21 November 2019
EMA/614876/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Spravato

International non-proprietary name: esketamine

Procedure No. EMEA/H/C/004535/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

(Study) SUI2001	(Study) ESKETINSUI2001
(Study) TRD2001	(Study) ESKETIVTRD2001
(Study) TRD2002	(Study) KETIVTRD2002
(Study) TRD2003	(Study) ESKETINTRD2003
(Study) TRD3001	(Study) ESKETINTRD3001
(Study) TRD3002	(Study) ESKETINTRD3002
(Study) TRD3003	(Study) ESKETINTRD3003
(Study) TRD3004	(Study) ESKETINTRD3004
(Study) TRD3005	(Study) ESKETINTRD3005
AD	antidepressant
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
App	Appendix (abbreviation used only in cross-references)
ATC	Anatomical Therapeutic Chemical
Att	Attachment (abbreviation used only in cross-references)
AUC	area under the plasma concentration-time curve
BCRP	breast cancer resistance protein
BfArM	Federal Institute for Drugs and Medical Devices
BP	blood pressure
BPRS+	Brief Psychiatric Rating Scale, 4-item Positive Symptom Subscale
C_{max}	maximum plasma concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
CADSS	Clinician Administered Dissociative States Scale
CGADR	Clinical Global Assessment of Discharge Readiness
CGI-S	Clinical Global Impression - Severity
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL_{CR}	creatinine clearance
CogState®	computerized cognitive test battery
CSR	Clinical Study Report
CYP	cytochrome P450
DB	double-blind
DBS	deep brain stimulation
DMF	Drug Master File
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition - Text Revision
DPP	Division of Psychiatry Products
ECG	electrocardiogram
ECT	electroconvulsive shock therapy
EMA	European Medicines Agency
EQ-5D-5L	European Quality of Life, 5-Dimension, 5-Level (questionnaire)
EQ-VAS	European Quality of Life – Visual Analogue Scale
Esk	esketamine (abbreviation used only in tables and figures where space is limited)
EU	European Union
FDA	Food and Drug Administration
GABA	γ-amino butyric acid

GAD-7	Generalized Anxiety Disorders – 7 item (scale)
HCl	Hydrochloride
HCP	healthcare professional
HVLT-R	Hopkins Verbal Learning Test - Revised
IA	interim analysis
ICD-C_{30}	Inventory of Depressive Symptomatology-Clinician rated, 30-item
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IM	intramuscular
IND	induction
IV	intravenous
KSS	Karolinska Sleepiness Scale
LOCF	last observation carried forward
LS	least squares
MA	maintenance
MAA	Marketing Authorisation Application
MADRS	Montgomery-Asberg Depression Rating Scale
MAR	maximum acceptable risk
MDD	major depressive disorder
MDSI	major depressive disorder with imminent risk for suicide
MEB	Medicines Evaluation Board
MedDRA	Medical Dictionary for Regulatory Activities
MGH-ATRQ	Massachusetts General Hospital – Antidepressant Treatment Response Questionnaire
MINI	Mini International Neuropsychiatric Interview
MMRM	mixed-effects model using repeated measures
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
NDA	New Drug Application
NMDA	N-methyl-D-aspartate
NMDAR	N-methyl-D-aspartate receptor
OATP	organic anion transport polypeptide
OL	open-label
OP	optimization
PD	pharmacodynamic
PDCO	Paediatric Committee
PHQ-9	9-item Patient Health Questionnaire
P-gp	P-glycoprotein
PIP	Paediatric Investigational Plan
PK	pharmacokinetic
PoC	proof-of-concept
PRO	patient-reported outcome
PWC-20	Physician Withdrawal Checklist; 20-Item
QIDS-SR16	Quick Inventory of Depressive Symptomatology – 16-item Self Report
QTcF	QT interval corrected by Fridericia's equation
rTMS	repetitive transcranial magnetic stimulation
SAP	statistical analysis plan
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SDLP	standard deviation of the lateral position
SDS	Sheehan Disability Scale
SE	standard error
SIGMA	Structured Interview Guide for the Montgomery-Asberg Depression Rating Scale

SOC	system organ class
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
the Applicant	Janssen Research & Development
$t_{1/2}$	terminal half life
tDCS	transcranial direct current stimulation
TEAE	treatment-emergent adverse event
TRD	treatment-resistant depression
ULN	upper limit of normal
UPSIT	University of Pennsylvania Smell Identification Test
US	United States
VNS	vagus nerve stimulation
WHO	World Health Organization
XR	extended release

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Janssen-Cilag International N.V. submitted on 10 October 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Spravato, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 July 2016. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant therapeutic innovation.

The applicant applied initially for the following indication "treatment resistant depression (Major Depressive Disorder in adults who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode)".

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that esketamine was considered to be a known active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0020/2017 on the agreement of a paediatric investigation plan (PIP), and the granting of a product-specific waiver.

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

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 applicant 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.

Applicant's requests for consideration

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004, which was declined by CHMP.

Scientific advice

The applicant received Scientific advice from the CHMP on the development for the indication from the CHMP on 15 November 2012 (EMEA/H/SA/2406/1/2012/III), 24 July 2014 (EMEA/H/SA/2406/1/FU/2/2014/II), 19 November 2015 (EMEA/H/SA/2406/1/FU/3/2015/I), 21 April 2017 (EMEA/H/SA/2406/1/FU/5/2017/I). The Scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- Quality aspects, including the development of the intranasal formulation and the intranasal delivery system: the applicant 's choice of starting material used in the manufacture; the use of a matrix based testing schedule for registration/validation drug product batches manufactured; acceptability of the release testing strategy for vials and intranasal devices; stability protocol and approach for manufacturing of registration batches; extractable and leachable testing plan
- Adequacy of the non -clinical program including: the proposal for intranasal esketamine administration.
- Adequacy of the clinical pharmacology program including: the proposal to not perform additional studies with inhibitors or inducers of hepatic CYP activity; assessing the disposition of intranasal esketamine; data collection to inform on the patient's ability to drive or operate machinery after intranasal esketamine administration.
- Appropriateness of the phase 3 program to support an authorisation of esketamine in the proposed indication (dose selection, primary and secondary endpoints, size of the safety database, scales for efficacy and safety assessments, number of EU patients in global program); the clinical development program for TRD in elderly patients; suitability of the healthcare supervision during esketamine administration.

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

The application was received by the EMA on	10 October 2018
The procedure started on	1 November 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	21 January 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	21 January 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	4 February 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	28 February 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	27 May 2019

The following inspection was requested by the CHMP and its outcome taken into consideration as part of the Safety/Efficacy assessment of the product:	
– A GCP inspection at 2 clinical study sites in Brazil and Malaysia and the Sponsor's site in Belgium between 28/01/2019 and 22/03/2019. The outcome of the inspection carried out was issued on	17-05-2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	1 July 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 July 2019
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	25 July 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	18 September 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	2 October 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Spravato on	17 October 2019
A revised opinion was adopted by the CHMP in order to provide further clarifications in relation to the clinical safety and the benefit-risk balance sections, on	21 November 2019

2. Scientific discussion

2.1. Problem statement

Major depressive disorder (MDD) is the leading cause of disability worldwide according to the World Health Organization (WHO) and is associated with a reduction in life expectancy by 10 years. According to the latest WHO estimates, more than 300 million individuals worldwide, including 40.2 million in Europe and 17.5 million in the US, are living with depression, an increase of more than 18% between 2005 and 2015. Only about two-thirds of patients with MDD are able to achieve remission after the first or second course of treatment using the currently approved drugs. Remission rates following subsequent steps of therapy are lower (approximately 13%), and relapse rates are higher and occur more quickly. Patients who have not responded to at least 2 different AD treatments, at an adequate dose for an adequate duration, in the current depressive episode are considered to have treatment-resistant depression (TRD).

2.1.1. Disease or condition

MDD is one of the most common psychiatric disorders, which is the fourth leading cause of global disease burden and affects about 15 % of the general population. MDD is not a benign disorder, it is associated with substantial psychosocial dysfunction and high individual mental strain as well as with excess morbidity and mortality - the risk of suicide is considerable.

Despite the many treatment options currently available for MDD, a relevant proportion of patients up to one third do not adequately respond to treatment and up to 20% are considered non-responders, even if there is good compliance and the treatment has been taken long enough with an adequate dosage. So there is a clear need for patients, in whom even "state of the art"-antidepressant therapy fails to elicit a sufficient treatment response. The clinical picture of TRD is common in everyday practice.

The approved therapeutic indication is:

Spravato, in combination with a SSRI or SNRI, is indicated for adults with treatment-resistant Major Depressive Disorder, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode

2.1.2. Epidemiology and risk factors

Depression is currently considered one of the most disabling medical conditions in the world and WHO predicts that depression will become the single most important illness in Europe and worldwide by 2030. MDD, one of the most common psychiatric disorders, is the fourth leading cause of global disease burden and affects about 15% of the general population. Recent meta-analyses from countries across Europe, Asia, North and South America, and Australia have found that the rates for 12-month MDD prevalence are in the region of 4.1%-4.6%, while recent estimates in US raise this percentage to 6.7% (overall in 12-month Prevalence of Major Depressive Episode Among U.S. Adults).

According to facts and figures from WHO, each year, 25% of the population suffer from depression or anxiety and neuropsychiatric disorders account for 19.5% of the burden of disease in the European Region, and 26% in European Union (EU) countries. These disorders account for up to 40% of years lived with disability, with depression as the main cause and up to 50% of chronic sick leaves are due to depression/anxiety.

2.1.3. Aetiology and pathogenesis

The pathogenesis of treatment resistant depression is not known. Some genetic factors which potentially affect response to antidepressants by influencing drug distribution and metabolism, serum and brain drug concentrations, and target molecules have been suggested. Structural and functional abnormalities in specific brain regions and neural networks have also been proposed as contributing factors for development of TRD. (Schosser et al 2012, GENDEP investigators 2013, Li et al 2015. Serra-Blasco et al 2013)

The pathogenesis of unipolar major depression with psychotic features is unknown. Studies have identified neurobiologic abnormalities, but it is not clear if these findings represent etiologic causes or sequelae because the studies investigated patients after they developed the disorder [https://www.uptodate.com/contents/unipolar-major-depression-with-psychotic-features-epidemiology-clinical-features-assessment-and-diagnosis?search=major%20depression%20pathogenesis&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1].

2.1.4. Clinical presentation, diagnosis and stage/prognosis

The detection of MDD requires the presence of mood disturbance or loss of interest and pleasure in activities accompanied by at least two (ICD-10) or four other symptoms of depression (DSM-5). At least one symptom must be either depressed mood or loss of interest or pleasure:

- Depressed mood most of the day, nearly every day
- Loss of interest or pleasure in most or all activities, nearly every day
- Insomnia or hypersomnia nearly every day
- Significant weight loss or weight gain (e.g., 5 percent within a month) or decrease or increase in appetite nearly every day
- Psychomotor retardation or agitation nearly every day that is observable by others
- Fatigue or low energy, nearly every day
- Decreased ability to concentrate, think, or make decisions, nearly every day
- Thoughts of worthlessness or excessive or inappropriate guilt, nearly every day
- Recurrent thoughts of death or suicidal ideation, or a suicide attempt.

These core symptoms may vary from patient to patient, however, they are typically seen for much of the day, almost always every day for at least two weeks and are associated with relevant psychological distress and considerable impairment of psychosocial and work functioning.

Symptoms of TRD follow those of MDD in general, for example depressed mood, loss of interest or pleasure, sleep disturbance, fatigue, neurocognitive dysfunction and changes in appetite and weight. Compared to patients with non-TRD MDD, patients with TRD show pronounced decreases in daily functioning and health-related quality of life. It has been suggested that all-cause mortality or suicide is greater in TRD as compared to non-TRD MDD, however the available data is limited. (Fekadu et al 2009, Olin et al 2012). Risk of relapse is estimated to be higher in TRD and the probability of remission seems to decrease with successive treatment failures. (Rush et al 2003, STAR*D study)

2.1.5. Management

Although there are many oral antidepressant (AD) pharmacotherapies available for use worldwide, all of these agents act primarily by modulating the same pathway (monoaminergic system) and require several weeks before a full clinical effect on depression symptoms is evident. The conventional treatments over the past 50 years have targeted monoamine neurotransmitters, including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).

There are several publications discussing the definition and potential treatments of TRD. Quetiapine prolonged released tablets (e.g. Seroquel XR) are licensed as add-on treatment of major depressive episodes in patients with Major Depressive Disorder (MDD) who have had sub-optimal response to antidepressant monotherapy; however the population was differently defined in comparison to a treatment - resistant population.

While an olanzapine-fluoxetine combination (Symbyax®) has been approved in the USA, there is currently no medicinal product specifically authorized for the treatment of TRD available in Europe. In the European guideline on clinical investigation of medicinal products in the treatment of depression (EMA/CHMP/185423/2010 Rev. 2), the difficulties even in the conceptual elaboration and definition of clear criteria for incomplete response and TRD are acknowledged together with the unavailability of specific approved treatments for this condition.

About the product

Esketamine (the S-enantiomer of racemic ketamine) is a known active substance, approved in some European Union and Latin American countries, and used for the induction and maintenance of anaesthesia via intramuscular (IM) or intravenous (IV) infusion.

Esketamine nasal spray has been developed as an antidepressant with a novel mechanism of action. It is a non-competitive, subtype non-selective, activity-dependent glutamate receptor modulator. The antidepressant effect of esketamine is mediated via antagonism of N-methyl-D-aspartate receptor (NMDAR) which produces a transient increase in glutamate release leading to increases in α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) stimulation, leading to an array of molecular and cellular events, including increases in brain-derived neurotrophic factor (BDNF) expression, synthesis and release, activations of neurotrophic signalling pathway such as extracellular signal regulated kinase/mitogen activated protein kinase (ERK/MAPK) and protein kinase B (AKT), inhibition of glycogen synthase kinase (GSK)-3, and activation of synaptic plasticity genes such as activity-regulated cytoskeleton (ARC)-associated protein. These changes are thought to further induce production of synaptic proteins and synaptogenesis, and eventually restoration of synaptic function. Additional effects mediated by modulation of monoaminergic neurotransmission cannot be excluded. In this respect it is noteworthy that acute and prolonged increases in dopamine levels in prefrontal cortex, striatum and nucleus accumbens occur immediately after administration of subanesthetic doses of esketamine.

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 proposed for marketing is a nasal spray solution: 28mg single-use nasal spray device. The pack sizes proposed are 1, 2, 3, or 6 nasal spray devices.

Type of Application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the following grounds:

- It was not entirely clear from the efficacy data that esketamine could fulfil the unmet medical need in TRD, since one study has shown statistically significant results

- The strength of evidence is challenged by issues related to study design, in particular lack of esketamine only comparison, starting two new treatments at the same time, unexpectedly high response in the AD+ intranasal placebo arm as well as reduced magnitude of response in the elderly (in spite of a wide range of doses), questioning whether the population was really TRD. All of those warrant a thorough discussion

that may not be possible within an accelerated assessment procedure:

- few substantiation for the claim of major public health interest/ major therapeutic innovation from an efficacy or safety perspective

- the actual amount of safety data from ongoing studies that would be submitted during the procedure is hardly predictable and assessment of an important amount of data submitted during the procedure would be difficult within an accelerated timetable.

2.2. Quality aspects

Introduction

The finished product is presented as nasal spray, solution containing 28 mg of esketamine (as hydrochloride) as active substance.

Other ingredients are: citric acid monohydrate, disodium edetate, sodium hydroxide (for pH adjustment) and water for injections.

The product is available in type I glass vial with a chlorobutyl rubber stopper. The filled and stoppered vial is assembled into a manually activated nasal spray device. The device dispenses two sprays delivering a total volume of 0.2 mL of solution, as described in section 6.5 of the SmPC.

Active substance

General information

The chemical name of esketamine hydrochloride is (*S*)-2-(o-chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride corresponding to the molecular formula $C_{13}H_{16}ClNO.HCl$. It has a molecular weight of 274.2 g/mol and the following structure:

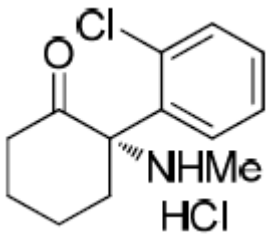


Figure 1: active substance structure

The chemical structure of esketamine hydrochloride was elucidated by a combination of mass spectrometry (MS), infrared (IR) spectroscopy, ultraviolet (UV) spectroscopy and nuclear magnetic resonance (NMR). The solid state properties of the active substance were measured by X-ray powder diffraction (XRPD), infrared (IR) spectroscopy, thermal gravimetric analysis (TGA), hot stage microscopy (HSM), and Differential Scanning Calorimetry (DSC).

The active substance is a white or almost white non-hygroscopic crystalline powder. It is freely soluble to slightly insoluble in aqueous media over pH range 3.1 - 6.9 and slightly soluble to freely soluble in organic solvents.

Esketamine exhibits stereoisomerism due to the presence of one chiral centre. Esketamine hydrochloride is a single enantiomer of racemic ketamine with the S configuration at C-2 position of the cyclohexanone ring. Stereoisomerism arises during the synthesis. The manufacturing process of the active substance consists of an optical (racemic) resolution step resulting in a single enantiomer, esketamine obtained by

crystallisation. Enantiomeric purity is routinely controlled in the active substance specifications as well as finished product release and shelf-life specifications using chiral HPLC.

Polymorphism has not been observed for esketamine hydrochloride. Only one crystalline form is known from literature (Form I). Nevertheless, a polymorph screen was initiated in order to ensure no other crystalline forms can be formed. Crystallization experiments were conducted with solvents that cover a broad range of properties such as polarity, dielectric constant, boiling point and hydrogen bond donor and acceptor propensity. Also included were solvent/water mixtures appropriate to identify possible hydrates. The experimental procedures included slurry tests at room and elevated temperature, solvent evaporation and cooling crystallization. Only Form I was found in all these experiments. The screening studies demonstrated that the active substance does not exhibit polymorphism. These results are consistent with the information found in literature.

The particle size of the active substance does not impact the manufacturability or quality of the finished product since the active substance is completely dissolved in the first step of the finished product manufacturing process.

The active substance has a monograph in the European Pharmacopoeia (Ph. Eur.), however the manufacturers of the active substance have not submitted a Certificate of Suitability of the European Pharmacopoeia (CEP) for esketamine hydrochloride.

Manufacture, characterisation and process controls

Two suppliers of the active substance are used. For one supplier the detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory. For the second supplier, complete information on manufacturing of the active substance has been provided in the dossier.

Active substance manufactured by the ASMF-supported manufacturer was used to produce the finished product used in all clinical trials throughout development. The comparability of active substance manufactured by both manufacturers has been demonstrated by batch analysis data and characterization studies.

Active substance is synthesized in five or six main steps, respectively, depending on the manufacturer, using well defined starting materials with acceptable specifications. One of the intermediates used in the synthesis by the ASMF-supported manufacturer is covered by a valid CEP.

For the manufacturer supported with complete information on manufacturing in the dossier a criticality analysis of the active substance manufacturing process has been performed to identify the critical steps. Based on the results obtained the steps 4 (formation of intermediate designed to obtain the (S)-enantiomer) and 5 (formation of esketamine hydrochloride) of the active substance synthesis process have been determined to have an influence on the critical quality attributes (CQAs) of the final active substance and are therefore designated as critical steps.

For the ASMF-supported manufacturer critical steps have been clearly defined and in-process controls have been adequately described. Appropriate limits have been set for intermediates.

The development of the manufacturing process has been described showing the differences between development batches and registration batches. Only minor changes have been made to optimize the manufacturing process and to increase the yield.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in double low-density polyethylene (LDPE) bags which comply with the EC directive 2002/72/EC and EC 10/2011 as amended. The bags are closed with a twist-tie or equivalent and placed in a closed container (plastic drum, fiber drum, or equivalent). Primary packaging of the active substance supplied by the ASMF-supported manufacturer are packaged in low density polyethylene film which is also in compliance with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for: appearance, appearance of solution (Ph. Eur.), identity (IR, HPLC), identification of chloride ion (Ph. Eur.), assay (UHPLC), chromatographic purity (UHPLC), enantiomeric purity (chiral HPCL), pH value (Ph. Eur.), residual solvents (GC), and residue on ignition (Ph. Eur.).

Potential impurities Ph. Eur Impurity A, HCl salt of synthesis intermediate (Step 1b), Ph. Eur Impurity B, rearrangement product of Impurity C, Ph. Eur Impurity C; synthesis impurity (Step 1b), and Ph. Eur Impurity D, enantiomer of the active substance are listed in the Ph. Eur monograph of esketamine hydrochloride and are also included in the active substance specification. It has been stated that active substance synthesis impurities, carryover impurities from starting and raw materials, as well as degradation products are not observed in the active substance above 0.05% (w/w).

A specific discussion as part of the overall discussion on impurities with regard to their mutagenic potential according to ICH M7 guideline has been provided for all known actual and potential impurities likely to be present in the active substance. Two SAR prediction methodologies that complement each other have been applied: DEREK (an expert rule-based methodology) and Leadscope (a statistical-based methodology). In case of a relevant structural alert, a bacterial mutagenicity assay (Ames test) has been conducted. Based on this mutagenic assessment, the evaluated impurities have been classified with respect to carcinogenic and mutagenic potential as defined in ICH M7 guideline. A TTC-based acceptable intake of 119 ppm has been calculated when assuming a 10-year impurity dose of 10 µg/day and a maximum daily active substance dose of 84 mg/day. A summary of the mutagenicity assessment and control has been provided.

Based on process control and purging factor considerations under the applicable process conditions, they are not expected to occur in the final active substance at levels above the TTC-based maximum allowable concentration. Therefore, no further specific control of these impurities is required.

Based on the chemical synthesis route and the bacteriostatic and fungistatic properties of the active substance it has been justified that no test for microbiological purity testing is warranted in the active substance specification.

A risk assessment for the potential presence of elemental impurities was conducted in accordance with the ICH Q3D Guideline for Elemental Impurities (see also "Product specification" section). Based on that no specifications for elemental impurities are required for the active substance specification.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on 11 batches (3 commercial scale and 9 development scale) from one and 20 batches (4 commercial scale and 16 development scale) from the second manufacturer of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 commercial scale and 4 development scale batches stored in the proposed commercial packaging from one manufacturer and 3 commercial scale and 11 development scale batches from the second manufacturer stored in the packaging simulating commercial packaging for up to 24 and 60 months respectively, under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Data from the first manufacturer included intermediate storage conditions as well. Photostability testing following the ICH guideline Q1B was performed on one batch by each manufacturer. Results on stress conditions (thermal, hydrolytic, oxidative and photochemical conditions) were also provided on one batch.

The following parameters were tested: appearance, assay, impurities, water content and pH value. The analytical methods used were stability indicating.

All tested parameters were within the specifications demonstrating the stability and photostability of the active substance. The active substance is stable when exposed to light and requires no special storage conditions. The active substance is prone to significant degradation under basic conditions and to some minor degradation under oxidative conditions. The active substance is stable under acidic conditions, under neutral conditions, and under dry thermal and humidity/thermal conditions.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 36 and 60 months respectively, with no special storage conditions in the proposed container.

Finished medicinal product

Description of the product and Pharmaceutical development

Spravato is a buffered, non-preserved aqueous solution containing esketamine hydrochloride as the active substance. The finished product is available in one single dosage strength, containing a nominal delivered dose of 28 mg esketamine base. The filled and stoppered vials are assembled into a manually activated single-use disposable nasal spray device (see Figure 2 below). The device dispenses two sprays (one for each nostril) delivering a total volume of 0.2 mL of the finished product.

Figure 2. The SPRAVATO nasal spray device

Qualitative and quantitative composition of the finished product is provided.

The aim of the pharmaceutical development was to develop an easy-to-administer esketamine formulation, which provides a pharmacokinetic profile comparable to intravenous (IV) administration. An intranasal formulation was chosen since it mimics the pharmacokinetic profile of IV dosing, allows for rapid systemic absorption and bypasses first pass metabolism. It is less invasive and more patient friendly than IV dosing.

A Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQA) for the finished product were defined and are presented in table 1.

Table 1: QTTP and CQAs of Spravato

Drug Product Attribute	QTPP Aspect	Drug Product CQA
Dosage Form	Preservative-free aqueous liquid	Appearance Drug Product Solution, Color and Clarity
Route of Administration	Intranasal	Appearance of Device
Dosing volume	200 µL	Fill volume
Dosage Strength	The nasal spray solution consists of esketamine HCl 161.4 mg/mL and a base equivalent concentration of 140 mg/mL Each 0.2 mL delivers 32.3 mg of esketamine hydrochloride or 28 mg of the free base form	Identification, Esketamine Assay, Fill Volume
Purity-organic/inorganic/degradants	Sufficiently low level of organic/inorganic/degradants	Purity-organic/inorganic/degradants, Particulate Matter, Disodium Edetate assay, pH, Appearance
Intranasal Delivery	Device Performance for adequate delivery of Drug Product Solution	Manual Operation of Device[a], Droplet Size Distribution[a], and Spray Content Uniformity by Weight [a]
pH	pH 3-10 acceptable; pH 4.5-6.5 preferred	pH
Osmolality	Isotonic or hypertonic	Osmolality
Viscosity, Surface Tension, and Density	Proper spray	Droplet size distribution[a]
Microbiological Purity	Sufficiently low level of microbial impurities	Microbiological Purity
Container Closure System	Type 1 clear glass vials sealed with rubber plunger stoppers and packaged in a single-use nasal spray device	Purity-organic/inorganic/degradants, Microbiological Purity, Particulate Matter, Esketamine Assay, disodium edetate Assay
Shelf-Life	Minimum 36 months[b]	Appearance, Esketamine Assay, Purity-organic/inorganic/degradants, Particulate matter, disodium edetate assay, Microbiological Purity, pH, Droplet Size Distribution[a], and Spray Content Uniformity by Weight[a]

[a] Combination product related quality attribute, further discussed in 3.2.P.5.4, Batch Analysis and 3.2.P.8.1, Stability Summary and Conclusion
[b] The QTPP target drug product shelf-life is 36 months. The actual shelf-life is based on available data as presented in 3.2.P.8.1, Stability Summary and Conclusion

The aqueous solubility of the active substance is approximately 200 mg/mL at room temperature. The solubility of the active substance has also been studied in various aqueous buffer systems across the pH range. Due to the basic nature of the active substance (pKa = 7.5 in aqueous solution at 20 ºC), the solubility is higher at low pH values and begins to drop as the pH rises above 5.0. These solubility characteristics support the finished product pH specification range.

For the development of the nasal spray of esketamine, the HCl salt of the drug was selected since it is already commercially available and exhibits chemical and physical stability at the conditions of use (room temperature). Also, the hydrochloride salt is freely soluble in water at the pH range which is suitable for the preparation of the finished product as a nasal spray solution.

As described in the active substance stability section, esketamine hydrochloride exhibits good chemical stability in the solid state at room temperature and ambient humidity. No impurities have been observed in the active substance above the reporting threshold of 0.05% (w/w) in representative batches manufactured according to the proposed commercial synthesis at release or during stability testing.

The finished product is manufactured by dissolving the active substance in aqueous vehicle. The active substance is freely soluble in water at the pH range which is the pH of the formulation. Manufacturing experiments indicate that the active substance dissolves instantaneously in the formulation vehicle, utilizing the process parameters and process equipment proposed for commercial production. Visual checks are included in the manufacturing process to ensure all active substance is dissolved following mixing.

Polymorphism is not a factor that will impact finished product manufacturability or performance since there is only one form (Form I) of the active substance that can be formed as discussed earlier in this report.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Stability studies have demonstrated that during storage of the finished product, the chemical and physical quality is maintained throughout the course of the stability studies. During these stability studies, real-time and accelerated storage conditions have been studied, and also storage under light conditions

have been evaluated. The results of these stability studies can be considered as supportive of overall excipient compatibility.

No preservative was used as the QTPP indicated a preference to have a preservative-free formulation and because of the antimicrobial properties of the active substance. Spravato nasal spray is not a sterile product.

A concentration of eq.140 mg/mL esketamine free base was selected based on pre-clinical and clinical PK studies. Subsequently a nasal spray formulation G001 (esketamine free base eq. 140 mg/mL nasal spray solution) was evaluated in Phase 1 studies. G001 is a preservative-free aqueous solution of the esketamine hydrochloride in water for injection at a base equivalent concentration of 140 mg/mL and adjusted to a final target pH of 4.5 using sodium hydroxide. The addition of penetration enhancers and viscosity increasing agents did not offer any relevant benefit and were therefore omitted. Esketamine formulations containing low levels of citric acid and EDTA, respectively exhibited improved stability compared to G001 and resulted in a stable solution pH over 24 months. The addition of citric acid and EDTA was also well tolerated with minimal unilateral histopathological changes. Therefore, formulation G005 (an aqueous solution of the esketamine hydrochloride in water for injection at a base equivalent concentration of 140 mg/mL, and adjusted to a final target pH of 4.5 using sodium hydroxide) was selected for evaluation in Phase 2 and Phase 3 studies, and used in subsequent Phase 1 studies as well. This formulation was selected for the final commercial formulation.

A concentration of eq. 140 mg/mL esketamine in the drug product solution was considered acceptable based on solubility of esketamine hydrochloride in the formulation vehicle. This esketamine concentration however resulted in a high osmolarity of the nasal solution (approximately 1050 mOsm/kg). The effect of the high osmotic pressure on the nasal irritation has been investigated in clinical studies and the outcomes demonstrated that the overall nasal tolerability profile was considered to be acceptable.

The primary packaging is type I glass vial with a chlorobutyl rubber stopper. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. The filled and stoppered vials are, subsequently, assembled into the nasal spray device.

The materials of the esketamine primary container closure and the nasal spray device in contact with the drug include glass, chlorobutyl rubber, stainless steel and polypropylene and are commonly used for pharmaceutical products.

An extractable study was performed to determine the extractable and/or potential leachable profiles of the primary container closure components including the glass vial and rubber stopper. The objective of the study was to identify extractables and provide a semi-quantitative estimation of their amounts. Subsequently, the potential leachables selected from the extractable experiment were followed during a leachables study. No organic or inorganic extractables of concern were found in the glass vial and stopper. From the list of extractables found for the primary container a selection was made of potential leachables which were monitored during the leachables study. Studies to determine the leachables from the Type-I glass vials and rubber stoppers were initiated through 36 months of the product to support the shelf-life. Through 6 months storage at accelerated conditions (40 °C/25% RH) and 24 months at 30 °C/35% RH, none of the compounds identified as potential leachables exceeded the 0.05 µg/vial analytical evaluation threshold in the study with the finished product in the primary container closure system. No unexpected leachables were observed by screening methods.

In addition, although the nasal spray device components are not packaged in contact with the finished product and have only brief contact, components which could potentially come in contact with the finished product, including, the cannula, spray pin and the actuator, were also evaluated for extractables and potential leachables. Based on all the data and evaluations for secondary container closure testing, no

extractables of concern were detected and, as there is only momentary contact with the finished product solution, there is no risk of leachables.

A microbial risk assessment was conducted on the finished product that evaluated the potential sources of microbial contamination to the finished product. Adequate risk controls including good manufacturing processes and routine cleaning procedures have been established to reduce the risk of microbial contamination for the esketamine nasal spray finished product. In addition, challenge tests conducted on the finished product solution demonstrate that the finished product solution is bacteriostatic and fungistatic.

Manufacture of the product and process controls

The manufacturing process consists of five main steps: compounding, filtration, filling and stoppering, assembly and packaging. The process is a standard manufacturing process.

Filtration and holding steps are considered critical steps and they are controlled with a bulk solution holding time.

The finished product is a solution produced by conventional manufacturing processes such as mixing and filled into the container closure system. Process validation will be performed prior to commercial distribution of the product. Three consecutive full-scale drug product validation batches will be produced at the commercial facility. Each batch will undergo appropriate testing throughout the manufacturing process to demonstrate that the manufacturing process consistently produces the finished product meeting the proposed specifications. The process validation scheme is provided and found acceptable.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications shown in Table 4 include appropriate tests for this kind of dosage form: appearance, colour and clarity (Ph. Eur.) identification of esketamine (UHPLC, UV), assay (UHPLC), chromatographic purity (UHPLC), enantiomeric purity (HPLC), assay of disodium edetate (UHPLC), pH (Ph. Eur.), particulate matter (Ph. Eur.), osmolality (Ph. Eur.), and fill volume (Ph. Eur.)

Release and shelf-life specifications for the drug-device combination product include tests for: appearance, appearance of solution, colour and clarity, device manual operation, esketamine identification (UHPLC, UV), esketamine assay (UHPLC), assay of disodium edetate, chromatographic purity (UHPLC), enantiomeric purity (HPLC), pH (Ph. Eur.), spray content uniformity, droplet size distribution, particulate matter, osmolality, fill volume and microbiological purity. Specifications of the assembled device were presented.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment and batch analyses data on 3 batches it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

The finished product primary registration lots and relevant clinical lots were monitored during stability studies for weight loss by gravimetrical method for up to 36 months at various conditions. During storage at the normal storage conditions and accelerated conditions, the weight loss is quite negligible as could be expected for product stored in glass vials (0 to 1%). Therefore, the weight loss test is not considered to

be relevant as a stability indicating test in support of the shelf life of the finished product and is not proposed as a commercial specification.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 31 development/clinical batches, 3 registration batches (15 L each) and one scale up batch at proposed commercial batch size (100 L) confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 primary stability batches of a scale size range from 2 – 15 L (or 2 – 15% of the commercial batch size) of the finished product manufactured using esketamine hydrochloride from both proposed active substance manufacturers and stored in vertical inverted, vertical upright and horizontal position for up to 12 months under long term conditions (25 ºC / 40% RH), intermediate conditions (30 ºC / 35% RH, 30 ºC / 75% RH)) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. The stability studies represent a complex matrixing stability strategy plan.

Supportive stability data from 4 batches of filled stoppered vials is also provided. In addition, supportive stability data from 2 Phase 3 clinical development batches of filled stoppered vials and combination product are also provided.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

Samples were tested for specifications as presented in tables 4 and 5. The analytical procedures used are stability indicating. No significant changes have been observed at any of the storage conditions including photostability testing except a slight tendency of the EDTA levels to decrease with storage of the finished product at the different storage conditions, but this trend is not considered a substantial stability related change. The finished product is sufficiently stable when exposed to light.

In accordance with EU GMP guidelines (6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union), any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Based on available stability data, the proposed shelf-life of 2 years and no special storage conditions as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Esketamine is a newly developed non-competitive, subtype non-selective, activity-dependent, N-methyl-D-aspartate receptor (NMDAR) modulator to be delivered nasally for use as a rapidly acting antidepressant in adults with treatment-resistant depression (TRD). Chemically, esketamine (S-ketamine) is the S-enantiomer of ketamine ([R,S]-ketamine) which is the racemic mixture of 50% esketamine and 50% arketamine (R-ketamine). Ketamine is marketed as anaesthetic agent applied via intravenous (IV) or intramuscular (IM) injection. Currently, the rapid antidepressant action of IV infused ketamine in small-scale clinical investigations in humans at subanaesthetic dose levels was published. A typical dosing regimen is 0.5 mg/kg IV infusion over 40 minutes. In the current application JRD developed a nasal spray containing esketamine hydrochloride, the maximum recommended human dose (MRHD) is 84 mg/person resulting in subanaesthetic plasma levels.

The pharmacology programme is based on a review of available published literature on ketamine its isomers and metabolites, complemented by pharmacodynamic studies and a safety pharmacology core battery performed by the Applicant.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Contributors to depression such as stress and other conditions are known to cause structural and functional impairment of synapses in brain regions involved with the regulation of mood and emotional behaviour. The antidepressant activity of esketamine is supposed to be mediated via inhibition of NMDARs which produces a transient increase in glutamate release leading to increases in α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor (AMPAR) stimulation that subsequently increases neurotrophic signalling and restores synaptic function in these brain regions. In order to establish this mode of action the published literature was reviewed and receptor binding studies and functional assays on calcium release were performed with ketamine its isomers and several metabolites.

In terms of NMDAR inhibition, esketamine was found to be the most potent as compared to ketamine, arketamine or their metabolites. In radioligand binding assays in rat cerebral cortex at the phencyclidine (PCP) binding site of the NMDAR, inhibitor constant (Ki)-values for esketamine were in the submicromolar range. This is very close to values described in the literature. In assays performed by JRD, esketamine was approximately 4-fold more potent than arketamine and 6-fold more potent than the metabolite noresketamine (M10). Based on published data esketamine can be considered to be 1.5- to 2.8-fold more potent than ketamine in terms of NMDAR inhibition. Esketamine derived metabolites 2S,6S-HNK (M4), 2S-5,6-DHNK (M9), noresketamine (M10) and keto-reduced 2S,6S-HNK (M19), also bind to NMDARs albeit with Ki-values in the micromolar range.

Esketamine, arketamine and noresketamine (M10) were active in functional fluorescence imaging plate reader (FLIPR) functional assay by measuring calcium flux in CHO cells stably expressing human NMDAR subunits at low micromolar concentrations, while other esketamine metabolites were inactive. No major differences were observed at different subunit compositions indicating that esketamine is a subtype unselective antagonist at the NMDARs. Published studies mainly performed with recombinant NMDAR expression systems (mouse/rat and xenopus oocytes) gave similar results with no differences of activities at different receptor compositions. Notably, in all experiments esketamine was more potent than arketamine under all conditions tested. Similarly, to what was observed in receptor binding studies, patch clamp experiments indicate that esketamine is about 2-3-fold more potent at the NMDAR than arketamine.

No dedicated in vivo studies in animal models of depression with (es)ketamine have been performed by the Applicant. However, the Applicant reviewed published literature of in vivo models of depression performed with either ketamine or esketamine. It is agreed that animal models of depression or antidepressant-sensitive behavioural tests are poorly predictive for the human situation. As reviewed in detail by the Applicant, many studies indicate antidepressant-like effects of ketamine and arketamine in rodent models at higher concentrations which are not reached after intranasal esketamine application while little is reported about esketamine effects in respective models. Despite the lack of in vivo studies with esketamine it is agreed that based on NMDAR activities of esketamine and sufficient evidence of pharmacodynamic activity of esketamine in humans at lower doses, further in vivo studies with esketamine would not add further value to the overall assessment.

Secondary pharmacodynamic studies

In order to address secondary pharmacodynamics, apart from a review of data in the public domain, esketamine, arketamine, ketamine, and esketamine-derived metabolites were screened in vitro in radioligand binding studies for binding on a series of receptors, ion channels and transporters. In addition, these compounds were tested in vitro apart from NMDAR for functional, α7 nicotinic acetylcholine-, and opioid receptor interactions. Furthermore, ketamine-derived metabolites were investigated for their γ-amino butyric acid A (GABAA)-receptor and benzodiazepine (BZD) site binding potential in vitro. In conclusion, it is considered unlikely, that esketamine or its isomers and metabolites display relevant activities at the tested receptors at clinically relevant concentrations as the estimated maximum brain free level of esketamine is 0.8 to 1.3 µM at the MRHD of 84 mg.

Safety pharmacology programme

The safety pharmacology assessment of esketamine was mainly based on dedicated studies performed by JRD or Javelin Pharmaceuticals. No relevant safety issues were identified in these studies. A thorough review on published data on esketamine's effects on the cardiovascular system and CNS was performed. However, it was concluded that in the majority of studies high anaesthetic doses were applied, which are not relevant to the clinical use of esketamine as nasal spray.

2.3.3. Pharmacokinetics

2.3.4. Toxicology

The Applicant has submitted a range of pharmacokinetic studies on absorption, plasma kinetics, distribution, metabolism and excretion of esketamine or ketamine in *in vitro*- and *in vivo* test systems. In addition, enzyme induction and inhibition studies, as well as transporter studies with esketamine and/or

its metabolites were conducted. Finally, several other studies were conducted along the development process of esketamine, including pharmaco/toxicokinetic studies of specific metabolites and their chiral characterization, and a study in simulated gastric fluid to demonstrate the absence of N-nitroso-esketamine formation after intranasal esketamine treatment.

Plasma assays for esketamine and its pharmacologically active metabolite noresketamine were validated according to US Food and Drug Administration (FDA) guidance and European Medicines Agency (EMA) guideline on bioanalytical method validation.

