• PL Section 2.<br>• Legal status: Special and restricted medical prescription with categorization at the Member State level.<br>**Additional risk minimization measures:**<br>• None. | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>• None<br>**Additional pharmacovigilance activities:**<br>• Pregnancy registry for psychiatric medications such as antidepressants including esketamine. |

Key: PBRER = Periodic Benefit Risk Evaluation Report; PL = Package Leaflet; PSUR = Periodic Safety Update Report; SmPC = Summary of Product Characteristics.

## *2.7. Update of the Product information*

The group of variations requested amendments to the Summary of Product Characteristics, Annex II, Labelling, Package Leaflet and Annex IV.

As a consequence of this new indication and this group of variations, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 6.5 of the SmPC have been updated.

B.II.e.5.a.2: Addition of a new pack size (multipack) of 24 nasal spray devices (multipack of 8 packs of 3 nasal spray devices) corresponding to 4 weeks of treatment in the new indication.

The Package Leaflet and labelling are updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to clarify the wording in Annex II.D.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed and accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of Hungary.

### 2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

Full user testing in compliance with the above-mentioned legislative requirements was recently performed (n= 20 participants) on the package leaflet developed for Spravato for the initial Marketing Authorisation Application, which received a positive opinion on 17 October 2019 by the Committee for

Medicinal Products for Human Use and a European Commission decision on 18 December 2019. The results confirmed that the Package Leaflet for Spravato complies with current EU requirements for User Testing.

With reference to the two examples included in the 'Guidance concerning consultations with target patient groups for the package leaflet' (May 2006) and the 'Guideline on the readability of the labelling and package leaflet of medicinal products for human use' (revision 1, 12 January 2009) for circumstances in which reference can be made to an already approved package leaflet (Same safety issues identified and Same class of medicinal product), the applicant considers the following points to be relevant:

- The same formulation for use in the treatment of TRD will be used in the new target indication and the abilities of patients with MDSI are similar to those diagnosed with TRD with respect to their ability to find and understand instructions communicated in the package leaflet. The user groups (patients and the health care professional directly supervising them) are broadly similar to those for the TRD indication.
- The updated package leaflet (Annex IIIB) submitted within the EUPI to support this Type II variation to extend the indication (Mod1.3.1) introduces minimal changes and will use the same leaflet format with previously approved leaflet.
    - No new warnings in the package leaflet
    - The new terms determined to be side effects for esketamine following the MDSI adverse drug reaction assessment are similar to those previously identified in the TRD data.

Based on the rationale described above, the applicant does not propose to conduct any user testing (or bridging) to support the new indication application, which is acceptable for CHMP.

### 2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Spravato (esketamine) is included in the additional monitoring list since it has measures for ensuring the safe use of the medicinal product included in the risk management system and it has conditions or restrictions with regard to the safe and effective use of the medicinal product.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

Depression is the leading cause of disability worldwide and a major contributor to the overall global burden of disease. Major Depressive Disorder is a serious, disabling psychiatric illness that can have a devastating impact on the lives of patients. Moreover, MDD is the psychiatric condition most commonly associated with suicide. Suicide-related morbidity and mortality in patients with MDD are a major public health concern. The reported prevalence of suicidal ideation in adult patients with MDD is as high as 60%

and the lifetime prevalence of attempted suicide in this population ranges between 10% and 20%. Further, the lifetime risk of completed suicide is estimated to be 3.4% in this population.

Many risk factors for committing a suicide have been identified in these patients, for example prior history of suicide attempt, more severe depression, hopelessness and comorbidity. It has been estimated that patients with depression are at approximately 20 times greater risk for suicide than the general population. Alterations in the glutamate signalling may have a role in depression pathogenesis. It has also been suggested that there are differences in the glutamate system between patients with MDD with or without suicidal ideation.

It has been estimated that nearly 45,000 people in the United States (CDC, 2018) and more than 800,000 worldwide die by suicide each year (GBD 2015).

Worldwide, the crude suicide mortality rates dropped between 2000 and 2016, by 16% in men and 20% in women. In 2016, nearly 800 000 deaths were due to suicide, equivalent to an annual global crude suicide mortality rate of 10.6 per 100 000 population or one person every 40 seconds.

Screening for suicide has not been shown to reduce mortality and the reported cases may not reflect the true problem due to misclassification of deaths.

The evaluation of a patient who may be suicidal includes an assessment of ideation, method, plan, and intent. Unfortunately, the ability to predict who will attempt suicide is limited; patients who die by suicide are similar to those who do not (Pirkis et al. 2002). As an example, one study of 4800 psychiatric inpatients who were evaluated using the risk factors found that trying to identify particular people who would or would not die by suicide was not feasible because of the low sensitivity and specificity of available identification procedures (Pokorny 1983). Similarly, among patients who have presented to an emergency department after an episode of self-harm, assessments by psychiatrists and emergency department staff have low sensitivity and specificity for predicting who will repeat self-harm (Kapur et al. 2005).

A number of standardized scales have been proposed to evaluate suicide risk, but none is associated with a high predictive value. Scales such as the Columbia Suicidality Severity Rating Scale, Columbia Classification Algorithm for Suicide Assessment and InterSePT Scale for Suicidal Thinking are primarily used to evaluate safety, and not efficacy, in suicidality. Depression rating scales are commonly used, but these are measures of the severity of depression and not specifically of suicide risk (Runeson et al 2017). In addition, more general health related outcomes are used. As an example, a study evaluated responses to item number nine from the Patient Health Questionnaire – Nine Item (PHQ-9) ("Over the last two weeks, how often have you been bothered by thoughts you would be better off dead or of hurting yourself in some way?"), and found that the cumulative risk of suicide over one year among outpatients who answered "nearly every day" was 4 percent (Simon et al, 2013). In cardiac inpatients with current emotional distress (n = 366), a positive response to item nine was endorsed by 21 percent, but a detailed suicide evaluation found that suicidal plans or intent were present in only 3 percent Suarez et al., 2015). Other studies also suggest that item nine is an insufficient assessment tool (Na et al., 2018).

Another option for identifying patients at high risk of suicide is the Beck Hopelessness Scale, which is a 20-item true/false questionnaire that correlates more closely with current suicide attempt than the severity of the depression. However, a meta-analysis found that the low specificity of the scale limits its applicability (McMillan et al., 2007; Uptodate.com Suicidal ideation and behavior in adults, accessed March 2020).