Across species, fast absorption occurred following intranasal administration of esketamine, with peak plasma concentrations reached usually within 30 min. The C_{max} levels of the active metabolite noresketamine were reached somewhat later than those of parent esketamine.

Single dose data are available in mouse, rat and dog. In mice and rats, mean C_{max} values of esketamine and noresketamine were comparable whereas the mean AUC values were higher for the metabolite than for the parent. Plasma kinetics of esketamine and noresketamine were not linear and tended to increase more than dose-proportionally. In the dog, the exposure to noresketamine after intranasal dosing of esketamine was up to 3-fold lower than the exposure to esketamine.

After repeated intranasal dosing of esketamine in mice and rats, noresketamine exposure was higher than that of esketamine, whereas in the dog it was the reverse. In the mouse, exposure to esketamine increased dose-proportionally, repeat-dose exposure was lower (males) and similar (females) than single dose exposure, and there were no major gender differences. In the rat, esketamine AUC values after repeated dosing increased generally less than dose-proportionally in males and in females at higher dose levels (between 3 and 9 mg), but more than dose-proportionally at lower dose levels (between 0.3 and 3 mg). The systemic exposure to esketamine and noresketamine was generally lower after repeated than after single dosing in the 6-month and 2-year study probably due to autoinduction of esketamine and noresketamine metabolising enzymes. The clinical relevance of this finding is unknown. However, in clinical studies no decrease in exposure to esketamine and noresketamine has been observed after repeated intermittent administration compared to single administration. Whereas there was no gender difference for esketamine and noresketamine exposures in the 2-year study and for esketamine in the 6-month study, esketamine and noresketamine AUC values were higher in females than in males in the 3-month study, and the latter was also true for noresketamine in the 6-month study. In the 3- and 9-month dog toxicity studies, exposure increased generally dose-proportionally up to 48 mg, where a plateau was reached. Repeat-dose TK at the end of the 9-month study was similar to TK at the end of the first week, and no consistent gender differences were observed.

In no studies with repeated esketamine application the $t_{1/2}$ values have been calculated. However, it is expected that as for ketamine, the plasma elimination of esketamine is very fast. In a single dose IV study in dogs with esketamine, the $t_{1/2}$ value was 1.29 h. In clinical studies the mean terminal $t_{1/2}$ in plasma of esketamine is 8.1 h.

After IV administration of esketamine in beagle dogs, a very fast clearance (exceeding liver blood flow) and high distribution volume was obtained. The exposure to noresketamine, represented by AUC values, after IV dosing was somewhat lower than the exposure to esketamine with a metabolite-to-parent ratio of 0.77.

In juvenile rats after SC dosing of esketamine, mean esketamine and noresketamine exposure values (C_{max} and AUC) increased largely dose-proportionally. Highest esketamine plasma concentrations were reached at 15 to 30 min. Accumulation was not observed. In general, the systemic exposure of noresketamine was comparable to that of esketamine.

The tissue distribution of (es)ketamine in rats is characterized by a fast equilibrium between plasma and well-perfused tissues leading to a rapid tissue uptake. Brain concentrations of esketamine were

significantly higher compared to those in the systemic circulation. The brain uptake of most more polar metabolites (noresketamine [M10], 2S,6S-HNK [M4], 2S-5,6-DHNK [M9]) was less efficient than for the parent drug. No radioactive tissue distribution or quantitative whole-body autoradiography study was performed for esketamine, which is acceptable due to the non-clinical and clinical data available for racemic ketamine and esketamine for use as anaesthetic.

There is evidence that esketamine crosses the placental barrier.

In blood, esketamine only marginally distributed to blood cells, as was derived from a blood/plasma concentration ratio of about 1 for racemic ketamine in rats, rabbits, dogs, pigs and humans.

The in vitro PPB of racemic ketamine was low in all species investigated (rat, dog, pig, human), and the fraction unbound ranged from about 46 to 72%. The PPB of esketamine was measured in pre-dose plasma samples from 2 Phase I single dose open-label studies with esketamine in male subjects with mild or moderate hepatic and renal impairment compared to matched subjects with normal hepatic or kidney function. The proportion of unbound esketamine in plasma of the cohorts of healthy subjects is on average 54.8% and 55.5%. The free fraction of noresketamine in the cohorts of healthy subjects is on average 56.4% and 62.0%. The degree to which esketamine is bound to plasma proteins is not dependent on hepatic or renal function.

The major in vitro biotransformation pathway of esketamine in liver microsomes and S9 fractions of mouse, rat, dog and human was N-demethylation to noresketamine (M10), followed by hydroxylation on different positions of the cyclohexanone ring, oxidative deamination and keto reduction. The metabolism was similar between the species and no human specific metabolites have been observed.

In vitro data indicated that CYP2B6 was the main enzyme involved in esketamine metabolism in human liver microsomes, with a contribution close to 60%, and the contribution of CYP3A4 was estimated at 35 to 40%. CYP2A6 and CYP2B6 were the major enzymes involved in the downstream metabolism of noresketamine.

In rats, 30 to 41% of the radioactive dose was excreted in the 0-24 h urine following IV administration. By far the major metabolites were noresketamine and hydroxynoresketamine of which the site of oxidation was not further elucidated. Traces of parent esketamine were present in rat urine.

In humans, following a single PO or IV dose, respectively 86.3% and 78.4% of the radiotracer dose was excreted in urine, and less than 2% was excreted in feces. Very low levels of unchanged drug were present in urine (less than 1% of the dose), indicating that esketamine is metabolically cleared. Metabolites where N-demethylation is involved (i.e. sum of noresketamine (M10) and 23 noresketamine-derived metabolites) make up 64.0% and 53.7% of the dose following PO and IV dosing, respectively, of which noresketamine itself accounts for 3.5 % and 2.3 % of the PO and IV dose, respectively. Metabolites where aliphatic hydroxylation is involved (n = 18) make up 44.1% and 36.7% of the dose following PO and IV dosing, respectively, and virtually all (except for M8 and M30) are formed in combination with N-demethylation. Metabolites where keto-reduction is involved (n = 10) make up 23.7% and 21.7% of the dose following PO and IV dosing, respectively, and all are formed in combination with N-demethylation (M21 and M32) and aliphatic hydroxylation. Metabolites where dehydrogenation is involved (i.e. M9 and M14) make up 14.4% and 13.8% of the dose following PO and IV dosing, respectively, and all are formed in combination with N-demethylation. N-Oxidation is mainly seen with noresketamine in combination with glucuronidation to M17, and in total (+M24 and M25) makes up 12.3% and 9.4% of the dose following PO and IV dosing, respectively. Metabolites where aromatic hydroxylation is involved (n = 4) make up 6.3% and 4.6% of the dose following PO and IV dosing, respectively, and all are formed in combination with N-demethylation and aliphatic hydroxylation (excluding M15 which does not contribute to the mass balance).

Based on group mean AUC, the 10% threshold of the total exposure to drug and metabolites, is only exceeded for noresketamine (M10), accounting for 12 to 14% of the total drug-derived exposure in the systemic circulation of humans. All other major phase-1 metabolites and all phase-2 metabolites represented less than 10% of the total drug related material in plasma. Similar results were obtained for plasma following PO and IV administration. Several other metabolites represent >25% of esketamine AUC following a nasal dose of 84 mg esketamine, and were therefore tested for their potential to inhibit enzymes or transporters. This was the case for 2S,6S-HNK (M4), 2S,5S-HNK (M5), 2S-5,6-DHNK (M9), noresketamine (M10) and keto-reduced 2S,6SHNK (M19).

Noresketamine (M10) was routinely measured in all clinical trials and in all pivotal in vivo nonclinical safety studies.

Renal is the main route of excretion of esketamine, mainly as its metabolites. After oral and IV radiolabelled esketamine administration to healthy male subjects, 86.3% and 78.4% of total radioactivity was excreted in urine, respectively. Only 1.70% and 1.81% of the oral and IV radiolabeled doses was recovered in feces, respectively, indicating that biliary excretion is not important in man. Less than 1% of the dose is excreted as parent esketamine, the majority of the radiolabeled dose is excreted under the form of numerous metabolites. Over a time period of 168 h the total radioactivity recovered in human feces and urine was 88.0% and 80.3% after PO and IV administration, respectively.

After IV administration of ^{14}C-labeled esketamine in human, the mean terminal $t_{1/2}$ of the total radioactivity (59.9 h) in plasma was much longer than the terminal $t_{1/2}$ values of esketamine (8.1 h) and noresketamine (M10; 9.8 h). The underlying mechanism leading to this is not completely clear. To some extent, this may be indicative for a slow redistribution from tissues, which has been described for ketamine in dogs.

There is evidence that esketamine is excreted in milk.

The induction potential of esketamine and its major circulating metabolites on CYP450 enzymes is expected to be low. Esketamine and its major circulating metabolites clearly had no effect on CYP1A2 in human hepatocytes. There were some inducing effects of esketamine on CYP3A4 and CYP2B6 in vitro in human hepatocytes.

In vitro, esketamine and its major circulating metabolites had a low inhibition potential against CYPs and UGTs. Only noresketamine showed a weak inhibition on CYP3A4 (IC_{50} = 1.9 µM) with testosterone as substrate but not for midazolam and nifedipine as CYP3A4 substrates.

Esketamine and its pharmacologically active metabolite noresketamine were not a substrate of investigated transporters (P-gp, BCRP, OATP1B1, OATP1B3 for esketamine, and P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2 for noresketamine). Given the C_{max} values of 0.63 µM for esketamine in humans after an intranasal dose of 84 mg, and with about 50 % unbound to plasma proteins, the concentration of esketamine of 0.3 µM tested in these experiments was in the same range as the concentration obtained in human after a therapeutic dose of esketamine.

Esketamine and none of its major circulating phase-1 metabolites (M10, M9, M4, M5 and M19) were found to be a relevant inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2K transporters.

Single dose toxicity

Single and repeated intranasal dosing of esketamine was investigated in rats and dogs, because of similarities in metabolic pathways of esketamine to those in humans, former experience with ketamine in

these animal species and presence of the pharmacologic target in both species. Single dose studies were also performed with ketamine as well as single and repeat-dose studies with (es)-ketamine using different ways of application. The clinical formulation of esketamine was used in a single dose toxicity study in dogs and in the long-term toxicity studies with esketamine in rats and dogs.

In the single dose studies with (es)-ketamine mainly CNS-related clinical signs were observed which could be attributed to the exaggerated pharmacology of esketamine and ketamine. Toxicokinetic parameters obtained within the single dose study in dogs showed low oral and relatively high intranasal bioavailability of esketamine (approximately 50 %).

Repeat dose toxicity

After repeated intranasal dosing of esketamine to rats and dogs, again dose-dependent CNS-related clinical signs due to the pharmacologic action of esketamine were observed in all dose groups. The 3-month studies included high dose recovery groups. Recovery of CNS-signs was shown in both animal species. CNS-related clinical signs were also frequently observed during phase 2 and phase 3 clinical trials with esketamine.

Common findings in dogs and rats after intranasal application of esketamine were histopathological changes in the nasal cavity. There was no evidence of ulceration, basal cell hyperplasia/metaplasia or inflammatory response in the nasal cavity. Therefore, nasal changes were considered to represent a local response to the repeated intranasal instillation of material, rather than an indication of toxicity.

Slight increases in heart rate were seen in the 3-month study in dogs in all treated animals; increases were not reversible in females. Increases in heart rate were also observed in safety pharmacology studies. Changes in cardiovascular parameters, like increases in heart rate, are known effects of (es)-ketamine in humans.

In summary, main findings after repeated intranasal application of esketamine to rats and dogs are pharmacology related clinical signs of the CNS and histopathological changes attributed to mild irritation provoked by repeated intranasal application. Exposures at the NOAEL of the intranasal studies were in general around human therapeutic exposure at the maximum recommended human dose (based on AUC). Clinical signs and changes in the nasal cavity were observed below human exposures.

A 2-week study with oral application of esketamine to rats showed hepatotoxicity in male rats at exposures corresponding to human therapeutic exposures based on AUC. Hepatotoxicity was observed with ketamine treatment in clinical use. However, hepatotoxicity of esketamine was only observed in male rats from the high dose group and not associated with increased liver enzymes or changes in bilirubin. Kidney toxicity was also observed in all treated males and was discussed to be due to α2µ-globulin nephropathy which is a male rat specific finding. Esketamine exposures at the NOAEL for female rats after oral application were about 5-times based on AUC at the MRHD.

Several repeat-dose toxicity studies have been performed with ketamine by Javelin Pharmaceuticals. Detailed study reports were not available for these studies; therefore, they are only considered as supportive for the assessment of esketamine. Taken together, CNS-related clinical signs, changes indicative of nasal irritation at large dose volumes, and bladder changes were observed in all species treated with ketamine. Beside bladder changes, these findings are fully in line with observations from repeat-dose toxicity studies with esketamine. After intranasal esketamine exposure changes in the urinary bladder were only observed in the 3-month dog study in one animal each of the mid and high dose group. Since findings had dissimilar histopathological characteristics, were not dose-related and were not observed after recovery, they were not considered treatment-related. However, literature reports

suggest that chronic ketamine abuse may be associated with ulcerative cystitis. The urinary tract symptoms observed with esketamine in clinical trials in general appeared to be reversible and did not suggest a risk of permanent bladder damage. Otherwise, the toxicity studies indicate no differences in the toxicities of ketamine and esketamine.

Genotoxicity and carcinogenicity

Ketamine was negative in a GLP-conform Ames test and an in vivo micronucleus test in mice performed by Javelin but was found to be mutagenic in a GLP-conform in vitro micronucleus test after metabolic activation performed by the same company. Subsequent in vivo testing of ketamine by Javelin in a micronucleus test performed in mice after IP dosing yielded negative results. To follow up the positive in vitro results JRD performed an in vitro micronucleus test with esketamine in TK6 lymphoblastoid cells, which again gave a positive result after metabolic activation. In accordance with ICH S2(R1) a second in vivo assay was conducted covering a different endpoint (Comet assay in rat liver). Esketamine was not genotoxic in the Comet assay following IV infusion of esketamine up to 50 mg/kg/day on three consecutive days with a mean concentration based safety margin of approximately 39 for esketamine and 22 for noresketamine to the MRHD at 84 mg/day. Overall, esketamine can be considered as non-genotoxic in vivo. The reason for the positive in vitro findings was not further evaluated by the Applicant but was assumed to be mediated by radical intermediates formed during metabolism in the absence of GSH in in vitro tests (see section pharmacokinetics for details). Based on the negative results of the in vivo genotoxicity tests and the negative carcinogenicity studies, it is considered acceptable not to further follow up these positive findings.

Esketamine was not carcinogenic after nasal instillation up to the maximum feasible dose in a long-term carcinogenicity study in rats. Safety margins to the MRHD of 84 mg for esketamine and noresketamine were low. The C_{max}- and AUC-based exposure ratios were approximately 1.2- and 0.5-fold, respectively, for esketamine, and 1.6- and 0.5-fold, respectively, for noresketamine (M10). It is agreed, that higher nasal dosing of rats is not feasible. In a subsequent SC 26-week carcinogenicity study in transgenic Tg.rasH2 mice no increase in tumour incidences was observed. Safety margins to the MRHD of 84 mg for esketamine and noresketamine were higher than in the rat carcinogenicity study. At 40 mg/kg/day, the C_{max}- and AUC-based safety margins for esketamine compared to the 84 mg MRHD were approximately 20- and 4-fold, respectively. For noresketamine (M10), these margins were approximately 16- and 4-fold, respectively. Based on the negative in vivo genotoxicity and carcinogenicity studies, esketamine is not considered to pose a carcinogenic risk to humans.

Reproduction Toxicity

In a rat fertility study with intranasal administered esketamine (up to 9 mg/day), no adverse effects on fertility and reproductive capacity and performance were found. Rat and rabbit embryo-foetal developmental toxicity studies were conducted with intranasal administered ketamine up to 150 and 50 mg/kg/day, respectively. In the rat, 15 mg/kg/day was considered the NOEL for maternal toxicity, and a dose of 150 mg/kg/day was considered the NOEL for developmental toxicity. In the rabbit, the highest dose level of 100 mg/kg/day was reduced to 50 mg/kg/day due to mortality. The dose of 10 mg/kg/day was considered the NOAEL for maternal and developmental toxicity in rabbits, solely driven by a decrease in foetal body weight at the mid dose in the presence of maternal toxicity (i.e., decreases in maternal food consumption and corrected maternal body weight gain). No statistically significant differences in external, visceral and skeletal malformations or variations were seen in foetuses. IV bridging TK studies demonstrated that esketamine comprised approximately 49 and 30% of the systemic exposures in

ketamine-treated pregnant rats and rabbits, respectively. Taken together, intranasal ketamine did not lead to reproductive toxicity.

In pre- and postnatal development in the Crl:CD(SD) rat with esketamine mainly CNS-related clinical signs were observed which could be attributed to the exaggerated pharmacology of esketamine. The NOAEL for the pre- and postnatal survival, growth, maturation, neurobehavioral development and reproductive performance of the F0 offspring was considered to be 9 mg/rat/day. In the F1 offspring at 9 mg/rat/day a dose dependent delay in Preyer response reflex was detected. However, histological evaluations showed that the brain, including the neuroanatomical structures responsible for the auditory pathway, was not affected.

NMDAR antagonists, including ketamine, are well known to induce apoptotic neurodegeneration in the developing neonatal rodent brain. Published data indicate that parenterally administered ketamine exerts developmental neurotoxicity in pregnant rats and monkeys, since it induces neuronal cell death in the brain of the offspring. Ketamine-induced neuronal cell death was also observed with early postnatal IP or SC treatment of rat and mice pups, a period of rapid brain growth. This period of brain development translates into the third trimester of human pregnancy. A similar risk of developmental neurotoxicity cannot be excluded for esketamine. It should be considered that Spravato is designated for long-term medication. Therefore, the use of esketamine during pregnancy is not recommended. Milk transfer of esketamine was not investigated. Animal milk transfer has been reported for racemic ketamine. For safety reasons it is advised not to take Spravato while breast-feeding or to discontinue breast-feeding.

Toxicokinetic data

Fast absorption occurred after intranasal administration of esketamine across species. Higher noresketamine (M10) than esketamine exposures were observed after repeated intranasal dosing in rats of both sexes whereas AUC values were higher for esketamine and noresketamine (M10) in females than in males. In dogs, esketamine exposures were generally higher than noresketamine (M10) exposures in both sexes and no important sex-related differences in exposures were observed. In the repeat-dose toxicity studies with esketamine, noresketamine (M10) was only adequately covered in the rat.

Exposure levels to metabolites M4 and M19 were compared for the long-term toxicity studies with esketamine in rats and dogs to human exposures at the MRHD. Exposure to M4 in rats exceeded human exposures whereas exposures to M4 in dogs were below human exposures based on AUC. Exposures to M19 were lower to significantly lower, in both species compared to humans. However, based on group mean AUC, the 10% threshold of exposure to drug and metabolites was only exceeded for noresketamine. All other metabolites represented less than 10% of the total drug related material.

Interspecies differences in local exposure to the nasal cavity were calculated. In long-term studies, rats received approximately the same dose volume per nasal cavity surface area as humans at the MRHD, while dogs received approximately half of it.

Local Tolerance

No specific studies were performed to investigate the local tolerance of intranasal application of esketamine. Local tolerance was evaluated within the intranasal repeat-dose studies in rats and dogs.

Other toxicity studies

Neurotoxicity studies

The neurotoxic potential of intranasal administered esketamine was investigated by detailed histopathological examination of the brain in a series of dedicated single dose and 14-day repeat-dose neurotoxicity studies in adult rats. The NMDAR antagonist [+]MK-801-maleate (dizocilpine) was used as the positive control in these studies. No histopathological brain lesions were noted even upon high exposures. Furthermore, in the 6- month rat and 9-month dog repeat-dose toxicity studies with intranasal administered esketamine, no evidence of neurotoxicity was found as judged by examinations of brain histopathology, and neurobehavioral endpoints in the rat and neurological assessments in the dog, respectively. The pre- and postnatal developmental toxicity study with intranasal esketamine in rats did not reveal neurotoxicity findings either.

Twice weekly SC administration of esketamine hydrochloride up to 150 mg /kg over a period of 14 days in juvenile rats led to prominent but transient clinical observations, but did not produce any evidence of neuropathological lesions after histopathological examination of the brains. In 6-month repeat-dose toxicity study in rats and 9-month repeat-dose toxicity study in dogs no neurological toxicity in juvenile animals was observed. However, Spravato is at present only indicated for adult patients.

In single dose neurotoxicity studies conducted with SC-dosed ketamine in adult rats, transient neuronal vacuolation was observed in female rats at the highest dose tested (60 mg/kg); there were no signs of neuronal necrosis. However, there was no evidence of vacuolation at 24 and 72 h post-dose nor was neuronal degeneration observed at any time point in this group. Also there was no apparent impact on motor skills or learning/memory functions.

Published data indicate that ketamine also exerts neurotoxicity in juvenile rats and monkeys inducing neuronal cell death in the brain.

Dependence

A human abuse potential study was conducted, in which intranasal esketamine was compared with an IV infusion of ketamine. This human study supersedes an animal study.

Ketamine is scheduled because of its well-established abuse potential. Given the pharmacological analogy, a similar risk is anticipated for esketamine.

Impurities

The synthesis impurity T003641 is considered to be safe up to the qualification threshold of NMT 0.2% and was negative in an Ames assays and studies on skin erosion and skin irritation and a local lymphnode assay.

Starting material T003642 concentration dependently increased reverse mutations in the E coli strain WP2uvrA in the absence and presence of S9 mix in an Ames assay and is thus considered to be mutagenic. T003642 is controlled according to ICH M7(R1) as described in the Quality AR.

2.3.5. Ecotoxicity/environmental risk assessment

The active substance is not expected to pose a risk to the surface water, groundwater as all risk quotients are below 1. An assessment of the risk to the terrestrial compartment is considered not necessary. Esketamine hydrochloride is 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). A risk to sediment organisms is not expected.

Table 1. Summary of main study results

Substance (INN/Invented Name): Esketamine hydrochloride			
CAS-number (if available): 33643-47-9			
PBT screening		Result	**Conclusion**

Bioaccumulation potential- log K_{ow}	OECD107	log Dow at pH 9 = 2.06			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	log Dow at pH 9 = 2.06			not B
Persistence	DT_{50}	738.4 days in sediment (12°C)			**vP**
Toxicity	NOEC or CMR	98.8 µg/L			not T
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, refined with treatment regime	0.038	µg/L			> 0.01 threshold (Y)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	Kf_{oc} sandy loam = 106 L/kg Kf_{oc} silt loam = 107 L/kg Kf_{oc} loam = 417 L/kg Kf_{oc} sludge = 9 L/kg Kf_{oc} sludge = 11 L/kg			Terrestrial studies not triggered
Ready Biodegradability Test	OECD 301B	1.4% (28d), not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 24.3d and 43.5d (dissipation) $DT_{50, sediment}$ = 537.8d and 738.4d $DT_{50, whole\ system}$ = 294.5d and 490.8d % shifting to sediment = 54% and 61%			All DT_{50} normalised to 12°C Very persistent (vP) in sediment
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Pseudokirchneriella subcapitata*	OECD 201	NOEC	14700	µg/L	*Pseudokirchner-iella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	98.8	µg/L	Significant increasing effects on reproduction (72-30%)
Fish, Early Life Stage Toxicity Test/*Danio rerio*	OECD 210	NOEC	341	µg/L	*Danio rerio*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	100000	µg/L	
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC	87.1	mg/kg dw	*Chironomus riparius* Normalised to 10% Corg

2.3.6. Discussion on non-clinical aspects

The Applicant has provided satisfactory response to all issues raised during the procedure.

From the non-clinical point of view the Applicant has investigated the pharmacodynamic and pharmacokinetic properties and the toxicity of esketamine hydrochloride to a sufficient extend to support the indication applied for.

2.3.7. Conclusion on the non-clinical aspects

From the preclinical point of view, there are no remaining issues and Marketing Authorisation can be granted.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1:	**Completed Phase 2 Efficacy Studies of Adjunctive Intranasal and Intravenous Ketamine and Esketamine for Indications Relevant to Major Depressive Disorder, Including Both Treatment-resistant Depression and Imminent Risk for Suicide**	
Full Study Code	**Study Title (ie, Design)**	**Double-blind Efficacy Populations [a]**

ESKETIV TRD2001	"A double-blind, double-randomization, placebo-controlled study of the efficacy of intravenous esketamine in adult subjects with treatment-resistant depression"	Total: 30 subjects, intravenous treatment for 1 week at 2x per week: [b]
		Day 1
		• Placebo: 10 subjects
		• Esketamine: 9 subjects at 0.20 mg/kg, 11 subjects at 0.40 mg/kg
		
		Day 4
		• Treatments to subjects who were in the Day 1 placebo group;
		  ○ Esketamine: 3 subjects at 0.20 mg/kg, 7 subjects at 0.40 mg/kg
		• Treatments to subjects who were in the Day 1 esketamine 0.20 mg/kg group;
		  ○ Esketamine: 6 subjects at 0.20 mg/kg, 3 subjects at 0.40 mg/kg
		• Treatments to subjects who were in the Day 1 esketamine 0.40 mg/kg group;
		  ○ Esketamine: 11 subjects at 0.40 mg/kg

KETIV TRD2002	"A double-blind, randomized, placebo-controlled, parallel group, dose frequency study of ketamine in subjects with treatment-resistant depression"	Total: 67 subjects, intravenous treatment for 4 weeks: [b] • Placebo: 16 subjects at 2x per week, 16 subjects at 3x per week • Ketamine 0.50 mg/kg: 18 subjects at 2x per week, 17 subjects at 3x per week
ESKETIN TRD2003	"A double-blind, doubly-randomized, placebo-controlled study of intranasal	Total: 108 subjects, intranasal treatment for 1 week each period at 2x per week: [b]

Table 1:	**Completed Phase 2 Efficacy Studies of Adjunctive Intranasal and Intravenous Ketamine and Esketamine for Indications Relevant to Major Depressive Disorder, Including Both Treatment-resistant Depression and Imminent Risk for Suicide**		
Full Study Code	**Study Title (ie, Design)**	**Double-blind Efficacy Populations [a]**	
	esketamine in an adaptive treatment protocol to assess safety and efficacy in treatment-resistant depression"	• Panel A, Period 1 (67 randomized): – Placebo: 33 subjects – Esketamine: ○ 28 mg: 11 subjects ○ 56 mg: 11 subjects ○ 84 mg: 12 subjects • Panel A, Period 2 (nonresponders to placebo in Period 1 were rerandomized): – Placebo: 6 subjects – Esketamine: ○ 28 mg: 8 subjects ○ 56 mg: 9 subjects ○ 84 mg: 5 subjects	• Panel B, Period 1 (41 randomized): – Placebo: 21 subjects – Esketamine: ○ 14 mg: 11 subjects ○ 56 mg: 9 subjects • Panel B, Period 2 (nonresponders to placebo in Period 1 were rerandomized): – Placebo: 5 subjects – Esketamine: ○ 14 mg: 5 subjects ○ 56 mg: 3 subjects
ESKETIN SUI2001	"A double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of intranasal esketamine for the rapid reduction of the symptoms of major depressive disorder, including suicidal ideation, in subjects assessed to be at imminent risk for suicide"	Total: 66 subjects, all subjects had standard of care antidepressant treatment, inpatient hospitalization, and intranasal treatment for 4 weeks at 2x per week: • Placebo nasal spray (permitting a one-time decrease in dose after Day 1): 31 subjects • Esketamine 84 mg (permitting a one-time decrease to 56 mg after Day 1): 35 subjects	

[a] The efficacy analyses were performed with the intent-to-treat analysis sets.
[b] After the double-blind study periods shown here, these studies also offered optional open-label treatment periods. The open-label treatment regimens were as follows:
- In Study TRD2001, the dosing magnitude was 0.40 or 0.30 mg/kg, the frequency was 2x per week, and the duration was 2 weeks.
- In Study TRD2002, the dosing magnitude was 0.50 mg/kg, the frequency was 2x or 3x per week, and the duration was 2 weeks.
- In Study TRD2003, the dosing magnitude started at 56 mg, with options for later titration down or up. The duration was up to 9 weeks in Panel A or up to 2 weeks in Panel B, during which time the frequency was 2x per week for 2 weeks (ie, 4 sessions at that frequency), then reduced to 1x per week for 3 weeks (ie, 3 sessions at that frequency), then reduced to every 2 weeks for the next 4 weeks (ie, 2 sessions at that frequency).

Sources: Clinical Study Reports (Mod5.3.5.1/TRD2001, Mod5.3.5.1/TRD2002, Mod5.3.5.1/TRD2003, and Mod5.3.5.1/SUI2001).

Table 2: Completed Phase 3 Efficacy Studies of Intranasal Esketamine in Treatment-resistant Depression

Full Study Code	**Study Title** (ie, Design; With *Emphasis* on Important Differences)	**Primary Objective**	**Esketamine Treatment**		**Efficacy Endpoints as Prespecified in the Protocol [b]**		**Efficacy Populations [c]**
			Dose [a]	**Duration**	**Primary**	**Secondary**	
Short-term Studies With DB Induction Phases							
ESKETIN-TRD3002	"A randomized, double-blind, multicenter, active-controlled study to evaluate the efficacy, safety, and tolerability of *flexible* doses of intranasal esketamine plus an oral antidepressant in *adult* subjects with treatment-resistant depression"	"To evaluate the efficacy of switching adult subjects with TRD from a prior antidepressant treatment to flexibly dosed intranasal esketamine plus a newly initiated oral antidepressant compared with switching to a newly initiated oral antidepressant … plus intranasal placebo …" [see primary efficacy endpoint column].	56 or 84 mg [a] (flexible); twice a week.	In DB induction phase: 4 weeks.	In DB induction phase: MADRS, change in total score from baseline to Day 28 or induction endpoint.	In DB induction phase: Key secondary: • MADRS-defined onset of response (Day 2 maintained through Day 28). • Change from baseline to Day 28 or induction endpoint in SDS total score and PHQ-9 total score. Other secondary: • Proportion of MADRS response and remission at Day 28 or induction endpoint. • Change from baseline to Day 28 or induction endpoint for CGI-S, GAD-7, and	In DB induction phase: • 114 subjects in intranasal Esk + oral AD group. • 109 subjects in the oral AD + intranasal placebo group.

Table 2: Completed Phase 3 Efficacy Studies of Intranasal Esketamine in Treatment-resistant Depression							
Full Study Code	**Study Title** (ie, Design; With *Emphasis* on Important Differences)	**Primary Objective**	**Esketamine Treatment**		**Efficacy Endpoints as Prespecified in the Protocol** [b]		**Efficacy Populations** [c]
			Dose [a]	**Duration**	**Primary**	**Secondary**	
						EQ-5D-5L.	
ESKETIN-TRD3001	"A randomized, double-blind, multicenter, active-controlled study to evaluate the efficacy, safety, and tolerability of *fixed* doses of intranasal esketamine plus an oral antidepressant in *adult* subjects with treatment-resistant depression"	"To evaluate the efficacy of switching adult subjects with treatment-resistant depression from a prior antidepressant treatment to intranasal esketamine plus a newly initiated oral antidepressant compared with switching to a newly initiated oral antidepressant … plus intranasal placebo …" [see primary efficacy endpoint column].	56 or 84 mg [a] (fixed); twice a week.	In DB induction phase: 4 weeks.	In DB induction phase: MADRS, change in total score baseline to the Day 28 or induction endpoint.	In DB induction phase: Key secondary: • MADRS-defined onset of response (Day 2 maintained through Day 28). • Change from baseline to the Day 28 or induction endpoint in SDS total score and PHQ-9 total score. Other secondary: • Proportion of MADRS response and remission at the Day 28 or induction endpoint. • Change from baseline to the Day 28 or induction endpoint for CGI-S, GAD-7, and EQ-5D-5L.	In DB induction phase: • In intranasal Esk + oral AD groups: – 115 subjects in Esk 56 mg group. – 114 subjects in Esk 84 mg group. • 113 subjects in oral AD + intranasal placebo group.
ESKETIN-TRD3005	"A randomized, double-blind, multicenter, active-controlled study to evaluate the efficacy, safety and tolerability of flexible doses of intranasal esketamine plus an oral antidepressant in *elderly* subjects with treatment-resistant depression"	"To evaluate the efficacy of switching elderly subjects with TRD from a prior antidepressant treatment (to which they have not responded) to flexibly dosed intranasal esketamine (28 mg, 56 mg or 84 mg) plus a newly initiated oral antidepressant, compared with switching to a newly initiated oral antidepressant … plus intranasal placebo…" [see primary efficacy endpoint column].	28, 56, or 84 mg [a] (flexible); twice a week.	In DB induction phase: 4 weeks.	In DB induction phase: MADRS, change in total score from baseline to the Day 28 or induction endpoint.	In DB induction phase: • Proportion of MADRS response and remission at the Day 28 or induction endpoint. • Change from baseline to the Day 28 or induction endpoint in CGI-S and EQ-5D-5L.	In DB induction phase: • 72 subjects in intranasal Esk + oral AD group. • 65 subjects in oral AD + intranasal placebo group.

Table 2: Completed Phase 3 Efficacy Studies of Intranasal Esketamine in Treatment-resistant Depression

Full Study Code	Study Title (ie, Design; With *Emphasis* on Important Differences)	Primary Objective	Esketamine Treatment		Efficacy Endpoints as Prespecified in the Protocol [b]		Efficacy Populations [c]
			Dose [a]	Duration	Primary	Secondary	
Long-term Studies With OL Induction Phases							
ESKETIN-TRD3003	"A randomized, double-blind, multicenter, active-controlled study of intranasal esketamine plus an oral antidepressant for *relapse prevention* in treatment-resistant depression"	"To assess the efficacy of intranasal esketamine plus an oral antidepressant compared with an oral antidepressant … plus intranasal placebo in delaying relapse of depressive symptoms in subjects with treatment-resistant depression who are in stable remission after an induction and optimization course of intranasal esketamine plus an oral antidepressant."	56 or 84 mg [a] (flexible); twice a week.	In OL induction phase: 4 weeks.	In OL induction phase: Not applicable.	In OL induction phase: Not applicable.	In OL induction phase: 430 subjects in intranasal Esk + oral AD group.
			56 or 84 mg; weekly for 4 weeks, then weekly or every other week for 8 weeks.	In DB/OL optimization phase: [d] 12 weeks.	In DB/OL optimization phase: Not applicable.	In DB/OL optimization phase: Not applicable.	In DB/OL optimization phase: 452 subjects in intranasal Esk + oral AD group.
			56 or 84 mg; weekly or every other week.	In DB maintenance phase: variable duration, medians ~10 weeks in placebo groups & ~20 weeks in Esk groups (see last column).	In DB maintenance phase: Time to relapse for subjects in stable remission after treatment with esketamine in earlier phases.	In DB maintenance phase: • Time to relapse for subjects showing stable response (but not showing stable remission) after treatment with esketamine in earlier phases. • Change from the maintenance phase baseline to the maintenance phase endpoint in MADRS, PHQ-9, CGI-S, GAD-7, EQ-5D-5L, and SDS.	In DB maintenance phase: • In intranasal Esk + oral AD group: – 90 stable remitters. – 62 stable responders. • In oral AD + intranasal placebo group: – 86 stable remitters. – 59 stable responders.
ESKETIN-TRD3004	"An *open-label, long-term*, safety and efficacy study of intranasal esketamine in treatment-resistant depression"	"To assess the long-term safety and tolerability of intranasal esketamine plus a newly initiated oral antidepressant in subjects with TRD…"	28,[a] 56, or 84 mg [a] (flexible); twice a week.	In OL induction phase: [d] 4 weeks.	Across phases: Not applicable.	Across phases: • Change from baseline of either phase, for the following: MADRS, PHQ-9, CGI-S, GAD-7, EQ-5D-5L, and SDS. • MADRS and PHQ-9 response and remission rates over time, from the induction phase baseline.	In OL induction phase: 779 subjects in intranasal Esk + oral AD group.
			28,[a] 56, or 84 mg; weekly for 4 weeks, then weekly or every other week.	In OL optimization/ maintenance phase: [e] up to 48 weeks; median = 29 weeks.			In OL optimization/ maintenance phase: 603 subjects in intranasal Esk + oral AD group.

Key: AD = antidepressant; CGI-S = Clinical Global Impression - Severity; DB = double-blind; EQ-5D-5L = European Quality of Life Group, 5-Dimension, 5-Level; GAD-7 = Generalized Anxiety Disorder, 7-item (scale); MADRS = Montgomery-Asberg Depression Rating Scale; OL = open-label; PHQ-9 = Patient Health Questionnaire, 9-item; SCE = Summary of Clinical Efficacy; SDS = Sheehan Disability Scale; TRD = treatment-resistant depression.

[a] **Dosing:**

- Magnitude:
  Start vs end, induction phases: In all studies, all esketamine treatment groups, and all age groups, the starting dose was lower than or equivalent to the ending dose. For example, in studies of 56 or 84 mg, all subjects started with 56 mg. Because early titration is more relevant to tolerability than to efficacy, the early titration schedules are not detailed here.
  Age-specific and country-specific options: In Study TRD3004, the 28-mg dose was applicable only to subjects aged ≥65 years and to subjects in Korea.
- Frequency, optimization and maintenance phases: the frequency of intranasal dosing was individualized (based on a MADRS-driven algorithm) to once weekly or every other week to achieve the lowest dosing frequency for an individual subject that could sustain initial improvements in depressive symptomatology. The treatment algorithms are described in the Clinical Study Reports (CSRs) and in Appendix 2 of this SCE.

Table 2: Completed Phase 3 Efficacy Studies of Intranasal Esketamine in Treatment-resistant Depression							
			Esketamine Treatment		Efficacy Endpoints as Prespecified in the Protocol [b]		
Full Study Code	Study Title (ie, Design; With *Emphasis* on Important Differences)	Primary Objective	Dose [a]	Duration	Primary	Secondary	Efficacy Populations [c]

[b] **Efficacy baselines and endpoints:** This column is primarily populated from the protocols, under "Study Evaluations" (Section 9 in the protocols for all 5 studies), subsection "Efficacy" (Sections 9.2 or 9.3 in the protocols), subsection "Endpoints" or "Efficacy Endpoints." Definitions of baselines and endpoints are provided in the protocols and the statistical analysis plans. The short-term studies with double-blind induction phases had prespecified 2 types of analyses: a mixed-effects model using repeated measures (MMRM) at Day 28, and an analysis of covariance (ANCOVA) model using last observation carried forward (LOCF) data at the double-blind induction phase endpoint. Within the multiphase studies and when transferring across the studies, more than 1 baseline was applicable (ie, baseline per each phase) and more than 1 corresponding endpoint was applicable.

[c] **Efficacy populations**: : This column provides the number of subjects in the full analysis sets used for the efficacy summaries and analyses. The full analysis sets in studies TRD3002, TRD3001, TRD3005 and TRD3003 included subjects who received at least 1 dose of intranasal study agent and 1 dose of oral antidepressant during the relevant phase. For study TRD3004 the full analysis sets included subjects who received at least one dose of intranasal study agent or 1 dose of oral antidepressant during the relevant phase. Complete definitions of analysis sets are provided in the CSRs, and have phase-specific labels clarified in parentheses where applicable.

[d] **Transfer of subjects between short-term and long-term studies or phases:** The footnoted phases in the long-term Studies TRD3003 and TRD3004 show the entry points for eligible subjects who had completed the short-term Studies TRD3002, TRD3001, or TRD3005.

Note: The screening/prospective observational phases and the follow-up phases are excluded from this table, since they are not highly relevant to efficacy.

Sources: The CSRs, protocols (which are in Appendix 1 of each CSR), and statistical analysis plans (which are in Appendix 9 of each CSR) for each study (Mod5.3.5.1/TRD3002, Mod5.3.5.1/TRD3001, Mod5.3.5.1/TRD3005, Mod5.3.5.1/TRD3003, and Mod5.3.5.2/TRD3004).

2.4.2. Pharmacokinetics

The pharmacokinetics of esketamine were investigated in 19 PK studies. One study was conducted in healthy Japanese subjects (TRD1002) and one in healthy Japanese, Chinese and Korean subjects (TRD1008). Subjects with a history of allergic rhinitis were enrolled to evaluate the effects of this condition and common comedication on the PK and tolerability of nasal esketamine (TRD1007). In addition, the PK of esketamine was evaluated in subjects with mild or moderate liver impairment (TRD1011), mild, moderate or severe renal impairment (TRD1014) and in elderly subjects (TRD1003, TRD1012, TRRD1018). To evaluate the interaction potential of esketamine four drug-drug interaction studies were conducted (TRD1010, TRD1008, TRD1020, TRD1009).

Methods

Non-chiral LC-MS/MS assays for the quantification of esketamine and noresketamine in human heparin plasma and urine were validated and used. In general, selected method and validation are acceptable.

Rich and sparse plasma concentration data of esketamine and noresketamine obtained form 13 clinical studies (Phases 1, 2 and 3) were pooled for population PK analysis. in order to characterise the PK of esketamine and its major metabolite noresketamine after intranasal (IN), IV or PO administration of single and multiple doses of esketamine to healthy volunteers and TRD patients. It is questionable if the low proportion of the data collected after PO and IV administration compared to the sample size after nasal administration allows an adequate estimation of the PK for all three routes of administration.

Absorption

The intended route of application for esketamine is to be intranasally via a disposable spray device containing 200 µl aqueous solution of esketamine HCl at an esketamine base equivalent concentration of 140 mg/mL. Esketamine is rapidly absorbed when administered into the nasal cavity as evidenced by the presence of the drug in plasma at the first sampling time of 7 minutes, following a 28-mg dose (TRD1001, TRD1002, TRD1003, TRD1011, and TRD1014). Nevertheless, application with a nasal device is a new application route whose impacts need to be assessed thoroughly. Physiologically based based Pharmacokinetics modelling (PBPK) data indicate, that 54% of intranasally administered esketamine is absorbed through the nasal cavity and 46% is swallowed with increasing fraction of swallowed

esketamine for every subsequent spray device. In phase I study TRD1009 esketamine's bioavailability was estimated to be 48% for intranasal application (84 mg esketamine) and 14 % for oral application. The expected absolute bioavailability, based on pharmacokinetic modelling, is slightly higher for the 28 mg and 56 mg doses of intranasal esketamine relative to the 84 mg dose. For every 28 mg dose step one spray in each nostril needs to be applied. Pharmacokinetic studies performed used different dosing regimens ranging from 28 mg to 112 mg intranasal esketamine, whereby 56 mg and 84 mg is intended to be the recommended starting dose for patients with TRD below the age of 65. In study TRD1001 the effects of different handling instructions have been investigated (pause time between each device 5 and 10 minutes, application angle, sniffing). Although PK data with altered instructions were in parts notably higher compared to administration without application instructions no statistical analysis of comparison was conducted. In addition, the effects of handling failures like application of two sprays in one nostril or sneezing as identified in human factors validation study DS-TEC-127301 on esketamine exposure were discussed in detail. Appropriate reflection of these data is presented in the SmPC and PL. Presented bioequivalence studies for formulation changes used inadequate cohorts and were not available with comparable cohorts using administration pauses of 5 minutes as proposed in the current SmPC version. However, the majority of esketamine pharmacokinetic data were generated with devices that contained Formulation G005, which is the one used in the Phase 2 and 3 studies.

Food effect was not evaluated. During phase 2 and phase 3 studies, esketamine nasal spray was administered under fasting conditions, therefore SmPC contains the same recommendation for the method of administration, which is agreed. The Applicant clarified that the rationale for the food restriction was to minimize the potential for adverse sequelae, given the potential for treatment-emergent nausea and vomiting observed on dosing days.

Distribution

Esketamine's plasma and tissue distribution have been investigated in non-clinical and clinical studies. In humans, distribution of intravenous administered esketamine was measured in study TRD1009 after a 40-min intravenous infusion of 28 mg esketamine. Mean distribution volume at steady state was 709 L. The rapid systemic clearance and large distribution volume observed are consistent with results on racemic ketamine and esketamine published previously. In non-clinical studies drug concentration in CNS was measured in rats only and showed that the brain to plasma ratio for esketamine was 1.8 at the first measurement time point of 1 hour postdose and 0.3 to 0.4 for noresketamine. This is in accordance with published data (Hartvig P et al. 1995). The blood to plasma ratio was measured in a radiolabelled mass balance study (TRD1016) and were similar for oral or intravenous application ranging from 0.738 to 0.937. Dialysis analysis shows, that esketamine has a rather low protein binding (55 to 57% unbound) which is not altered by renal or hepatic impairment (TRD1011 and TRD1014). Non clinical data indicate, that esketamine is not a subject of common transporters.

Elimination

In study TRD1009 maximum plasma concentrations of esketamine were observed at a median of 0.67 hours after 40 minute intravenous esketamine (28 mg), oral (84 mg) and nasal (84 mg). Decrease of plasma levels after each treatment showed half-lives of 10.7, 7.8 and 12 hrs for intravenous, oral and nasal treatment, respectively. The mean clearance of esketamine administered by the intravenous route in healthy subjects was approximately 89 L/h.

- Metabolism

Results from in vitro data show that esketamine is extensively metabolized in humans through phase I and subsequent phase II reactions. In all species, the most important primary metabolic pathway was N-demethylation at the secondary amine to noresketamine and to a smaller extent keto-reduction, hydroxylation, oxidation and glucuronidation to metabolites M19, 4, 17, 9, 13, 8, 15, 20 and 18 in decreasing order. CYP3A4 and CYP2B6 are the primary CYP enzymes responsible for the clearance of esketamine. The metabolite profiles were similar in plasma following either route of administration (intravenous, oral, intranasal). In subjects with moderate hepatic impairment, esketamine to noresketamine ratio was lower compared to healthy subject. Esketamine is not a substrate of common transporters.

According to results from mass-balance study TRD1016 esketamine and noresketamine reach the same Cmax of approximately 0.6 µM at 40 minutes and at 2 hours, respectively, following a single intranasal dose of 84 mg esketamine (given over a period of 20 minutes). Median tmax in plasma was 0.75 hours after dosing for esketamine and noresketamine, with comparable ranges of individual values.

According to published data no in vivo back-conversion of esketamine occurs.

- Excretion

Mass balance study TRD1016 shows that an average of 86.3% and 78.4% of the administered total radioactivity was recovered in urine and 1.70% and 1.81% was recovered in feces of the oral and IV radiolabelled doses, respectively, which is in accordance with published data. Esketamine is metabolized extensively with a high first-pass effect with under <1% and <2.5% of unchanged esketamine being excreted renally in subjects with and without renal or hepatic impairment, respectively.

Dose proportionality and time dependencies

According to a cross-study analysis including PK data from healthy Caucasian and Japanese subjects (Mod5.3.5.3/SAPDDPS, Mod5.3.5.3/SAPDPS Output) dose-proportionality for the 28 mg, 56 mg and 84 mg dose could not be shown, it increases in a less than dose-proportional manner. Nevertheless dose-proportionality could be shown with pairwise-comparison for the 56 mg and 84 mg dose only. Since the 28 mg dose is the recommended starting dose for elderly patients, the Applicant was asked to further discuss the implications of non-dose-proportional pharmacokinetics for the proposed dose adjustments in elderly patients. Discussion showed, that proposed dose adjustments are appropriate.

In line with its rather short half-life of 7 to 12 hrs PK data after 25 days of twice weekly esketamine treatment showed time-independent PK in healthy subjects and patients with TRD (TRD1010).

Inter and Intra-individual variability

According to a cross-study analysis including PK data from healthy Caucasian subjects from phase I studies Cmax values are ranging from 27.3 to 66.4 % and it is not surprising that it increases with the amount of spray devices used. Values for AUClast are ranging from 18.3 to 44.6%. For this parameter an increase in variability is only seen from the 28 mg dose to the the 56 mg dose. Variability of the 56 mg dose is comparable to the 84 mg dose.

No studies for intra-individual variability were presented.

Inter-individual variabilities found in the population analyses were low to high (23.2%CV for Qh and 132% for kapo). Different covariates were found to explain the interindividual variability: Dose on FRn, Japanese race on FRn, age on Qh, Asian race on kel and Asian race on CLn/F. Some additional parameters seem to influence PK of esketamine or noresketamine as parameters of hepatic and renal impairment.

Since the covariate analyses are considered to have some deficiencies, the impact of renal and hepatic impairment cannot be finally evaluated. The following points need to be clarified:

The criteria for inclusion of covariates are not fully agreed. Therefore, the covariate analyses cannot be fully supported. According to the forest plots comparing AUC ratios for subpopulations, it seems that not all relevant covariates have been found by the conducted covariate analyses. Values of parameters reflecting liver- and renal function seem to additionally influence PK of esketamine. The covariate analyses should be re-evaluated accordingly. Potentially, the influence of age on the PK were disentangled by the influence of renal and hepatic impairment. Dose adjustments for patients with renal / hepatic impairment taking into consideration the results of the population PK analysis have been submitted and appropriate guidance regarding hepatic and renal impairments in section 4.2 of the SmPC has been proposed (please see below Population pharmacokinetics).

A justification is also required, for the conclusion that dose adjustments based on the identified covariates (Japanese on FRn, Asian on kel and CLn/F) are not warranted. This should be discussed also in the light that based on the deterministic model-based simulations Asian (non-Japanese and Japanese) are expected to have an up to 48 % higher noresketamine AUC, and in addition, Japanese are expected to have higher esketamine AUC and Cmax values (up to 38 %). This is reflected appropriately in the SmPC.

With respect to the covariate "age": Exposure metrics could only be found for 18 or 70 year old simulated subjects (Table 8) and thus results comparing 70 year old Caucasians and Asians to those below 60 years of age cannot be followed but were described. In addition, 70-year-old Japanese were not compared to other subpopulations. Based on the population pharmacokinetic model, hepatic blood flow (Qh) decreased at a rate of 21.9 L/h×10 years in subjects ≥60 years of age. To illustrate this relationship, *Qh* is expected to be 25% lower in subjects from 77 years onwards than in adult subjects younger than 60 years old. Furthermore, individual estimates of parameters of the final pharmacokinetic model indicated the geometric mean esketamine AUC ratio (90% confidence interval) for subjects >60 years of age versus those 40 to 60 years of age did not deviate greatly from unity (1.05 [0.99, 1.11]).

PK parameters in target population/patients with TRD

No obvious changes in PK parameters were detected comparing phase II and III studies in patients with TRD with phase I studies in healthy subjects. According to the presented mechanism of action and pharmacokinetic profile of esketamine, no changes in PK parameters were expected.

The pharmacokinetics for esketamine and noresketamine were best described with a combined three-compartment and two-compartment model, respectively. After nasal administration absorption followed a first-order rate while oral absorption was described by a sequential zero- and first-order absorption. A hepatic compartment resembles the hepato-portal system. Furthermore, the model assumed that esketamine in the hepatic compartment is metabolised either to noresketamine or to other metabolites through a linear process. The biotransformation of esketamine to noresketamine was characterised by a first-order rate constant while the elimination of esketamine through other metabolic routes was characterized by a first-order rate constant. The presented population PK model seems to describe the data adequately with good precision, although VPCs reveal some small remaining over- or under-prediction in particular in the elimination phase, but which may be tolerated.

Generally, all parameter estimates of the base and the final population PK model should be presented including information on shrinkage. It should be kept in mind that visual inspection of covariate relations is only valid with low shrinkages.

The model revealed, that hepatic flow (Qh) changes with age. An explanation , why noresketamine plasma concentrations are not decreased with decreasing Qh was provided

Special populations

Elderly

Esketamine shows a significant increase in Cmax and AUC for elderly patients >65 years (21% and 18%) compared to younger adults despite other covariates as race, and target population. The mean esketamine Cmax and AUC∞ values produced by an 84-mg dose were 67% and 38% higher in elderly subjects (age range 75 to 85 years) compared with younger adult subjects. Dose reduction recommendations were proposed for elderly patients with starting doses of 28 mg intranasal esketamine. No specific studies have been performed for elderly subjects above 85 years of age.

Population PK analyses revealed the following covariates included in the final model: dose on FRn, Japanese on FRn, Age on Qh, Asians on kel and Asians on CLn/F. Parameters of renal and hepatic impairment were not included as covariates until now but seem to have an additional effect on the PK of esketamine and noresketamine, which should be clarified (see above).

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
TRD1003	14/34	N/A	N/A
TRD1012	N/A	8/16	N/A
TRD1018	19/37	N/A	N/A
TRD3005	49/137	10/137	N/A

Gender

No clinically relevant differences in esketamine exposure could be observed for renal impairment, weight and gender.

Hepatic impairment

In study TRD1011 subjects with moderate hepatic impairment showed mean AUC∞ values of 213.7% of according AUC∞ in healthy subjects. In addition, mean Cmax values are 44% lower and t1/2 significantly longer for its main metabolite noresketamine. A detailed discussion on the lack of dose recommendation for patients with moderate to severe hepatic impairment and a warning under section 4.4 of the SmPC like in many European Products for intravenous ketamine is necessary (German Ketanest S, UK Ketamine 50 mg/ml for injection PL 01502/ 0099 or SE Ketamin Abcur) . Plasma protein binding of esketamine was independent from hepatic function and the fraction unbound ranged between 56% and 61% in subjects with mild and moderate hepatic impairment and 57% in healthy subjects.

Ethnicity

Although pharmacokinetic parameters are elevated for Han-Chinese, Korean and especially Japanese subjects (Cmax 41%, AUC∞ 40% after 56 mg intranasal esketamine in Japanese; TRD1008) no dose recommendations were proposed, because values are within the inter-subject variability. Although this is true, conclusion is hampered because the referenced inter-individual variability was calculated from a pooled analysis of healthy Caucasian subjects. Elevated esketamine exposure for the Asian and Japanese subjects could be on top of inter-individual variability possibly increasing the individual esketamine exposure especially for Japanese subjects above tolerated concentrations. Appropriate wording for patients of Japanese ancestry has been introduced in the SmPC.

Based on the safety data, it seems that Japanese subjects experienced more adverse events than Caucasian subjects (total adverse events reported: 80% vs. 50%). Moreover, reporting of adverse events in Japanese subjects appears to be dose dependent (35.7% [28mg], 50.0% [56mg], 69.2% [84mg), though this isn't reflected in any particular adverse events. This is in contrast to what has been observed in Caucasian subjects (15.4% [28mg], 35.7% [56mg] and 23.1% [84mg]). It also seems that the reporting of adverse events in Japanese subjects are more specific to esketamine (headache, vertigo, vomiting and nausea) whereas in the Caucasian population it is more sporadic.

CYP2B6 Polymorphism

The Applicant graphically showed in its comprehensive cross-study pharmacokinetic analysis (Mod5.3.3.3/54135419CD170056) on CYP2B6 polymorphism extensive overlap in the range of plasma Cmax and AUClast values of esketamine following administration as a nasal spray in subjects classified as extensive, intermediate, or poor Metabolizers of CYP2B6 substrates. The Applicant evaluated pharmacokinetics of esketamine graphically, separately in young adult and elderly, and in Japanese elderly at each dose level and concluded that CYP2B6 genotype does not have an impact of intranasally administered esketamine. Overall, based on the presented scatterplots, there was an overlap in PK parameter values for esketamine between CYP2B6 genotypes.

Pharmacokinetic interaction studies

Esketamine's interaction potential has been studied intensively *in vitro.* There were no indications for transporter interactions and only low inhibition/induction potential for most CYP's and none for UGTS. Only noresketamine showed a weak inhibition potential for CYP3A4 with an IC50 of 1.92 µM for testosterone, whereas the IC50 was >30 µM for midazolam and nifedipine. Esketamine showed a minor induction potential for CYP3A4 and CYP2B6 with positive induction criteria (% of positive control, and fold change versus the negative control) reached at the highest concentration tested only (10 µM). *In vivo* studies were conducted to evaluate the clinical relevance of these effects.

In vitro, esketamine was found to be mainly metabolized by CYP2B6 (60%) and by CYP3A4 (35 to 40%), therefore drug-drug interactions were performed towards those enzymes.

In vivo study TRD1010 on the induction and inhibition potential of esketamine did not show significant increases or decreases in CYP3A4 (midazolam) and CYP2B6 (bupropion) substrates. On the other side, studies TRD1009 and TRD1020 showed that esketamine's exposure was altered in the range of 5% to 29% (mean values for AUC ∞), respectively by comedication of common CYP3A4 (TRD1009, clarithromycin) and CYP2B6 (TRD1020, ticlopidine) inhibitors. Study TRD1008 showed, that mean esketamine AUC∞ values were decreased by 28% by comedication of a common CYP3A4 and CYP2B6 inducer (rifampicin). The corresponding 90% confidence intervals were clearly below or above the common range of 80-125 % for bioequivalence. In addition, this effect may be underestimated as rifampicin was stopped (Day -1) before administration of esketamine on Day 1 in Period 2. Although these effects are significant, clinical relevance cannot be estimated at this point. Proposed informative sections in 5.2 are therefore supported, and were expanded to include changes in esketamine exposure from ticlopidine comedication.

The effect of comedication has been studied for intranasal corticosteroids in healthy subjects and decongestants in subjects with allergic rhinitis. In study TRD1007 subjects with allergic rhinitis did not show clinically relevant differences in esketamine exposure when compared to healthy subjects. When a decongestant (oxymetazoline HCl) or corticosteroid (mometasone furoate) was administered 1 hr prior to the treatment, as commonly used in this population, esketamine exposure was similar. According to the

trial setup SmPC recommendations to use intranasal decongestants or corticosteroids at least 1 hr prior to the esketamine administration were proposed.

After, a more detailed discussion on possible effects of sneezing and the mucosity of nasal discharge e.g. during common colds on esketamine exposure, inclusion of appropriate sections in SmpC and PL have been introduced.

No dedicated studies have been presented to evaluate the effect of antidepressant drugs as co-medication on esketamine exposure. Retrospectively presented individual esketamine PK parameters under co-administration with the allowed antidepressant drugs used (duloxetine, escitalopram, sertraline and venlafaxine) were compared to healthy subject data and otherwise justified. Any significant influence on esketamine PK was sufficiently excluded.

2.4.3. Pharmacodynamics

Esketamine (the S-enantiomer of racemic ketamine) is a known active substance, approved (in some European Union [EU] countries) and used for the induction and maintenance of anesthesia via intramuscular (IM) or intravenous (IV) infusion. Its growing off-label use as antidepressant, predominantly in the USA, was one reason to establish a clinical trial program to assess esketamine's efficacy and safety.

Mechanism of action

The *in vitro* binding potential of esketamine, arketamine and ketamine was investigated against a panel of receptors, ion channels and transporters showing, that ketamine and esketamine are non-competitive, subtype non-selective, activity dependent NMDAR antagonists. For a more detailed review on the mechanism of action and *in vitro* data please refer to the nonclinical Assessment Report. Evidence within the literature (Duman RS et al. 2016 and Murrough JW et al. 2017) suggests that, transient increase in glutamate release leads to increases in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) stimulation, which in turn increases brain-derived neurotrophic factor (BDNF) expression, synthesis and release, activations of neurotrophic signaling pathway and activation of synaptic plasticity genes such as activity-regulated cytoskeleton (ARC)-associated protein. These changes are thought to further induce production of synaptic proteins and synaptogenesis, and eventually restoration of synaptic function. However, there are data available suggesting that these changes in synapses are temporary and are lost after a short period of time. In conjunction to this, the proposed dosing recommendation with dosing frequency twice a week – once in two weeks has not been adequately justified. Altogether it has not been fully elucidated what are the structural changes in CNS that produce antidepressant effects, lasting for longer periods of time. Furthermore, the (long-term) impact of these changes on for example cognition and suicidality remain unknown. The Applicant provided a discussion on the claimed effect of esketamine on synaptogenesis and restoration of synaptic function and their persistence and also touched upon potential differences in elderly in comparison to younger adults.

Additional effects mediated by modulation of monoaminergic neurotransmission cannot be excluded. In this respect it is noteworthy that acute and prolonged increases in dopamine levels in prefrontal cortex, striatum and nucleus accumbens occur immediately after administration of subanaesthetic doses of esketamine.

Primary and Secondary pharmacology

It is unclear whether the increased exposure of esketamine in Japanese subjects leads to any safety issues, given contradictory results from the phase 1 studies. The Applicant is requested to provide an

interim analysis of phase 2b study TRD2005 (if available) to allow for evaluation of the safety profile in Japanese subjects.

The Applicant has not discussed the possible genetic differences in PD response, and there are data suggesting that in patients with BDNF Val66Met polymorphism, the antidepressant efficacy of ketamine may be lower. The Applicant performed an analysis of the effect of Val66Met polymorphism on MADRS response, based on data from studies TRD3001 and TRD3002. The Applicant provided very little information on this analysis and results are only presented for study TRD3002. The results suggest that response to esketamine is similar irrespective of Val66Met phenotype, however the numbers are low, in particular the met/met phenotype. The applicant has provided some more information on the analysis performed and the results for study TRD3001. Altogether the results indicate that in contrast to animal data, clinical response in humans is not dependent on Val66Met polymorphism, based on data from >300 patients.

For a more detailed assessment on PD interactions, please refer to the Safety Assessment in section on the Safety related to drug-drug interactions and other interactions.

Primary pharmacology

Because direct measurement of NMDAR inhibition in humans is hardly applicable, no primary pharmacodynamic *in vivo* studies have been performed in humans. To estimate the indirect primary pharmacodynamic effect changes in the placebo corrected MADRS score from baseline were used in phase II studies TRD2001, TRD2002 and SUI2001. For a more detailed review please refer to the Efficacy Assessment in section 3.3.5. Although the results of the study suggest than an add-on IV ketamine treatment can reduce the severity of depressive symptoms in average from moderate/severe to mild intensity, data on the long-term effect had not been provided in phase II studies.

In addition study TRD1001 evaluated the proportion of antidepressant activity of esketamine's metabolites after nasal application. Since noresketamine is the only metabolite with clinically relevant binding potential for NMDAR it was the only one to be investigated further. Taking the dissociative constant (Ki), circulating concentrations and the brain distribution properties of the 2 compounds into consideration noresketamine's antidepressant activity is estimated to be 11- to 30-times lower at Cmax than that of esketamine at Cmax. In view of the not yet completely elucidated mechanism of action, it must be emphasized that this is to be regarded only as hypothetical contributions.

Secondary pharmacology

In the light of known secondary pharmacology effects of racemic ketamine, five pharmacodynamic studies have been conducted with esketamine.

Thorough QT/QTc study

The effect of esketamine on the QT interval was evaluated in study TRD1013 in 60 healthy subjects with 84 mg intranasal esketamine, 0,8 mg/kg intravenous esketamine and 400 mg Moxifloxacin as positive control. The design of the QT study follows the ICHE14 guideline and is acceptable. In no case the upper bound of the 90% one-sided confidence interval for the largest time-matched mean effect of the drug on the QTc interval exceeded 10 ms, the study is hence negative and no impact on QT prolongation could be found.

Cognitive Function

In study TRD1005 the effect of 84 mg intranasal esketamine on cognitive function was investigated using a computerized test battery. Results were significantly higher after esketamine application compared to placebo. The mental effort required, was restored to comparable levels in subjects by 2 hours postdose. The Karolinska sleepiness scale (KSS) showed significant differences between esketamine and placebo observed at 40 min and 2 hours postdose, returning to comparable levels by 4 hours. The detected impairment subsides within a few hours, and repeated esketamine administration did not affect cognitive functioning of patients in long-term treatment. In addition, the mean age of subjects included in this study was 25.3 years, it is unclear to what extent the results can be extrapolated to elderly.

On-road Driving

On-road driving tests were performed according to current scientific knowledge driving a 100-km primary highway circuit with the standard deviation from lateral position (SDLP; Verster et al. 2011) as primary objective as same-day driving in healthy subjects (TRD1006) and after multiple-doses in subjects with major depressive disorders (MDD; TRD1019 Part B) and next day driving after single dose in subjects with MDD (TRD1019, Part A).

In study TRD1006 the effect of 84 mg esketamine was compared to placebo and mirtazapine as a positive control. On-road driving test was performed 8 hours post-dose. Although the least square (LS) means (SE) of the SDLP were not significantly higher for esketamine compared to placebo (17.10 (0.92) cm and 17.25 (0.92) cm, respectively) statistically significant more effort was reported for each active treatment (ie, esketamine and mirtazapine) compared with placebo. These results have been adequately reflected in the SmPC proposing to only actively taking part in road traffic after a restful night of sleep.

In Study TRD1019 Part A a driving-test after a single 84 mg dose was performed 18 hours post-dose. The difference in mean SDLP (LS mean) between esketamine and placebo was -0.22 cm. As the upper limit of the two-sided 95% CI of the mean difference between the treatments was 0.70 cm, the difference was not statistically significant (p=0.655). Study Part B was still ongoing, presentation of the data is still expected. Nevertheless statistical significance of both study parts is still a subject of discussion since prespecified population size of 24 subjects have not been met (Part A 23 subjects, Part B 18 subjects). Study results were presented after completion and are acceptable.

Abuse potential

The primary objective of Study TRD1015 was to evaluate the abuse potential of esketamine nasal spray in healthy, nondependent, recreational polydrug users of perception altering drugs. The results of this study confirmed the abuse potential of both ketamine and esketamine. For a more detailed discussion and raised OC please refer to section 4.3.5 of the Safety Report.

PK/PD

Two different and complementary approaches were used to deal with the dose up titration in TRD3002 study and the dose differences in TRD3001. One approach consisted in a dose-response analysis using ΔMADRS as efficacy parameter linked to the dose via a linear model. The other approach was a PKPD model using individual (model derived) plasma concentrations linked via an effect compartment to an Emax model of the MADRS Total scores. Safety parameters (systolic and diastolic blood pressure and CADSS) were linearly linked to blood concentrations. A tolerance effect was included for blood pressure and CADSS effects over time. With respect to the modelling approach open points were clarified.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The pharmacokinetics of esketamine were investigated in 19 PK studies. The Applicant provided a comprehensive dossier presenting adequate information on esketamine's elimination, distribution and metabolism. There were studies presented on the bioavailability and bioequivalence for the intranasal application of esketamine via a disposable spray device. Upon request, the applicant provided detailed discussion on the effect of application instructions and handling failures exposure to esketamine, together with appropriate recommendations in the SmPC.

Furthermore the applicant sufficiently explained that the cut-off age of 65 years, which is used in the posology section of the SmPC is for consistency with the conduct of the Phase 3 studies. The recommendation for dose adjustment (ie, a starting dose of 28 mg intranasal esketamine) for subjects ≥65 years of age were mainly done to improve tolerability in older patients.

Population Pharmacokinetics:

To assess the PK/PD relationship a PKPD model using individual (model derived) plasma concentrations linked via an effect compartment to an Emax model of the MADRS Total scores was applied. A number of questions were raised regarding the population PK and PKPD analysis. In particular, further clarification on the covariate analysis was needed. The Applicant provided detailed information on the stepwise evaluation of the covariates. Furthermore, regarding the identified covariates age, renal / hepatic impairment and race (i.e. Japanese and non-Japanese Asian) from the presented studies, the Applicant was requested to further discuss the need for dose adjustment taking into consideration the results of the population pharmacokinetic analysis. The Applicant subsequently proposed the following guidance for these patients in the SmPC section 4.2 Posology and method of administration as follows:

Special populations

Hepatic impairment

No dose adjustment is necessary in patients with mild (Child Pugh class A) or moderate (Child Pugh class B) hepatic impairment. However, the maximum dose of 84 mg should be used with caution in patients with moderate hepatic impairment.

Spravato has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

Use in this population is not recommended (see section 4.4 and 5.2).

Renal impairment

No dose adjustment is necessary in patients with mild to severe renal impairment. Patients on dialysis were not studied.

Race

For patients of Japanese ancestry, initial Spravato dose is 28 mg esketamine (day 1, starting dose, see Table 3). Subsequent doses should be increased in increments of 28 mg up to 56 mg or 84 mg, based on efficacy and tolerability.

This guidance was further detailed using a Table and included detailed recommendations for the induction phase (starting and subsequent doses) and maintenance phase.

Since Japanese patients are expected to reach higher 14 % and 33 % higher C_{max} and AUC_{∞} levels after a single 56 mg dose, compared to non-Japanese patients, the Applicant proposed the following guidance in section 4.2 of the SmPC *Posology and method of administration*, which was agreed:

The above mentioned SmPC modifications were considered appropriate and acceptable.

Pharmacodynamics

The mechanism of action in terms of receptor binding and subsequent cascade of molecular events has been adequately described and discussed. The most important secondary pharmacological effects of esketamine have been adequately investigated and reflected in the proposed SmPC.

The Applicant has provided satisfactory response to all issues raised during the procedure.

2.4.5. Conclusions on clinical pharmacology

From the clinical pharmacology point of view, there are no remaining issues and Marketing Authorisation can be granted.

2.5. Clinical efficacy

The final proposed indication for esketamine is, in combination with a SSRI or SNRI, 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.

Esketamine is intended to be self-administered intranasally using a single-use device under the supervision of a healthcare professional.

The proposed dosage recommendations for esketamine nasal spray are shown in the following table. It is recommended to maintain the dosage the patient receives at the end of the induction phase in the maintenance phase. Dose adjustments should be made based on efficacy and tolerability to the previous dose.

Induction Phase	**Maintenance Phase**
Weeks 1-4 (two treatment sessions/week): Starting Day 1 dose:* 56 mg Subsequent doses: 56 mg or 84 mg	Weeks 5-8: 56 mg or 84 mg once weekly From Week 9: 56 mg or 84 mg every 2 weeks or once weekly**
Evidence of therapeutic benefit should be evaluated at the end of induction phase to determine need for continued treatment.	Periodically reexamine the need for continued treatment.

* For patients ≥65 years Day 1 starting dose is 28 mg

** Dosing frequency should be individualized to the lowest frequency to maintain remission/response.

After depressive symptoms improve, treatment is recommended for at least 6 months.

A recommendation for Post administration Observation is also included in the Posology and Method of Administration section of the SmPC:

During and after Spravato administration at each treatment session, patients should be observed under the supervision of a healthcare professional until the patient is stable based on clinical judgment (see section 4.4 of the SmPC). Before Spravato administration, instruct patients not to engage in potentially hazardous activities, such as driving a motor vehicle or operating machinery until the next day after a restful sleep (see section 4.7 of the SmPC).

2.5.1. Dose response study(ies)

The Applicant's initial Phase 2 studies in subjects with TRD investigated the efficacy and safety of 2 doses of intravenous esketamine (in Study TRD2001) or 2 dosing frequencies of intravenous ketamine (in Study TRD2002).

Initial Phase 1 studies with the nasal spray formulation in healthy subjects demonstrated that: (i) nasally administered esketamine was rapidly absorbed; (ii) plasma levels similar to those achieved after 0.2 or 0.4 mg/kg IV esketamine could be achieved after nasal administration at doses of 28 to 84 mg esketamine; and (iii) esketamine nasal spray had good local tolerability.

The nasal route of administration offers two advantages: a) a fixed dosage unit for multiple administration reduces likelihood of error and b) nasal mucosa facilitates rapid and appreciable absorption.

In Study TRD2003 a broad range of dose regimens (14 to 84 mg esketamine nasal spray) was used. The 1 week primary efficacy endpoint of the double-blind phase for Panel A demonstrated that treatment with the 28-, 56-, and 84 mg doses of esketamine nasal spray, when added to an existing oral AD, significantly improved depressive symptoms (per MADRS total score) in subjects with TRD compared with placebo (please see also below in Main studies section). After 1 week of treatment (twice a week dosing session), a dose-response analysis demonstrated a statistically significant relationship between esketamine dose and change in MADRS total score.

Sixty-seven participants (38 women, mean [SD] age, 44.7 [10.0] years) were included in the efficacy and safety analyses. Change (least-squares mean [SE] difference vs placebo) in MADRS total score (both periods combined) in all 3 esketamine groups was superior to placebo (esketamine 28 mg: -4.2 [2.09], 1-sided P=.02; 56 mg: -6.3 [2.07], 1-sided P=.001; 84 mg: -9.0 [2.13], 1-sided P<.001), with a significant ascending dose-response relationship (1-sided P<.001). Forty-one participants (17 women, mean [SD] age, 44.5 [8.03] years) were included in the efficacy and safety analyses of Panel B. In Period 1, the change (least-squares mean [SE] difference vs placebo) in MADRS total score was significant at the 1-sided 0.10 level for the esketamine 56 mg group (-3.7 [2.81], 1-sided p=0.096) vs placebo, but not for the esketamine 14 mg group (+1.8 [2.62], 1-sided p=0.751) vs placebo. In Period 2, the change (least-squares mean [SE] difference vs placebo) in MADRS total score was greater for the esketamine 14 mg group (-5.9 [5.58]) vs placebo than for the esketamine 56 mg group (-0.5 [6.25]) vs placebo.

In addition, after 2 weeks of treatment, the rate of remission (when defined as MADRS total score of $\leq$12 points, the same as the definition in the Phase 3 studies) at endpoint was lowest in the adjunctive oral AD + intranasal placebo group (at 10.0%) and ascendingly higher for each dose level in the esketamine + oral AD groups (at 12.5%, 27.3%, and 40.0% for esketamine doses of 28, 56, and 84 mg, respectively). In Panel B, with only Japanese subjects treated with oral AD + intranasal placebo and 14-, or 56-mg doses of esketamine nasal spray + existing oral AD, small improvements in MADRS total score were observed in the 14-mg group and dose-response was detected.

In the Applicant's Study SUI2001 efficacy of esketamine was further supported in a related population of patients with major depressive disorder with imminent risk for suicide (MDSI). The 84 mg dose of esketamine nasal spray, when added to optimized antidepressant treatment in inpatient hospitalization, demonstrated statistically significant (and clinically meaningful) efficacy on the primary endpoint at 4 hours postdose and on Day 2 (approximately 24 hours postdose).

Esketamine will be administered as add-on therapy concomitantly with an oral antidepressant. The Applicant has investigated both intravenous and intranasal administration of esketamine and has correlated the plasma levels achieved via the two routes. In this dedicated dose response study TRD2003, the efficacy parameters (improvement of depressive symptoms using MADRS) provided adequate data showing higher improvement with higher doses of intranasal esketamine.

With depressed patients a flexibility in the dosing schedule is considered common clinical practice, depending on the observed efficacy and the undesirable effects. The treating physician after the patient's evaluation is expected to suggest modifications to the treatment and it is not considered uncommon to increase the amount of antidepressants or decrease them to the minimum effective dose or even modify the dosing frequency in order to achieve the maximum possible effect for the patient with the maximum tolerability.

The available data are considered supportive of a flexible dosing scheme.

2.5.2. Main study(ies)

Tables and Figures with a letter e.g. A, B, C, etc. have been compiled by the assessment teams. Tables and Figures with numbers have been extracted from the Applicant's documentation.

The clinical program of intranasal esketamine comprises 5 completed Phase 3 studies investigating efficacy and safety in adults with TRD (TRD3001 or TRANSFORM-1, TRD3002 or TRANSFORM-2) including a relapse prevention study (TRD3003 or SUSTAIN-1) and a study in patients 65 years and older (TRD3005 or TRANSFORM-3). Limited safety data are also included in this application from 2 ongoing studies in adults with TRD (TRD3004 or SUSTAIN-2) and ongoing Phase 3 studies in adult subjects with MDSI (including 2 double-blind (DB) and psychoactive placebo-controlled clinical studies and 1 open label (OL) safety study). It is announced that data from a third ongoing study in TRD [TRD3006] and other ongoing studies will be available with the Day 120 responses.

The completed Phase 2 efficacy studies of adjunctive intranasal and intravenous ketamine and esketamine for indications relevant to major depressive disorder, including both treatment-resistant depression and imminent risk for suicide and the completed Phase 3 efficacy studies of intranasal esketamine in treatment-resistant depression have been summarised in the tabular overview of studies above.

It is of note the studies in MDSI will be submitted at a later stage and are not included in the efficacy package for TRD.

Methods

Table A: Summary of Phase 2 and 3 clinical studies with intranasal esketamine

Study	Design
Phase 2 studies	
TRD2003	DB, doubly-randomized, delayed-start, placebo-controlled study in adults (20-64 years) with TRD.
SUI2001	DB, randomized, placebo-controlled, multicenter study in adults (19-64 years) with MDD assessed to be at imminent risk for suicide.
Phase 3 Short term Studies	
TRD3001 (TRANSFORM-1)	Randomized, DB, multicenter, controlled study in adults (18-64 years) with TRD.
TRD3002 (TRANSFORM-2)	Randomized, DB, multicenter, controlled study in adults (18-64 years) with TRD.
TRD3005 (TRANSFORM-3)	Randomized, DB, multicenter, controlled study of flexible doses in elderly subjects (≥65 years) with TRD.
Phase 3 Relapse Prevention Study	
TRD3003 (SUSTAIN-1)	DB, randomized withdrawal design, multicenter, controlled study of esketamine plus oral AD in delaying relapse of depressive symptoms in adults (18-64 years) with TRD.
Phase 3 Long-term OL Study	
TRD3004 (SUSTAIN-2)	OL, multicenter, long-term safety study in adult and elderly subjects with TRD.

The Phase 3 long-term, uncontrolled, open-label study TRD3004 was primarily designed to obtain longer-term data on safety, including the incidence, severity, and persistence of AEs over time with esketamine + oral AD in a population with TRD.

In the dossier two more phase 2 studies with IV ketamine and IV esketamine were also included

Table B: Summary of Phase 2 clinical studies with intravenous ketamine and esketamine

Study	Design
Phase 2 studies with IV esketamine and IV ketamine	
TRD2001	A double-blind, double-randomization, placebo-controlled study of the efficacy of intravenous esketamine in adult subjects with TRD
TRD2002	A double-blind, randomized, placebo-controlled, parallel group, dose frequency study of ketamine in subjects with TRD

AD: antidepressant; DB: double-blind; Esk: esketamine; MA: maintenance; MDD: major depressive disorder; OL: open-label; OP: optimization; TRD: Treatment-resistant depression

A number of studies have been submitted to support the proposed indication for the treatment of TRD with the proposed flexible dosing regimen. The clinical development program can be considered as comprehensive and conforming to the requirements of the EU adopted Guideline on clinical investigation of medicinal products in the treatment of depression (EMA/CHMP/185423/2010 Rev. 2, 30 May 2013) (please see also below comments on study design).

It is noted however that all studies were performed in an adjunctive setting plus an oral antidepressant for TRD and esketamine has not been used as a single therapeutic agent in TRD.

Key study design features

According to the current adopted Guideline on clinical investigation of medicinal products in the treatment of depression (EMA/CHMP/185423/2010 Rev. 2, 30 May 2013), the minimum requirement for the development of a medicinal product for the treatment of major depressive disorder is at least one short term randomised double blind study parallel group compared to placebo or active comparator in a superiority design and one study investigating the maintenance of effect for at least 6 months. Replication of the scientific results is usually also expected with the submission of a second phase 3 randomised, parallel group, controlled, double bind, short-term study.

Choice of control (newly-initiated oral AD + intranasal placebo).

The use of placebo alone in clinical studies of outpatients with MDD (and by extension, TRD) is ethically controversial; however, the need to provide reliable evidence of antidepressant efficacy is essential in clinical trials of any new investigational product. From a scientific perspective, showing superiority over an active comparator is an acceptable alternative to conventional randomized DB comparisons versus placebo to permit adequate evaluation of efficacy in MDD.

For esketamine, three randomized double-blind placebo-controlled short term studies, including one study in the elderly, were submitted. All studies were conducted with esketamine administered concomitantly with a newly initiated antidepressant. Since in the EU there is currently no product approved for the treatment of TRD that would have been adequate as a comparator, the placebo control is adequate. However, according to the Applicant, the design of the Phase 3 short-term studies was neither an inactive comparator (i.e., placebo) only design nor a classical 'add-on' design.

Initiating a new oral AD in the induction phase of the Phase 3 short-term studies increased the difficulty of showing a statistically significant difference between the esketamine + oral AD and oral AD + intranasal placebo treatment groups as there was likely to be some antidepressant effect of the new oral AD.

In addition, the following was taken into consideration:

Electroconvulsive shock therapy (ECT) model for TRD. The development of esketamine for use in TRD was modelled after the use of ECT in this condition, where ECT plus an AD has been shown to result in better antidepressant efficacy compared to ECT alone or AD treatment alone in patients with TRD.