The patients in the phase 3 studies with Spravato were identified by answering in MINI that they think about harming or hurting or injuring themselves and that they intend to act on thoughts of killing themselves.

### 3.1.2. Available therapies and unmet medical need

Patients with MDD who have a current suicidal ideation reflect an acutely ill population that requires immediate intervention. Management of the suicidal individual should include:

- Hospitalisation
- Medical stabilization
- Reducing immediate risk and treatment planning
- Managing underlying factors and psychiatric disorders
- Monitoring and follow-up

There may be differences between countries in the approach to reducing the immediate risk which may concern inpatient hospitalization, partial hospitalization or an outpatient program.

However, there are no approved pharmacological treatments for the rapid reduction of the symptoms of depression and suicidality in this patient population. Furthermore, only limited information is available to guide clinical decisions, since this population has typically been excluded from antidepressant drug trials in the past. Standard antidepressants may take several weeks to exert their full effect, limiting their utility in crisis situations. Additionally, hospitalizations are temporary and not completely effective, and the risks for attempted and completed suicide remain high in the weeks immediately after discharge.

Some studies in the literature suggest that patients with MDD who have suicidal ideation show a worse response to antidepressant treatment than MDD patients without suicidal ideation. In one study evaluating the response to a new antidepressant after 6 weeks of treatment in 4,041 depressed outpatients, suicidal patients were less likely to improve or attain remission than non-suicidal patients. In the multivariate analyses, active suicidal ideation (odds ratio] = 1.40; 95% confidence interval [CI]: 1.18-1.65) and a history of suicide attempt (odds ratio = 1.39; 95% CI: 1.16-1.66) were the best predictors of non-remission, independent of the class of antidepressant treatment (Lopez-Castroman et al 2016).

Patients with MDD who have active suicidal ideation/thoughts and/or behavior reflect a severely ill population that requires immediate intervention. Current approach for treating these patients is mainly initiation or optimisation with antidepressants and frequently hospitalisation. However, antidepressants have been associated with suicide risk.

There is a clear unmet medical need for the treatment of patients who suffer from suicidal ideation and/or behaviour. There are options such as structured and protective environment for the management of the suicidality of these patients. If the patients can be identified most important rapid management would still be hospitalization and oral antidepressants. Clear benefit would have been if outpatient pharmacological treatment became possible.

### 3.1.3. Main clinical studies

Two phase 3 studies were conducted. The design of these pivotal studies was identical: double-blind, randomized, placebo-controlled, multi-center, international studies in adults with MDD, who have responded that they think about harming or of hurting or of injuring themselves and who intend to act on thoughts of killing themselves (question B3 and B10 of MINI).

Sample size calculation was appropriate based on an effect size for the MADRS total score and a number of 451 patients in total (with 226 patients receiving Esketamine + SOC and 225 on placebo + SOC) can be considered sufficient. Randomisation was also implemented. Blinding was maintained by adding a bittering agent to the placebo nasal spray (as in the studies for TRD) and by using different raters to perform efficacy and safety assessments.

The primary endpoint was considered appropriate to investigate the depressive symptoms (MADRS). With respect to the suicidality issue (key secondary endpoint CGI-SS-R and other indices such as MADRS Suicidal thoughts, CGI-SR-I, CGI-FoST, Patient reported FoST) it is unclear whether the scales/instruments used were appropriate. The statistical methods are generally considered acceptable.

## *3.2. Favourable effects*

A rapid reduction of depressive symptoms was observed in the study population. In study SUI3001, the mean change in MADRS total score (SD) from baseline to 24 hours was -12.8 (10.73) for the SOC + placebo group and -16.4 (11.95) for the SOC + esketamine group. In study SUI3002, the mean change in MADRS total score (SD) from baseline to 24 hours was -12.4 (10.43) for the SOC + placebo group and -15.7 (11.56) for the SOC + esketamine group. For the primary endpoint a LS mean treatment difference in the change of MADRS total score from baseline to 24 hours after the first dose (Day 2) was observed in both studies [SUI3001: -3.8 (-6.56; -1.09) (SE=1.39); p=0.006 and SUI3002: -3.9 (-6.60; -1.11) (SE=1.39); p=0.006]. For the pooled studies, the LS mean treatment difference (95% CI) at 24 hours after the first dose was -3.8 (-5.75; -1.89).

A larger proportion of patients in the esketamine group (compared to placebo) achieved remission of depressive symptoms (MADRS total score ≤12). In study SUI3001, remission rate at 24 hours was 8.9% in the SOC + placebo group and 18.8% in the SOC + esketamine group. Response rate at 24 hours was 26.8% in the SOC + placebo group and 33.9% in the SOC + esketamine group. In study SUI3002, remission rate at 24 hours was 10.6% in the SOC + placebo group and 21.9% in the SOC + esketamine group. Response rate at 24 hours was 23.9% in the SOC + placebo group and 35.1% in the SOC + esketamine group. At the double-blind endpoint Day 25 (4 hours postdose), 50% of subjects in the esketamine + SOC group and 37% in placebo + SOC group had a MADRS total score ≤12. The corresponding treatment difference (95% CI) was 13.1% (4.03; 22.19).

## *3.3. Uncertainties and limitations about favourable effects*

Suicides can occur impulsively and the time period between onset of suicidal ideation and suicide attempt can be very short from minutes to a few hours. In addition, it is very difficult to predict which patients will proceed to committing suicide or not. Specific and sensitive instruments have not been identified yet. It has also been reported that no diagnostic tool has demonstrated clinical value for the assessment of short-term suicide risk among high-risk individuals (Hawes et al 2017). The necessity for reliable diagnostic tools for the short-term suicide risk assessment has been recognised (Calati et al 2020).

Several scales have been proposed to evaluate suicide risk, but without a high predictive value. Scales such as the Columbia Suicidality Severity Rating Scale (C-SSRS), Columbia Classification Algorithm for Suicide Assessment (C-CASA) and InterSePT Scale for Suicidal Thinking are primarily used to evaluate safety, and not efficacy, in suicidality. Depression scales are a measure of severity of depression and not necessarily of the suicide risk. In addition, a high degree of complexity is associated with suicidal behaviours.

Taking all the above into consideration, it is questionable whether a population of "*adult patients with a moderate to severe episode of MDD who have current suicidal ideation with intent*" can truly be identified in clinical practice.

A notably high percentage of 37% of patients on placebo achieved remission of depressive symptoms (MADRS total score ≤12). This may be explained by the fact that these patients received optimal SOC. However, the beneficial effects on esketamine versus placebo in reducing depressive symptoms, as measured by MADRS, did not translate into more pronounced reduction of suicidal ideation and/or behaviour.

The key secondary endpoint, change in CGI-SS-R score from baseline to 24 hours after the first dose (Day 2) failed to show a statistically significant difference between the treatment groups and also failed to show a convincing trend in favour of Esketamine + SOC [LS means in -0.3 in study SUI3001; -0.1 in study SUI3002 and -0.2 for the pooled studies]. The treatment groups did not separate at any time-point throughout the studies, neither in CGI-SS-R or the investigator assessed risk of suicide (GCI-SR-I). In study SUI3001, the median change from baseline to 24 hours in severity of suicidal ideation as measured by the Clinical Global Impression – Severity of Suicidality (CGI-SS-R) was -1.0 (-5; 1) in the SOC + placebo group and -1.0 (-6; 2) in the SOC + esketamine group. The Hodges-Lehmann estimate of the treatment difference (95% CI) was 0.0 (-1.00; 0.00). (2-sided p=0.107). In study SUI3002, the median change from baseline to 24 hours in severity of suicidal ideation as measured by the CGI-SS-R was -1.0 (-6; 2) in the SOC + esketamine group and -1.0 (-5; 2) in the SOC + placebo. The Hodges-Lehmann estimate of the treatment difference (95% CI) was 0.0 (0.00; 0.00) (2-sided p=0.379). The CGI-SS-R is part of the SIBAT, which was subject to a qualification advice procedure (EMA/CHMP/SAWP/705316/2018, Procedure No.: EMEA/H/SAB/051/1/FU/1/2018). It was stated that the final utility of the scale will only be determined once the phase 3 data is available. The small numerical difference favouring Esketamine + SOC cannot be considered as evidence of an effect of esketamine in reducing suicidal ideation or suicide risk and it does not demonstrate the clinical relevance of CGI-SS-R. It is unclear whether the studies failing to show an effect is due to esketamine having no relevant effect on suicidal behavior, or whether it can be attributed to the beneficial effects of hospitalization with extensive clinical care during the double-blind treatment phase, which may make it difficult to show an additional effect compared to placebo. Therefore, the observed result on CGI-SS-R could be either failure of the treatment or failure of the assessment scale, which is currently not validated.

Another secondary endpoint was the percentage of subjects achieving resolution of suicidality based on CGI-SS-R score at different time points. However, the CGI-SS-R scale, which is part of the SIBAT tool, is currently not validated. In the overall clinical trial population, the between group differences were 13.2%, 1.6% and 7.3% at Days 1, 2 and 25, respectively. In the subpopulation with severe depression (baseline MADRS ≥35), the between group differences were similar, i.e. 16.2%, 4.6% and 5.6% at Days 1, 2 and 25, respectively. Overall, these differences were small but most visible on Day 1, in line with the early onset of antidepressant effect of esketamine.

For the key secondary endpoint, several different analyses were also pre-defined to describe the size of the treatment effect. It is not clear whether the calculation of LS means using ANCOVA based on the actual values is valid as CGI-SS-R is an ordinal scale. The item response analysis resulting in an odds ratio for achieving a lower score is an interesting explorative analysis but also difficult to interpret. Firstly, the

application of the Bayesian framework is not standard in the regulatory context. Secondly, the interpretation of odds ratios in terms of clinical relevance is generally difficult and not intuitive, particularly for ordinal scales.

All of the suicide indices including MADRS suicidal thoughts, CGI-SS-R scores, CGI-SR-I scores, clinician-rated FoST, and patient-reported FoST showed improvement from baseline to the end of the double-blind treatment phase for both treatment groups. There were only small differences observed between placebo + SOC and Esketamine + SOC [MADRS suicidal thoughts -0.20; CGI-SS-R -0.18; CGI-SR-I -0.16; CGI-FoST -0.09 and Patient reported FoST -0.05].

Hospitalization was recommend to be continued for at least 5 days, however this could have been longer or shorter based on clinical judgement. It is unclear whether there is differential effect on duration of hospitalization.

In study SUI3002, local SOC and regional requirements led to the increase in some EU countries to 14 days of hospitalization. This together with other factors such as higher proportion of randomized subjects who received an antidepressant + augmentation therapy, longer mean duration of illness, higher proportion of patients who had a recent suicide attempt and higher number of discontinuations in SUI3002 compared to SUI3001 led to some differences in effects between the studies. The results for the placebo + SOC group in the study SUI3002 appeared to be somewhat better than in study SUI3001 and the between-group difference favouring esketamine + SOC smaller. However, the results of the primary and important key secondary efficacy variables were similar for the two studies and do not raise any concerns.

## *3.4. Unfavourable effects*

The clinical development program for esketamine in MDSI provided safety data for 262 subjects who received at least 1 dose of esketamine + SOC in the Phase 2 and 3 studies, representing a combined cumulative exposure to esketamine of 15.8 patient-years. The safety and tolerability of esketamine is further supported by data collected during the extensive clinical development program in patients with TRD, including 1,708 subjects who received esketamine in the completed Phase 2 and 3 TRD studies (611 patient-years exposure), and 1,140 subjects who went on to receive esketamine in the ongoing long-term OL extension safety study TRD3008 (1,198 patient-years exposure). As of 31 December 2018, across completed and ongoing Phase 3 TRD studies, 1,739 subjects had received at least one dose of esketamine 56 mg (611 patient-years of exposure) and 1,279 subjects had received at least one dose of esketamine 84 mg (1,151 patient-years of exposure). Key safety observations are summarized below.