Facilitating optimization of longer-term antidepressant effect. In contrast to available data about the short-term antidepressant effects of esketamine/ketamine, much less was known at the time the clinical program for esketamine was being designed about how the antidepressant effect of these compounds are sustained over the long term. As esketamine was not intended to be used as monotherapy in TRD, an important question to be asked in the Phase 3 program was whether, among subjects with confirmed stable remission/stable response to initial esketamine + oral AD therapy, treatment with esketamine could be stopped and longer-term maintenance be achieved with the oral AD alone (please see also study TRD3003). This was the main reason a new oral AD was initiated in the induction phase of TRD3001, TRD3002, and TRD3003, as the use of a newly-initiated oral AD (instead of one to which subjects had previously not responded) was thought to provide subjects a greater likelihood of achieving sustained improvement following discontinuation of esketamine. Recent studies have demonstrated that pharmacotherapy started earlier at the same time as ECT is significantly more effective in maintaining the induction of response with a course of ECT.

Ethical considerations in continuing therapy with a failed drug. Initiating a new AD, instead of continuing a failed medication to which a subject had demonstrated no clinically meaningful response after an adequate treatment course with an optimized dose, is consistent with international depression clinical treatment recommendations to switch to a different agent.

Recommendation of FDA. In a Type B meeting held with FDA in March 2014 concerning the development program for TRD, the Division of Psychiatry Products expressed their opinion that continuing a patient on an AD medication that was demonstrated to be ineffective was not sound clinical practice and recommended that the Phase 3 study design include esketamine given with a newly-initiated AD.

Imbalances at baseline in terms of tolerance and treatment duration are reduced. As all study medication was newly initiated at the start of the DB phase, the potential for bias in terms of duration of concurrent oral AD treatment and tolerance to study medication side effects was reduced. An optional, up to 3-week taper period prior to the induction phase was included, if clinically indicated, to avoid any carry-over effect of the discontinued (failed) oral AD.

The specific oral AD administered could be selected from 2 different classes of treatments, a selective serotonin reuptake inhibitor (SSRI) (escitalopram or sertraline) or a serotonin and norepinephrine reuptake inhibitor (SNRI) (duloxetine or venlafaxine extended release), that the subject had not: (i) previously shown nonresponse to in the current depressive episode and/or (ii) demonstrated intolerance to (lifetime). The selection of these 4 oral ADs was based on global availability and the need to provide a range of appropriate choices for subjects with TRD that were consistent with the current standard of care; these drugs were considered by the Applicant fully representative of the 2 main classes of ADs.

The argumentation presented by the Applicant for the concomitant administration of a newly initiated oral AD is considered valid and acceptable although the initiation of two new therapies at the same time has not been considered common practice so far. Furthermore, contemporary treatment guidelines are not recommending a depressed patient to remain on a treatment that is not useful for its condition from both ethical and clinical practice perspectives. Either add-on or switch therapies are consequently explored. During scientific advice procedure when different designs were presented by the Applicant, the initiation

of a new AD at the same time as initiation of esketamine treatment was finally favoured compared to continuation of an antidepressant to which no response was shown (Scientific Advice Clarification letter EMA/605499/2014).

However, it was clarified that there were no sufficient efficacy or safety data available for the combination of TCAs or MAOIs (these were excluded in the phase 3 studies) and intranasal, esketamine from the phase 3 studies. As such, extrapolation from SSRIs and SNRIs to all oral ADs was not considered appropriate and the indication was restricted accordingly.

Length of induction phase (duration of phase 3 short term studies)

The 4-week duration of the induction phase to investigate the antidepressant effect of esketamine is considered appropriate and within the recommendations of the EU Depression Guideline. Furthermore, based on an FDA conducted meta-analysis of data from 24 short-term AD trials submitted to this US agency over a 10-year period, the AD-placebo treatment difference was consistent for trials of 4 to 8 weeks' duration, suggesting that it is plausible to shorten AD trial duration to 4 weeks.

Maintenance of effect

According to the same Guideline, for authorisation it should be shown that a short-term effect can be maintained during the index episode. For this a randomised withdrawal study, allowing to study relapse prevention is probably the best design. The Applicant has included a relapse prevention study in the clinical development program for esketamine.

The Applicant has also included a study in older patients and an open label long term study. It is noted that a long term double blind study investigating the prevention of the next episode(s) or recurrence prevention is not a mandatory part of a registration package for treatment of MDD episodes.

It should be noted, however, that the initial proposed indication for this application was considered broad and not supported by the clinical program, since esketamine has been used only as an add-on therapy administered concomitantly with a newly initiated oral AD and monotherapy data were not available. With respect to the role of esketamine as monotherapy in the treatment armamentarium of TRD, the Applicant is currently considering various design options and objectives for the monotherapy study.

The Applicant agreed to modify the proposed indication for SPRAVATO to better describe the patient population evaluated in the clinical development program, as follows:

- *SPRAVATO, in combination with a SSRI or SNRI, is indicated for adults with treatment-resistant Major Depressive Disorder, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode (see section 5.1).*

Study Participants

Phase 2 studies

In Panel A of study TRD2003, 60 subjects were planned to be randomly assigned to treatment to receive placebo, 28mg, 56mg or 84 mg intranasal esketamine and 40 subjects in Panel B to receive placebo, 14mg or 56 mg intranasal esketamine, concomitantly with an antidepressant.

In study SUI2001, Sixty-eight adult subjects (man or woman), were randomized to intranasal esketamine 84 mg (n = 36) or intranasal placebo (n = 32), and included in safety, efficacy, and pharmacokinetic/pharmacodynamics analyses, by treatment arm.

Phase 3 studies

All Phase 3 studies enrolled subjects who had moderate to severe depression and who had not responded to 2 or more different oral AD treatments for the current depression episode, the last of which was assessed prospectively during the screening/observational phase, except in the case of the long-term TRD3004 study, which used retrospective confirmation.

In all controlled Phase 3 studies, treatment resistance was defined in accordance with the regulatory definition, i.e., a lack of clinically meaningful improvement (defined for Phase 3 studies as ≤25%) in the current episode of depression after treatment with at least 2 different AD agents prescribed in adequate dosages for an adequate duration (defined for Phase 3 studies as at least 6 weeks).

Short term phase 3 studies.

Subjects were required to meet Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (DSM-5) diagnostic criteria for recurrent MDD or single-episode MDD (duration ≥2 years) without psychotic features, which was verified by the structured Mini International Neuropsychiatric Interview (MINI).

In addition, subjects had to have a MADRS total score of ≥28 for TRD3001 and TRD3002 and ≥24 for TRD3005 based on assessment by a remote, independent rater at Weeks 1, 2, and 4 of the screening/observational phase with a no more than 25% improvement from Weeks 1 through 4.

The subjects were 67.1% women and 32.9% men; were white in 83.2% of cases; were enrolled in North America for 43.2% of subjects, in Europe for 38.8% of subjects, and in Central or South America for 18.1% of subjects; and had a mean (SD) age of 46.1 (11.46) years. Population from EU was sufficiently represented in the studies (conforming to CHMP Scientific Advice). The Applicant also attempted to fulfil the commitment to CHMP to include as many subjects ≥75 years of age as possible to evaluate efficacy in an elderly population in the study TRD3005 (please see also section on outcomes).

Study sites/countries

The Phase 2 study in TRD (TRD2003) was conducted in Belgium and the US (Panel A) as well as in Japan (Panel B), while the Phase 2 study in MDSI (SUI2001) was conducted at US sites. As MDD is a worldwide disorder showing no geographic boundaries, the four Phase 3 DB controlled studies of esketamine in TRD were conducted in 21 different countries across 4 continents. The Phase 3 long-term OL study, TRD3004, was also international in scope, conducted in 21 countries across Europe, North America, Asia, Africa, South and Central America, and Australia. Study TRD3002 was conducted at 47 sites in 5 countries (Czech Republic, Germany, Poland, Spain, and United States), study TRD3001 at 42 sires in 9 countries and study TRD3005 at 57 sites in 13 countries.

Consistent with scientific advice from the CHMP, at least 30% (278/702) of subjects across these studies were enrolled and treated at sites in the EU (overall: 39.6% [24.9% in TRD3001, 60.1% in TRD3002, and 43.1% in TRD3005]). Between 39.9% and 51.1% of subjects in the 3 short-term Phase 3 studies were enrolled at sites in the North America (US) and between 24.9% and 60.1% were enrolled at sites in Europe.

Age

In TRD3001 and TRD3002, subjects 18 to 64 years (inclusive) were eligible for enrolment; TRD2003 enrolled subjects aged 20 to 64 years (inclusive). Study TRD3005 targeted the elderly and the very elderly population with TRD (subjects ≥65 years). The evaluation of esketamine in an elderly population was important as TRD in this population is more severe and less responsive to treatment. Furthermore, treatment of depression in the elderly is challenging as patients not only commonly suffer from disability,

functional decline, and diminished quality of life from TRD, but also as a consequence of comorbid medical conditions.

Gender

For each of these 3 short term studies, approximately two-thirds of subjects were women (61.9% to 70.5%), which is consistent with the gender distribution in the prevalence of MDD reported in community-based epidemiology studies.

Previous antidepressant medications

In each of the Phase 3 short-term studies (ie, Studies TRD3002, TRD3001, and TRD3005), all subjects met inclusion criterion for having had a nonresponse to at least 2 antidepressants (1 retrospective and 1 assessed prospectively) in the current depression episode prior to randomization (unless otherwise specified in the sections about protocol deviations).

The Massachusetts General Hospital – Antidepressant Treatment Response Questionnaire (MGH-ATRQ), a reliable, and validated scale to determine treatment resistance in MDD, was used to document oral AD use and response (medication, dose, duration of treatment) in the current depression episode. Finally, written documentation of the MDD diagnosis and prior AD use from medical/pharmacy records was obtained. At the start of screening, as indicated in the MGH-ATRQ, nonresponse to 2 or more antidepressants was documented in 89.7% of subjects, and for the remaining 10.3% of subjects, nonresponse had been documented for 1 antidepressant.

At baseline, all subjects had moderate to severe depression, a current depression episode that had persisted for an average of 2 to 4 years, and considerable functional impairment and a poor health-related quality of life at randomization. Additional independent qualitative and quantitative assessments were performed, including review of medical record documentation, to ensure that subjects without TRD were not enrolled in the studies.

Retrospective assessment of prior AD nonresponse in current episode of depression: all subjects in the Phase 3 short-term studies were required to have had documented nonresponse (≤25% improvement in MADRS total score per clinical judgment) to at least 1 oral AD treatment taken for the current episode of depression prior to the initial screening visit, at adequate dosage and for an adequate duration, as assessed on the MGH-ATRQ and confirmed by structured interview and documented records. As the Phase 3 studies were conducted globally, with variability in both the availability and accessibility to specific AD treatments, standardization of the type and maximum duration of AD treatments received prior to the first screening visit was not implemented as it would have hindered recruitment and limited the generalizability of the study results. The newly initiated AD treatments during the induction phase were restricted to only four: duloxetine, escitalopram, sertraline and venlafaxine XR.

Prospective assessment of AD nonresponse: at the initial screening visit, subjects must have been receiving treatment for the current depression episode with a different oral AD for at least 2 weeks at or above the minimum therapeutic dose (per MGH-ATRQ). This drug was continued prospectively for 4 weeks during the screening/prospective observational phase. Only subjects who demonstrated (prospectively) nonresponse to the current oral AD after at least 6 weeks (≤25% improvement on MADRS total score from Week 1 to 4, together with a MADRS total score of ≥28 on Week 2 and Week 4 [≥24 for elderly subjects in TRD3005]), were eligible for randomization. Medication adherence was documented on the Patient Adherence Questionnaire during the screening/prospective observational phase to ensure that subjects took at least a minimum therapeutic dose of the current oral AD.

All 3 short-term studies started by requiring prior nonresponse to ≥2 antidepressants in the current episode of depression, documented retrospectively at the start of the screening/prospective observational phase. These studies later were amended to allow prior nonresponse to ≥1 oral

antidepressants at the start of the phase but still ≥2 oral antidepressants by the end of the phase prior to randomization (with prospective confirmation of nonresponse to the ongoing antidepressant during the phase).

The number of classes of previous failed antidepressant medication received prior to randomization for the short term DB phase 3 studies are summarised in the following Table.

According to the EU Guideline on depression (EMA/CHMP/185423/2010 Rev. 2, 30 May 2013), patients who have not responded to at least 2 different AD treatments, at an adequate dose for an adequate duration, in the current depressive episode are considered to have TRD. As such it should be made evident that the study participants belong to this patient group and have certain characteristics with special focus on treatment failures. The Applicant has used the conservative definition of Treatment-resistant depression with at least two treatment failures one of which prospectively shown and made a considerable effort to recruit treatment-resistant depressed patients according to the definition which exists in the current EU Depression Guideline. The severity of a subject's depressive symptoms in the current major depressive episode was also confirmed using a Site Independent Qualification Assessment (SIQA).

It is noted that a high percentage of patients in the short term studies (~89.4% and 89.5% in TRD3001 and ~92.1% in TRD3002 in the Esketamine + Oral AD group) had treatment failures with 2 or more specific antidepressant medications and (~74% and 78% in TRD3001 and ~80% in TRD3002 in the Esketamine + Oral AD group) had treatment failures with 2 or more classes of antidepressant medications. For the esketamine + oral AD group (N=343) 53.7% had 2 treatment failures, 25.2% had 3 treatment failures, 8.5% had 4 treatment failures and 2.9% had 5 treatment failures or more. Prior to randomization in the 3 short-term studies, and to be considered to have TRD, subjects were required to demonstrate nonresponse to at least 2 different prior antidepressants in the current depressive episode, with nonresponse to 1 antidepressant demonstrated prospectively. To assess nonresponse, all studies used the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ). In addition, prior antidepressant use for the current episode of depression was verified by a site independent qualification assessment and confirmed with written documentation (eg, medical/pharmacy/prescription records or a letter from the treating physician, etc.). According to the Applicant, the severity of the depressive symptomatology at the time of randomization (ie, after treatment with at least 2 prior oral ADs), as well as the duration of the current episode, further supported the treatment-resistant nature of the depression experienced by subjects in the Phase 3 short-term double-blind studies. The various analyses provided for the population selected to be included in the studies are further reassuring that these patients belonged to the TRD spectrum.

It should also be noted that in addition nonresponse to at least 1 antidepressant was assessed prospectively during the screening/prospective observational phase. It could be argued that 1 treatment failure assessed prospectively can suffice to define a treatment-resistant depressed patient, since TRD develops in a continuum with progressively higher resistance depending on the number and nature of interventions failed. With this in mind the population studied with esketamine can be considered as treatment-resistant depressed patients.

Table 3: Duration and Number (of Specific Antidepressants and General Classes) of Prior Oral Antidepressants: Nonresponses During Screening in Studies TRD3002, TRD3001, and TRD3005 (Full Analysis Set)

Prior Oral Antidepressants With Nonresponse (ie, Failed Antidepressants)	Study TRD3002 Adult Subjects (N=223)	Study TRD3001 Adult Subjects (N=342)	Study TRD3005 Elderly Subjects (N=137)
Number of specific antidepressants, n (%) [a]			
N	223	340	137
1	27 (12.1%)	31 (9.1%)	21 (15.3%)
2	123 (55.2%)	174 (51.2%)	63 (46.0%)
3	46 (20.6%)	94 (27.6%)	30 (21.9%)
4	20 (9.0%)	34 (10.0%)	16 (11.7%)
5	4 (1.8%)	6 (1.8%)	5 (3.6%)
6, 7, 8, or 9	≤1% each category	≤1% each category	≤1% each category
Number of general classes, n (%) [b]			
N	223	342	137
1	49 (22.0%)	75 (21.9%)	32 (23.4%)
2	134 (60.1%)	208 (60.8%)	79 (57.7%)
>2	40 (17.9%)	59 (17.3%)	26 (19.0%)
Duration, days [c]			
N	217	329	108
Mean (standard deviation)	374.9 (614.10)	458.5 (901.93)	727.1 (1202.30)
Median	152	183	341
Range	(42; 4894)	(42; 7556)	(42; 7148)

[a] **Specific antidepressants:** In accordance with the protocols subjects entering the induction phase met the inclusion criterion for having had a nonresponse to at least 2 ADs (1 retrospective and 1 assessed prospectively). The data presented are the number of antidepressants with nonresponse (defined as ≤25% improvement) taken for at least 6 weeks during the current episode as obtained at the start of screening from the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ) results. See also Section of this document for further information about definitions of nonresponse.

[b] **General classes:** The general classes recorded on the MGH-ATRQ were as follows: monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants; serotonin and norepinephrine reuptake inhibitor (SNRI); selective serotonin reuptake inhibitor (SSRI); or other.

[c] **Duration:** Prior antidepressant ongoing at screening was included in the analysis. For a subject with no ongoing prior antidepressant at screening, the last antidepressant taken within 1 week prior to screening was included. For a subject with multiple medications ongoing at screening, the medication with the longest duration was included in the analysis.

Sources: The data are adapted from the TSIDEM table series presented in (or attached to) the sections about demographic and baseline characteristics in the Clinical Study Reports (Mod5.3.5.1/TRD3002/Sec4.2, Mod5.3.5.1/TRD3001/Sec4.2, and Mod5.3.5.1/TRD3005/Sec4.2), as well as tables in Appendix 6 of this document.

The Applicant has also provided an analysis with the number of failed previous antidepressant medications. It appears that the percentage of patients who had only one failed previous AD medication, prior to randomisation and inclusion in the study (in order to investigate prospectively one more AD failure or not) were very low from 0.77% to 4.38%.

Table Q95_1: Number of Failed Previous Oral Antidepressant Medications in the Current Episode Prior to Randomization/Study Entry

Number of failed previous AD medications, n (%)	Number of Failed ADs Prior to Randomization in the Short-Term Studies			Number of Failed ADs Prior to Entry in the Longer-Term Studies	
	TRD3001 (N=342)[a]	TRD3002 (N=223)[b]	TRD3005 (N=137)[c]	TRD3003 (N=430)[d]	TRD3004 (N=779)[e]
2	167 (48.8%)	136 (61.0%)	68 (49.6%)	248 (57.7%)	452 (58.0%)
3	116 (33.9%)	53 (23.8%)	34 (24.8%)	111 (25.8%)	182 (23.4%)
≥4	51 (14.9%)	29 (13.0%)	24 (17.5%)	59 (13.7%)	132 (16.9%)

[a] 8 subjects are not included in the summary; of these subjects, 4 failed at least 2 oral ADs (based on other data in the database) and 4 failed 1 oral AD.
[b] 5 subjects are not included in the summary; all 5 subjects failed at least 2 oral ADs (based on other data in the database).
[c] 11 subjects are not included in the summary; of these subjects, 5 failed at least 2 oral ADs (based on other data in the database) and 6 failed 1 oral AD.
[d] 12 subjects are not included in the summary; of these subjects, 6 failed at least 2 oral ADs (based on other data in the database), 5 failed 1 oral AD, and 1 failed 0 oral AD.
[e] 13 subjects are not included in the summary; of these subjects, 7 (5 of whom were transferred-entry non-responders) failed at least 2 oral ADs (based on other data in the database) and 6 (all of whom were transferred-entry non-responders) took 1 AD.

Source: Attachment Q95_ORALAD_3001_T206; Attachment Q95_ORALAD_3002_T207; Attachment Q95_ORALAD_3005_T212; Attachment Q95_ORALAD_3003_T208; Attachment Q95_ORALAD_3004_T211

Phase 3 Relapse prevention Study in TRD (TRD3003)

The study population consisted of adult men or women, 18 to 64 years of age (inclusive), who met the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) diagnostic criteria for recurrent or single-episode major depressive disorder (MDD) (if single must have been ≥2 years) without psychotic features, based upon clinical assessment, and confirmed by the Mini International Neuropsychiatric Interview (MINI). In addition, subjects were required to have an Inventory of Depressive Symptomatology - Clinician-rated, 30 item (IDS-C30) total score of ≥34 (corresponding to moderate to severe depression). Treatment-resistant depression was defined as a lack of clinically meaningful improvement after treatment with at least 2 different antidepressant agents prescribed in adequate dosages for adequate duration. At the start of the 4-week screening/prospective observational phase, subjects were required to have had documented non-response to ≥1 but ≤5 oral antidepressant treatments taken at adequate dosage and for adequate duration, as assessed on the Massachusetts General Hospital - Antidepressant Treatment Response Questionnaire (MGH-ATRQ) for the current episode of depression and confirmed by documented records. Nonresponse at the end of the screening/prospective observational phase was defined as ≤25% improvement in the Montgomery-Asberg Depression Rating Scale (MADRS) total score from Week 1 to Week 4 and a MADRS total score of ≥28 on Week 2 and Week 4. Subjects were excluded from the study who had: a current or prior DSM-5 diagnosis of a psychotic disorder; a history of suicidal behavior in the past 1 year; intent or suicidal ideation within 6 months before screening as clinically assessed by the investigator or based on the Columbia-Suicide Severity Rating Scale (C-SSRS) scale; a history of moderate or severe substance or alcohol use disorder according to DSM-5 criteria.

Of the 705 enrolled subjects, 437 (62.0%) were directly enrolled into the 3003 study, 150 (21.3%) were transferred from the acute fixed dose study TRD3001, and 118 (16.7%) were transferred from the acute flexibly dosed study TRD3002.

Phase 3 OL Long-term Safety Study in TRD (TRD3004)

Eligibility criteria for direct-entry subjects in TRD3004 were generally consistent with those specified for the Phase 3 short-term DB studies. Subjects were to be at least 18 years of age; have met DSM-5 diagnostic criteria for recurrent or single-episode MDD, without psychotic features, and confirmed by the MINI; at the start of the screening phase, patients were to have had a nonresponse to at least 2 oral AD treatments in the current episode of depression as assessed retrospectively by the MGH-ATRQ and confirmed by documented records; and had a MADRS total score of ≥22 at screening.

Unlike the Phase 3 DB studies (TRD3001, TRD3002, TRD3005, TRD3003), prospective confirmation of nonresponse to at least 1 oral AD was not required in the Study TRD3004 as this OL study was primarily designed for safety rather than efficacy objectives.

The absence of prospective confirmation of nonresponse to at last 1 oral AD for the OL (mainly safety) study TRD3004 is not considered to be of concern, since the adjunctive antidepressant effect of esketamine has been investigated in one phase 3 study and in the relapse prevention study TRD3003.

Treatments

Initial Phase 1 studies with the nasal spray formulation in healthy subjects demonstrated that: (i) nasally administered esketamine was rapidly absorbed; (ii) plasma levels similar to those achieved after 0.2 or 0.4 mg/kg IV esketamine could be achieved after nasal administration at doses of 28 to 84 mg esketamine; and (iii) esketamine nasal spray had good local tolerability.

Phase 2 studies

Study TRD2003

Panel A: At the beginning of Period 1, 67 subjects were randomly assigned to receive treatment with placebo, esketamine 28 mg, 56 mg, or 84 mg in a 3:1:1:1 ratio. At the end of Period 1, 28 subjects in the placebo group with QIDS-SR16 score ≥11 (ie, subjects who did not respond to placebo treatment) were randomly reassigned to a treatment group for Period 2.

Panel B: At the beginning of Period 1, 41 subjects in Panel B were randomly assigned to receive treatment with placebo, esketamine 14 mg or esketamine 56 mg in a 2:1:1 ratio. At the end of Period 1, 13 subjects in the placebo group with QIDS-SR16 score ≥11 were randomly reassigned to treatment for Period 2.

In both panels, each subject participated in up to 4 phases: a screening phase of up to 4 weeks, a double-blind treatment phase (Day 1 to Day 15) which included two 1-week treatment periods (Period 1 and Period 2), an optional open-label treatment phase (Panel A: Day 15 to 74; Panel B: Day 15 to 25), and an 8-week post-treatment (follow-up) phase.

Concomitant medications

Panel A: In Period 1, the most common concomitant medication was bupropion, taken by a total of 17 subjects. The next most common concomitant medications, each taken by 9 subjects during Period 1, were citalopram, clonazepam, sertraline, and vitamins.

For the 28 subjects who were in the placebo group during Period 1 then reassigned to treatment in Period 2, the most common concomitant medication in Period 2 was bupropion, taken by a total of 10 subjects. The next most common concomitant medications were clonazepam, sertraline, and vitamins.

Panel B: In Period 1, the most common concomitant medication was mirtazapine, taken by a total of 17 subjects. The next most common concomitant medication was duloxetine (taken by 15 subjects during Period 1).

For the 13 subjects who were in the placebo group during Period 1 and then reassigned to treatment in Period 2, the most common concomitant medications taken in Period 2 were duloxetine and etizolam, each taken by a total of 5 subjects.

Study SUI2001

Standard of care antidepressant treatment was initiated or optimized for all subjects on Day 1. Subjects who had been taking a recently initiated antidepressant treatment at Screening (initiated <2 weeks prior) were permitted to continue taking the antidepressant at the same dose through to the end of the double-blind treatment phase (Day 25), if considered appropriate by the investigator.

Two groups were evaluated during the DB period:

Intranasal esketamine 84 mg, administered two times per week for 4 weeks, on Days 1, 4, 8, 11, 15, 18, 22 and 25 + standard of care antidepressant treatment.

Intranasal placebo, administered two times per week for 4 weeks, on Days 1, 4, 8, 11, 15, 18, 22, and 25 + standard of care antidepressant treatment.

Phase 3 studies

Amount of intranasal esketamine

Dose selection was informed by the efficacy and safety results from the Phase 2 dose response study TRD2003. The lowest intranasal dose evaluated in Study TRD2003, 14 mg, was not carried into the Phase 3 program for adult or elderly subjects due to insufficient efficacy.

Across the Phase 3 studies, esketamine was administered at doses of 28 mg (elderly subjects ≥65 years only), 56 mg, or 84 mg. The Phase 3 short-term DB study TRD3001 evaluated 2 fixed doses of esketamine (56 mg or 84 mg). Flexible dosing of esketamine was evaluated in the other Phase 3 short-term studies, TRD3002 (56 mg and 84 mg) and TRD3005 (28, 56 mg, or 84 mg), as well as in the relapse prevention study TRD3003 and long-term OL study TRD3004.

The final dose range (after titration) was chosen as 56 or 84 mg for adult subjects and 28, 56, or 84 mg for elderly subjects. For tolerability, all starting doses (56 mg for adults and 28 mg for elderly subjects) were lower than or equivalent to the ending dose.

The fixed dose design in Study TRD3001 was used to separately evaluate the superiority of esketamine doses of 56 mg and 84 mg plus an oral AD to the oral AD + intranasal placebo comparator treatment.

In the case of flexible dosing (pivotal) study TRD3002, the following scheme was allowed according to the protocol as described in the following Table.

Table 4: Intranasal Treatment Administration during the Double-blind Induction Phase

	Time of Intranasal Device Administration[c]		
Intranasal Treatment	**0[a]**	**5 minutes**	**10 minutes**
Intranasal Device[b]	1st	2nd	3rd
Placebo	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
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 is defined as the time of administration of the first intranasal spray to one nostril from the first intranasal device.
[b] One device will be used at each time point. Each individual intranasal device contains 2 sprays. The intranasal devices containing esketamine deliver 14 mg per spray, for a total of 28 mg per individual device (ie, 2 sprays).
[c] The 3 intranasal devices for each intranasal treatment session should be administered in the medication kit order provided by the IWRS

In this flexible dose Study TRD3002, 66.7% of patients in the esketamine nasal spray plus oral AD arm received 84 mg dose of esketamine nasal spray, indicating the need for up-titration to this dose in a substantial proportion of subjects.

Frequency

Data from the up to 9-week OL phase of TRD2003 showed that reducing the dosing frequency from twice weekly to weekly or every other week did not impact the ability to maintain the antidepressant activity of esketamine. In the longer-term Phase 3 studies (TRD3003 and TRD3004), the frequency of nasal dosing after the induction phase was individualized to once weekly or every other week to achieve the lowest dosing frequency for an individual subject that could sustain initial improvements in depressive symptomatology.

The amount of esketamine and the dosing frequency used in the phase 3 trials is supported by data from the phase 2 studies. The use of a flexible dosing scheme is considered part of the everyday clinical practice, with which the depressed patient is being evaluated by the physician for its response and tolerability to treatment. It is not considered unusual to increase or decrease the amount of antidepressants to the minimum effective dose or modify the dosing frequency in order to achieve the best possible effect with good tolerability for the patient.

Use of a new oral AD + intranasal placebo

As mentioned above, key study design features, the use of placebo alone in clinical studies of outpatients with MDD (and by extension, TRD) was considered ethically controversial. For this reason, the design of the Phase 3 short-term studies included initiation of a new oral AD for all subjects at the start of the DB induction phase which, together with placebo nasal spray (to ensure blinding), served as the comparator treatment. In order for all subjects in the Phase 3 studies to receive a clinically optimized antidepressant treatment, consistent with various international depression treatment and some regulatory guidelines, a new open-label oral antidepressant was initiated on Day 1 of the double blind induction phase. This was taken daily for the duration of this phase and no other changes were allowed.

Objectives

The study designs for the completed Phase 2 and 3 studies were used to assess the efficacy, safety, and tolerability of induction and maintenance treatment with esketamine in depression.

The objectives of the phase 3 studies to demonstrate the efficacy and safety of esketamine in the treatment of TRD can be misinterpreted, since the data submitted support the adjunctive use of esketamine as add-on therapy in the treatment of TRD.

Outcomes/endpoints

The primary efficacy endpoint in the controlled Phase 3 short term studies was based on the change in depressive symptoms, as evaluated using the clinician rated MADRS. The MADRS is a clinician-rated scale designed to measure depression severity and detect changes due to antidepressant treatment. The MADRS was performed by independent remote raters during the study, using the Structured Interview Guide for the Montgomery-Asberg Depression Rating Scale (SIGMA).

Key Secondary Efficacy Evaluations

- Onset of Clinical Response by Day 2 (24 hours): The MADRS was also administered using a modified recall period of 24 hours for the key secondary efficacy evaluation related to onset of clinical response by Day 2 (24 hours) that was maintained for the duration of the double-blind induction phase with one excursion allowed.

- Patient Health Questionnaire - 9-Item: The Patient Health Questionnaire - 9-Item (PHQ-9) is a 9-item, subject-reported outcome measure that was used to assess depressive symptoms. The PHQ-9 was used to assess depressive symptom domains of the nine DSM-5 MDD criteria and provide a complementary perspective to the clinician-reported MADRS (see Mod5.3.5.3/PHQ-9 for a measurement summary of this endpoint in TRD);

- Sheehan Disability Scale: The Sheehan Disability Scale (SDS) was used to assess the key secondary objective of functional impact and associated disability. The SDS is a widely used PRO to measure disruption to occupational, social and family function as functional impairment and disability in work/school, social and family life is not adequately captured in the MADRS

Other secondary efficacy evaluations also included patient-reported outcome (PRO) measures evaluated in the Phase 3 studies in TRD such as:

- Onset of Clinical Response by Day 8: The MADRS assessment with a recall period of 7 days was used for the secondary efficacy evaluation related to onset of clinical response by Day 8 that was maintained for the duration of the double-blind induction phase with one excursion allowed.

- Clinical Global Impression of Severity: The Clinical Global Impression of Severity (CGI-S) provides an overall clinician-determined summary measure of the severity of the subject's illness that takes into account all available information, including knowledge of the subject's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the subject's ability to function.

- Generalized Anxiety Disorder 7-Item Scale: The 7-item subject-reported Generalized Anxiety Disorder, 7-Item Scale (GAD-7) was used to measure the secondary objective of symptoms of anxiety, as MDD with comorbid anxiety disorder has been associated with poor clinical outcomes and treatment nonresponse.

- European Quality of Life - 5 Dimension - 5 Level: The European Quality of Life - 5 Dimension - 5 Level (EQ-5D-5L) is a standardized instrument used as a measure of health outcome, primarily designed for self-completion by respondents. The EQ-5D-5L consisting of the EQ-5D-5L descriptive system of subjects' current general health status across 5 dimensions and the European Quality of Life - Visual Analogue Scale (EQ-VAS) recording overall health status.

Remission was defined as MADRS total score of ≤12, PHQ-9 total score ≤4 or SDS score ≤2 for each item and total score ≤6 at a given time point. **Stable remission** was defined as a MADRS total score ≤12 for at least 3 of the last 4 weeks of the optimization phase, with 1 excursion of a MADRS total score >12 or one

missing MADRS assessment permitted at optimization Week 13 or 14 only. **Response** was defined as ≥ 50% improvement in MADRS total score or ≥50% improvement PHQ-9 total score or SDS score of ≤4 for each item and total score ≤12 at a given time point. **Stable response** was defined as ≥50% reduction in the MADRS total score from baseline (Day 1 of induction phase, prior to the first intranasal dose) in each of the last 2 weeks of the optimization phase, but without meeting criteria for stable remission.

Relapse was defined as a MADRS total score ≥22 for 2 consecutive assessments separated by 5 to 15 days and/or hospitalization for worsening depression or any other clinically relevant event determined per clinical judgment to be suggestive of a relapse of depressive illness such as suicide attempt, completed suicide, or hospitalization for suicide prevention.

Each of these assessments were conducted predose at clinic visits.

The MADRS was used to calculate the primary efficacy endpoint in the Phase 2 and 3 short-term DB studies (TRD2003, TRD3001, TRD3002, TRD3005), as well as the secondary efficacy endpoints of onset of clinical response by Day 2 (TRD2003, TRD3001, TRD3002), response and remission rates (TRD2003, all Phase 3 studies), and long-term efficacy (TRD3004).

The primary endpoint in the TRD3003 relapse prevention study was time to relapse. Secondary endpoints included evaluations of response and remission (based on improvement of depression symptoms using MADRS) as well as subject-rated outcome measures shown to be important in TRD.

Study TRD3004 was primarily focused on safety and tolerability, but also had secondary efficacy endpoints, as described further in the Table with the completed Phase 3 studies (above) and in the Table below.

Table C. Summary of endpoints used in Phase 2 and 3 Clinical studies with intranasal esketamine

Endpoint	**TRD2003**	**TRD3001 Short term DB fixed dosing**	**TRD3002 Short term DB, flexible dosing**	**TRD3005 Short term DB in elderly**	**TRD3003 Relapse prevention**	**TRD3004 Open label long term safety**
Primary: change from baseline (or maintenance phase baseline) in MADRS total score at Day 28/endpoint	X (from Baseline to Day 8)	X	X	X	X (as secondary)	X
Key secondary: proportion of subjects with onset of clinical response by Day 2 that was maintained until Day 28/endpoint		X	X			
changes from baseline in SDS total score at Day 28/endpoint		X	X	X	X	X
changes from baseline and PHQ-9 total score at Day 28/endpoint		X	X	X	X	X
proportion of subjects with MADRS-defined response and remission		X	X	X		
changes from baseline in CGI-S		X	X	X	X	X
changes from baseline in GAD-7		X	X		X	X

Endpoint	TRD2003	TRD3001 Short term DB fixed dosing	TRD3002 Short term DB, flexible dosing	TRD3005 Short term DB in elderly	TRD3003 Relapse prevention	TRD3004 Open label long term safety
changes from baseline in EQ-5D-5L		X	X	X	X	X
time to relapse for stable remitters					X (as primary)	
time to relapse for stable responders					X (as secondary)	

Study SUI2001: The primary efficacy endpoint was change in score from baseline to 4 hours after initial dose on the Montgomery-Asberg Depression Rating Scale (MADRS). Clinician global judgment of suicide risk (from the Suicide Ideation and Behavior Assessment Tool) was also assessed. Secondary endpoints included these measures at 24 hours and double-blind endpoint at day 25.

The selection of the endpoints, the measurement of MADRS change from baseline to end point (after 4 weeks in double-blind induction phase) and the difference of this change between treatments is considered appropriate and in accordance with the current guidelines, available literature and clinical practice. The randomised withdrawal design to evaluate relapse prevention is according to the current EU Depression Guideline. The long term study was not aiming to investigate recurrence prevention of the next episode, but this is not mandatory for marketing authorisation. The efficacy data collected together with the safety data should be able to provide useful information for the effect of intranasal esketamine as add-on therapy in TRD.

Randomisation and blinding (masking)

Sample size calculations and randomisation methods in the phase 3 studies were performed centrally and can be considered appropriate.

With respect to blinding, the investigator was not provided with randomization codes. Due to the dissociative effects with esketamine, independent remote (by phone) blinded raters for MADRS assessment were used to maintain the blinding of the studies. Furthermore, the use of a bittering agent in the intranasal placebo and the use of 3 devices in each treatment session were additional precautionary measures to ensure that blinding was maintained and as such these are considered appropriate.

Statistical methods

For the short-term induction studies, the target of estimation (estimand) according to the Applicant was the hypothetical treatment effect when the drug was taken as intended in the protocol. However, the treatment effect that is of primary interest from a regulatory point of view is the effect regardless of treatment discontinuations, and if patients changing treatment to an alternative AD therapy had simply discontinued corresponding treatment(s) instead. Actually, it is somewhat unclear what treatment effect is targeted by the primary analysis ANCOVA (LOCF). However, ANCOVA (BOCF) that was provided as sensitivity analysis for studies 3001 and 3002, which was already recommended in the CHMP scientific advice as a possibility for missing data imputation, could be considered as a conservative analysis in accordance with the target of estimation of primary regulatory interest because BOCF assumes that all benefits potentially achieved from treatment are lost.

The primary analysis set for all efficacy analyses in Studies TRD3001, TRD3002, and TRD3005 included all randomized subjects who received at least 1 dose of nasal study medication and 1 dose of oral AD medication during the DB induction phase (termed, full analysis set).

For the EU dossier, the primary efficacy variable, change from baseline in MADRS total score at Day 28, was analyzed based on an analysis of covariance (ANCOVA) model using change from baseline to Day 28 with last observation carried forward (LOCF) data with the model including factors for treatment, country (TRD3002) or region (TRD3001, TRD3005), and class of oral AD and the baseline MADRS total score as a covariate. Missing data in primary analysis were replaced using LOCF, whereby the last post-baseline value was to be carried forward; patients without post-baseline data were excluded from analysis, which is not considered appropriate, but numbers were negligible. For non-EU countries, the primary efficacy variable was analyzed based on a mixed-effects model using repeated measures (MMRM) based on observed case data.

Additional post-hoc sensitivity analyses were performed for the ANCOVA analysis of change in MADRS total score at endpoint using baseline observation carried forward (BOCF) and worst observation carried forward (WOCF) methods of imputation.

Study TRD3001 applied a truncated fixed-sequence, parallel gate-keeping approach, and Study TRD3002 applied a fixed sequence approach, to control type I error across the primary (change in MADRS total score) and the 3 prespecified key secondary endpoints.

For studies 3001 and 3005, pre-planned interim analyses were conducted to re-estimate the sample size, or to stop the study for futility. The procedures that were put in place to ensure confidentiality of interim results to assure the integrity of the study were adequate. The interim analysis was appropriately taken into account for statistical testing and estimation.

The treatment group difference in the proportion of subjects showing onset of clinical response by Day 2 (24 hours) that was maintained for the duration of the DB induction phase was analyzed using a Cochran-Mantel-Haenszel (CMH) chi-square test adjusting for country and class of antidepressant (SSRI or SNRI) in TRD3002 and using a weighted Fisher's exact test for TRD3001. Changes from baseline at Day 28 (or DB end point) in the SDS total score and PHQ-9 total score were analyzed using the same models as described for the primary analysis.

In the relapse prevention study, the target of estimation (estimand) according to the Applicant was the effect 'while on initially randomised treatment'. However, this is not the treatment effect of primary interest for assessment of maintenance of effect from a regulatory point of view because this effect is only related to the subset of the population that is on treatment, which changes with time because of treatment drop-outs. The treatment effect that is actually of primary interest is the effect regardless of treatment discontinuations and if patients changing treatment to an alternative AD therapy had simply discontinued corresponding treatment(s) instead. However, as the proportion of patients who discontinued treatment during the maintenance phase was relatively small (~10%), the strategy how intercurrent events are addressed is not of critical importance for the conclusions from the study. Furthermore, the pre-sensitivity analysis which was originally intended to serve another purpose can also be considered as sensitivity analysis for the effect of primary regulatory interest.