- In the completed Phase 2 and 3 MDSI studies, 1 death was reported in 262 subjects who had been assigned to esketamine + SOC treatment in the double-blind treatment phase (15.8 patient-years of exposure) and 0 deaths were observed in 256 subjects who had been assigned to placebo + SOC (15.7 patient-years of exposure). No deaths were observed during the double-blind treatment phase of the SUI2001, SUI3001, or SUI3002 studies.in the controlled Phase 2 and 3 MDSI studies. Across all completed and ongoing studies of esketamine in MDSI and TRD indications, 8 deaths have been reported in subjects who had received treatment with esketamine. Four deaths were reported in the completed Phase 2 and 3 TRD studies in 1,708 subjects who had been assigned to esketamine + oral antidepressant treatment, and no deaths in 486 subjects who received oral antidepressant + placebo. In the ongoing long-term OL extension study TRD3008, 3 deaths were reported in 1,140 esketamine-treated subjects through 31 December 2018. In each of the 8 cases, the AEs were considered by the investigator as not related or doubtfully related to esketamine nasal spray. Of the 8 deaths reported in subjects who received esketamine during the MDSI and TRD clinical studies, 4 were completed suicides. This corresponds to an incidence of 0.22 completed suicides per 100 patient

years of exposure, which is comparable to the rate reported in a meta-analysis of studies in MDD patients treated with oral antidepressants (0.22 per 100 patient years) (Braun et al. Psychother. Psychosom. 2016;85) and lower than the rate reported in another meta-analysis in TRD patients receiving various treatments (0.47 per 100 patient years) (Bergfeld et al. J Affect Disord. 2018;235).

- Overall, esketamine nasal spray 84 mg was safe and tolerated in the Phase 2 and 3 MDSI studies when used in conjunction with comprehensive SOC. The adverse events reported in these studies were generally consistent with the safety profile of esketamine observed in previous studies in subjects with TRD. There were no new or unexpected safety concerns noted with the administration of esketamine in the completed MDSI clinical studies, or in the ongoing studies in subjects with TRD or MDSI.
- As observed in the TRD clinical program, most TEAEs reported during esketamine treatment in the Phase 2 and 3 MDSI studies, including the most common anticipated TEAEs, were mild or moderate in severity, were observed postdose on the day of dosing, and resolved the same day.
- In the pooled Phase 3 studies (SUI3001/3002), the following common TEAEs (reported in at least 10% of subjects) were observed more frequently in subjects treated with esketamine + SOC compared with those receiving placebo + SOC: dizziness, dissociation, nausea, somnolence, dysgeusia, vision blurred, paresthesia, vomiting, blood pressure increased, sedation, and anxiety. A similar pattern of TEAE reporting was observed for the Phase 2 study (SUI2001).
- Based on an analysis of ADRs across TRD and MDSI clinical programs, esketamine was shown to have a consistent risk profile in both populations and the ADRs determined were not considered indication specific.
- In the pooled Phase 3 studies SUI3001/3002, SAEs were reported during the double-blind phase in esketamine-treated subjects at rates that were low and generally similar to those in subjects receiving placebo + SOC (9 [4.0%] vs. 12 [5.3%] subjects, respectively). In the Phase 2 SUI2001 study, SAEs were reported during the double-blind phase in 4 (11.4%) vs. 0 subjects, respectively. The most frequently reported SAEs were in the psychiatric disorders category and were associated with the underlying disease state.
- The rates of discontinuation of treatment due to TEAEs were reported at higher rates in the esketamine + SOC group compared with the placebo + SOC group in the pooled Phase 3 studies (14 [6.2%] vs 8 [3.6%] subjects, respectively) and Phase 2 study SUI2001 (5 [14.3%] vs. 1 [3.2%], respectively). Main reasons for discontinuations were nervous system disorders such as dissociation, depersonalisation/derealisation, hallucination, sedation/somnolence and others.
- Dissociative/perceptual changes (based on the CADSS) and sedative effects (based on MOAA/S) were observed at higher rates in the esketamine + SOC group than the placebo + SOC group in the Phase 2 and 3 MDSI studies. These events had an onset shortly after dosing, peaked by 40 minutes postdose, and typically resolved within 1.5 hours. The TEAEs associated with these symptoms were primarily mild or moderate in severity, occurred on the day of dosing, and resolved the same day.
- No cases of respiratory depression or TEAEs that required cardiopulmonary resuscitation or other medical intervention were observed.
- The Phase 2 and 3 MDSI studies enrolled subjects with MDD who had active suicidal ideation with intent, and a large proportion of these subjects (~60%) had a history of prior suicide attempt. It is important to note that these studies were designed to evaluate the efficacy of esketamine in reducing the severity of suicidality and were not designed to evaluate the effectiveness of esketamine in preventing suicide. Overall, the rates of AEs potentially related to suicidality (including suicide attempts and 1 completed suicide) in the Phase 2 and 3 studies were similar between the esketamine

+ SOC and placebo + SOC treatment groups during the double-blind and follow-up phases. Given the high-risk status of the population enrolled in these studies, the observed rate of suicidality-related events during the Phase 2 and 3 MDSI studies was not unexpected. The Sponsor has included a warning in the proposed label to highlight that esketamine has not been studied or proven to be effective in preventing suicide, and that the use of esketamine does not preclude the need for hospitalization, if clinically warranted. This is included with the class warning statement regarding suicide/suicidal thoughts or clinical worsening in Section 4.4 of the proposed SmPC.

- Transient increases in systolic and diastolic blood pressure were observed following administration of esketamine nasal spray in the Phase 2 and 3 MDSI clinical studies, with maximum elevations typically observed around 40 minutes after dosing and values returning to, or close to, pretreatment levels by 1.5 hours postdose. The blood pressure elevations generally did not require intervention and were not associated with adverse clinical outcomes. Few subjects discontinued esketamine treatment due to increased blood pressure.
- There were no new data obtained from the Phase 2 and 3 MDSI studies or other ongoing studies that would warrant changes to the existing sections in the esketamine SmPC related to pregnancy/lactation, overdose, abuse potential, withdrawal and rebound, effects on the ability to drive or operate machinery, or cognitive and memory impairment.

In conclusion, the safety profile of esketamine in patients with MDSI was consistent with that observed in the TRD program, and no new safety signals were observed. Taken together, the safety data from the completed Phase 2 and 3 MDSI clinical studies and the TRD program support the conclusion that the overall safety profile of esketamine nasal spray, despite uncertainties, has not changed when it is used in conjunction with oral antidepressant therapy for the rapid reduction of depressive symptoms in a subgroup of adult patients with MDD.

## *3.5. Uncertainties and limitations about unfavourable effects*

The patient population investigated in the pivotal Phase 3 studies is defined as adults with Major Depressive Disorder (MDD) assessed to be at imminent risk for suicide. Patients were identified by the answer "yes" to the questions B3 and B10 of the MINI. In clinical routine suicidal ideation is a symptom common in patients with depression but not a separate diagnostic criterion. Biologically, patients with major depressive disorder either with or without suicidal ideation would not be distinguishable.

All patients with major depressive disorder have an increased risk for suicides and suicide attempts. Oral anti-depressive drugs can be associated with initially increased risk for suicides. This risk can vary with factors like disease stage or age of the patients and are usually identified through post-marketing data and meta analyses. In major depressive disorder so far no anti-depressive drug has been identified that is proven to actually effectively reduce the number of suicides and suicide attempts.

Four suicides have so far occurred in all studies of esketamine in patients with treatment resistant depression (TRD) or major depressive disorder with suicidal ideation (MDSI). Two of these suicides occurred in the follow-up phase of patients previously on esketamine during the placebo-controlled phase of the MDSI and TRD studies, three days and 20 days respectively, after last intake of study drug. The other two occurred during the uncontrolled active induction/maintenance phases within the TRD studies. No suicides occurred in patients that were either on treatment with placebo or in follow-up after placebo treatment.

Due to the small sample size these data are difficult to interpret. Taken together with the lack of efficacy on suicidality scores, they show however that there is remaining uncertainty how esketamine use might actually affect suicidality in patients with depression.

In the TRD studies discussed in the original MAA, suicidality did not appear to be increased during the initial weeks of treatment. Events were reported in the esketamine groups with an incidence of around < 4% for the induction and maintenance phases of the studies. In the MDSI studies an incidence of 7.5% is reported in the esketamine group during initial treatment (double blind).

Because of a numerical imbalance that suggested that esketamine treated subjects engage more in suicidal behaviour, the temporal relation of the suicidality related AEs suicide attempt, intentional self-injury, intentional overdose, and completed suicide to esketamine dosing was analysed. Based on the pooled Phase 3 studies (SUI3001/3002), the proportion of subjects reporting one of the selected potential suicidality-related events for esketamine vs. placebo was 4.4% vs. 3.1% during the double-blind phase, but 5.3% vs. 1.6% during the follow-up phase. This numerical difference was largely due to a higher rate of suicide attempt in the esketamine + SOC group vs. placebo group during the follow-up phase (3.7% vs. 1.6%).

A history of one or more prior suicide attempts was reported for approximately 60% of the 518 MDD subjects with current suicidal ideation and intent in the Phase 2 and 3 MDSI studies. Study SUI3002 had a higher percentage of subjects in the esketamine group that reported a suicide attempt within the last month before study entry compared the placebo group (31.6% versus 21.2%). A history of prior suicide, and in particular recent prior attempt, is one of the most important predictors for future suicidal behaviour. Therefore, this imbalance may have contributed to the observed differences in the number of suicide attempts during the follow-up phase. In the Phase 2 study SUI2001, more suicide attempts were reported in the placebo group than in the esketamine group (3 subjects versus none) during the follow-up phase. There was an imbalance at baseline in the proportion of subjects with recent suicide attempts with 41.9% vs. 30.3% for the placebo versus esketamine group. In the pooled data of the Phase 2 and Phase 3 studies the rate of suicide attempt during the follow-up phase was 3.2% vs. 2.9% for esketamine versus placebo.

Analysis of the time since the last study drug dose to the onset of the first selected AE potentially related to suicidality showed these events were dispersed over the follow-up phase, without an apparent pattern suggestive of rebound. In the pooled Phase 3 studies, the median time from the last dose of study drug to the first AE in the follow-up phase was longer in the esketamine + SOC group than the placebo + SOC group (30 vs. 7 days). Similar results were observed for the pooled Phase 2 and 3 studies (24 vs. 8.5 days).

The only completed suicide occurred 3 days after the last dose of esketamine in a subject that appeared to be in remission. However, the clinical narrative supports the investigator's assessment, that the event was not related to study drug. The subject showed a clear pattern of a chronic disease and a possible major relapse close to the suicide was indicated (after the subject had completed the study).

There was also a higher rate of AEs potentially related to suicidality in the younger age group (18 to 24 years) compared with the older age group (>24 years), regardless of treatment assignment. Within the age range of 18 to 24 years the incidence of these events was however higher in the placebo group than in the esketamine group. Also, only 79 subjects within this age range were included in the pooled Phase 3 studies, therefore the sample size is small and has to be interpreted with caution. Generally, the finding of higher incidence of AEs potentially related to suicidality in the younger subgroup (18-24 years) compared with the older subgroup (>24 years) is consistent with the scientific literature. It might also be further confounded by concomitant intake of oral anti-depressive drugs, which are known to increase suicidal behavior especially in children and young adults.

Overall, while a slight numerical imbalance exists for suicide related events towards the esketamine group, these data are very limited. The observation might also be explained by slight differences in the

composition of the patient groups within the treatment arms. Therefore, no specific safety signal can be identified at this time for patients with MDD and suicidal ideation or behaviour.

## *3.6. Effects Table*

**Table 46: Effects Table for [SPRAVATO for the rapid reduction of depressive symptoms in adult patients with a moderate to severe episode of MDD who have current suicidal ideation with intent] (data cut-off: May 2019)**