The analysis set used for analysis of the primary endpoint included all randomized subjects who were in stable remission at the end of the OP phase and who received at least 1 dose of nasal study drug and 1 dose of oral AD during the MA phase (ie, full [stable remitter] analysis set). The primary efficacy endpoint was the time from randomization to the first relapse during the maintenance phase in esketamine-treated subjects who achieved stable remission at the end of the optimization phase. The treatment groups were compared using the log-rank test statistic. The estimate of the hazard ratio and its 95% confidence

interval (CI) were calculated. The cumulative distribution function of the time to relapse was estimated by the Kaplan-Meier method.

Study TRD3003 was designed with an interim analysis that allowed early termination of the MA phase for efficacy or to re-estimate the sample size (ie, required number of relapses). The two- stage design with sample size estimation at interim was adequately taken into account for statistical testing and for estimation.

For MADRS, PHQ-9, CGI-S, GAD-7 and SDS, the change from baseline (for the maintenance phase) at each visit, including observed case and LOCF data, during the double-blind maintenance phase and at end point for the maintenance phase were analyzed using an analysis of covariance (ANCOVA) model (rank-based for CGI-S) with factors for treatment and country and baseline (maintenance phase) score as a covariate. Least-squares estimates of the treatment differences and 95% CIs are presented.

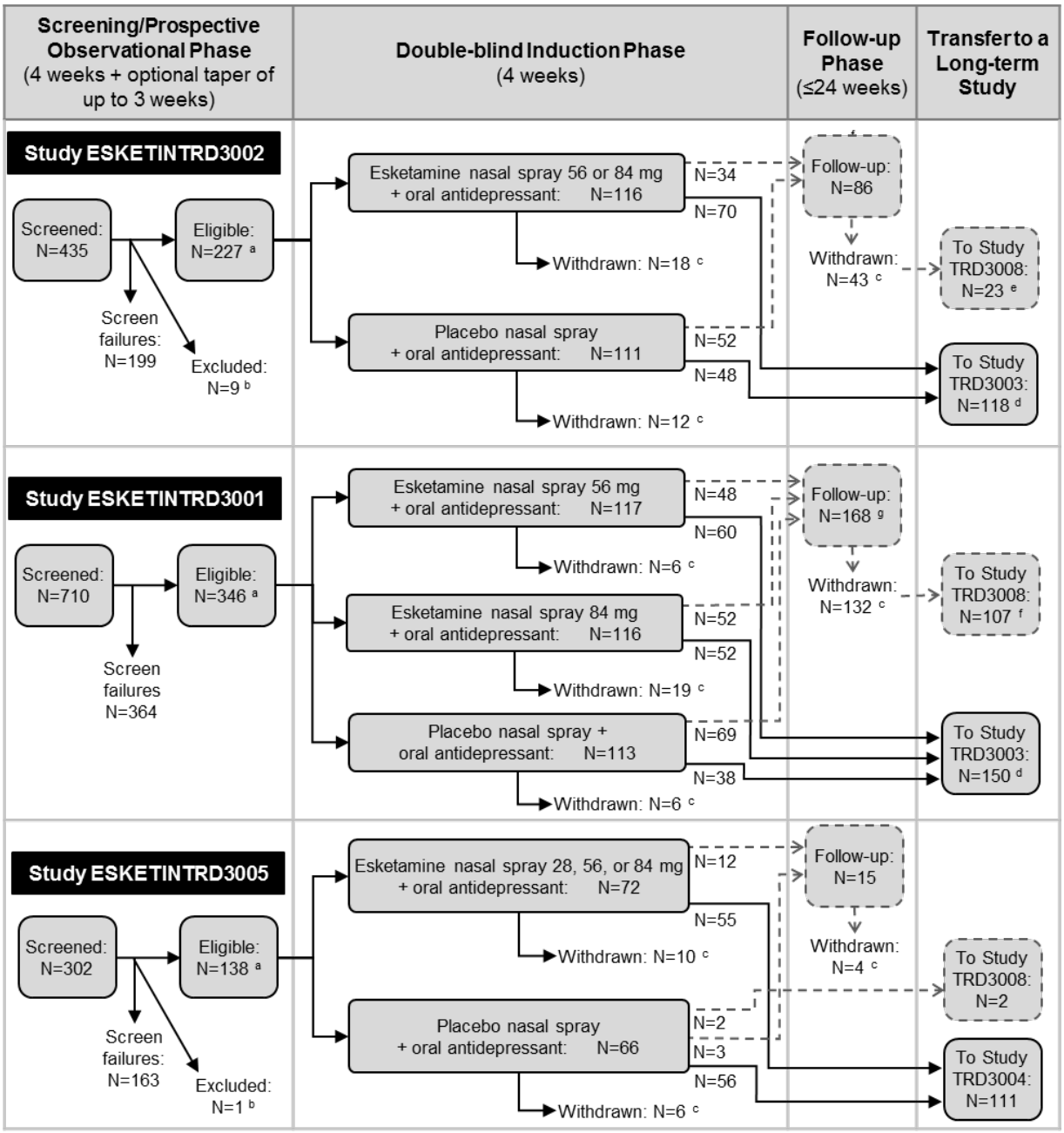
Results

Participant flow

Phase 3 studies

For the 3 short-term studies [ie, for Studies TRD3002 (short term DB flexible dosing), TRD3001 (short term DB fixed dosing), and TRD3005 (elderly patients)], overall participant flow is shown in following Figure and reasons for withdrawal are shown in the Table below.

Figure 3: Participant Flow Diagram through Studies TRD3002, TRD3001, and TRD3005

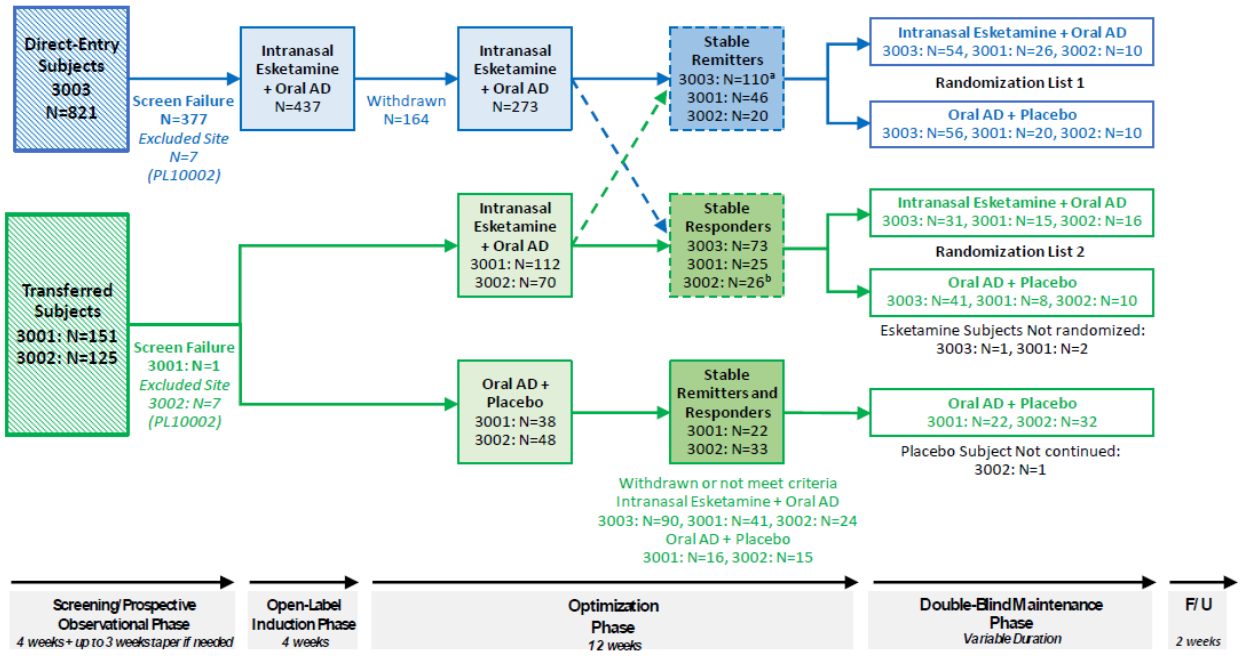


[a] Only subjects whose current depressive episode had demonstrated nonresponse to at least 2 oral antidepressants prior to randomization were eligible to participate in these studies.
[b] These subjects were excluded from the analysis sets due to Good Clinical Practice issues found at 1 site during an audit, as described in the Clinical Study Reports (CSRs).
[c] Itemized reasons for withdrawal are described in Table 3 (for the double-blind induction phase) and in the CSRs (for all phases).
[d] Only subjects who met predefined criteria for response were eligible to continue to Study TRD3003.
[e] In Study TRD3002, N=6 from the esketamine + oral antidepressant (AD) group and N=17 from the intranasal placebo + oral AD group were withdrawn to participate in Study TRD3008.
[f] In Study TRD3001, N=34 from the esketamine 56 mg + oral AD group, N=29 the esketamine 84 mg + oral AD group, and N=44 from the intranasal placebo + oral AD group were withdrawn to participate in Study TRD3008.
[g] Although 169 subjects entered the follow-up phase, 1 subject in the esketamine 56 mg + oral AD group discontinued prior to performing the first scheduled visit; therefore, this subject is not counted as participating in the follow-up phase.

Notes: The dashed lines (- -) show phases and studies that are not relevant to this Summary of Clinical Efficacy (SCE). In the follow-up phases, no esketamine was administered. In Study 54135419TRD3008, which was ongoing when this SCE was issued, no primary efficacy objectives had been prespecified in the protocol; no secondary efficacy data were available for this SCE; safety results are described in the Summary of Clinical Safety (Mod2.7.4/SCS). The solid lines (—) show phases and studies that are more relevant to this SCE.

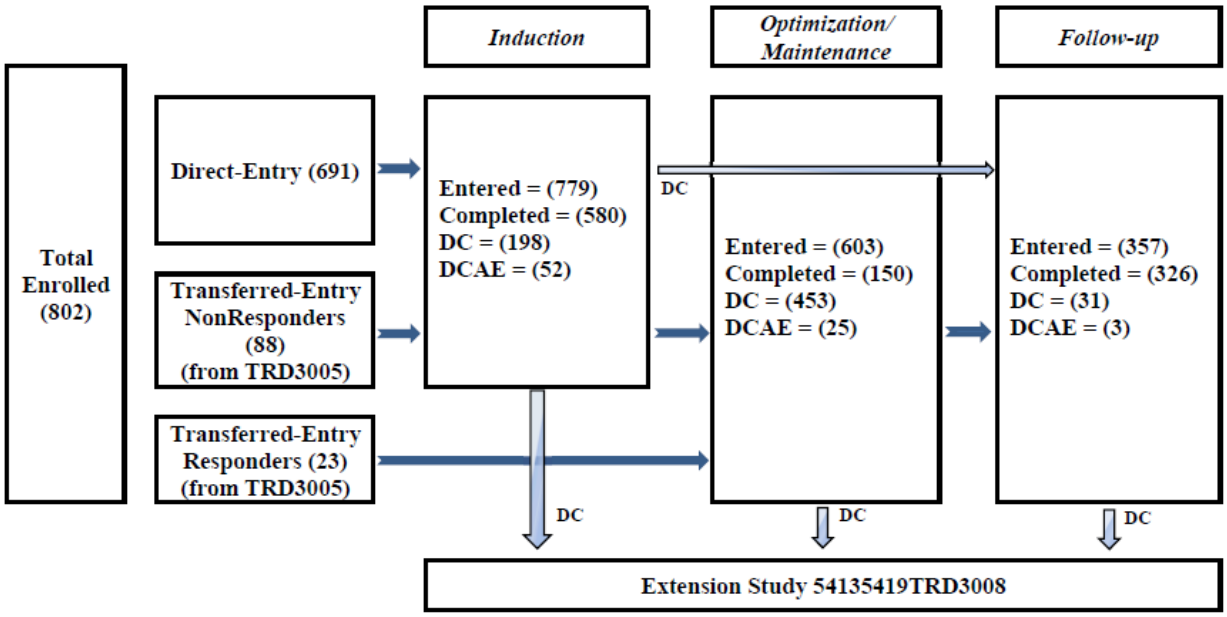
Sources: This diagram is adapted from the individual participant flow diagram and information in table TSIDS02 in each CSR (Mod5.3.5.1/TRD3002/Sec4.1, Mod5.3.5.1/TRD3001/Sec4.1, and Mod5.3.5.1/TRD3005/Sec4.1).

Figure 4: Participant Flow diagram for Study 3003



(a) 1 stable responder was incorrectly randomized as a stable remitter.
(b) 1 subject not meeting either stable remission or stable response criteria at the end of the optimization phase was incorrectly randomized as a stable responder

Figure 5: Disposition of subjects in Study 3004



Cross reference: Attachment TSIDS01; Attachment TSIDS02; Attachment TSIDS03; Attachment TSIDS04; Attachment TSIDS04A
Note: DC=discontinuation, DCAE=discontinuation due to adverse event

Interim analysis

During all 3 short-term studies, several measures were implemented to improve study execution and enhance the quality of study conduct. While these measures were independent of the interim analyses in Studies TRD3001 and TRD3005, the measures may have contributed to the observed differential treatment effect on the primary endpoint for subjects enrolled prior to the interim analysis (Stage 1) or after the interim analysis (Stage 2), as the timing of these initiatives were considered to have the greatest impact on Stage 2. An analysis for Study TRD3002 evaluated whether similar differences between stages would have been observed had there been an interim analysis. Results were consistent with by stage analyses for Studies TRD3001 and TRD3005 in showing a larger treatment group difference for subjects who were enrolled later. Regarding a potential concern on confidentiality of interim results, it is reassuring that study 3002 without interim analysis showed a larger treatment group difference for subjects who were enrolled later in the analysis mimicking a by stage evaluation. As there were only slight differences in patient characteristics between stage 1 and stage 2, it cannot be concluded that there is a difference in patient populations between stage 1 and 2. Therefore a patient population in which esketamine on top of an oral AD would have a greater efficacy cannot be defined and it is considered that the observed effect estimates in the short-term studies can be generalized to the target patient population.

Baseline data

Across these studies, the mean baseline MADRS total score ranged from 35.2 to 37.6 (MADRS score >31 signals severe depression71), and 75.2% to 83.3% of subjects across these studies were considered markedly to extremely ill based on Clinical Global Impression – Severity (CGI-S) scores at baseline.

The mean duration of the current depression episode was >2 years in all studies (115 weeks [~2.2 years] in TRD3002, 203 weeks [~3.9 years] in TRD3001, and 216 weeks [~4.2 years] in TRD3005), and a substantial proportion of subjects (41% to 63%) had a family history of depression.

All subjects had non-response to at least 2 antidepressant treatments prior to randomization.

Study TRD3001 (short term DB fixed dosing)

In general, the treatment groups were similar with respect to baseline characteristics. The mean (standard deviation [SD]) age of all subjects was 46.3 (11.19) years, range: 18 to 64 years. The majority of subjects entering the study were female (70.5%) and white (76.6%). Medical history of hypertension was observed in 21.1% of subjects. The majority (57.3%) of the subjects initiated oral antidepressant treatment with an SNRI; 39.8% of subjects received duloxetine. The greatest percentage of subjects enrolled was in the United States (39.5%), followed by Brazil (16.7%), Mexico (13.2%), France (9.1%), Belgium (8.5%), Canada (5.8%), Estonia and Slovakia (2.9% each), and Hungary (1.5%).

The mean (SD) baseline MADRS total score was 37.6 (5.51), ranging from 18 to 53, which is considered severe depression. Based on CGI-S scores, the majority of subjects (57.3%) were markedly ill (CGI-S score of 5). The mean (SD) duration of the current episode of depression was 202.9 (290.24) weeks. Subjects reported a family history of depression (62.9%), alcohol abuse (17.5%), and anxiety disorder (12.3%). Approximately 39.6% of subjects had a history (lifetime) of suicidal ideation as assessed using the C-SSRS, and 24.3% had a history (lifetime) of suicidal behavior.

Study TRD3002 (short term DB flexible dosing)

The treatment groups were similar with respect to baseline characteristics. The mean (SD) age of all subjects was 45.7 (11.89) years, ranging from 19 to 64 years. The majority of subjects entering the study were female (61.9%) and white (93.3%). In addition, the majority (68.2%) initiated oral antidepressant

treatment with an SNRI, and more than half of subjects (54.3%) received duloxetine. The greatest percentage of subjects was enrolled in the United States (39.9%), followed by the Czech Republic (26.0%), Poland (17.0%), Germany (9.0%), and Spain (8.1%). A total of 20.2% of subjects reported a medical history of hypertension.

The mean (SD) baseline MADRS total score was 37.1 (5.67), ranging from 21 to 52. Based on CGI-S scores, the majority of subjects (57.0%) were markedly ill. The mean (SD) duration of the current episode of depression was 114.6 (157.96) weeks. Subjects reported a family history of depression (48.0%), alcohol abuse (17.0%), and anxiety disorder (11.7%). Approximately one third (33.2%) of subjects had a history (lifetime) of suicidal ideation as assessed using the C-SSRS, and 10.3% had a history of suicidal behavior.

Study TRD3005 (elderly patients)

The treatment groups were similar with respect to baseline characteristics. The mean (SD) age of all subjects at baseline was 70.0 (4.52) years and ranged from 65 to 86 years. Most subjects entering the study were female (62.0%) and white (94.9%). In addition, the majority (55.5%) initiated oral antidepressant treatment with an SSRI. The greatest percentage of subjects was enrolled in the United States (51.1%), followed by Sweden (10.2%), Italy (6.6%), Spain (5.8%), Poland (5.1%), South Africa (5.1%), and France (5.1%). A total of 53.3% of subjects reported a history of hypertension.

The mean (SD) baseline MADRS total score was 35.2 (6.16), ranging from 19 to 51. Based on CGI-S scores, approximately half of the subjects (49.6%) were markedly ill and approximately one quarter of the subjects (24.8%) were severely ill. The mean (SD) duration of the current episode of depression was 215.8 (341.7) weeks. Subjects reported a family history of depression (40.9%), anxiety disorder (8.0%), and alcohol abuse (7.3%). Approximately one-third (31.9%) of subjects had a history (lifetime) of suicidal ideation as assessed using the C-SSRS, and 14.1% had a history of suicidal behavior.

Study TRD3003 (relapse prevention)

The mean (standard deviation [SD]) age of all subjects was 46.1 (11.10) years, ranging from 18 to 64 years. The majority of subjects entering the study were female (64.8%) and white (90.1%). In addition, the majority of subjects (62.9%) initiated oral antidepressant treatment with an SNRI and 46.2% of subjects received duloxetine. Medical history of hypertension was observed in 20.9% of subjects. The highest percentage of subjects was enrolled in the United States (27.0%), followed by Poland (18.7%), the Czech Republic (14.0%), Brazil (9.1%), and Turkey (7.5%);

The mean (SD) baseline MADRS total score was 37.9 (5.50), ranging from 4 (1 subject, with a score >28 at screening with an unexpected significant score decrease on Day 1, who ultimately discontinued after the induction phase) to 53. Based on CGI-S scores, the majority of subjects (58.4%) were markedly ill (CGI-S score of 5). The mean (SD) duration of the current episode of depression was 132.2 (209.18) weeks (median 64.0 weeks). Subjects reported a family history of depression (45.1%), alcohol abuse (13.5%), and anxiety disorder (9.1%). A total of 27.4% of subjects had a history (lifetime) of suicidal ideation as assessed using the C-SSRS and 14.9% had a history of suicidal behavior. The mean (SD) IDS-C30 total score at screening was 47.2 (7.26), corresponding to severe depression.

Study TRD3004 (OL long term safety)

A higher percentage of subjects were women (62.6%) and white (85.5%) (Table 13). The median age was 53.5 years (range 18 to 86 years). Elderly subjects (≥65 years) made up 22.2% (178) of subjects enrolled and of these elderly subjects, there were 19 subjects ≥75 years of age. The mean (SD) weight was 78.51 (18.426) kg, with 256 subjects who were either obese (28.4%) or morbidly obese (3.5%). A similar percentage of subjects received SNRIs or SSRIs for the oral antidepressant initiated on Day 1 of

the induction phase (see Section 3.6). Approximately 30% of subjects each received duloxetine or escitalopram, and approximately 20% of subjects each received sertraline or venlafaxine extended release. The highest percentage of subjects was enrolled in the United States (18.3%), followed by the Argentina (13.2%), Bulgaria (11.7%), Sweden (11.2%), South Africa (8.0%), Brazil (6.5%), and Spain (5.2%). A total of 27.4% of subjects reported a medical history of hypertension.

Baseline psychiatric medical history and previous use of antidepressant medication was generally consistent with the inclusion and exclusion criteria (following Table from study TRD3004 CSR). The median age at time of diagnosis with MDD was 35 years (range [8; 72]). The mean (SD) baseline MADRS total score was 31.4 (5.39). Based on CGI-S scores, half of the subjects (51.0%) were considered markedly ill. The mean (SD) duration of the current episode of depression was 160.5 (261.80) weeks (median: 66.5 weeks and range [6; 2184]). Of the subjects in this study, approximately 40% of subjects were not responsive to 3 or more antidepressant medications. Subjects reported 1) a family history of depression (43.1%), 2) alcohol abuse (7.6%), and 3) anxiety disorder (7.6%). Approximately one-quarter (25.4%) of subjects had a history (lifetime) of suicidal ideation as assessed using the C-SSRS, and 15.4% had a prior history of suicidal behavior. Also based on the C-SSRS, 26.9% reported suicidal ideation within the past 6 months and 0.3% (2 subjects) reported suicidal behavior in the past 12 months

Numbers analysed

Phase 3 studies

Across the Phase 3 short-term DB studies, a total of 711 subjects were randomized and assigned to DB treatment at the start of the induction phase, of whom 702 were included in the full analysis sets used for primary analyses of efficacy in these studies (342 in TRD3001; 223 in TRD3002; 137 in TRD3005). In each of these studies, the overall proportions of subjects completing the DB induction phase was 86.8% to 91.0%.

In the relapse prevention study TRD3003 stable remitters were 176 patients, from which 90 received esketamine and oral AD and 86 received oral AD and intranasal placebo.

The open-label long term Study TRD3004 had no efficacy endpoints prespecified in the protocol and 779 patients entered the induction phase while 603 entered the optimisation/maintenance phase.

The following Table is summarising the number of patients in the phase 3 studies.

Table G: Number of patients included and analysed in Phase 3 studies

Study code	Patients
Short term DB studies	
TRD3001	710 patients were screened, 346 subjects were randomized, and 315 subjects completed the double-blind induction phase.
TRD3002	435 patients were screened, 227 subjects were randomized, and 197 subjects completed the double-blind induction phase.
TRD3005	302 patients were screened, 138 subjects were randomized, and 122 subjects completed the double blind induction phase.
Relapse prevention study	
TRD3003	1097 patients were screened (705 subjects direct or transfer entry), 455 subjects entered the optimization phase, 297 subjects (176 stable remitters and 121 stable responders) were randomized into the maintenance phase, and 272 subjects (159 stable remitters and 113 stable responders) completed the maintenance phase.
Open Label long term study	
TRD3004	The study enrolled 802 subjects, of whom 691 were direct-entry subjects and 111 were transferred-entry subjects (88 transferred nonresponders and 23 transferred

	responders). The induction phase was entered by 779 subjects and completed by 580 subjects. The optimization/maintenance phase was entered by 603 subjects and completed by 150 subjects when the Applicant terminated the study because specific exposure numbers had been met.

Outcomes and estimation

Study TRD2001

Of the enrolled patients, 97% (29 of 30) completed the study. The least-squares mean changes (SE) from baseline to Day 2 in Montgomery-Asberg Depression Rating Scale total score for the esketamine 0.20 mg/kg and 0.40 mg/kg dose groups were -16.8 (3.00) and -16.9 (2.61), respectively, and showed significant improvement (one-sided p=.001 for both groups) compared with placebo (-3.8 [2.97]). Esketamine showed a rapid (within 2 hours) and robust antidepressant effect.

Study TRD2002

In total, 67 (45 women) of 68 randomized patients received treatment. In the twice-weekly dosing groups, the mean change in MADRS score at Day 15 was -18.4 (SD=12.0) for ketamine and -5.7 (SD=10.2) for placebo; in the thrice-weekly groups, it was -17.7 (SD=7.3) for ketamine and -3.1 (SD=5.7) for placebo. Similar observations were noted for ketamine during the open-label phase (twice-weekly, -12.2 [SD=12.8] on Day 4; thrice-weekly, -14.0 [SD=12.5] on Day 5).

Phase 2 Studies with Intranasal Administration

Study TRD2003

In the adaptive delayed-start design study TRD2003, consisting of a 2-week DB phase that included two 1-week treatment periods, twice-weekly esketamine significantly improved depressive symptoms in adults with TRD. Efficacy was dose related, with doses of 56 mg and 84 mg demonstrating significantly greater efficacy than placebo. The 28 mg dose had a shorter duration of response, and the 14 mg dose was ineffective. The clinical effect was observed as early as 2 hours after the first dose. In the open-label (OL) phase (Days 15-74) following the DB period, in which the frequency of esketamine dosing was reduced to once weekly for 2 weeks and then to every 2 weeks, the antidepressant response appeared to persist for approximately 2 months after the last dose of esketamine

The results for Panel A of Study TRD2003 have been published.

Sixty-seven participants (38 women, mean [SD] age, 44.7 [10.0] years) were included in the efficacy and safety analyses. Change (least-squares mean [SE] difference vs placebo) in MADRS total score (both periods combined) in all 3 esketamine groups was superior to placebo (esketamine 28 mg: -4.2 [2.09], 1-sided P=.02; 56 mg: -6.3 [2.07], 1-sided P=.001; 84 mg: -9.0 [2.13], 1-sided P<.001), with a significant ascending dose-response relationship (1-sided P<.001). Improvement in depressive symptoms appeared to be sustained (-7.2 [1.84]) despite reduced dosing frequency in the open-label phase.

The results for Panel B of Study TRD2003 (conducted in Japan) have not been published but have been presented by the Applicant as an abstract.

Forty-one participants (17 women, mean [SD] age, 44.5 [8.03] years) were included in the efficacy and safety analyses. In Period 1, the change (least-squares mean [SE] difference vs placebo) in MADRS total score was significant at the 1-sided 0.10 level for the esketamine 56 mg group (-3.7 [2.81], 1-sided p=0.096) vs placebo, but not for the esketamine 14 mg group (+1.8 [2.62], 1-sided p=0.751) vs placebo. Results suggested a potential interaction of treatment with baseline MADRS total score: outcomes favoured the placebo group for subjects with higher baseline MADRS total scores and favoured

the esketamine groups for subjects with lower baseline MADRS total scores. In Period 2, the change (least-squares mean [SE] difference vs placebo) in MADRS total score was greater for the esketamine 14 mg group (-5.9 [5.58]) vs placebo than for the esketamine 56 mg group (-0.5 [6.25]) vs placebo.

Study SUI2001

In Study SUI2001, the efficacy of esketamine was demonstrated in an associated population of subjects with MDSI. In this study, esketamine at a dose of 84 mg (given twice weekly over 4 weeks), when added to optimized AD treatment and inpatient hospitalization, resulted in clinically meaningful and statistically significant reductions in depressive symptoms at 4 hours after the first dose

Phase 3 short term studies

Primary endpoint

ANCOVA LOCF analysis of the change in MADRS total score from baseline to endpoint (please see also Table below with MMRM and ANCOV LOCF analyses results):

For Study TRD3002, the results statistically favoured treatment with esketamine + oral AD over oral AD + intranasal placebo; the estimated difference in MADRS change from baseline to Day 28/endpoint (95% CI) compared to oral AD + intranasal placebo treatment was -4.0 (-7.31; -0.64) points by MMRM, -3.5 (-6.67; -0.26) points by ANCOVA LOCF and -3.5 (-6.70; -0.27) by ANCOVA BOCF analysis methods. The BOCF method of analysis is considered the most relevant.

With respect to change in MADRS total score over time, the LS mean (95% CI) treatment differences (based on ANCOVA [LOCF]) were 3.6 (-6.05; -1.21), 2.8 (-5.08; -0.57), -2.1 (4.92; 0.64), and -3.4 (6.43; 0.28) at Days 2, 8, 15, and 22, respectively.

Table H: Enrolment by country and treatment group in study TRD3002

Country	Intranasal Esk + Oral AD (N=116)	Oral AD + intranasal placebo (N=111)	Total (N=227)
Czech Republic (6 sites)	30 (25.9%)	29 (26.1%)	59 (26.0%)
Germany (9 sites)	10 (8.6%)	10 (9.0%)	20 (8.8%)
Poland (6 sites)	21 (18.1%)	18 (16.2%)	39 (17.2%)
Spain (7 sites)	9 (7.8%)	9 (8.1%)	18 (7.9%)
United States (10 sites)	46 (39.7%)	45 (40.5%)	91 (40.1%)

In this study which is considered the pivotal that showed statistically significant results, the disposition of the patients across study sites is such that a specific study site did not dominate the results.

For Study TRD3001,

- for esketamine 84 mg + oral AD, the median unbiased estimate (95% CI) for the treatment difference versus oral AD + intranasal_placebo was -2.0 (-5.52; +1.42). The least-squares mean difference (95% CI) using the most relevant analysis of the change in MADRS (ANCOVA BOCF) was -1.2 (-4.66; -2.32) (2-sided p=0.513). The results numerically favoured esketamine 84 mg + oral AD but did not reach statistical significance (2 sided p=0.250).
- for esketamine 56 mg + oral AD, the median unbiased estimate (95% CI) numerically favoured esketamine 56 mg + oral AD at -4.1 (-7.53; -0.60). The least-squares mean difference (95% CI) using the most relevant analysis of the change in MADRS (ANCOVA BOCF) was -4.3 (-7.79; -0.80) (2-sided p=0.017). Because the difference between the esketamine 84 mg + oral AD group and the oral AD + intranasal placebo group was not statistically significant, esketamine 56 mg + oral AD group versus the oral AD + intranasal placebo group could not be formally evaluated for treatment difference based on the predefined testing sequence.

For Study TRD3005, the estimated treatment difference (95% CI) of -3.6 (-7.20; +0.07) by MMRM and -3.6 (-7.16; -0.03) by ANCOVA LOCF analysis methods for esketamine + oral AD over oral AD + intranasal placebo suggests a clinically meaningful benefit. The results numerically favoured esketamine + oral AD but did not reach statistical significance (2 sided p=0.052).

The least-squares mean changes in the MADRS total score over time in Studies TRD3002 and TRD3001 showed an improvement in clinician-rated depression symptoms that was apparent as early as 24 hours after the first dose of esketamine + oral AD (i.e., Day 2) that continued throughout the duration of the 4-week induction phase. The mean treatment differences at Day 2 (based on MMRM analysis) were -3.3 for the esketamine + oral AD group in Study TRD3002 and -3.0 and -2.2 for the esketamine 56 mg and 84 mg + oral AD groups, respectively, in Study TRD3001 (corresponding values based on ANCOVA LOCF analysis were -3.6 for TRD3002, and -2.9 and -2.0 respectively, for TRD3001).

MMRM was primary analysis only for non-EU countries; for EU, ANCOVA (LOCF) was primary. ANCOVA (BOCF) is considered the most relevant method of analysis.

The results are presented using the BOCF analysis in the Summary of Product Characteristics.

Table 5: MADRS Total Score: Change from Baseline to Day 28 by MMRM or to Endpoint by ANCOVA LOCF for the Double-blind Induction Phases in Studies TRD3002, TRD3001, and TRD3005 (Full Analysis Sets)

	Study TRD3002 (Adult Subjects)				Study TRD3001 (Adult Subjects)						Study TRD3005 (Elderly Subjects)			
	To Day 28 by MMRM		To Endpoint by ANCOVA LOCF		To Day 28 by MMRM			To Endpoint by ANCOVA LOCF			To Day 28 by MMRM		To Endpoint by ANCOVA LOCF	
	Esk (56 or 84 mg) + Oral AD (N=114)	Oral AD + Placebo (N=109)	Esk (56 or 84 mg) + Oral AD (N=114)	Oral AD + Placebo (N=109)	Esk (56 mg) + Oral AD (N=115)	Esk (84 mg) + Oral AD (N=114)	Oral AD + Placebo (N=113)	Esk (56 mg) + Oral AD (N=115)	Esk (84 mg) + Oral AD (N=114)	Oral AD + Placebo (N=113)	Esk (28, 56, or 84 mg) + Oral AD (N=72)	Oral AD + Placebo (N=65)	Esk (28, 56, or 84 mg) + Oral AD (N=72)	Oral AD + Placebo (N=65)
Baseline														
N	114	109	114	109	115	114	113	115	114	113	72	65	72	65
Mean	37.0	37.3	37.0	37.3	37.4	37.8	37.5	37.4	37.8	37.5	35.5	34.8	35.5	34.8
Standard deviation	5.69	5.66	5.69	5.66	4.76	5.58	6.16	4.76	5.58	6.16	5.91	6.44	5.91	6.44
Day 28 or endpoint														
N	101	100	112	109	111	98	108	115	113	113	63	60	71	64
Mean	15.5	20.6	17.4	21.0	18.5	19.4	22.8	19.1	20.6	23.1	25.4	28.7	26.3	29.2
Standard deviation	10.67	12.70	12.18	12.86	13.25	13.89	13.68	13.51	14.02	13.58	12.70	10.11	12.29	10.06
Change, baseline to Day 28 or endpoint														
N	101	100	112	109	111	98	108	115	113	113	63	60	71	64
Mean	-21.4	-17.0	-19.6	-16.3	-19.0	-18.8	-14.8	-18.3	-17.4	-14.3	-10.0	-6.3	-9.3	-5.6
Standard deviation	12.32	13.88	13.58	14.24	13.86	14.12	15.07	14.21	14.25	15.00	12.74	8.86	12.28	9.11
Statistical analysis [a]														
Difference [b]	-4.0		-3.5		-4.1	-3.2		-4.1	-2.0		-3.6		-3.6	
95% CI [c]	-7.31; -0.64		-6.67; -0.26		-7.67; -0.49	-6.88; 0.45		-7.53; -0.60	-5.52; 1.42		-7.20; 0.07		-7.16; -0.03	
2-sided p-value [d]	0.020		0.034		N/A[e]	0.088		N/A[e]	0.250		0.059		0.052	

Key: AD = antidepressant; ANCOVA = analysis of covariance; Esk = esketamine; CI = confidence interval; LOCF = last observation carried forward; MADRS = Montgomery-Asberg Depression Rating Scale; MMRM = mixed model using repeated measures; n/a = not applicable.

[a] **For both MMRM and ANCOVA analyses**, a negative difference favors esketamine.

- MMRM: For all 3 studies, the test for treatment effect is based on MMRM with change from baseline as the response variable and the fixed effect model terms for treatment, day, geographic area, class of oral AD (serotonin and norepinephrine reuptake inhibitor [SNRI] or selective serotonin reuptake inhibitor [SSRI]), and treatment-by-day, and baseline value as a covariate.
- ANCOVA: For all 3 studies, the test for treatment effect is based on ANCOVA model with change from baseline as the response variable and factors for treatment, geographic area, and class of oral AD (SNRI or SSRI), and baseline value as a covariate.
- Both MMRM and ANCOVA: *For treatment:* in Studies TRD3002 and TRD3005 the terms or factors are Esk + oral AD and oral AD + intranasal placebo; in Study TRD3001 the terms or factors are Esk 56 mg + oral AD, Esk 84 mg + oral AD, and oral AD + intranasal placebo. *For geographic area:* in Studies TRD3001 and TRD3005 the terms or factors are regions; in Study TRD3002 the term or factor is country.

[b] **Difference:** For Studies TRD3001 and TRD3005, the difference from placebo is the median unbiased estimate, which is a weighted combination of the least-squares means of the difference from placebo. For Study TRD3002, the difference from placebo is the least-squares mean difference between Esk + oral AD and oral AD + intranasal placebo.

[c] **95% CI:** For Studies TRD3001 and TRD3005, this value is the 2-sided flexible CI for the difference from placebo.

[d] **P-values:** For Studies TRD3001 and TRD3005, the p-values are based on the weighted combination test statistic.

[e] **Sequential p-values:** Because the 84 mg dose was not statistically significant, 56 mg cannot be formally evaluated for treatment difference. The fixed sequence procedure is described in the Clinical Study Report (Mod5.3.5.1/TRD3001/Sec3.11.2.4).

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: The data are adapted from the TEFMAD table series presented in (or attached to) the sections about primary efficacy analyses in the Clinical Study Reports (Mod5.3.5.1/TRD3002/Sec6.2, Mod5.3.5.1/TRD3001/Sec6.2, and Mod5.3.5.1/TRD3005/Sec6.2).

MADRS Total Score: Least-squares Mean Changes (±SE) Over Time by ANCOVA LOCF for the Double-blind Induction Phases in Studies TRD3002, TRD3001, and TRD3005 (Full Analysis Sets)

Figure 6A: Studies TRD3002 and TRD3001; Adult Subjects

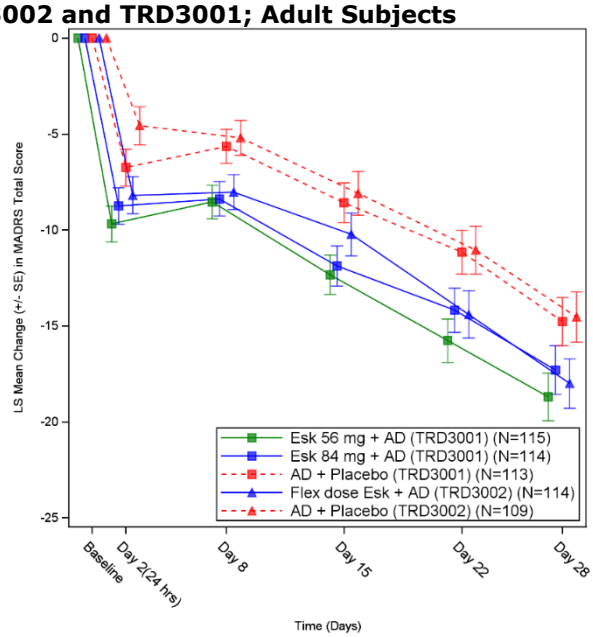
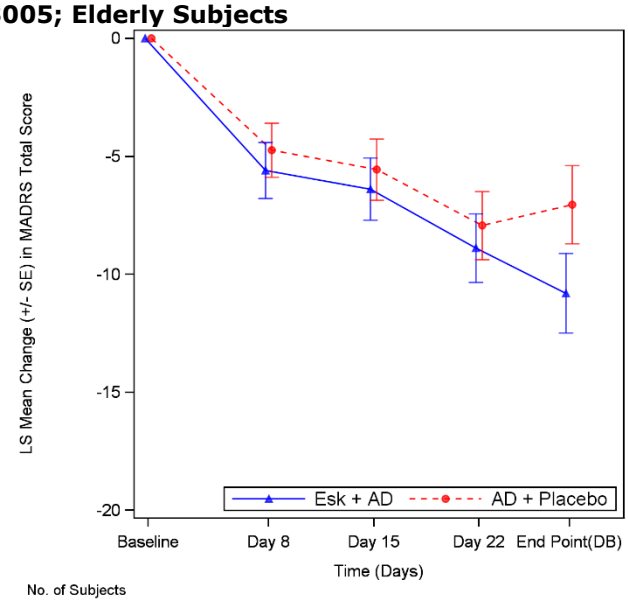


Figure 6B: Study TRD3005; Elderly Subjects



No. of Subjects

Esk + AD	72	66	71	71	71
AD + Placebo	65	63	64	64	64

Key: AD = antidepressant; ANCOVA = analysis of covariance; DB = double-blind; Esk = esketamine; SE = standard error; LOCF = last observation carried forward; LS = least-squares; MADRS = Montgomery-Asberg Depression Rating Scale.

Notes: The LS mean and SE values were based on ANCOVA fitted separately for each study with change from baseline as the response variable and factors for treatment, geographic area, and class of oral AD (serotonin and norepinephrine reuptake inhibitor [SNRI] or selective serotonin reuptake inhibitor [SSRI]), and baseline value as a covariate. *For treatment:* In Studies TRD3002 and TRD3005 the factors are Esk + oral AD and oral AD + intranasal placebo; in Study TRD3001, the factors are Esk 56 mg + oral AD, Esk 84 mg + oral AD, and oral AD + intranasal placebo. *For geographic area*: In Studies TRD3001 and TRD3005 the factors are regions; in Study TRD3002, the factor is country. Results are not adjusted for sample size re-estimation in Studies TRD3001 and TRD3005. Negative change in score indicates improvement. On the x-axes, the "Day 28" by LOCF (Figure 6A) is the same as "Endpoint (DB)" (eg, as shown for Figure 6B).