| Effect | Short description | Unit | Treatment | Control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| Change in MADRS total score | MADRS Total Score: Change From Baseline to 24 Hours After the First Dose (Day 2) | | -16.4 | -12.8 | SoE: Difference of LS means (SE) -3.8 (1.39), p=0.006 | Study SUI3001 |
| Change in MADRS total score | MADRS Total Score: Change From Baseline to 24 Hours After the First Dose (Day 2) | | -15.7 | -12.4 | SoE: Difference of LS means (SE) -3.9 (1.39), p=0.006 | Study SUI3002 |
| Change in CGI-SS-R Score | Clinical Global Impression – Severity of Suicidality - Revised (CGI-SS-R) Score: Change From Baseline to 24 Hours After the First Dose (Day 2) by ANCOVA LOCF | | -1.0 | -1.0 | Uncertainty: Hodges-Lehmann Estimate of Treatment Diff, (95% CI), 2-sided p-value 0.0 (-1.00; 0.00), p=0.107 | Study SUI3001 |
| Change in CGI-SS-R Score | Clinical Global Impression – Severity of Suicidality - Revised (CGI-SS-R) Score: Change From Baseline to 24 Hours After the First Dose (Day 2) by ANCOVA LOCF | | -1.0 | -1.0 | Uncertainty: Hodges-Lehmann Estimate of Treatment Diff, (95% CI), 2-sided p-value 0.0 (0.00; 0.00), p=0.379 | Study SUI3002 |
| MADRS Remission of MDD | MADRS percentage of patients who achieved remission (MADRS total score ≤12) at the double-blind endpoint (Day 25, 4 hours postdose) | | 50% | 37% | Uncertainty: treatment difference [95% CI]: 13.1% [4.03; 22.19] | Pooled Phase 3 studies |
| **Unfavourable Effects** | | | | | | |
| Death | Serious Adverse Events: Deaths | | 8 | 0 | Uncertainty: All 8 cases were considered by the investigators to be not related or doubtfully related to the study medication | All available studies with esketamine |
| Suicide attempt | Suicide attempts (N) | | 4 | 4 | Uncertainty: Increase in suicide | Pooled Phase 3 |

| Effect | Short description | Unit | Treatment | Control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| in double-blind phase | | | | | attempts after treatment discontinuation (see below) | studies double-blind phase (Table 18) |
| Suicide attempt in follow-up | Suicide attempts (N) | | 7 | 3 | Uncertainty: higher number in Esketamine + SOC group | Pooled Phase 3 studies Follow-Up Phase (Table 19) |
| Intentional self-injury | Self-injury (N) | | 7 | 3 | Uncertainty: higher number in Esketamine + SOC group | Pooled Phase 3 studies Double-blind Phase (Table 18) |
| Transient dissociative/perceptual changes | Incidence of Derealisation, depersonalization, distortion of time and space and illusions (N) | | 77 (33.9%) | 13 (5.8%) | Placebo + SOC: 34/35 (97.1%) Esketamine + SOC: 358/360 (99.4%) | Pooled Phase 3 studies (Table 8) |
| Paresthesia | Paresthesia | | 26 (11.5%) | 7 (3.1%) | Higher rates in the esketamine + SOC group | Pooled Phase 3 studies (Table 8) |
| Dizziness | | | 87 (38.3%) | 31 (13.8%) | Higher rates in the esketamine + SOC group | Pooled Phase 3 studies (Table 8) |
| Transient increase BP | Incidence of abnormal BP elevation (SBP to ≥180 mm Hg or DBP to ≥110 mm Hg, i.e. acute hypertension (N) | | 26 (11.5%) | 9 (4.0%) | Higher rates in the esketamine + SOC group | Pooled Phase 3 studies (Table 8) |
| Somnolence | Incidence of Somnolence | | 47 (20.7%) | 23 (10.2%) | Higher rates in the esketamine + SOC group | Pooled Phase 3 studies (Table 8) |
| Sedation | Sedation (N) | | 23 (10.1%) | 5 (2.2%) | Higher rates in the esketamine + SOC group | Pooled Phase 3 studies (Table 8) |

Abbreviations:

Notes:

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

The population of depressed patients who have suicidal behavior and/or ideation/thoughts is a vulnerable subgroup of MDD patients. However, there are difficulties in identifying this population in the clinical

practice, perform a prospective assessment and ultimately predict and prevent their actions with regard to attempting or committing suicide.

There is a clear unmet medical need for the treatment of patients who suffer from suicidal ideation and/or behaviour. There are options such as structured and protective environment for the management of the suicidality of these patients. If the patients can be identified, most important rapid management would still be hospitalization and optimization of oral antidepressants.

A reduction in depressive symptoms as measured by the change in the MADRS scale from baseline to 24 hours after the first dose (Day 2) and from baseline to end of treatment (Day 25) showed large effect sizes for the esketamine 84mg + SOC group compared to placebo + SOC. The currently available antidepressive medications may take several weeks to work. The observed rapid reduction of depressive symptoms in a patient population with a moderate to severe episode of MDD and current suicidal ideation or behaviour is therefore considered as an important benefit.

These favourable results, however, did not translate into a meaningful reduction in suicidality indices, as it would have been expected. There were no relevant differences in scales measuring suicidality and suicide risk between esketamine and the combination of hospitalisation, oral antidepressants, benzodiazepines and psychotherapy which were included in the comprehensive SOC. The key secondary objective of the Phase 3 studies related to reduction of suicidality was not achieved.

The failure of the key secondary endpoint (as well as suicidality indices) to show a favourable effect of the esketamine 84mg + SOC treatment could be due to the overall optimized management of patients during the double-blind treatment phase, since a remarkable improvement was observed also for the placebo group. However, despite that statistical significance has not been reached, a trend favouring esketamine + SOC has been observed in some secondary efficacy endpoints, including some suicidality indices (e.g. resolution of suicidality and reduction of hopelessness using BHS) and patient-reported outcome (PRO) measures (e.g. quality of life using QLDS) on top of comprehensive SOC. The differences however, were small and of questionable clinical relevance.

There is a concern that it would be difficult for prescribers to predict future suicidal behavior, and that currently available scales have limited utility in reliably identifying those patients who will go on to attempt or complete suicide. Communication and education of healthcare professionals will be required to ensure that the appropriate population receives esketamine and to inform about what effects should and should not be expected. The following information was considered more appropriate for section 4.4. instead of section 4.1:

> "The effectiveness of Spravato in preventing suicide or in reducing suicidal ideation or behaviour has not been demonstrated. Use of Spravato does not preclude the need for hospitalisation if clinically warranted, even if patients experience improvement after an initial dose of Spravato."

The Committee considered that a reference in the therapeutic indication together with a boxed warning mentioning suicidal ideation or behaviour may cause misinterpretations.