Sources: [GEFMAD03B_SQR.RTF] [JNJ-54135419\Z_SCE\DBR_2018\RE_2018\PROD\GEFMAD03B_SQR.SAS] 15JUN2018, 13:58 and [GEFMAD04A_SQR.RTF] [JNJ-54135419\TRD3005\DBR_FINAL\RE_CSR\PROD\GEFMAD04A_SQR.SAS] 26JUN2018, 12:07

Clinically Meaningful Improvement in Assessment of Antidepressant Efficacy

Currently 2 rating scales are accepted by health authorities: the Montgomery-Asberg Depression Rating Scale (MADRS) and the Hamilton Depression Rating Scale, 17-item version (HAMD). The primary endpoint most often used is difference in change in total scores of MADRS or HAM-D between new antidepressant and comparator at endpoint.

The average treatment effect by HAM-D was -3.0 (SD=2.4) in studies conducted before 1995 and then was -1.8 (SD=1.0) in studies conducted since 1995. The average 2-point difference between antidepressants and placebo translates into a clinically meaningful treatment difference for well accepted antidepressants with proven efficacy.

In studies which have used both HAM-D and MADRS scales, the differences at endpoint between drug and comparator is approximately 2-points for both scales10 and this is widely believed by academics to be sufficient as a criterion establishing obvious clinically meaningful benefit.

According to the Applicant the data from some of the recently approved antidepressants for adjunctive treatment of depression and treatment-resistant depression are summarized in the table below, as examples of change in MADRS total scores. It is noted that not all of the active substances are approved in EU for the treatment of depression (e.g. aripiprazole, brexpiprazole and the combination of olanzapine + fluoxetine are only approved in US for use in depression).

Table 6: Summary Statistics of Treatment Effect Sizes for Approved Antidepressant Drugs Based on Change in MADRS Total Score

	Difference From Reference	
Study Drug	MADRS Mean	Median (Range)
Quetiapine	-2.67	-2.79 (-3.05; -1.90)
Aripiprazole	-3.17	-3.00 (-3.70; -2.80)
Brexpiprazole	-1.94	-1.52 (-3.12; -1.19)
Vortioxetine	-3.23	-2.50 (-7.10, -0.50)
Olanzapine + fluoxetine	-2.54	-1.40 (-6.90; -0.20)

According to the Applicant, in the Phase 3 DB short-term studies with esketamine, the LS mean treatment group difference for the primary endpoint ranged from -2.0 to -4.1 across studies, dose regimens, and analyses. These treatment differences are at least as large as the median treatment differences reported in placebo controlled clinical studies of currently marketed antidepressants in patients with an inadequate response to previous AD therapy or in active comparator-controlled (i.e., failed oral AD) studies of the olanzapine-fluoxetine combination (Symbayx).

The effect size of -3.5 or -4.3, which was observed in the esketamine short term DB studies, is considered clinically relevant, since a difference of 2 between the test and the reference treatment or placebo has been previously considered sufficient to demonstrate efficacy in the regulatory setting for monotherapy. However, in a number of publications provided by the Applicant there was a range in the treatment effect sizes for MADRS total score reported in individual published studies of approved antidepressant drugs either as monotherapy or add-on treatment, i.e. the MADRS difference of treatment from placebo was for quetiapine (add-on) from -1.19 to -3.05, aripiprazole (add-on) from -2.80 to -3.70, for brexpiprazole

(add-on) from -1.19 to -3.12 and for vortioxetine from -0.5 to -7.1. Hence, the treatment effect observed with esketamine in TRD population is considered clinically relevant and meaningful.

Table 7: Treatment Effect Size for MADRS Total Score Reported in Individual Published Studies of Drugs Approved for use in Depression

Study Drug	Study	Treatment Arm	MADRS Difference From Placebo
Quetiapine	Bauer et al.[2]	150 mg	-3.05
		300 mg	-2.73
	El Khalili et al.[6]	150 mg	-1.90
		300 mg	-3.00
	Bauer et al.[1]	150 mg	-2.50
		300 mg	-2.85
Aripiprazole	Berman et al.[4]	2-20 mg	-3.00
	Marcus et al.[8]	2-20 mg	-2.80
	Berman et al.[3]	2-20 mg	-3.70
Brexpiprazole	Thase et al.[14]	1 mg	-1.19
		3 mg	-1.52
	Thase et al.[13]	2 mg	-3.12
Vortioxetine	11492A[15]	5 mg	-5.9
		10 mg	-5.7
	13267A[15]	15 mg	-5.5
		20 mg	-7.1
	315[15]	15 mg	-1.5
		20 mg	-2.8
	316[15]	10 mg	-2.2
		20 mg	-3.6
	11984A[15]	5 mg	-1.7
		10 mg	-1.5
	317[15]	10 mg	-0.8
		15 mg	-0.5
		Reference Treatment Arm	**MADRS Difference From Reference**
Olanzapine + fluoxetine	Thase et al.[12]	Fluoxetine	-5.60
		Olanzapine	-6.90
	Thase et al.[12]	Fluoxetine	-1.40
		Olanzapine	-0.70
	Shelton et al.[11]	Fluoxetine	-0.20
		Olanzapine	-1.76
		Nortriptyline	-1.25

Response and Remission Rate Based on MADRS Total Scores

Differences in MADRS or HAM-D total scores versus placebo are considered important, but differences in response rates should also be demonstrated.

For the 3 short-term studies (i.e., Studies TRD3002, TRD3001, and TRD3005), results for response and remission rates, defined using the MADRS total scores, at the end of the double-blind induction phase are shown in the following Table.

In study TRD3001, the response and remission rates at Day 28 in the esketamine + oral AD groups were 54.1% and 36.0% (for the esketamine 56-mg group), 53.1% and 38.8% (for the esketamine 84-mg group), and 38.9% and 30.6% in the oral AD + intranasal placebo group. In study TRD3002 the response and remission rates at Day 28 were 69.3% and 52.5% of the esketamine + oral AD group versus 52.0% and 31.0% for the oral AD + intranasal placebo. The differences in response and remission rates can be considered at least comparable or even higher than those previously observed in studies with approved antidepressants. The statement by the Applicant that "a treatment difference of the magnitude observed in the end point (DB LOCF) response rates between esketamine + oral AD and oral AD + intranasal placebo in the Phase 3 short-term studies (i.e., 11% to 16%) has been considered clinically meaningful for approval of other ADs" is considered valid.

As shown in the table across studies (for the 223 subjects in Study TRD3002, the 342 subjects in Study TRD3001, and the 137 subjects in Study TRD3005):

- Remission rates at Day 28 of the double-blind induction phase were higher in the esketamine + oral AD groups than in the oral AD + intranasal placebo groups across all 3 short-term studies. Remission rates ranged from approximately 36% to 53% for adult subjects or 17% for elderly subjects in the esketamine + oral AD groups and were 31% for adult subjects or 7% for elderly subjects in the oral AD + intranasal placebo groups.
- Response rates at Day 28 of the double-blind induction phase were higher in the esketamine + oral AD groups than in the oral AD + intranasal placebo groups across all 3 short-term studies. At Day 28, response rates in the esketamine + oral AD groups were 69% in TRD3002 (versus 52% for oral AD + intranasal placebo), and 54% and 53% in the 56 mg and 84 mg dose groups respectively of TRD3001 (versus 39% for oral AD + intranasal placebo). In the "*vulnerable and difficult-to-treat*" elderly population in TRD3005, the response rate was 27% in the esketamine + oral AD group (versus 13% for oral AD + intranasal placebo). Furthermore, response rate data for TRD3002 and TRD3001 provide further support for the rapid onset of antidepressant activity for esketamine, with rates after the first dose ranging from 16% to 19% in the esketamine + oral AD groups compared with 8% to 11% for the oral AD + intranasal placebo groups (as mentioned earlier, MADRS was not assessed at Day 2 in Study TRD3005).

In the esketamine + oral AD groups, remission rates (MADRS total score $\leq$12) at end point (DB LOCF) among adult subjects were 48.2% in TRD3002 and 34.8% and 35.4% in the 56 mg and 84 mg dose groups of TRD3001 (vs 30.3% and 29.2% for oral AD + intranasal placebo groups of both studies), and were 15.5% in the elderly population in TRD3005 (vs 6.3% in elderly oral AD + intranasal placebo group).

Table 8: MADRS Total Score: Response and Remission Rates at Day 28 (Observed Case) or Endpoint (LOCF) for the Double-blind Induction Phases in Studies TRD3002, TRD3001, and TRD3005 (Full Analysis Sets)

	Study TRD3002 (Adult Subjects)		Study TRD3001 (Adult Subjects)			Study TRD3005 (Elderly Subjects)	
	Esketamine (56 or 84 mg) + Oral AD (N=114)	Oral AD + Placebo (N=109)	Esketamine (56 mg) + Oral AD (N=115)	Esketamine (84 mg) + Oral AD (N=114)	Oral AD + Placebo (N=113)	Esketamine (28, 56, or 84 mg) + Oral AD (N=72)	Oral AD + Placebo (N=65)
Subjects showing response							
Day 28 (observed case)							
N	101	100	111	98	108	63	60
≥50% improvement	70 (69.3%)	52 (52.0%)	60 (54.1%)	52 (53.1%)	42 (38.9%)	17 (27.0%)	8 (13.3%)
Endpoint (LOCF)							
N	112	109	115	113	113	71	64
≥50% improvement	71 (63.4%)	54 (49.5%)	61 (53.0%)	54 (47.8%)	42 (37.2%)	17 (23.9%)	8 (12.5%)
Subjects in remission							
Day 28 (observed case)							
N	101	100	111	98	108	63	60
Score ≤12 points	53 (52.5%)	31 (31.0%)	40 (36.0%)	38 (38.8%)	33 (30.6%)	11 (17.5%)	4 (6.7%)
Endpoint (LOCF)							
N	112	109	115	113	113	71	64
Score ≤12 points	54 (48.2%)	33 (30.3%)	40 (34.8%)	40 (35.4%)	33 (29.2%)	11 (15.5%)	4 (6.3%)

Key: AD = antidepressant; LOCF = last observation carried forward; MADRS = Montgomery-Asberg Depression Rating Scale.
Notes: A subject was defined as a responder at a given time point if the percent improvement from baseline in MADRS total score was at least 50%. A subject was defined as being in remission at a given time point if the MADRS total score was ≤12 points.
Sources: The data are adapted from the TEFMADRP and TEFMADRM table series presented in (or attached to) the sections about response and remission rates based on MADRS total scores in the Clinical Study Reports (Mod5.3.5.1/TRD3002/Sec6.4.1 and Sec6.4.2; Mod5.3.5.1/TRD3001/Sec6.4.1 and Sec6.4.2; and Mod5.3.5.1/TRD3005/Sec6.3.1 and Sec6.3.2).

Response rate

Response rate, defined as ≥50% decrease in MADRS total score, over time for studies TRD3001 and TRD3002 are presented in the following Table 9 and for study TRD3005 in Table 10.

Table 9: Response rate over time in studies TRD3002 and TRD3001

TRD3002			**TRD3001**		
	oral AD + esketamine (N=114)	**oral AD + intranasal placebo (N=102)**	**oral AD + Esk 56 mg (N=115)**	**oral AD + Esk 84 mg (N=114)**	**Oral AD + intranasal placebo (N=113)**
Day 2 (24 hrs) N ≥50% improvement	 109 18 (16.5%)	 102 11 (10.8%)	 105 20 (19.0%)	 104 17 (16.3%)	 101 8 (7.9%)
Day 8 N ≥50% improvement	 109 15 (13.8%)	 105 13 (12.4%)	 114 21 (18.4%)	 107 16 (15.0%)	 111 5 (4.5%)
Day 15 N ≥50% improvement	 107 29 (27.1%)	 102 23 (22.5%)	 110 29 (26.4%)	 99 25 (25.3%)	 106 15 (14.2%)
Day 22 N ≥50% improvement	 103 54 (52.4%)	 104 35 (33.7%)	 107 52 (48.6%)	 96 33 (34.4%)	 105 25 (23.8%)
Day 28 N ≥50% improvement	 101 70 (69.3%)	 100 52 (52.0%)	 111 60 (54.1%)	 98 52 (53.1%)	 108 42 (38.9%)

Table 10: Response Based on MADRS Total Score Over Time observed cases LOCF, study TRD3005

	oral AD + Esketamine (N=72)	**Oral AD + intranasal placebo (N=65)**
Day 8 N ≥50% improvement	 66 4 (6.1%)	 63 3 (4.8%)
Day 15 N ≥50% improvement	 68 4 (5.9%)	 62 8 (12.9%)
Day 22 N ≥50% improvement	 60 9 (15.0%)	 56 8 (14.3%)
Day 28 N ≥50% improvement	 63 17 (27.0%)	 60 8 (13.3%)

Remission rate

Remission rate, defined as ≤12 total MADRS score, over time in studies TRD3001 and TRD3002 are presented in the following Table 11 and for study TRD3005 in Table 12

Table 11: Remission rate over time in studies TRD3002 and TRD3001.

TRD3002			TRD3001		
	oral AD + esketamine (N=114)	**Oral AD + intranasal placebo (N=109)**	**oral AD + Esk 56 mg (N=115)**	**oral AD + Esk 84 mg (N=114)**	**Oral AD + intranasal placebo (N=113)**
Day 2 (24 hrs)					
N	109	102	105	104	101
≤12	10 (9.2%)	6 (5.9%)	11 (10.5%)	8 (7.7%)	3 (3.0%)
Day 8					
N	109	105	114	107	111
≤12	8 (7.3%)	7 (6.7%)	9 (7.9%)	11 (10.3%)	1 (0.9%)
Day 15					
N	107	102	110	99	106
≤12	13 (12.1%)	13 (12.7%)	20 (18.2%)	15 (15.2%)	9 (8.5%)
Day 22					
N	103	104	107	96	105
≤12	32 (31.1%)	20 (19.2%)	29 (27.1%)	21 (21.9%)	17 (16.2%)
Day 28					
N	101	100	111	98	108
≤12	53 (52.5%)	31 (31.0%)	40 (36.0%)	38 (38.8%)	33 (30.6%)

Table 12: Remission Based on MADRS Total Score Over Time for Observed Case study TRD3005

	oral AD + esketamine (N=72)	**Oral AD + intranasal placebo (N=65)**
Day 8		
N	66	63
≤12	4 (6.1%)	1 (1.6%)
Day 15		
N	68	62
≤12	2 (2.9%)	5 (8.1%)
Day 22		
N	60	56
≤12	4 (6.7%)	4 (7.1%)
Day 28		
N	63	60
≤12	11 (17.5%)	4 (6.7%)

Higher than Expected Response to Oral AD + intranasal Placebo

In short term DB studies TRD3001 and TRD3002, response rates after the first dose ranged from 16% to 19% in the esketamine + oral AD group compared with 8% to 11% for the oral AD + intranasal placebo group (Mod2.7.3/App13). At end point (DB LOCF), response rates in the esketamine + oral AD groups were 63.4% in TRD3002 (vs 49.5% for oral AD + intranasal placebo) and 53.0% and 47.8% in the esketamine 56 mg + oral AD and esketamine 84 mg + oral AD groups of TRD3001, respectively (vs 37.2% for oral AD + intranasal placebo). In elderly patients' study TRD3005, the response rate at end point (DB LOCF) of the induction phase was 23.9% in the esketamine + oral AD group (vs 12.5% for oral AD + intranasal placebo).

According to the Applicant, the response and remission rates in TRD3002 and TRD3001 for the oral AD + intranasal placebo group were considerably higher than expected based on those reported in the STAR*D trial (16.8% and 13.7%, respectively, based on 16-item Quick Inventory of Depressive Symptomatology) for adult patients with MDD at treatment step 3 (ie, comparable level of treatment resistance).

The United Kingdom's National Institute of Clinical Excellence (NICE) uses a 10% difference in response rate to assess for clinically meaningful difference between 2 new antidepressant treatments. An assessment on efficacy of antidepressants by the CHMP set a 16% difference in response rates between antidepressant and placebo to be a clinically meaningful difference and noted that the difference in response rates for most approved antidepressants was between 13.1% and 19.5%.

Despite the high percentages observed for oral AD+placebo, a consistent and increasing percentage of responders and remitters over time was observed during the short term DB studies further supporting the antidepressant effect of esketamine.

A number of factors are known to increase the placebo response in trials of ADs. Some of the factors that likely contributed to the higher than expected response and remission rates observed for the oral AD + intranasal placebo groups in Studies TRD3002 and TRD3001 are highlighted below.

- Use of a newly-initiated AD (to which the subject had not shown a previous nonresponse) in the comparator arm (ie, not a true placebo control)
- High frequency of subject interaction with clinic staff due to the need for twice weekly visits (of approximately one-half day in length) during the induction phase, which imparts a high degree of attention and care.
- Use of nasal spray delivery system leading to a subject expectation of 'something novel'
- High patient expectation of benefit due to the portrayal in the media of ketamine as a 'magical' new treatment option for depression.
- Nocebo response (ie, pseudo-adverse effect following an 'inert' treatment) as noted by an increase in CADSS scores after placebo nasal spray administration to which a bittering agent had been added to facilitate blinding

Each of the above contribute to a significant expectation of benefit, which is one of the principal mediators of placebo response. While considerable care was taken to minimize other contributors to a placebo response in the Phase 3 studies with esketamine (eg, diagnostic uncertainty, rater drift), expectation of benefit is difficult to control.

The argumentation provided by the Applicant is considered valid and reflecting the expectations of the depressed patients and the general situation in the field of major depressive disorder. The Applicant provided an analysis with the number of previous treatment failures in the patients who showed response. In TRD3001, the majority of oral AD + intranasal placebo responder subjects at endpoint had 2 failures (57.1%), followed by 3 (28.6%), and ≥4 (14.3%). In TRD3002, the majority of oral AD + intranasal placebo responder at endpoint subjects had 2 failures (77.8%), followed by 3 (11.1%), and ≥4 (11.1%).

Key secondary efficacy endpoints

The following 3 key secondary efficacy endpoints were analyzed sequentially in Studies TRD3002 and TRD3001 according to the prespecified hierarchy: onset of clinical response by Day 2 [24 hours], change in SDS total score, and change in PHQ-9 total score to adjust for multiplicity and control type I error.

Onset of clinical response. With respect to the onset of clinical response, the proportion of subjects with at least a 50% improvement from baseline in the MADRS total score by Day 2 that was maintained to Day 28, was numerically higher for the esketamine + oral AD groups (ranging from ~8% to 10%) than for the oral AD + intranasal placebo group (ranging from ~2% to 5%). The odds ratio (95% CI) for onset of clinical response for the esketamine + oral AD group vs the oral AD + intranasal placebo group was 1.79

(0.57, 5.67) for Study TRD3002, and was 6.47 (1.38, 60.45) and 5.34 (1.09, 50.91) for the esketamine 56 mg and 84 mg dose groups, respectively, in Study TRD3001.

The treatment difference of this key secondary endpoint was not statistically significant for TRD3002 (2-sided p=0.321), and in the case of study TRD3001 it could not be tested statistically since the primary endpoint in the testing hierarchy was not significant for the esketamine 84 mg + oral AD group.

Changes from baseline in SDS and PHQ-9 total scores. For both TRD3002 and TRD3001, the other 2 key secondary endpoints (change in SDS and PHQ-9) in the statistical hierarchy could not be formally tested. Nevertheless, results for both of these subject-rated clinical measures numerically favoured treatment with esketamine + oral AD.

SDS total score. The LS mean (95% CI) treatment differences (based on ANCOVA [LOCF] analysis) for the SDS total score at end point (DB [LOCF]) in favour of esketamine + oral AD were -3.5 (5.85, -1.16) for TRD3002; -2.7 (-5.33, -0.01) and -1.7 (4.35, 0.85) and for the esketamine 56 mg and esketamine 84 mg groups, respectively, in TRD3001 (based on median unbiased estimate); and -2.8 (-6.39, 0.75) for TRD3005.

PHQ-9 total score. The LS mean (95% CI) treatment differences (ANCOVA [LOCF] analysis) at end point (DB [LOCF]) for the PHQ-9 total score in favour of esketamine + oral AD were -2.2 (-3.93, -0.40) for TRD3002; -2.5 (4.53, 0.54) and -1.9 (-3.87, 0.08) for esketamine 56 mg and esketamine 84 mg groups, respectively, in TRD3001 (based on median unbiased estimate); and -2.7 (5.02, 0.45) for TRD3005.

The results for key secondary efficacy endpoints cannot be used in a confirmatory way since they could not be analysed due to the fact that the most important prioritised endpoint in the hierarchical testing sequence (the onset of clinical response by Day 2 in TRD3002 and the primary endpoint for esk84mg+oral AD in TRD3001) did not show statistical significance. However, the results from the key secondary endpoints, cannot be disregarded and they did show a trend favouring esketamine + oral AD versus oral AD + intranasal placebo. The other secondary endpoints also showed a trend in favour of esketamine + oral AD versus oral AD+placebo, further supporting the antidepressant primary efficacy results.

It should be noted that for the onset of clinical response at Day 2 (24 hours) in TRD3001 showed higher numerical values for esketamine 56mg + oral AD (10.4%, 1-sided p=0.010) and esketamine 84mg + oral AD (8.8%, 1-sided p=0.041>p=0.025) vs oral AD + intranasal placebo (1.8%). Similarly, in TRD3002 the percentage that showed onset of clinical response by Day 2 (24 hours) was 7.9% for esketamine + oral AD and 4.6% for oral AD + intranasal placebo (p=0.321). Despite the fact that statistical significance was not achieved, it is obvious that a rapid onset of effect by Day 2 for esketamine + oral AD was observed in both double blind phase 3 studies TRD3001 and TD3002.

However, it is also noted that there is a considerable change in MADRS total score from Day 0 (BL) to Day 2 (24hrs) (please see below Table with results from TRD3002 from TEFMAD03A: Montgomery-Asberg Depression Rating Scale (MADRS) Total Score: Means and Mean Changes from Baseline Over Time; Double-blind Induction Phase (Study ESKETINTRD3002: Full Analysis Set). Furthermore, this decrease does not follow the same rate of decline between Day 2 (24hrs) and Day 8. From day 8 onwards MADRS total score continue to decline considerably (Figure 6a with Least-squares Mean Changes (±SE) Over Time by ANCOVA LOCF for the Double-blind Induction Phases in Studies TRD3002, TRD3001). The "plateau phase" observed in the change of MADRS total score between Day 2 (24 hours) and Day 8 may be representative of the overlapping recall periods of these 2 assessments.

For the first time it is noticed that efficacy starts earlier with a medicinal product in comparison to already approved conventional ADs (which usually requires a start of the effect at 2 weeks). This can be considered an important advantage, although a claim cannot be made due to the lack of statistical significance and a direct comparison.

Other Secondary Efficacy Endpoints

Change in CGI-S score. Results for the clinician-rated CGI-S also showed greater improvements in depression ratings for esketamine + oral AD in each of the 3 short-term studies.

Change in EQ-VAS score. Mean improvements from baseline to end point (DB) in the EQ-VAS score, which allows subjects to factor in concepts specific to their own situation in evaluating the best and worst health imaginable, were consistently numerically larger for the esketamine + oral AD groups compared with the oral AD + intranasal placebo groups in Studies TRD3002 (mean changes: 29.1 vs 20.9) and TRD3001 (mean changes: 20.9 and 19.1 [56 and 84 mg dose groups, respectively] vs 14.9)

Change in GAD-7 total score. A larger improvement in anxiety symptoms, based on the change from baseline in the GAD-7 total score, was observed for the esketamine + oral AD 56 and 84 mg groups compared with the oral AD + intranasal placebo group (LS mean treatment differences [95% CI] of -1.5 [-2.84, -0.20] and -1.4 [-2.77, -0.12], respectively) in Study TRD3001 (Mod2.7.3/Sec2.3.2.2). A similar treatment difference for the change in GAD-7 total score favoring esketamine + oral AD was not observed in Study TRD3002 (LS mean treatment difference [95% CI] of -1.0 [-2.34, 0.34]).

The other secondary endpoints also showed a trend in favour of esketamine + oral AD versus oral AD+ intranasal placebo, further supporting the antidepressant primary efficacy results

Subgroup analyses

Subgroup analyses, performed to explore the consistency of results for the primary endpoint using pooled data for Studies TRD3001/TRD3002 (to provide additional precision as some of the subgroups were small in the individual studies), showed no major differences in the results as a function of age, gender, race, baseline MADRS total score, number of previous treatment failures in the current episode, functional impairment (based on baseline SDS total score), country, region, class of newly-initiated oral AD, or oral AD class history. Similarly, subgroup analyses based on data from TRD3005 showed no notable differences in treatment effects as a function of various subgroups. Subgroup analyses were supportive of the results for the primary analysis of the primary endpoint.

Phase 3 long term studies - Study TRD3003 relapse prevention

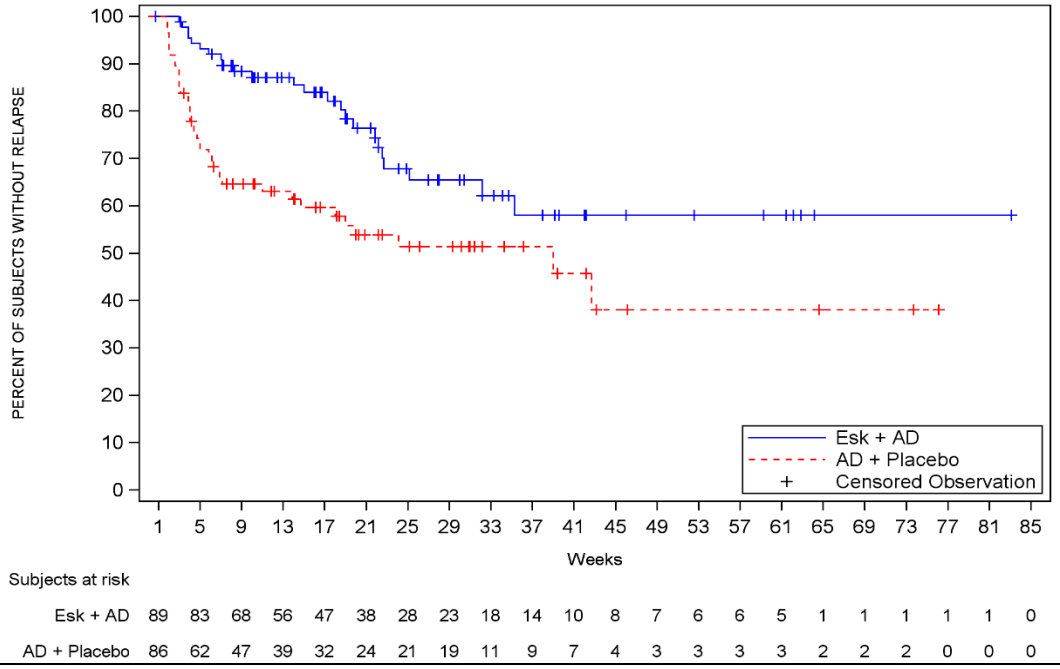
Primary endpoint

Study TRD3003 relapse prevention

A total of 705 subjects were enrolled and treated in Study TRD3003, including 437 (62.0%) who were directly enrolled, 150 (21.3%) who were transferred from TRD3001, and 118 (16.7%) who were transferred from TRD3002. A total of 121 esketamine-treated subjects demonstrated stable response at the end of the OP phase, were randomized to DB treatment in the MA phase, and were included in the full (stable responders) analysis set. In the combined group of stable remitters or stable responders randomized to continued esketamine treatment at the start of the DB MA phase in TRD3003, 60.5% received the 84 mg dose (55.6% of stable remitters) and 39.5% received the 56 mg dose (44% of stable remitters). The primary efficacy endpoint was time to relapse in subjects achieving stable remission on esketamine + oral AD.

In the full (stable remitters) analysis set, relapse events occurred during the MA phase for 26.7% subjects in the esketamine + oral AD group and 45.3% of subjects in the oral AD + intranasal placebo group. The estimated hazard ratio of esketamine + oral AD relative to oral AD + intranasal placebo based on weighted estimates was 0.49 (95% CI: 0.29; 0.84), indicating that subjects who were stable remitters and were randomized to continue treatment with esketamine were, on average, 51% less likely to relapse than subjects who were stable remitters and were randomized to discontinue esketamine. The difference between treatment groups for the time to relapse was statistically significant (2-sided p=0.003).

Figure 6: Cumulative Proportion (Kaplan-Meier Estimates) of Stable Remitter Subjects Who Remained Relapse Free During the Maintenance Phase of Study TRD3003



Key: AD = antidepressant; Esk = esketamine.
Note: The data represent the full (stable remitters) analysis set, which included 175 stable remitters and 1 stable responder (who was incorrectly randomized as a stable remitter).

[GEFREL01A.RTF] [JNJ-54135419\TRD3003\DBR_FINAL\RE_CSR\PROD\GEFREL01A.SAS] 13JUN2018
Source: Mod2.7.3/Fig9

Table 13: Time to Relapse and Number (%) of Subjects That Remained Relapse Free; Maintenance Phase (Study TRD3003: Full (Stable Responders) Analysis Set)

	Intranasal Esk + Oral AD	Oral AD + Intranasal Placebo
Time to Relapse (days) (a)		
Number assessed	62	59
Number censored (%)	46 (74.2%)	25 (42.4%)
Number of relapses (%)	16 (25.8%)	34 (57.6%)
25% percentile (95% CI)	217.0 (56.0; 635.0)	24.0 (17.0; 46.0)
Median (95% CI)	635.0 (264.0; 635.0)	88.0 (46.0; 196.0)
75% percentile (95% CI)	635.0 (NE)	NE
Hazard Ratio (95% CI)(b)	0.30 (0.16; 0.55)	
Two-sided P-value(c)	<0.001	

(a) Based on Kaplan-Meier product limit estimates.
(b) Regression analysis of survival data based on Cox proportional hazards model with treatment as a factor.
(c) Log-rank test.
Note: NE stands for Not Estimable.

Secondary Efficacy Endpoint

The secondary efficacy results for the time to relapse by stable responders (but who were not in remission) showed a statistically significantly longer time to relapse in subjects randomized to continue esketamine compared to those randomized to discontinue esketamine (2-sided p<0.001). The estimated hazard ratio of esketamine + oral AD relative to oral AD + intranasal placebo was 0.30 (95% CI: 0.16; 0.55), indicating that relapse was, on average, 70% less likely for stable responders who continued on esketamine treatment than for those who discontinued esketamine treatment

Other Secondary Efficacy Endpoints

Outcomes have been reported for assessments at the end of the maintenance phase, first for the stable remitters and then for the stable responders. Secondary efficacy endpoints numerically favoured the continuation of esketamine in measures of clinician-rated severity of depressive illness (MADRS and CGI S), subject-reported depressive symptoms (PHQ 9), anxiety symptoms (GAD 7), functioning and associated disability (SDS), and health-related quality of life and health status (EQ 5D 5L).

Subgroup analyses

Results of analyses of the primary endpoint in various subpopulations by gender, age group, region, number of previous treatment failures in the current episode, functional impairment, race, class of oral AD medication, country, consented protocol (before or after Protocol Amendment 4 [in which criteria for stable remission were amended] was adopted), entry source (direct entry or transferred entry), and oral AD medication (performed using the full [stable remitters] analysis set) generally showed a longer time to relapse for the esketamine + oral AD treatment group compared with the oral AD + intranasal placebo group, as indicated by the forest plots.

Relapse prevention study

As already mentioned above a relapse prevention study is required for a MAA in order to demonstrate the maintenance of the antidepressant effect. Study TRD3003 served as a relapse prevention study with a statistical significance in favour of esketamine + oral AD versus oral AD+ intranasal placebo. Results showed a statistically significantly longer time to relapse in patients randomized to continue esketamine compared with those randomized to discontinue esketamine among those who were in stable remission after 16 weeks of treatment with esketamine + oral AD, as well as among those who were in stable response (but not remission) after 16 weeks of treatment with esketamine + oral AD (2-sided p=0.003).

Subgroup analyses and secondary efficacy endpoints were supportive of the results of the primary and key secondary endpoints.

The proportional hazards assumption is obviously not fulfilled for the analysis of time to relapse. After an early separation of the curves shortly after start of maintenance phase, the difference between the curves remains almost constant over time, suggesting a large hazard ratio at the beginning and a hazard ratio around 1 afterwards. Therefore, the hazard ratio is not considered as the optimal summary measure to describe the difference in relapse risk, in particular because the overall hazard ratio as the 'mean hazard ratio over event times' is dominated by the early phase where most patients are at risk and most events are observed. Relapse proportion differences at fixed time points provide a better description of the treatment effect than hazard ratio. After 12 weeks, the relapse proportions (Kaplan-Meier estimates) were 13% in the esketamine + oral AD arm and 37% in the oral AD + intranasal placebo arm, corresponding to a difference of −24.0% (95% CI: −35.2%; −10.7%). After 24 weeks, the relapse proportions were 32% in the esketamine + oral AD arm and 46% in the oral AD + intranasal placebo arm, corresponding to a difference of −14.0% (95% CI: −28.1%; 2.7%).A tipping point sensitivity analysis showed that a 50 times increased risk (hazard ratio) after drop-out in the esketamine + AD group would be needed to change the conclusion of the trial (assuming that drop-out has no effect on relapse risk in placebo + AD group). As an increase in risk after treatment discontinuation at this size is considered unrealistic, the conclusions from the study are considered valid also when the treatment effect disregarding study discontinuation is of interest, which is of primary relevance from a regulatory point of view.

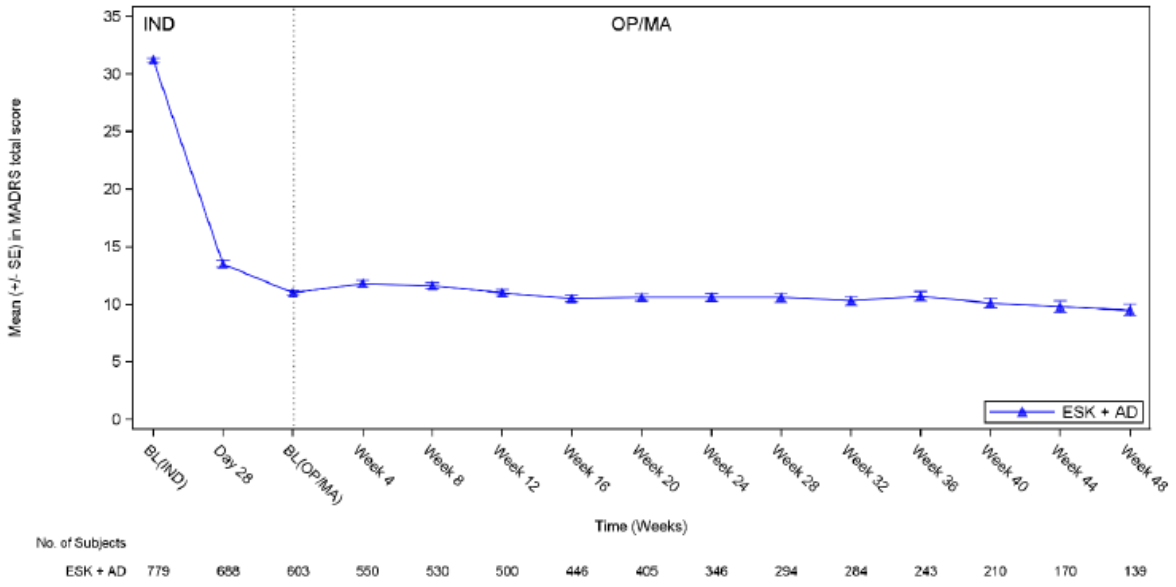
Phase 3 long term studies - Study TRD3004 OL long term safety

Of the 779 subjects who entered the induction phase, most subjects (74.5%; 580 subjects) continued to the optimization/maintenance phase. A total of 603 subjects entered the optimization/maintenance phase (580 from the induction phase and 23 responders from study ESKETINTRD300599), approximately 25% of subjects completed the optimization/maintenance phase (24.9%; 150 subjects).

Subjects treated with intranasal esketamine plus oral antidepressant in the induction phase showed a decrease (indicative of improvement in depression) from baseline (IND) in MADRS total score at endpoint (IND): mean change (SD) was -16.4 (8.76). The mean (SD) change from baseline in the MADRS total score remained largely unchanged throughout the 48-week OP/MA phase for those subjects who entered that phase, with the mean (SD) change from the baseline to end point of the OP/MA phase being 0.3 (8.12).

At the induction endpoint, the response rate (defined as ≥50% reduction in the MADRS total score from baseline) was 78.4% (593/756) and the remission rate (defined as a MADRS total score ≤12) was 47.2% (357/756). Of the subjects proceeding to the OP/MA phase, 76.5% (461/603) had met the criteria for response and 58.2% (351/603) were in remission at end point (OP/MA).

Figure 7: Arithmetic Means (+/- SE) for Montgomery-Asberg Depression Rating Scale (MADRS) Total Score Over Time Observed Case; (Study ESKETINTRD3004: All Enrolled Analysis Set)



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A similar pattern was observed for PHQ-9, GAD-7 and SDS. CGI-S and EQ-5D-5L and EQ-VAS score appeared to support the findings of the MADRS total score and the improvement of the health status in the induction phase (IND), which was maintained in the optimisation/maintenance phase (OP/MA).

It appears that there were improvements in measurements of depression in the induction phase of this open label long term study and these were consistent across multiple assessments of depressive symptoms over the 4-week induction phase. In addition, these improvements appeared to be maintained in subjects who continued treatment up to the 1-year exposure. This provides further evidence of the maintenance of the antidepressant effect of esketamine in an adjunctive setting. The analysis for the 150 subjects who completed the optimisation/maintenance phase from the baseline of the induction phase presented the same pattern as the total population.

Ancillary analyses

Phase 3 short term studies

MMRM analysis of the change in MADRS total score from baseline to Day 28:

For Study TRD3002, the least-squares mean treatment difference (95% CI) of esketamine + oral AD from oral AD + intranasal placebo was 4.0 (-7.31; -0.64); this difference was statistically significant (2 sided p=0.020) in favour of esketamine + oral AD.

For Study TRD3001,

- For esketamine 84 mg, the median unbiased estimate (95% CI) for the treatment difference versus oral AD + intranasal placebo was -3.2 (-6.88; +0.45). The results numerically favoured esketamine 84 mg + oral AD but the treatment difference was not statistically significant (2-sided p=0.088).
- For esketamine 56 mg, the median unbiased estimate (95% CI) for the treatment difference versus oral AD + intranasal placebo was -4.1 (-7.67; -0.49). The results numerically favoured esketamine 56 mg + oral AD. However, because the difference between the esketamine 84 mg + oral AD group and the oral AD + intranasal placebo group was not statistically significant, the esketamine 56 mg + oral AD group versus the oral AD + intranasal placebo group could not be formally evaluated for treatment difference based on the predefined testing sequence.

For Study TRD3005, the median unbiased estimate (95% CI) for the treatment difference of esketamine + oral AD versus oral AD +placebo was -3.6 (-7.20; +0.07). The results numerically favoured esketamine + oral AD but did not reach statistical significance (2-sided p=0.059).

It is noted that analysis of the results with MMRM provided the same effect size as that with ANCOVA LOCF analysis. This can be reassuring with respect to the outcome of the phase 3 studies. BOCF is considered the most relevant analysis and the results for phase 3 study in older patients were reanalysed using BOCF analysis, as in the case of studies TRD3001 and TRD3002.

Ancillary analyses

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 later sections).