Overall, the safety profile of esketamine has not changed from the initial MA in TRD. The same AEs have been observed in the studies in this subgroup of patients with MDD. Major safety risks are still considered dissociative effects, perceptual changes, increases in BP, somnolence and sedation, as well as an abuse potential, which put considerable limitations for the intended use. A numerical imbalance in deaths, suicides and suicide attempts for the esketamine 84mg + SOC increases the uncertainty. In particular, compared to placebo, suicidal behaviour in the form of intentional self-injury, suicide attempt, completed suicide and intentional overdose occurred more frequently in esketamine treated subjects. Further analyses show that a clear signal for suicidality cannot be established due to the low numbers and that the differences may be explained by baseline imbalances in suicidality risk, but the numerical difference

between esketamine and placebo treated subjects still remain. Thus, a relationship can therefore not be excluded. This is considered to be sufficiently covered by the suicidality warning in the SmPC of Spravato.

## 3.7.2. Balance of benefits and risks

A sizeable positive effect of esketamine treatment in rapidly reducing depressive symptoms as measured by changes in the MADRS scale, is observed. A high percentage of patients showed remission of depressive symptoms (MADRS total score ≤12) in both treatment groups with a clinically relevant difference in favour of esketamine. The rapid onset of effect is in line with previous study findings in TRD.

Scales attempting to measure a reduction in suicidality, suicidal ideation/thoughts/behavior did not yield statistically significant results in favour of the esketamine 84mg + SOC in patients who have responded positively that they *Think [even momentarily] about harming or of hurting or of injuring themselves: with at least some intent or awareness that they might die as a result; or think about suicide [i.e., about killing themselves]*) and who *Intend to act on thoughts of killing themselves.* Other secondary endpoints assessing suicidal ideation and/or behaviour did not yield results favouring the esketamine + SOC group.

A clear clinical benefit for this specific subgroup of patients with MDD, in the form of an improvement in suicidal indices would have been expected, in addition to the reduction of depressive symptoms. It can only be speculated why this objective has not been met. The identification of patients with suicidal ideation who will in fact attempt suicide is not reliably possible, factors other than severity of depression add to suicidality, the scales used may not be suitable or not sensitive enough, the large effect of optimized SOC in the comparator arm made it difficult to show a statistically significant additional benefit, or esketamine may indeed have no or only a marginal effect on suicidality. Even a (temporary) negative effect on suicidality can currently not be excluded. It is important to mention that, so far, a favourable effect on suicidality has also not been shown for other currently approved antidepressive medications and that risk of suicidality may even be increased during initial treatment. However, the fact remains that the secondary objective of demonstrating a beneficial effect of esketamine - on top of oral antidepressive therapy and optimized non-pharmacological measures - on suicidality in adult patients with a moderate to severe episode of MDD and current suicidal ideation or behaviour has not been met.

This has been acknowledged by the Applicant and a note was initially proposed to be included in section 4.1 of the SmPC to clearly state that the effectiveness of esketamine in preventing suicide or in reducing suicidal ideation or behaviour has not been demonstrated. Because of the high relevance of this information for the safety of patients, the Rapporteur suggested going a step further and having this information as a boxed warning. The Committee considered more appropriate that these issues are flagged in section 4.4.

The Applicant proposes to carefully educate healthcare professionals to ensure that the appropriate population receives esketamine and on effects that should and should not be expected. The educational material for the prescribers has been provided together with a description of a plan for HCPs with a variety of medical education activities, for example at psychiatric scientific congresses (1), or as standalone activities (2).

As a last point, the survey conducted on behalf of the Applicant by a third-party research organization, Cello Health Insight, has been prepared and submitted. In early 2018 Janssen EMEA commissioned the independent healthcare market research company, Cello Health Insight, to conduct a market research study, designed to quantify the patient population with major depressive disorder with imminent risk of suicide (MDSI), as well as to understand the potential role esketamine might have for the treatment of this patient population. The survey was conducted with 671 European psychiatrists and physicians (including General Psychiatrists, excluding office-based psychiatrists, Accident and Emergency Physicians and Primary Care Physicians, plus office-based psychiatrists). The results outlined in the survey suggest

that prescribers are proficient at recognizing and identifying acute suicidal ideation and behaviour in patients with MDD, considering a wide range of factors, and that most do so based on factors that can be broadly categorised as clinical evaluations and/or interviews. Most participants in the survey (91%) indicated that they assessed acute suicidality based on clinical evaluation and interview, including such elements as clinical/medical history, clinical assessment of suicidal ideation/intent and history of suicidality, psychological evaluation, discussion with the patient and family/caregivers. The findings in this report are in agreement with the knowledge that the assessment teams have accumulated up to now.

It is evident that nobody can reliably predict who will go on and attempt or commit suicide. However, psychiatrists, as part of their everyday clinical practice, are evaluating MDD patients for suicidal ideation and behaviour.

The adverse event profile of esketamine observed in the submitted studies is generally in line with that observed in TRD patients. There are relevant safety issues but they are considered manageable with the RMMs already in place (e.g. monitoring of patient's blood pressure, administration in a setting with appropriate resuscitation equipment and healthcare professionals with training in cardiopulmonary resuscitation are available and monitoring of patients by a healthcare professional until they are considered clinically stable and ready to leave the healthcare setting).

Overall, the benefit of rapid reduction of depressive symptoms in a severely affected subpopulation with MDD is considered to outweigh the risks.

## 3.7.3. Additional considerations on the benefit-risk balance

The Applicant has taken into consideration the Committee's concerns (that key secondary objective of the Phase 3 studies related to suicidality was not achieved) and is currently proposing a revised wording for the indications:

The applicant has modified the initially proposed wording of the indication and is currently seeking approval of SPRAVATO for the following indication:

> *Spravato, co-administered with oral antidepressant therapy, is indicated as acute short-term treatment for the rapid reduction of depressive symptoms,* ***~~when this is urgently required~~ in a psychiatric emergency,*** *as per clinical judgement, in adult patients with a moderate to severe episode of MDD (see section 5.1* ***for a description of the population studied****)* ***~~and~~*** *~~current suicidal ideation~~* ***~~or behaviour~~****.*

The phrase "when this is urgently required" is considered broad and could be misinterpreted by physicians. The currently proposed wording ***"in a psychiatric emergency"*** is restricting the use of Spravato to the patients most in need of the treatment, describes better the population included in the clinical studies and avoids any reference to suicidal thoughts or suicidal behavior.