Table 2. Summary of Efficacy for trial ESKETINTRD3001 (TRANSFORM-1)

Title: A Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Fixed Doses of Intranasal Esketamine Plus an Oral Antidepressant in Adult Subjects with Treatment-resistant Depression **Study name:** Trial of Rapid-acting Intranasal Esketamine for Treatment-resistant Major Depressive Disorder (TRANSFORM-1)		
Study identifier	ESKETINTRD3001, EudraCT Number: 2014-004584-20, NCT No.: NCT02417064, Clinical Registry No.: CR107146 EDMS number: Report Body: EDMS-ERI-144473122, 1.0	
Design	Randomized, double-blind, active-controlled, multicenter study conducted at multiple sites in Belgium, Brazil, Canada, Estonia, France, Hungary, Mexico, Slovakia, and the United States to evaluate the efficacy, safety, and tolerability of fixed doses of intranasal esketamine (56 mg or 84 mg) plus a newly initiated oral antidepressant (duloxetine, escitalopram, sertraline or venlafaxine extended release [XR]), compared with a newly initiated oral antidepressant (active comparator) plus intranasal placebo, in adult subjects with TRD. 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:	a 4-week double-blind induction phase
	Duration of Run-in phase:	a 4-week screening/prospective observational phase, followed by an optional up to 3-week period to taper the current antidepressant medication

	Duration of Extension phase:		24-week post-treatment follow-up phase Subjects who were responders to the end of the 4-week double-blind induction phase were eligible to participate in a maintenance of effect study (ESKETINTRD3003), and all subjects who were not eligible or who chose to not participate in the ESKETINTRD3003 study were to proceed to the follow-up phase of this study.
Hypothesis	Superiority: to evaluate the efficacy of switching adult subjects with treatment-resistant depression (TRD) from a prior antidepressant treatment (to which they had not responded) to intranasal esketamine (56 mg or 84 mg) plus a newly initiated oral antidepressant, compared with switching to a newly initiated oral antidepressant (active comparator) plus intranasal placebo		
Treatments groups	Intranasal Esk 56mg + Oral AD		Intranasal Esketamine 56mg + New Oral OL AD duration: double-blind induction phase 4 weeks, follow-up phase: 24 weeks , n=117
	Intranasal Esk 84mg + Oral AD		Intranasal Esketamine 84mg + New Oral OL AD, duration: double-blind induction phase 4 weeks, follow-up phase: 24 weeks, n=116
	Oral AD + Intranasal PBO		Active comparator (New Oral OL AD) + Intranasal Placebo, duration: double-blind induction phase 4 weeks, follow-up phase: 24 weeks, n=113
Endpoints and definitions	Primary endpoint	MADRS total score To end point LOCF ANCOVA	Montgomery-Asberg Depression Rating Scale (MADRS) total score: change from baseline to end point (double-blind) LOCF ANCOVA; double-blind induction phase
	Primary endpoint	MADRS total score To end point BOCF ANCOVA	Montgomery-Asberg Depression Rating Scale (MADRS) total score: Change from baseline to end point (DB) baseline observation carried forward (BOCF) ANCOVA; double-blind induction phase
	The first of 3 key secondary endpoints in the testing sequence was the proportion of subjects with onset of clinical response by Day 2 (24 hours) that was maintained to Day 28 with one excursion allowed.		
	Key Secondary endpoint	MADRS total score ONSET of response by Day 2	Onset of clinical response based on Montgomery-Asberg Depression Rating Scale (MADRS) total score by Day 2 (24hours) Fisher's Exact test; double-blind induction phase
	Key Secondary endpoint	SDS to end point LOCF ANCOVA	Sheehan Disability Scale (SDS) total score: change from baseline to end point (double-blind) LOCF ANCOVA; double-blind induction phase
	Key Secondary endpoint	PHQ-9 to end point LOCF ANCOVA	Patient Health Questionnaire (PHQ-9) total score: change from baseline to end point (double-blind) LOCF ANCOVA; double-blind induction phase
	Secondary endpoint	CGI-S to end point LOCF ANCOVA	Clinical Global Impression–Severity (CGI-S): change from baseline to end point (DB) LOCF ANCOVA on ranks; double-blind induction phase

	Secondary endpoint	GAD-7 to end point ANCOVA	Generalized Anxiety Disorder (GAD-7) total score: change from baseline to end point (DB) ANCOVA; double-blind induction phase
	Secondary endpoint	CGI-S over time	Clinical Global Impression–Severity (CGI-S): change from baseline over time ANCOVA on ranks; double-blind induction phase
Database lock	There were 2 database locks planned for this study as indicated in the protocol. The first database lock was on 17 November 2017 and included data from the double-blind phase and data from subjects who had completed the first 2 weeks of the follow-up phase. The analyses for these data were provided following this first database lock. The second database lock was on 21 March 2018 and included data from the remainder of the follow-up phase (up to 6 months). **Study Period**: 3 September 2015 (date first subject signed informed consent) to 20 February 2018 (date of last observation for last subject recorded as part of the database).		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set: The efficacy analyses of data in the double-blind induction phase were based on the full analysis set. The full analysis set was defined as all randomized subjects who received at least 1 dose of intranasal study medication			
Descriptive statistics and estimate variability	Treatment group	Intranasal Esk 56 mg + Oral AD	Intranasal Esk 84 mg + Oral AD	Oral AD + Intranasal Placebo
	Number of subject	N=115	N=114	N=113
Primary endpoint	MADRS total score To end point LOCF ANCOVA Mean (SD)	-18.3 (14.21)	-17.4 (14.25)	-14.3 (15.00)
Effect estimate per comparison	Diff. of LS means (Esk+AD minus AD+Placebo), 95% CI, 2-sided p-value	-4.1 -7.53; -0.60 p=0.022	-2.0 -5.52; +1.42 p=0.250	
Primary endpoint	**MADRS total score To end point BOCF ANCOVA Mean (SD)**	**-18.4 (14.06)**	**-16.1 (14.63)**	**-14.2 (15.06)**
Effect estimate per comparison	**Diff. of LS means (Esk+AD minus AD+Placebo), 95% CI, 2-sided p-value**	**-4.3 -7.79; -0.80 p=0.017**	**-1.2 -4.66; +2.32 p=0.513**	
Key Secondary endpoint	MADRS total score ONSET of response by Day 2	YES 12 (10.4%) NO 103 (89.6%)	YES 10 (8.8%) NO 104 (91.2%)	YES 2 (1.8%) NO 111 (98.2%)
Effect estimate per comparison	Fisher's Exact test (c) 2-sided p-value (esk+AD vs. AD+placebo) Odds ratio	0.019 6.47 (1.38; 60.45)	0.082 5.34 (1.09; 50.91)	

	(95% CI)			
Key Secondary endpoint	SDS to end point LOCF ANCOVA Mean (SD)	-10.7 (9.39)	-10.2 (10.00)	-8.1 (9.57)
Effect estimate per comparison	ANCOVA (a) Diff. of LS means (Esk+AD minus AD+Placebo) (b) 95% confidence interval on diff. (c) 2-sided p-value (esk + AD minus AD + intranasal placebo) (d)	-2.7 -5.33; -0.01 p = 0.051	-1.7 -4.35; 0.85 p = 0.190	
Key Secondary endpoint	PHQ-9 to end point LOCF ANCOVA Mean (SD)	-10.9 (8.26)	-10.9 (7.81)	-8.9 (8.37)
Effect estimate per comparison	ANCOVA (a) Diff. of LS means (Esk+AD minus AD+Placebo) (b) 95% confidence interval on diff. (c) 2-sided p-value (esk + AD minus AD + intranasal placebo) (d)	-2.5 -4.53; -0.54 p = 0.013	-1.9 -3.87; 0.08 p = 0.062	
Secondary endpoint	CGI-S to end point LOCF ANCOVA Median (Range)	-2.0 (-5; 1)	-2.0 (-5; 1)	-1.0 (-6; 3)
Effect estimate per comparison	2-sided p-value (a) (Esk+AD minus AD+Placebo)	p = 0.011	p = 0.041	
Secondary endpoint	GAD-7 to end point ANCOVA Mean (SD)	-7.4 (5.94)	7.7 (5.72)	-6.0 (6.01)
Effect estimate per comparison	ANCOVA (a) Difference from Placebo(SE) 95% confidence interval on diff. (b) 2-sided p-value (esk + AD minus AD + intranasal placebo) (c)	-1.5 (0.67) -2.84; -0.20 p = 0.024	-1.4 (0.67) -2.77; -0.12 p = 0.033	
Secondary endpoint	CGI-S over time End point (DB) Change from Baseline	-2.0 p = 0.011		-1.0
Secondary endpoint	CGI-S over time End point (DB) Change from Baseline		-2.0 p = 0.041	-1.0
Notes	ANCOVA (LOCF) was the pre-specified method for primary analysis. However, ANCOVA (BOCF) is considered more in line with the target of estimation that is of primary interest from a regulatory point of view Subject Disposition and Study Completion/Withdrawal Information			

	Outlet 1 (0.9%) 4 (3.4%) 2 (1.8%) 7 (2.0%) [TSIDS01A.RTF] [JNJ-54135419\TRD3001\DBR_FINAL2\RE_CSR\PROD\TSIDS01A.SAS] 21MAR2018, 17:41 Abbreviations: AD: antidepressant; Esk: esketamine.
Analysis description	(N=117) (N=116) (N=113) (N=346) All randomized 117 (100.0%) 116 (100.0%) 113 (100.0%) 346 (100.0%) Full 115 (98.3%) 114 (98.3%) 113 (100.0%) 342 (98.8%) Safety 115 (98.3%) 116 (100.0%) 113 (100.0%) 344 (99.4%) Follow-up 47 (40.2%) 52 (44.8%) 69 (61.1%) 168 (48.6%) [TSIDEM01.RTF] [JNJ-54135419\TRD3001\DBR_FINAL2\RE_CSR\PROD\TSIDEM01.SAS] 21MAR2018, 17:39 Abbreviations: AD: antidepressant; Esk: esketamine.

Table I: Summary of efficacy for trial ESKETINTRD3002 (TRANSFORM-2)

Title: A Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of **Flexible Doses** of Intranasal Esketamine Plus an Oral Antidepressant in Adult Subjects with Treatment-resistant Depression **Study name:** Trial of Rapid-acting Intranasal Esketamine for Treatment-resistant Major Depressive Disorder (TRANSFORM-2)		
Study identifier	ESKETINTRD3002, EudraCT Number: 2014-004585-22, NCT No.: NCT02418585, Clinical Registry No.: CR107147, EDMS number: Report Body: EDMS-ERI-139094789, 3.0	
Design	Randomized, double-blind, active-controlled, multicenter study conducted at multiple sites in the Czech Republic, Germany, Poland, Spain, and the United States to evaluate the efficacy, safety, and tolerability of **flexibly dosed intranasal esketamine (56 mg or 84 mg)** plus a newly initiated oral antidepressant (duloxetine, escitalopram, sertraline or venlafaxine extended release [XR]), compared with a newly initiated oral antidepressant (active comparator) plus intranasal placebo, in adult subjects with TRD. 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:	a 4-week double-blind induction phase
	Duration of Run-in phase:	a 4-week screening/prospective observational phase, followed by an optional up to 3-week period to taper the current antidepressant medication
	Duration of Extension phase:	24-week post-treatment follow-up phase
		The maximum duration of the study was 11 weeks (subjects who continued into the efficacy maintenance study ESKETINTRD3003) or 35 weeks (subjects who completed the follow-up phase). The study had 3 phases: a 4-week screening/prospective observational phase with an optional up to 3-week period to taper the current antidepressant medication; a 4-week double-blind induction phase with intranasal treatment sessions twice weekly; and a 24-week post-treatment follow-up phase.
Hypothesis	The primary objective of this study was to evaluate the efficacy of switching adult subjects with treatment-resistant depression (TRD) from a prior antidepressant treatment (to which they have not responded) to flexibly dosed intranasal esketamine (56 mg or 84 mg) plus a newly initiated oral antidepressant compared with switching to a newly initiated oral antidepressant	

	(active comparator) plus intranasal placebo, in improving depressive symptoms, as assessed by the change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score from Day 1 (pre-randomization) to the end of the 4-week double-blind induction phase.		
Treatments groups	Intranasal Esk 56mg or 84mg flexibly dosed + Oral AD		Intranasal Esketamine 56mg or 84mg flexibly dosed + New Oral OL AD duration: double-blind induction phase 4 weeks, follow-up phase: 24 weeks , n=116
	Oral AD + Intranasal PBO		Active comparator (New Oral OL AD) + Intranasal Placebo, duration: double-blind induction phase 4 weeks, follow-up phase: 24 weeks, n=111
Endpoints and definitions	Primary endpoint	Change in MADRS total score from BL To end point LOCF ANCOVA	Montgomery-Asberg Depression Rating Scale (MADRS) total score: change from baseline (BL) to end point (double-blind) LOCF ANCOVA; double-blind induction phase
	Primary endpoint	Change in MADRS total score from BL To end point BOCF ANCOVA	Montgomery-Asberg Depression Rating Scale (MADRS) total score: Change from baseline (BL) to end point (DB) baseline observation carried forward (BOCF) ANCOVA; double-blind induction phase
	The 3 key secondary endpoints were analyzed sequentially (in the following order: onset of clinical response by Day 2 [24 hours], change in SDS total score, and change in PHQ-9 total score) and were considered statistically significant only if the endpoint was individually significant and previous endpoints in the hierarchy were significant, including the primary endpoint.		
	Key Secondary endpoint	MADRS total score ONSET of response by Day 2	Onset of clinical response based on Montgomery-Asberg Depression Rating Scale (MADRS) total score by Day 2 (24 hours) Fisher's Exact test; double-blind induction phase
	Key Secondary endpoint	SDS to end point LOCF ANCOVA	Sheehan Disability Scale (SDS) total score: change from baseline to end point (double-blind) LOCF ANCOVA; double-blind induction phase
	Key Secondary endpoint	PHQ-9 to end point LOCF ANCOVA	Patient Health Questionnaire (PHQ-9) total score: change from baseline to end point (double-blind) LOCF ANCOVA; double-blind induction phase
	Secondary endpoint	CGI-S to end point LOCF ANCOVA	Clinical Global Impression–Severity (CGI-S): change from baseline to end point (DB) LOCF ANCOVA on ranks; double-blind induction phase
	Secondary endpoint	GAD-7 to end point ANCOVA	Generalized Anxiety Disorder (GAD-7) total score: change from baseline to end point (DB) ANCOVA; double-blind induction phase
	Secondary endpoint	CGI-S over time	Clinical Global Impression–Severity (CGI-S): change from baseline over time ANCOVA on ranks; double-blind induction phase
	Secondary endpoint	EQ-5D-5L	The EQ-5D-5L assessment is a 2-part, subject-reported instrument, consisting of the EQ-5D-5L descriptive system and the EQ-VAS, which is used as a measure of health outcome.

Database lock	Two database locks were planned for this study as indicated in the protocol. The first database lock was on 11 July 2017 and included data from the double-blind phase and data from subjects who had completed the first 2 weeks of the follow-up phase. The analyses for these data were run following this first database lock. The subject treatment assignment was revealed only to the Applicant's study staff. The investigators and the site personnel remained blinded to the treatment assignment until all subjects completed study participation through the follow-up phase. The second database lock was on 18 December 2017, for the remaining follow-up phase data (up to 6 months). **Study Period**: 07 August 2015 (date first subject signed informed consent) to 06 November 2017 (date of last observation for last subject recorded as part of the database).		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set: The efficacy analyses of data in the double-blind induction phase were based on the full analysis set. The full analysis set was defined as all randomized subjects who received at least 1 dose of intranasal study		
Descriptive statistics and estimate variability	Treatment group	Intranasal flexible dosing Esk 56 or 84 mg + Oral AD	Oral AD + Intranasal Placebo
	Number of subject	N=112	N=111
Primary endpoint	Change in MADRS total score from BL To end point LOCF ANCOVA Mean (SD)	N=112 -19.6 (13.58)	N=109 -16.3 (14.24)
Effect estimate per comparison	Diff. of LS means (Esk+AD minus AD+Placebo), (SE) 95% CI, 1-sided p-value	-3.5 (1.63) -6.67; -0.26 p=0.017	
Primary endpoint	**Change in MADRS total score from BL To end point BOCF ANCOVA Mean (SD)**	**N=114 -19.0 (13.46)**	**N=109 -15.6 (14.10)**
Effect estimate per comparison	**Diff. of LS means (Esk+AD minus AD+Placebo), (SE), 95% CI, 1-sided p-value**	**-3.5 (1.63) -6.70; -0.27 p=0.017**	
	MADRS total score at baseline, Mean (SD)	N=114 37.0 (5.69)	N=109 37.3 (5.66)
	MADRS total score at Day 28, Mean (SD)	N=101 15.5 (10.67)	N=100 20.6 (12.70)
Key Secondary endpoint	MADRS total score ONSET of response by Day 2	N=114 YES 9 (7.9%) NO 105 (92.1%)	N=109 YES 5 (4.6%) NO 104 (95.4%)
Effect estimate per comparison	Generalized Cochran-Mantel-Haenszel test (b) 1-sided p-value (esk+AD vs. AD+placebo) Odds ratio (95% CI)	p=0.161 1.79 (0.57; 5.67)	
Key Secondary	SDS to end point LOCF ANCOVA	N = 95	N = 89

endpoint	Mean (SD)	-12.5 (8.85)	-9.3 (8.39)
Effect estimate per comparison	ANCOVA (a) Diff. of LS means (Esk+AD minus AD+Placebo) (SE) 95% confidence interval on diff. 2-sided p-value (esk + AD minus AD + intranasal placebo)	-3.5 (1.19) -5.85; -1.16 p = 0.002	
Key Secondary endpoint	PHQ-9 to end point LOCF ANCOVA Mean (SD)	N = 111 -12.2 (6.87)	N = 105 -10.1 (7.87)
Effect estimate per comparison	ANCOVA (a) Diff. of LS means (Esk+AD minus AD+Placebo) (SE) 95% confidence interval on diff. 2-sided p-value (esk + AD minus AD + intranasal placebo)	-2.2 (0.89) -3.93; -0.40 p = 0.008	
Secondary endpoint	CGI-S to end point LOCF ANCOVA Median (Range)	N = 111 -2.0 (-5; 1)	N = 109 -2.0 (-5; 1)
Effect estimate per comparison	1-sided p-value (a) (Esk+AD minus AD+Placebo)	p = 0.017	
Secondary endpoint	GAD-7 to end point ANCOVA Mean (SD)	N = 110 -7.9 (6.12)	N = 102 -6.8 (5.75)
Effect estimate per comparison	ANCOVA (a) Difference from Placebo(SE), 95% confidence interval on diff. 2-sided p-value (esk + AD minus AD + intranasal placebo)	-1.0 (0.67) -2.35; -0.28 p = 0.061	
	EQ-5D-5L Mean (SD) changes in health status index from baseline to the endpoint of the double-blind induction phase	N = 114 0.288 (0.2317)	N = 109 0.231 (0.2506)
	Mean sum score also improved from baseline to the endpoint of the double-blind induction phase	-23.2 (16.64)	-17.1 (19.66)
	EQ-VAS score also improved frombaseline to the endpoint of the double-blind induction phase	29.1 (26.32)	20.9 (26.60)
Notes	ANCOVA (LOCF) was the pre-specified method for primary analysis. However, ANCOVA (BOCF) is considered more in line with the target of estimation that is of primary interest from a regulatory point of view.		
Analysis description			

	(N=116)	(N=111)	(N=227)
All randomized	116 (100.0%)	111 (100.0%)	227 (100.0%)
Full	114 (98.3%)	109 (98.2%)	223 (98.2%)
Safety	115 (99.1%)	109 (98.2%)	224 (98.7%)
Follow-up	34 (29.3%)	52 (46.8%)	86 (37.9%)

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Table J: Summary of efficacy for trial ESKETINTRD3005 (TRANSFORM-3)

Title: Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Intranasal Esketamine Plus an Oral Antidepressant in Elderly Subjects with Treatment-resistant Depression **Study name:** Trial of Rapid-acting Intranasal Esketamine for Treatment-resistant Major Depressive Disorder (TRANSFORM-3)		
Study identifier	ESKETINTRD3005, EudraCT Number: 2014-004588-19, NCT No.: NCT02422186, Clinical Registry No.: CR107129	
Design	randomized, double-blind, active-controlled, multicenter study in Belgium, Brazil, Bulgaria, Finland, France, Italy, Lithuania, Poland, South Africa, Spain, Sweden, United Kingdom and the United States to evaluate the efficacy, safety, and tolerability of **flexibly dosed intranasal esketamine (28 mg, 56 mg or 84 mg)** plus a newly initiated oral antidepressant (duloxetine, escitalopram, sertraline or venlafaxine extended release [XR]), compared with a newly initiated oral antidepressant (active comparator) plus intranasal placebo in male and female elderly subjects with TRD. An Independent Data Monitoring Committee (IDMC) was established to monitor data to ensure the continuing safety of the subjects enrolled in this study. In addition, the committee was to review 1 interim analysis (IA) for a potential sample size re-estimation or to stop the study for futility.	
	Duration of screening/prospective observational phase: Duration of double-blind induction phase: Duration of post-treatment follow-up phase:	a 4-week screening/prospective observational phase, followed by an optional up to 3-week period to taper the current antidepressant medication or to optimize medical management 4-weeks 2-weeks The maximum duration of a subject's participation in the current study was 8 to 11 weeks (for subjects continuing into ESKETINTRD3004) or 13 weeks (for subjects completing the follow up phase).
Hypothesis	The primary objective of this study was to evaluate the efficacy of switching elderly subjects with treatment-resistant depression (TRD) from a prior antidepressant treatment (to which they have not responded) to flexibly dosed intranasal esketamine (28 mg, 56 mg or 84 mg) plus a newly initiated oral antidepressant compared with switching to a newly initiated oral antidepressant (active comparator) plus intranasal placebo, in improving depressive symptoms, as assessed by the change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score from Day 1 (pre randomization) to the end of the 4-week double-blind induction phase.	
Treatments groups	Intranasal Esk 28mg or 56mg or 84mg flexibly dosed + Oral AD	Intranasal Esketamine 28mg or 56mg or 84mg flexibly dosed + New Oral OL AD all randomised analysis set, n=72
	Oral AD + Intranasal PBO	Active comparator (New Oral OL AD) + Intranasal Placebo, all randomised analysis set, n=66

Endpoints and definitions	Primary endpoint	Change in MADRS total score from BL To end point LOCF ANCOVA	Montgomery-Asberg Depression Rating Scale (MADRS) total score: change from baseline (BL) to end point (double-blind) LOCF ANCOVA; double-blind induction phase, full analysis set
	Secondary endpoint	Change From Baseline Over Time MMRM; Double-blind Induction Phase (Study ESKETINTRD3005: Full Analysis Set)	Montgomery-Asberg Depression Rating Scale (MADRS) total score over time: Change From Baseline Over Time MMRM; Double-blind Induction Phase (Study ESKETINTRD3005: Full Analysis Set),
	Secondary endpoint	Change From Baseline Over Time ANCOVA; Double-blind Induction Phase (Study ESKETINTRD3005: Full Analysis Set)	Montgomery-Asberg Depression Rating Scale (MADRS) total score over time: Change From Baseline Over Time ANCOVA; Double-blind Induction Phase (Study ESKETINTRD3005: Full Analysis Set)
	Secondary endpoint	Change in SDS over time, LOCF ANCOVA	Sheehan Disability Scale (SDS) total score: change from baseline to end point (double-blind) LOCF ANCOVA; double-blind induction phase
	Secondary endpoint	Change in PHQ-9 over time LOCF ANCOVA	Patient Health Questionnaire (PHQ-9) total score: change from baseline over time LOCF ANCOVA; double-blind induction phase (Study ESKETINTRD3005: Full Analysis Set)
	Secondary endpoint	CGI-S to end point LOCF ANCOVA	Clinical Global Impression–Severity (CGI-S): Change From Baseline to End Point (DB) LOCF ANCOVA on Ranks; Double-blind Induction Phase (Study ESKETINTRD3005: Full Analysis Set)
	Secondary endpoint	CGI-S over time	Clinical Global Impression–Severity (CGI-S): change from baseline over time ANCOVA on ranks; double-blind induction phase
Database lock	The first database lock was on 11 September 2017 and included all data from the double-blind induction phase and the follow-up phase. The analyses for these data were run following this first database lock. Following a regulatory agency's review of the AE coding, the database was re-opened to recode certain preferred terms in the Phase 3 program to facilitate the agency's review of the marketing application. A list of terms that were revised are provided in Attachment Revised Terms. The database was re-locked on 3 May 2018 and 8 June 2018 after recoding the adverse events. At the time of the first database lock, it was noted that some of the Database Release Plan specifications were not met and that the database was locked with exceptions. In addition,		

	discrepancies were found in the clinical database after database lock. Please refer to Attachment DB_Exceptions for a list of exceptions noted at the time of database lock and discrepancies found after database lock. The Applicant considers that the discrepancies in the database did not impact the conclusions of the study.		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set: The efficacy analyses of data in the double-blind induction phase were based on the full analysis set. The full analysis set was defined as all randomized subjects who received at least 1 dose of intranasal study medication		
Descriptive statistics and estimate variability	Treatment group	Intranasal flexible dosing Esk 56 or 84 mg + Oral AD	Oral AD + Intranasal Placebo
	Number of subjects	N=112	N=111
	MADRS total score at baseline, Mean (SD)	N=72 35.5 (5.91)	N=65 34.8 (6.44)
	MADRS total score at Day 28, Mean (SD)	N=101 25.4 (12.70)	N=60 28.7 (10.11)
Primary endpoint	Change in MADRS total score from BL to end point **LOCF ANCOVA** Mean (SD)	N=71 -9.3 (12.28)	N=64 -5.6 (9.11)
Effect estimate per comparison	Diff. of LS means (Esk+AD minus AD+Placebo), 95% CI, 1-sided p-value	-3.6 -7.16; -0.03 p=0.026	
Primary endpoint	**Change in MADRS total score from BL To end point BOCF ANCOVA Mean**	**N=72** **-10.1**	**N=65** **-6.8**
Effect estimate per comparison	**Diff. of LS means (Esk+oral AD minus oral AD+Placebo), (SE), 95% CI, 1-sided p-value**	**-3.2 (1.82)** **-6.85; 0.36** **p=0.039**	
Secondary endpoint	Change in MADRS From Baseline Over Time, MMRM; Double-blind Induction Phase (Study ESKETINTRD3005: Full Analysis Set), LS Mean	N=63 -10.2	N=60 -6.2
Effect estimate per comparison	Testing-Reference (esk+AD vs. AD+placebo) LS Mean, (95% CI) SE, 2-sided p-value	-4.0 (-7.71; -0.25) 1.88 p=0.037	
Secondary endpoint	Change in MADRS From Baseline Over Time ANCOVA; Double-blind Induction Phase (Study ESKETINTRD3005: Full Analysis Set), LS Mean	N=71 -10.9	N=64 -6.9
	Testing-Reference (esk+AD vs. AD+placebo) LS Mean, (95% CI) SE, 2-sided p-value	-3.9 (-7.56; -0.31) 1.83 p=0.034	

Secondary endpoint	Change in SDS over time, LOCF ANCOVA LS Mean (SD)	N = 35 -6.7	N = 36 -3.8
Effect estimate per comparison	ANCOVA (a) Diff. of LS means (Esk+AD minus AD+Placebo) (SE) 95% confidence interval on diff., SE, 2-sided p-value (esk + AD minus AD + intranasal placebo)	-2.8 (-6.39; 0.75) 1.79 p = 0.119	
Secondary endpoint	Change in PHQ-9 over time, LOCF ANCOVA LS Mean (SD)	N = 69 -6.7	N = 61 -3.9
Effect estimate per comparison	ANCOVA (a) Diff. of LS means (Esk+AD minus AD+Placebo) (95% confidence interval on diff.) SE, 2-sided p-value (esk + AD minus AD + intranasal placebo)	-2.7 (-3.93; -0.40) 1.16 p = 0.020	
Secondary endpoint	CGI-S to end point LOCF ANCOVA Median (Range)	N = 71 -1.0 (-4; 1)	N = 65 0.0 (-4; 3)
Effect estimate per comparison	2-sided p-value (Esk+AD minus AD+Placebo)	p < 0.001	
Secondary endpoint	CGI-S to end point over time ANCOVA, Median (range)	N = 71 -1.0 (-4; 1)	N =65 0.00 (-4; 1)
Effect estimate per comparison	2-sided p-value (Esk+AD minus AD+Placebo)	p < 0.001	
Notes	During this study, a for cause clinical site audit for a different study (ESKETINTRD3004) was performed at Site US10009. At the time of the audit 3 subjects were screened, 2 were screen failures, and the remaining subject was discontinued after the Day 8 induction phase visit in ESKETINTRD3005. None of the subject source data or Trial Center File for this protocol was reviewed. The same staff that conducted ESKETINTRD3004 also conducted the ESKETINTRD3005 trial. Because of the audit findings, the one subject enrolled at the site was not included in any of the analysis sets for the study (ie, not included in the all randomized analysis set, full analysis set, safety analysis set, or follow-up analysis set). The instances of GCP noncompliance at Site US10009 are not considered to have had an impact on the overall conclusions of the study. This site was closed due to GCP noncompliance and reported to the Office of Scientific Investigations. Data from this study for the 1 subject at Site US10009 are presented in the tables and listings in this CSR as listed in Table 12.		
Analysis description			

	Intranasal Esk + Oral AD (N=72)	Oral AD + Intranasal Placebo (N=66)	Total (N=138)
All randomized analysis set	72 (100.0%)	66 (100.0%)	138 (100.0%)
Full analysis set	72 (100.0%)	65 (98.5%)	137 (99.3%)
Safety analysis set	72 (100.0%)	65 (98.5%)	137 (99.3%)
Follow-up analysis set	12 (16.7%))	3 (4.5%))	15 (10.9%))

There were 2 analysis phases defined in this study: double-blind induction phase and follow-up (post-treatment) phase.

Table K: Summary of efficacy for trial ESKETINTRD3003 (SUSTAIN-1)

Title: A Randomized, Double-blind, Multicenter, Active-controlled Study of Intranasal Esketamine Plus an Oral Antidepressant for **Relapse Prevention** in Treatment-resistant Depression **Study name:** Sustenance of Esketamine Treatment Response with Repeated Doses at Intervals Determined by Symptom Severity (SUSTAIN-1)		
Study identifier	EudraCT Number: 2014-004586-24, NCT No.: NCT02493868, Clinical Registry No.: CR107128	
Design	Double-blind, multicenter, relapse prevention study using a randomized withdrawal design in adult men and women with TRD who had achieved stable remission or stable response after an induction and optimization course of treatment with intranasal esketamine + oral antidepressant. The study assessed the relative safety and efficacy of continuation versus discontinuation of intranasal esketamine, in the presence of an ongoing oral antidepressant, in subjects who were in stable remission. This study had 5 phases: a screening/prospective observational phase (direct-entry subjects only); an open-label induction phase (direct-entry subjects only); an optimization phase (both direct-entry and transferred-entry subjects); a maintenance phase (both direct-entry and transferred-entry subjects); and a 2-week post-treatment follow-up phase.	
	Duration of screening/prospective observational phase	(direct-entry subjects only) 4 weeks in duration with an optional 3-week taper period for oral antidepressant (direct-entry subjects only), open label
	Duration of induction phase:	(direct-entry subjects only) 4-week open label induction phase (intranasal esketamine + oral antidepressant; direct entry subjects only)
	Duration of optimisation phase:	(both direct-entry and transferred-entry subjects) 12 weeks (intranasal esketamine + oral antidepressant or oral antidepressant + intranasal placebo; all subjects)
	Duration of maintenance phase:	(both direct-entry and transferred-entry subjects) a variable length of time until subjects experienced a relapse event, met discontinuation/withdrawal criteria, or until the required number of relapses occurred among randomized subjects in stable remission based on interim analysis (IA) results.
	Duration of follow-up phase:	2 weeks post-treatment follow-up phase (subjects who do not enter the open-label safety extension study 54135419TRD3008)
Hypothesis	The primary objective of this study was to assess the efficacy of intranasal esketamine + oral antidepressant compared with an oral antidepressant + intranasal placebo in delaying relapse of depressive symptoms in subjects with treatment-resistant depression (TRD) who were in stable remission after an induction and optimization course of intranasal esketamine + oral antidepressant.	
Treatments groups	Intranasal Esk 56mg or 84mg flexibly dosed + Oral AD	Intranasal Esketamine 56mg or 84mg flexible dosed + Oral AD n=90 Full Analysis Set (stable remitters)

	Oral AD + Intranasal PBO		Active comparator (Oral AD) + Intranasal Placebo, n=86
	Of the 705 enrolled subjects, 437 were direct-entry subjects, and 268 were transferred-entry subjects. Of the subjects who directly entered the open-label induction phase and transferred-entry subjects on intranasal esketamine + oral antidepressant, 455 met the criteria for response and started the optimization phase. Of the 455 subjects who entered the optimization phase, 175 met the criteria for stable remission + one stable responder.		
Endpoints and definitions	Primary endpoint	Time to first relapse during maintenanc e phase	Time from randomization to the first relapse during the maintenance phase in esketamine-treated subjects who achieved stable remission at the end of the optimization phase.
	Secondary endpoint	Time to relapse in stable responders	Time to relapse in stable responders (who were not stable remitters) in maintenance phase, time to relapse was summarized and the cumulative distribution function of time to relapse was estimated by the Kaplan-Meier
	Secondary endpoint	Change in MADRS total score To end point LOCF ANCOVA (stable remitters)	Montgomery-Asberg Depression Rating Scale (MADRS) total score: Change from Baseline (MA) to Endpoint (MA) LOCF ANCOVA; Maintenance Phase (Study ESKETINTRD3003: Full (Stable Remitters) Analysis Set)
	Secondary endpoint	Change in MADRS total score To end point LOCF ANCOVA (stable responders)	Montgomery-Asberg Depression Rating Scale (MADRS) Total Score: Change from Baseline (MA) to Endpoint (MA) LOCF ANCOVA; Maintenance Phase (Study ESKETINTRD3003: Full (Stable Responders) Analysis Set)
	Secondary endpoint	Change in SDS total score (stable remitters)	Sheehan Disability Scale (SDS) Total Score: Change from Baseline (MA) to Endpoint (MA) LOCF ANCOVA; Maintenance Phase (Study ESKETINTRD3003: Full (Stable Remitters) Analysis Set)
	Secondary endpoint	Change in SDS total score (stable responders)	Sheehan Disability Scale (SDS) Total Score: Change From Baseline (MA) to Endpoint (MA) LOCF ANCOVA; Maintenance Phase (Study ESKETINTRD3003: Full (Stable Responders) Analysis Set)
	Secondary endpoint	Change in PHQ-9 Total Score (stable remitters)	Patient Health Questionnaire (PHQ-9) Total Score: Change from Baseline (MA) to Endpoint (MA) LOCF ANCOVA; Maintenance Phase (Study ESKETINTRD3003: Full (Stable Remitters) Analysis Set)
	Secondary endpoint	Change in PHQ-9 Total Score (stable responders)	Patient Health Questionnaire (PHQ-9) Total Score: Change from Baseline (MA) to Endpoint (MA) LOCF ANCOVA; Maintenance Phase (Study ESKETINTRD3003: Full (Stable Responders) Analysis Set)

	Secondary endpoint	CGI-S to end point frequency distribution (stable remitters)	Clinical Global Impression–Severity (CGI-S): Frequency Distribution at Baseline (MA) and End Point (MA); Maintenance Phase (Study ESKETINTRD3003: Full (Stable Remitters) Analysis Set)
	Secondary endpoint	CGI-S to end point frequency distribution (stable responders)	Clinical Global Impression–Severity (CGI-S): Frequency Distribution at Baseline (MA) and End Point (MA); Maintenance Phase (Study ESKETINTRD3003: Full (Stable Responders) Analysis Set)
	Secondary endpoint	Change in GAD-7 total score (stable remitters)	Generalized Anxiety Disorder (GAD-7) Total Score: Change From Baseline (MA) to Endpoint (MA) LOCF ANCOVA; Maintenance Phase (Study ESKETINTRD3003: Full (Stable Remitters) Analysis Set) at baseline (BL) and at endpoint (EP)
	Secondary endpoint	Change in GAD-7 total score (stable responders)	Generalized Anxiety Disorder (GAD-7) Total Score: Change From Baseline (MA) to Endpoint (MA) LOCF ANCOVA; Maintenance Phase (Study ESKETINTRD3003: Full (Stable Responders) Analysis Set) at baseline (BL) and at endpoint (EP)
	Secondary endpoint	EQ-5D-5L Mean (SD) EQ-VAS Scores maintenance phase (stable remitters)	The EQ-5D-5L assessment is a 2-part, subject-reported instrument, consisting of the EQ-5D-5L descriptive system and the EQ-VAS, which is used as a measure of health outcome. Mean (SD) EQ-VAS Scores maintenance phase (stable remitters) at baseline (BL) and at endpoint (EP)
	Secondary endpoint	EQ-5D-5L Mean (SD) EQ-VAS Scores maintenance phase (stable responders)	The EQ-5D-5L assessment is a 2-part, subject-reported instrument, consisting of the EQ-5D-5L descriptive system and the EQ-VAS, which is used as a measure of health outcome. Mean (SD) EQ-VAS Scores maintenance phase (stable responders) at baseline (BL) and at endpoint (EP)
Database lock	Two database locks were planned for this study as indicated in the protocol. The first database lock was on 11 July 2017 and included data from the double-blind phase and data from subjects who had completed the first 2 weeks of the follow-up phase. The analyses for these data were run following this first database lock. The subject treatment assignment was revealed only to the Applicant's study staff. The investigators and the site personnel remained blinded to the treatment assignment until all subjects completed study participation through the follow-up phase. The second database lock was on 18 December 2017, for the remaining follow-up phase data (up to 6 months). **Study Period**: 07 August 2015 (date first subject signed informed consent) to 06 November 2017 (date of last observation for last subject recorded as part of the database).		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Sets There were 4 full analysis sets used for the evaluation of efficacy: • Full (IND): All subjects who received at least 1 dose of intranasal study drug and 1 dose of oral antidepressant in the open-label induction phase		

	(direct-entry subjects only). • Full (OP): All subjects who received at least 1 dose of intranasal esketamine study drug and 1 dose of oral antidepressant in the optimization phase. • There were 2 full analyses sets defined for the maintenance phase: - Full (stable remitters): used to perform primary and secondary efficacy evaluations on randomized subjects who were in stable remission at the end of the optimization phase and who received at least 1 dose of intranasal study drug and 1 dose of oral antidepressant during the maintenance phase. - Full (stable responders): used to perform secondary efficacy evaluations on randomized subjects who were stable responders (who were not stable remitters) at the end of the optimization phase and who received at least 1 dose of intranasal study drug and 1 dose of oral antidepressant during the maintenance phase.		
Descriptive statistics and estimate variability	Treatment group	Intranasal flexible dosing Esk 56 or 84 mg + Oral AD	Oral AD + Intranasal Placebo
	Number of subject	N=90	N=86
Primary endpoint	Total number of subjects with relapse (%)	24 (26.7%)	39 (45.3%)
Effect estimate per comparison	Hazard ratio, 95% CI, Two-sided P-value	0.47 0.28; 0.78 0.003	
Effect estimate per comparison	Sensitivity analysis based on the cut-off date of the 59th event actually included 61 relapses, as 3 relapses occurred on the same date Two-sided P-value	0.46 0.27; 0.77 0.003	
Secondary endpoint	Time to relapse in stable responders, number of relapses (%)	N=62 16 (25.8%)	N=59 34 (57.6%)
Effect estimate per comparison	Hazard ratio, 95% CI, Two-sided P-value	0.30 0.16; 0.55 P<0.001	
Secondary endpoint	Change in MADRS total score To end point LOCF ANCOVA (stable remitters) Mean (SD)	N=89 7.5 (11.59)	N=86 12.5 (13.63)
Effect estimate per comparison	ANCOVA (a) Diff. of LS means (SE) (Esk+AD minus AD+Placebo) 95% confidence interval on diff. Two-sided p-value (b)	-5.2 (1.82) (-8.77; -1.58) p = 0.005	
Secondary endpoint	Change in MADRS total score To end point LOCF ANCOVA (stable responders) Mean (SD)	N=62 4.4 (11.38)	N=59 11.4 (12.00)
Effect estimate per comparison	ANCOVA (a) Diff. of LS means (SE) (Esk+AD minus AD+Placebo) 95% confidence interval on diff.	-7.4 (1.95) -11.30; -3.55	

	Two-sided p-value (b)	p < 0.001	
Secondary endpoint	Change in SDS Total Score (stable remitters) Mean (SD)	N = 82 4.7 (7.34)	N = 77 7.2 (10.44)
Effect estimate per comparison	ANCOVA (a) Diff. of LS means (SE) (Esk+AD minus AD+Placebo) 95% confidence interval on diff. Two-sided p-value (b)	-2.9 (1.30) -5.51; -0.38 p = 0.025	
Secondary endpoint	Change in SDS Total Score (stable responders) Mean (SD)	N = 58 2.2 (6.63)	N = 53 6.8 (7.64)
Effect estimate per comparison	ANCOVA (a) Diff. of LS means (Esk+AD minus AD+Placebo) (SE) 95% confidence interval on diff. 2-sided p-value (esk + AD minus AD + intranasal placebo) Two-sided p-value	-4.7 (1.31) -7.30; -2.10 p < 0.001	
Secondary endpoint	Change in PHQ-9 Total Score (stable remitters) Mean (SD)	N = 89 3.3 (5.36)	N = 86 5.9 (7.09)
Effect estimate per comparison	ANCOVA (a) Diff. of LS means (SE) (Esk+AD minus AD+Placebo) 95% confidence interval on diff. Two-sided p-value (b)	-2.4 (0.90) -4.20; -0.65 p = 0.008	
Secondary endpoint	Change in PHQ-9 Total Score (stable responders) Mean (SD)	N = 61 1.7 (5.02)	N = 58 4.7 (5.48)
Effect estimate per comparison	ANCOVA (a) Diff. of LS means (SE) (Esk+AD minus AD+Placebo) 95% confidence interval on diff. Two-sided p-value (b)	-3.0 (0.93) -4.87; -1.18 p = 0.002	
Secondary endpoint	CGI-S to end point frequency distribution (stable remitters) % Normal/ Borderline/Mild	BL: N = 90 97.8% EP: N = 89 74.2%	BL: N = 86 98.8% EP: N = 86 60.5%
Secondary endpoint	CGI-S to end point frequency distribution (stable responders) % Normal/ Borderline/Mild	BL: N = 62 93.5% EP: N = 62 67.7%	BL: N = 59 91.5% EP: N = 58 46.6%
Secondary endpoint	Change in GAD-7 total score (stable remitters)	N = 89	N = 86

	Men (SD)	2.2 (4.45)	4.0 (5.93)
Effect estimate per comparison	ANCOVA (a) Diff. of LS means (SE) (Esk+AD minus AD+Placebo) 95% confidence interval on diff. Two-sided p-value (b)	-1.7 (0.72) -3.12; -0.28 p = 0.020	
Secondary endpoint	Change in GAD-7 total score (stable responders) Men (SD)	N = 61 1.4 (3.76)	N = 58 2.6 (4.26)
Effect estimate per comparison	ANCOVA (a) Diff. of LS means (SE) (Esk+AD minus AD+Placebo) 95% confidence interval on diff. Two-sided p-value (b)	-1.1 (0.72) -2.56; 0.31 p = 0.123	
	EQ-5D-5L Mean (SD) EQ-VAS Scores maintenance phase (stable remitters)	BL: 88.4 (9.23) EP: 77.9 (20.80)	BL: 86.6 (9.77) EP: 70.6 (21.51)
	EQ-5D-5L Mean (SD) EQ-VAS Scores maintenance phase (stable responders)	BL: 77.0 (17.37) EP: 76.0 (17.67)	BL: 79.1 (14.27) EP: 65.4 (18.99)

Notes

Remission was defined as MADRS total score of ⩽12, PHQ-9 total score ⩽4 or SDS score ⩽2 for each item and total score ⩽6 at a given time point. **Stable remission** was defined as a MADRS total score ⩽12 for at least 3 of the last 4 weeks of the optimization phase, with 1 excursion of a MADRS total score >12 or one missing MADRS assessment permitted at optimization Week 13 or 14 only. **Response** was defined as ⩾50% improvement in MADRS total score or ⩾50% improvement PHQ-9 total score or SDS score of ⩽4 for each item and total score ⩽12 at a given time point. **Stable response** was defined as ⩾50% reduction in the MADRS total score from baseline (Day 1 of induction phase, prior to the first intranasal dose) in each of the last 2 weeks of the optimization phase, but without meeting criteria for stable remission.