The wording ***"for a description of the population studied"***, encourages physicians to read section 5.1 for more details and the presentation of the clinical evidence. The Applicant's position is acknowledged.

However, this latest indication as worded above was considered as too broad and implied that Spravato could be given in any psychiatric emergency which could be driven by complex psycho-social events and not necessarily be caused by the underlying depression; therefore the CHMP proposed the below indication which was agreed by the company:

"*Spravato, co-administered with oral antidepressant therapy, is indicated in adults with a moderate to severe episode of major depressive disorder, as acute short term treatment, for the rapid reduction of*

*depressive symptoms,* ***which according to clinical judgement constitute a psychiatric emergency*** *(see section 5.1 for a description of the population studied)"*

The proposed text, highlighting that "effectiveness of Spravato in preventing suicide or in reducing suicidal ideation or behaviour has not been demonstrated" and that there may be a need for hospitalisation, was included at the beginning of section 4.4.

### *3.8. Conclusions*

The overall B/R of Spravato is positive.

# 4. Recommendations

### *Outcome*

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

| **Variations accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| B.II.e.5.a.2 | B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes | Type IB | None |
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I, II, IIIA, IIIB and IV |

C.I.6(a): Extension of Indication to include a new indication for Spravato: Spravato, co-administered with oral antidepressant therapy, is indicated in adults with a moderate to severe episode of major depressive disorder, as acute short term treatment, for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency (see section 5.1 for a description of the population studied).

As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 6.5 of the SmPC are updated. The RMP version 2.5 has also been agreed.

B.II.e.5.a.2: Addition of a new pack size (multipack) of 24 nasal spray devices (multipack of 8 packs of 3 nasal spray devices) corresponding to 4 weeks of treatment in the new indication.

The Package Leaflet and labelling are updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to clarify the wording in Annex II.D.

### *Amendments to the marketing authorisation*

In view of the data submitted with the group of variations, amendments to Annex(es) I, II, IIIA, IIIB and addition to IV and amendments to the Risk Management Plan are recommended.

## *Conditions or restrictions with regard to the safe and effective use of the medicinal product*

## Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

## Additional risk minimisation measures

Prior to the launch of SPRAVATO in each Member State (MS), the Marketing Authorisation Holder (MAH) must agree about the content and format of the **educational materials (EM) and the controlled access programme (CAP)**, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).

The MAH shall ensure that in each MS where SPRAVATO is marketed a CAP is implemented to prevent/minimise the important identified risk of Drug abuse.

SPRAVATO is intended to be self-administered by the patient under direct Healthcare Professional (HCP) supervision and should be dispensed to the healthcare settings where administration takes place, as agreed at the MS level, based on local legal requirements and/or local healthcare systems. When the administration is intended for outpatients, it should only be reserved to an environment where the patient is appropriately followed-up. SPRAVATO may induce transient sedation, dissociative and perception disorders and/or increase blood pressure. Patients must, therefore, be monitored by a HCP during and after each treatment session including an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting. In patients with clinically significant or unstable cardiovascular or respiratory conditions, SPRAVATO should be administered in a setting where appropriate resuscitation equipment and healthcare professionals with training in cardiopulmonary resuscitation are available.

The following EM should be provided to HCPs (and acknowledgement of receipt recorded):

- **The HCP guide**, aiming at addressing the risks of Transient dissociative states and perception disorders, Drug abuse, Disturbances in consciousness, and Blood pressure increased, should incorporate adequate reference to patient's safety, and highlight that:
    - All patients must be monitored accordingly after SPRAVATO administration until considered clinically stable to leave the healthcare setting;
    - In patients with clinically significant or unstable cardiovascular or respiratory conditions, SPRAVATO should be administered in a clinical setting where equipment for cardiopulmonary resuscitation and staff trained in cardiopulmonary resuscitation are available;
    - Due to the potential risk of cardiac adverse events, the patient's blood pressure should be carefully monitored before and after SPRAVATO intake.
- The **readiness to leave checklist for HCPs** (attached to the HCP guide): the objective of this EM is to aid HCPs in evaluating when, following SPRAVATO administration, a patient is deemed stable and safely allowed to leave the clinic/facility where SPRAVATO has been administered.

The following EM should be provided to patients:

- The **guide for patients**, aiming at addressing the risks of Transient dissociative states and perception disorders, Drug abuse, Disturbances in consciousness and Blood pressure increased. The objective of this EM is to detail:
    - Which adverse effects to expect following SPRAVATO administration, and how to minimize those effects;
    - Risk factors/groups/ signs of abuse and dependence, which should be regularly assessed and monitored;
    - The procedure for SPRAVATO intranasal administration, including preparation (fasting for 2 hours, no drinking for 30 minutes) and patient's monitoring;

    The guide for patients also aims at increasing awareness about:

    - The steps for SPRAVATO self-administration under direct HCP supervision;
    - Monitoring of blood pressure before and after SPRAVATO dosing;
    - Requirements for HCP supervision and post-dose observation, until the HCP confirms the patient is clinically stable and is allowed to leave the clinic/facility where SPRAVATO has been administered;
    - The influence of SPRAVATO on the patient's ability to drive or operate machinery

## Obligation to conduct post-authorisation measures

N/A

## *Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States*

The Member States (MS) should ensure that all conditions or restrictions with regards to the safe and effective use of SPRAVATO, as described below, are implemented.

Prior to its launch in each MS, the Marketing Authorisation Holder (MAH) must agree with the National Competent Authority (NCA) all aspects of the controlled access programme (CAP) for SPRAVATO, implemented to prevent/minimise the important identified risk of drug abuse.

SPRAVATO is intended to be self-administered by the patient under direct Healthcare Professional (HCP) supervision and should be dispensed to the healthcare settings where administration takes place, as agreed at the MS level, based on local legal requirements and/or local healthcare systems. When the administration is intended for outpatients, it should only be reserved to an environment where the patient is appropriately followed-up.

SPRAVATO may induce transient sedation, dissociative and perception disorders and/or increase blood pressure. Patients must, therefore, be monitored by an HCP during and after each treatment session, including an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting. In patients with clinically significant or unstable cardiovascular or respiratory conditions, SPRAVATO should be administered in a setting where appropriate resuscitation equipment and healthcare professionals with training in cardiopulmonary resuscitation are available.