Relapse was defined as a MADRS total score ⩾22 for 2 consecutive assessments separated by 5 to 15 days and/or hospitalization for worsening depression or any other clinically relevant event determined per clinical judgment to be suggestive of a relapse of depressive illness such as suicide attempt, completed suicide, or hospitalization for suicide prevention.

Table 22 (study TRD3003 CSR): Time to Relapse Censoring Subjects with a Relapse within Weeks 1,2,3 and 4; Maintenance Phase (Study ESKETINTRD3003: Full (Stable Remitters) Analysis Set)

	Number of relapses (%) (a)		
	Intranasal Esk + Oral AD	Oral AD + Intranasal Placebo	Hazard ratio (95% CI)
Week 1	0	0	0.47 (0.28; 0.78)
Week 2	0	6 (15.4%)	0.54 (0.32; 0.91)
Week 3	1 (4.2%)	13 (33.3%)	0.64 (0.37; 1.12)
Week 4	4 (16.7%)	19 (48.7%)	0.71 (0.38; 1.31)

(a) The number of relapses occurred within weeks 1,2,3 and 4.
Note: Regression analysis of survival data based on Cox proportional hazards model with treatment as a factor. The oral AD + intranasal placebo is the reference group.

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Study Completion/Withdrawal Information; Open-label Induction Phase (Study ESKETINTRD3003: Safety (IND) Analysis Set)

	Intranasal Esk + Oral AD (N=437) Continued to optimization phase 273 (62.5%) Withdrawn during open-label induction phase 164 (37.5%) Adverse event 22 (5.0%) Lack of efficacy 2 (0.5%) Lost to follow-up 1 (0.2%) Protocol violation 2 (0.5%) Withdrawal by subject 15 (3.4%) Other 8 (1.8%) Subject does not meet criteria for continuing into the next phase 114 (26.1%) [TSIDS04.RTF] [JNJ-54135419\TRD3003\DBR_FINAL\RE_CSR\PROD\TSIDS04.SAS] 14JUN2018, 00:06 During this study, a for-cause clinical site audit was performed at site PL10002 (Poland), because the Applicant was informed by local representatives of possible GCP noncompliance at the site. Seven subjects from this site were transferred entry from ESKETINTRD3002 and 7 were directly enrolled. The instances of GCP noncompliance at Site PL10002 were not considered to have had an impact on the overall conclusions of the study, as none of these subjects met the criteria for stable remission. However, as a result of these audit findings, the 14 subjects from site PL10002 were not included in any of the analysis sets for the study (ie, not included in the all randomized analysis set, full analysis set, or follow-up analysis set).
Analysis description	Follow-up phase Follow-up 481 64 545 (a) Transferred entry subjects who continued to receive an oral antidepressant plus intranasal Placebo. (b) Full (Stable Remitters) analysis set at the time of Interim analysis. Note: Stable Remission: MADRS total score <=12 for at least 3 of the last 4 weeks of the optimization phase, but one excursion of a MADRS total score >12 or one missing MADRS assessment is permitted at Optimization week 13 or 14 only. The MADRS total score at weeks 15 and 16 must be <=12. Stable Response: >=50% reduction in the MADRS total score from baseline (Day 1 of induction phase; pre-randomization/prior to the first intranasal dose) in each of the last 2 weeks of the optimization phase, but does not meet criteria for stable remission. For transferred-entry subjects, Day 1 of the open-label induction phase will take place in studies ESKETINTRD3001 or ESKETINTRD3002. In addition to the subgroup analysis of pre/post Amendment 4 (Section 6.2.5), the Cox proportional hazards model and unweighted log-rank test was performed post-hoc on the 167 subjects who met the more stringent definition per pre-Amendment 4 to evaluate the robustness of the results. The HR (95% CI) for the 167 subjects was 0.44 (0.26; 0.74) with a 2-sided p-value of 0.002 (Attachment TEFREL02B). This result was consistent with the primary efficacy analysis.

Table L: Summary of efficacy for trial ESKETINTRD3004 (SUSTAIN-2)

Title: An Open-label, Long-term, Safety and Efficacy Study of Intranasal Esketamine in Treatment-resistant Depression **Study Name:** Safety and Sustenance of Esketamine Treatment Response with Repeated Doses at Intervals Determined by Symptom Severity (**SUSTAIN-2**)	
Study identifier	EudraCT Number: 2014-004587-38, NCT No.: NCT02497287, Clinical Registry No.: CR107148
Design	1-year open-label, long-term study conducted at multiple sites in Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Finland, France, Germany, Italy, Malaysia, Mexico, Poland, Republic of Korea, South Africa, Spain, Sweden, Taiwan, Turkey, United Kingdom, and United States. This study evaluated intranasal esketamine plus a newly initiated oral antidepressant (duloxetine, escitalopram, sertraline or venlafaxine extended release [XR]) in adult subjects with treatment-resistant depression. An Independent Data Monitoring Committee (IDMC) was established to monitor data to ensure the continuing safety of the subjects enrolled in this study. This long-term study included 4 phases: ≤4-week screening phase (direct-entry subjects only), a 4-week induction phase (direct-entry subjects and transferred-entry non-responder subjects), and a 48-week

	optimization/maintenance phase (all responder subjects from the open-label induction phase of this study, and transferred-entry responder subjects), and 4-week follow-up phase (available for all subjects). The maximum duration of a subject's participation in this study was to be 60 weeks for direct-entry subjects; 56 weeks for transferred-entry non-responder subjects, and 52 weeks for transferred-entry responder subjects. The end of the study occurred when at least 300 subjects received treatment with esketamine for 6 months and at least 100 subjects for 12 months including both direct-entry and transfer-entry subjects.		
	Duration of screening phase Duration of induction phase: Duration of optimisation/ maintenance phase: Duration of follow-up phase:		⩽4-weeks 4 weeks 48 weeks 4 weeks
Hypothesis	The primary objective of the study was to assess the long-term safety and tolerability of intranasal esketamine plus a newly initiated oral antidepressant in subjects with treatment-resistant depression (TRD), with special attention to the following: potential effects on cognitive function; potential treatment-emergent symptoms of cystitis and/or lower urinary tract symptoms; potential withdrawal and/or rebound symptoms following cessation of intranasal esketamine treatment.		
Treatments groups	Intranasal Esk 28mg or 56mg or 84mg flexibly dosed + Oral AD		Intranasal Esketamine 28mg or 56mg or 84mg flexible dosed + Oral AD n=802
	Without Active comparator		
	A total of 802 subjects were enrolled in this study. Of the 779 subjects who entered the induction phase (included 88 non-responders from study ESKETINTRD3005), most subjects (74.5%; 580 of 779 subjects) continued to the optimization/maintenance phase. Of the 802 subjects enrolled, 364 subjects (45.4%) were treated for 6 months and 136 subjects (17.0%) for 12 months.		
Endpoints and definitions	Efficacy was considered a secondary objective of this study because this was an open-label study with no comparator group. Therefore, only descriptive summaries of efficacy rating scales are presented. Both observed case and LOCF analyses were performed.		
	Secondary endpoint	Change in MADRS total score To end point, induction phase	Montgomery-Asberg Depression Rating Scale (MADRS) total score: Change from Baseline (IND) to Endpoint (IND); Induction Phase (Study ESKETINTRD3004: Full (IND) Analysis Set)
	Secondary endpoint	Change in MADRS total score To end point, optimisation /maintenance phase	Montgomery-Asberg Depression Rating Scale (MADRS) total score: Change from Baseline OP/MA) to Endpoint (OP/MA); Induction Phase (Study ESKETINTRD3004: Full (OP/MA) Analysis Set)

	Secondary endpoint	Change in PHQ-9 Total Score (induction phase)	Patient Health Questionnaire (PHQ-9) Total Score: Change from Baseline (IND) to Endpoint (IND); Induction Phase (Study ESKETINTRD3004 Full (IND) Analysis Set)
	Secondary endpoint	Change in PHQ-9 Total Score (optimisation/maintenance phase)	Patient Health Questionnaire (PHQ-9) Total Score: Change from Baseline (OP/MA) to Endpoint (OP/MA); Optimisation/Maintenance Phase (Study ESKETINTRD3004: Full (OP/MA) Analysis Set)
	Secondary endpoint	Change in CGI-S to end point (induction phase)	Clinical Global Impression–Severity (CGI-S): Change from Baseline (IND) to End Point (IND); Induction Phase (Study ESKETINTRD3004: Full (IND) Analysis Set)
	Secondary endpoint	Change in CGI-S to end point (optimisation/maintenance phase)	Clinical Global Impression–Severity (CGI-S): Change from Baseline (OP/MA) to End Point (OP/MA); Optimisation/Maintenance Phase (Study ESKETINTRD3004: Full (OP/MA) Analysis Set)
	Secondary endpoint	Change in GAD-7 total score (induction phase)	Generalized Anxiety Disorder (GAD-7) Total Score: Change From Baseline (IND) to Endpoint (IND); Induction Phase (Study ESKETINTRD3004: Full (IND) Analysis Set)
	Secondary endpoint	Change in GAD-7 total score (optimisation/maintenance phase)	Generalized Anxiety Disorder (GAD-7) Total Score: Change From Baseline (OP/MA) to Endpoint (OP/MA); Optimisation/Maintenance Phase (Study ESKETINTRD3004: Full (OP/MA) Analysis Set)
	Secondary endpoint	Change in SDS total score (induction phase)	Sheehan Disability Scale (SDS) Total Score: Change from Baseline (IND) to Endpoint (IND); Induction Phase (Study ESKETINTRD3004: Full (IND) Analysis Set)
	Secondary endpoint	Change in SDS total score (optimisation/maintenance phase)	Sheehan Disability Scale (SDS) Total Score: Change from Baseline (OP/MA) to Endpoint (OP/MA); Optimisation/Maintenance Phase (Study ESKETINTRD3004: Full (OP/MA) Analysis Set)
	Secondary endpoint	Change in EQ-5D-5L Health Status Index, EQ-VAS and Sum Score (induction phase)	The EQ-5D-5L descriptive system comprised the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression and the EQ-VAS, which is used as a measure of health outcome. Change in EQ-5D-5L, EQ-VAS Scores and Sum Score (IND) from baseline (BL) to endpoint (EP)

	Secondary endpoint	Change in EQ-5D-5L Health Status Index, EQ-VAS and Sum Score (optimisation /maintenanc e phase)	The EQ-5D-5L descriptive system comprised the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression and the EQ-VAS, which is used as a measure of health outcome. Change in EQ-5D-5L, EQ-VAS Scores and Sum Score (OP/MA) from baseline (BL) to endpoint (EP)
Database lock	At database lock for this study on 11 January 2018, it was noted that some of the Database Release Plan specifications were not met and that the database was locked with exceptions. In addition, discrepancies were found in the clinical database after database lock. Please refer to Attachment DB Exceptions for a list of exceptions noted at the time of database lock and discrepancies found after database lock. The medical history of spontaneous abortion of subjects 40540102 and 40900503 were not entered into the eCRF (Attachment DB_Exceptions) but were reported in the CIOMS reports. The subjects were reported as pregnant during treatment. Both subjects experienced a spontaneous abortion, one occurred during the optimization/maintenance phase the other occurred after the study (See Section 7.4.12 of the CSR). The Applicant considers that the discrepancies in the database did not impact the conclusions of the study. Following a regulatory agency's review of the adverse event coding, the database was re-locked for this study on 3 May 2018 and 13 June 2018 to recode specific preferred terms in the Phase 3 program in order to facilitate the agency's review of the marketing application. A list of terms that were revised are provided in Attachment Revised Terms.		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	In addition to direct entry subjects, subjects who were nonresponders from a previous study (ESKETINTRD3005) after having had 4 weeks of treatment with either esketamine plus oral antidepressant or placebo plus oral antidepressant in the previous study, entered the induction phase. Not all subjects who entered the induction phase progressed to the optimization/maintenance phase. Only subjects who completed the induction phase and were responders, entered the optimization/maintenance phase. In addition, responders from study ESKETINTRD3005 were allowed to enter the optimization/maintenance phase after having had 4 weeks of treatment with either esketamine plus oral antidepressant or placebo plus oral antidepressant. Because the study was considered completed based on the exposure criteria, some subjects could not complete the full duration of the optimization/maintenance phase. Efficacy analyses of data from the induction phase and optimization/maintenance phase were based on the full analysis sets, that were defined as subjects who received at least 1 dose of esketamine or 1 dose of oral antidepressant medication during the respective phase. Subjects in the follow-up phase were those who entered that phase. Due to GCP issues at one study site, 21 subjects from this site were not included in the analysis sets; however, data for this site are presented in listings.		
Descriptive statistics and estimate variability	Treatment group (Without active comparator)	Intranasal flexible dosing Esk 28 or 56 or 84 mg + Oral AD	
	Number of subjects Induction phase	N=779	
	Number of subjects Optimisation/Maintenance phase	N=603	
Secondary endpoint	Change in MADRS total score To end point, induction phase, Mean (SD)	N=756	

		-16.4 (8.76)
Secondary endpoint	Change in MADRS total score To end point, optimisation/ maintenance phase, Mean (SD)	N = 603 0.3 (8.12)
	MADRS total score at baseline (IND), Mean (SD)	31.2 (5.29)
	MADRS total score at endpoint (OP/MA), Mean (SD)	11.3 (7.87)
Secondary endpoint	Change in PHQ-9 Total Score (induction phase), Mean (SD)	N=746 -8.9 (6.67)
Secondary endpoint	Change in PHQ-9 Total Score (optimisation/maintenance phase)	N=603 -0.2 (5.65)
Secondary endpoint	Change in CGI-S to end point (induction phase), Median (range)	N = 763 -2.0 (-6;2)
Secondary endpoint	Change in CGI-S to end point (optimisation/maintenance phase), Median (range)	N = 603 0.0 (-3;4)
Secondary endpoint	Change in GAD-7 total score (induction phase), Mean (SD)	N = 724 -5.9 (5.85)
Secondary endpoint	Change in GAD-7 total score (optimisation/maintenance phase)	N = 574 0.2 (4.23)
Secondary endpoint	Change in SDS total score (induction phase), Mean (SD)	N = 626 -9.3 (7.86)
Secondary endpoint	Change in SDS total score (optimisation/maintenance phase), Mean (SD)	N = 541 -1.6 (8.25)
Secondary endpoint	Change in EQ-5D-5L Health Status Index, EQ-VAS and Sum Score (induction phase), Mean (SD)	N = 745 HSI 0.190 (0.2138) N= 746 EQ VAS 17.0 (21.69) N= 745 Sum Score -15.3 (16.26)
Secondary endpoint	Change in EQ-5D-5L Health Status Index, EQ-VAS and Sum Score (optimisation/maintenance phase), Mean (SD)	N = 603 HSI -0.009 (0.1411) N= 603 EQ VAS 1.6 (18.51) N= 603 Sum Score -0.7 (13.19)
Notes	Because this was an open-label study without a comparator group, the interpretation of the efficacy results is limited. Assessment of efficacy was a secondary objective of this study. Indicators of improvement were consistently observed for depression symptoms and other efficacy assessments by the end of the 4-week induction phase, and appeared to be sustained in subjects who continued treatment up to 1-year of exposure. It should be noted that subjects in the induction phase were either direct-entry or nonresponders from the 4-week induction phase of another study (ESKETINTRD3005). In addition, only responding subjects from the induction phase of study ESKETINTRD3004 were	

	allowed to enter the optimization/maintenance phase and were supplemented by responders from the 4-week induction phase of study ESKETINTRD3005. Subjects treated with esketamine plus a newly initiated oral antidepressant at the start of the induction phase showed a decrease (ie, improvement) in MADRS total score: mean change (SD) from baseline of the induction phase in MADRS total score to the endpoint of the induction phase was -16.4 (8.76) in 756 subjects. Of note, the mean (SD) MADRS total score at baseline of the induction phase was 31.4 (5.39) among enrolled subjects. During the optimization/maintenance phase (n=603): mean change (SD) in MADRS total score from baseline of the optimization/maintenance phase to the endpoint of the optimization/maintenance phase was 0.3 (8.12). The main limitation of this study was that treatment was open-label with no comparator group. Based on predefined criteria related to achieving the required number of exposures at 6 and 12 months (ie, 364/802 and 136/802, respectively), not all enrolled subjects completed the full planned duration of the study. Table 11: Completion/Withdrawal Information; Optimization/Maintenance Phase (Study ESKETINTRD3004: Full (OP/MA) Analysis Set) **Intranasal Esk + Oral AD (N=603)** Completed optimization/maintenance phase: 150 (24.9%) Withdrawn during optimization/maintenance phase: 453 (75.1%) Study terminated by sponsor: 331 (54.9%) Withdrawal by subject: 30 (5.0%) Adverse event: 25 (4.1%) Lack of efficacy: 25 (4.1%) Lost to follow-up: 10 (1.7%) Protocol violation: 3 (0.5%) Subject missed assessments or treatment sessions: 3 (0.5%) Death: 2 (0.3%) Pregnancy: 2 (0.3%) Non-compliance with study drug: 1 (0.2%) Other: 21 (3.5%) [TSIDS04.RTF] [JNJ-54135419\TRD3004\DBR_FINAL\RE_CSR\PROD\TSIDS04.SAS] 11JAN2018, 21:07 An internal audit was conducted from 22-Jun-2016 thru 24-Jun-2016 based on previous findings from a Janssen Site Manager during data reviews of site US10025. There were serious data integrity issues due to lack of PI oversight and a lack of adverse event reporting. In addition, vital sign data did not show the expected variability. The site was closed on 06-Jul-2016 and all subjects were withdrawn from the study (Appendix 8 Audit Certificate). Because of these audit findings, data from 21 subjects from Site US10025 (19 who received esketamine treatment and 2 who did not receive esketamine treatment) were not included in any of the analysis sets for the study (Appendix 17 LSIEXPE01A). The instances of GCP noncompliance at Site US10025 were not considered to have had an impact on the overall conclusions of the study. Data from this study for the 21 subjects at Site US10025 are presented separately and not included in summary tables.
Analysis description	Efficacy measures were summarized descriptively at each scheduled visit for each phase, using both last observation carried forward and observed data. Efficacy measures were summarized descriptively at each scheduled visit for each phase, using both last observation carried forward and observed data. Efficacy summaries were provided for the full analysis sets for the induction and optimization/maintenance phases, and for the follow-up phase. Table 8: Number of Subjects Entered from Study ESKETINTRD3005 (By Responder Status) and Direct-Entry Subjects (Study ESKETINTRD3004: All Enrolled Analysis Set)

[TSIDS01.RTF] [JNJ-54135419\TRD3004\DBR_FINAL\RE_CSR\PROD\TSIDS01.SAS] 11JAN2018, 21:07

	Intranasal Esk + Oral AD (N=802)
Induction phase	
Full (IND)	779 (97.1%)
Optimization/maintenance phase	
Full (OP/MA)	603 (75.2%)
Follow-up phase	
Follow-up	357 (44.5%)

[TSIDS02.RTF] [JNJ-54135419\TRD3004\DBR_FINAL\RE_CSR\PROD\TSIDS02.SAS] 11JAN2018, 21:07

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

Results for Studies TRD3002 and TRD3001 generally were not pooled due to differences in study design. However, analyses are provided here for efficacy in select subpopulations using data pooled for adults in Studies TRD3002 and TRD3001.

According to the Applicant, the results for Studies TRD3002 and TRD3001 generally were not pooled due to differences in study design. This section is an exception in accordance with the ICH guideline, which states for the "Comparison of Results in Subpopulations" section of an SCE that "given the limited sample sizes in individual studies, analyses across multiple studies should be performed." Accordingly, analyses have been provided for efficacy in select subpopulations using data pooled for adults in Studies TRD3002 and TRD3001. These analyses of pooled data were performed to increase the precision of efficacy estimates in adult subpopulations.

For psychiatric history and the severity of MDD at baseline, the MADRS total score had a mean (SD) value of 37.4 (5.57) points, which represented severe depression (as described in Section 3.2.3 of this SCE). The CGI S results indicated that 57.2% of subjects were markedly ill (with a score of 5 out of 7 points), 24.1% of subjects were severely ill (with a score of 6 out of 7 points), and 17.0% of subjects were moderately ill (with a score of 4 out of 7 points), with <2% of subjects in any of the other categories each.

For the 2 short-term studies of adults (i.e., for Studies TRD3002 and TRD3001), pooled information about prior oral antidepressants is shown in the following Table. The prior oral antidepressants were generally similar across treatment groups. A summary for the overall population of 565 adult subjects is provided below.

Exposure-response

The Applicant has performed a descriptive analysis to assess the improvement in efficacy of the 84 mg dose of esketamine over the 56 mg dose by evaluating the proportion of subjects who achieved clinical response or remission in the double-blind phase of the studies TRD3001, TRD3002, and TRD3005. The results are presented in the following Figures.

Figure 8: Proportion of responders (left panel) and remitters (right panel) by treatment group vs placebo, study TRD3001.

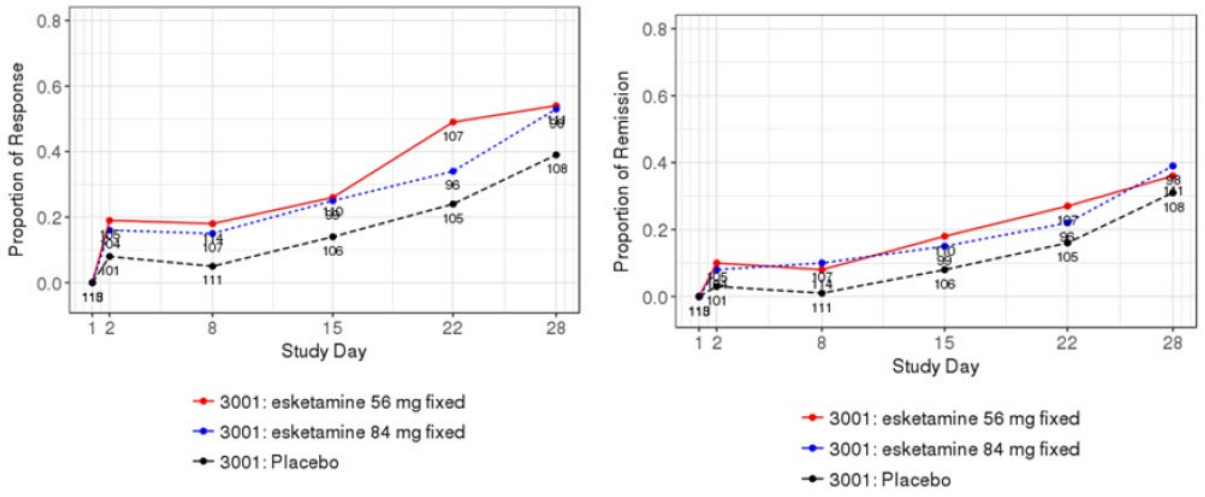


Figure 9: Proportion of responders (left panel) and remitters (right panel) with or without esketamine dose titration vs placebo, study TRD3002.

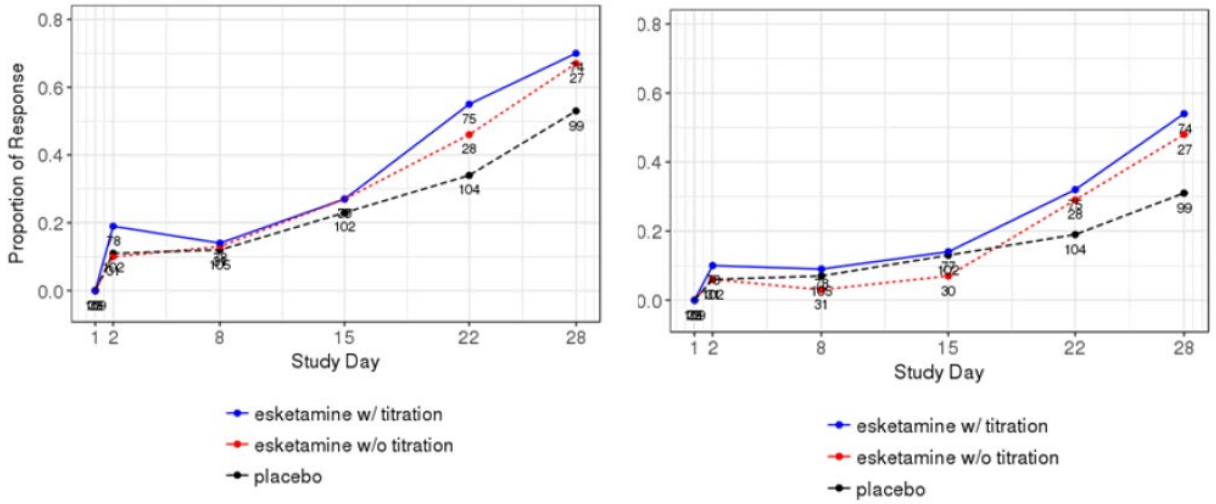
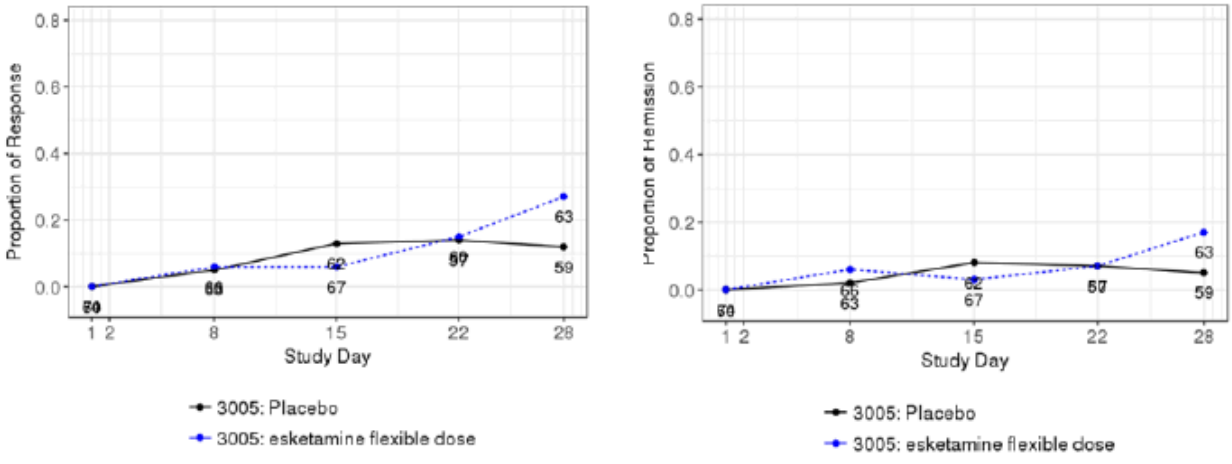


Figure 10: Proportion of responders (left panel) and remitters (right panel) by treatment group vs placebo, study TRD3005.

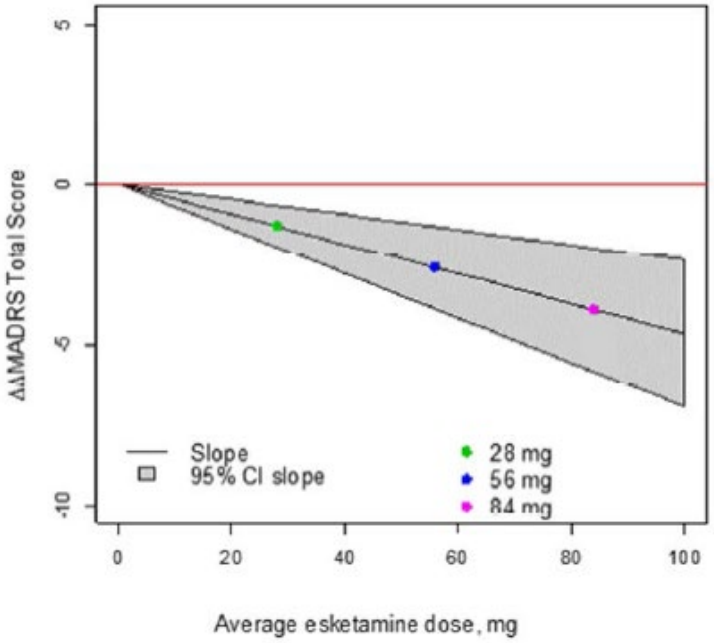


The Applicant has also performed an exposure-response analysis to explore the dose (or exposure) vs. response relationships of esketamine, using the change in MADRS scores from baseline as response. Data

from 696 subjects (410 subjects who administered a new OA and nasal esketamine, and 286 subjects who administered nasal placebo and a new OA) who were enrolled in studies TRD3001, TRD3002, and TRD3005 were included in the exposure-response analysis.

Linear drug effect was estimated with good precision in young adult subjects (TRD3001 and TRD3002) but not in elderly subjects (TRD3005). Therefore, a pooled analysis was performed on studies TRD3001 and TRD3002. Figure 12 shows the linear relationship between the average esketamine dose and the esketamine placebo-corrected ΔMADRS effect, based on these data. The esketamine effect on ΔMADRS was estimated to be 1.308 (95%CI: 0.666; 1.950) points per 28-mg increase in the average esketamine dose.

Figure 11: Linear Relationship Between the Average Esketamine Dose and Placebo-Corrected ΔMADRS Based on Data From Studies TRD3001 and TRD3002.



Prior oral antidepressants during screening:

Specific types of antidepressants: In accordance with the protocol, subjects demonstrated nonresponse to at least 2 antidepressant treatments prior to randomization, nonresponse to at least 1 antidepressant was assessed prospectively during the screening/prospective observational phase. At the start of screening, as indicated in the MGH-ATRQ, nonresponse to 2 or more antidepressants was documented in 89.7% of subjects, and for the remaining 10.3% of subjects, nonresponse had been documented for 1 antidepressant. The number of nonresponses reported in the MGH-ATRQ was most commonly 2 prior oral antidepressants (for 52.8% of subjects), followed by 3 prior oral antidepressants (for 24.9% subjects).

General classes of antidepressants:

- Number: The majority of subjects (60.5%) had demonstrated nonresponse to 2 classes of prior oral antidepressants. The remaining subjects were approximately evenly split, with 21.9% nonresponsive to <2 prior classes and 17.5% nonresponsive >2 prior classes.
- Class: The prior oral antidepressant classes that had failed most often during screening were SSRIs (to which 35.2% of subjects had demonstrated nonresponse), followed by SNRIs (for

24.7% of subjects) and the "multiple" category (for 21.6% of subjects), which included subjects who were treated with more than 1 class of antidepressant.

Duration: The treatment with prior oral antidepressant that was ongoing at screening had a mean (SD) duration of >1 year, at 425.2 (800.45) days.

- New oral antidepressants initiated at randomization: The class was more often an SNRI (for 61.6% of subjects) than an SSRI (for 38.4% of subjects). The type was most often duloxetine (for 45.5% of subjects); the other 3 types (escitalopram, sertraline, and venlafaxine XR) each were prescribed to <20% of subjects.

Table 14: Prior and Concomitant Oral Antidepressants in Pooled Studies TRD3002 and TRD3001 (Full Analysis Sets)

	Esketamine + Oral AD (N=343)	Oral AD + Placebo (N=222)	Total (N=565)
Prior Oral ADs With Nonresponse (ie, Failed Antidepressants) at Screening			
Number of specific ADs types, n (%) [a]			
N	341	222	563
1	33 (9.7%)	25 (11.3%)	58 (10.3%)
2	183 (53.7%)	114 (51.4%)	297 (52.8%)
3	86 (25.2%)	54 (24.3%)	140 (24.9%)
4	29 (8.5%)	25 (11.3%)	54 (9.6%)
5	7 (2.1%)	3 (1.4%)	10 (1.8%)
6 or 9	<1% either category	<1% either category	<1% either category
Number and groups of general AD classes			
Number, n (%) [b]			
N	343	222	565
1	77 (22.4%)	47 (21.2%)	124 (21.9%)
2	203 (59.2%)	139 (62.6%)	342 (60.5%)
>2	63 (18.4%)	36 (16.2%)	99 (17.5%)
Type, n (%) [c]			
N	328	218	546
SSRI	114 (34.8%)	78 (35.8%)	192 (35.2%)
SNRI	80 (24.4%)	55 (25.2%)	135 (24.7%)
Multiple	70 (21.3%)	48 (22.0%)	118 (21.6%)
Other	46 (14.0%)	30 (13.8%)	76 (13.9%)
MAOI / tricyclic antidepressants	18 (5.5%)	7 (3.2%)	25 (4.6%)
Duration, days [d]			
N	328	218	546
Mean (standard deviation)	426.9 (797.81)	422.8 (806.23)	425.2 (800.45)
Median	174.5	163.5	172.0
Range	(42; 6824)	(42; 7556)	(42; 7556)
New Oral ADs Initiated at Randomization			
N	343	222	565
Specific antidepressants			
Duloxetine	152 (44.3%)	105 (47.3%)	257 (45.5%)
Escitalopram	70 (20.4%)	41 (18.5%)	111 (19.6%)
Sertraline	64 (18.7%)	41 (18.5%)	105 (18.6%)
Venlafaxine XR	57 (16.6%)	35 (15.8%)	92 (16.3%)
General class			
SNRI	209 (60.9%)	139 (62.6%)	348 (61.6%)
SSRI	134 (39.1%)	83 (37.4%)	217 (38.4%)

Key: AD = antidepressant; MAOI = monoamine oxidase inhibitor; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; XR = extended-release.

[a] **Specific antidepressants:** These were the number of antidepressants with nonresponse (defined as ≤25% improvement) taken for at least 6 weeks during the current episode as obtained from the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ) results. See also Section of this document for further information about definitions of nonresponse.

[b] **Number of general classes:** These rows summarize all antidepressant medications that were captured retrospectively as well as those that were ongoing at screening.

[c] **Types of general classes:** These rows summarize only those medications that were ongoing at screening. The "multiple" category includes subjects treated with more than 1 class of antidepressant. The "other" category includes bupropion, mianserin, mirtazapine, trazodone, vilazodone, and vortioxetine.

[d] **Duration:** Prior antidepressant ongoing at screening was included in the analysis. For a subject with no ongoing prior antidepressant at screening, the last antidepressant taken within 1 week prior to screening was included. For a subject with multiple medications ongoing at screening, the medication with the longest duration was included in the analysis.

Sources: Adapted from TSIDEM01_SCE and TSIDEM02_SCE in Appendix 14.

With respect to subgroup analyses of efficacy results by age for adult population, for the 2 short-term studies of adults (i.e., for Studies TRD3002 and TRD3001), the Statistical Analysis Plan had prespecified that the efficacy results of MADRS total scores would be analyzed for the subpopulations of ages <45 years and ≥45 years. Efficacy results were generally consistent between these adult age subpopulations. In the pooled analyses, the mean difference in MADRS total scores at endpoint favoured treatment with esketamine + oral AD over treatment with oral AD + intranasal placebo for the older adults (ages 45 to 64 years) and for the younger adults (ages 18 to 44 years), with a slightly larger estimated effect for the older adults.

In the exploratory pooled analysis of Studies TRD3002 and TRD3001, forest plots were generated to show the least-squares mean treatment differences of change from baseline (95% CI) to Day 28 or endpoint for the same prespecified adult demographic variables as in the CSRs.

In the pooled adult population of studies TRD3001 and TRD3002 no major differences in the results could be observed in the various subgroups. Only two subgroups in country and one in functional impairment functions did not favour esketamine + oral AD.

Esketamine + oral AD was generally favoured over oral AD + intranasal placebo in the various demographic subpopulations in the pooled adult studies. Some exceptions occurred in subpopulations with numbers of subjects that were small; for example, for black race with 20 subjects in the esketamine group but 7 subjects in the oral AD + intranasal placebo group. Some exceptions were driven by results of one study but not the other; for example, for baseline functional impairment, esketamine was favoured in all 3 categories in Study TRD3001, and 2 categories (marked and extreme impairment) in Study TRD3002. Moreover, these potential exceptions in race and functional impairment in the short-term studies were not observed in the long-term study.

For the prior oral antidepressants in the pooled studies TRD3002 and TRD3001, it is noted that a small percentage ~10% (9.7% for the esketamine + oral AD and 11.3% for oral AD + intranasal placebo) had only one treatment failure. The various analyses provided for the population selected to be included in the studies are further reassuring that these patients belonged to the TRD spectrum.

With respect to the concomitant oral AD, it is observed that there were no major differences between esketamine + oral AD and for oral AD + intranasal placebo groups and percentages were similar with respect to the selected newly initiated oral AD between the two groups, with duloxetine being the most preferable choice (44.3% for esk+oral AD and 47.3% for oral AD+PL).

Clinical studies in special populations

The evaluation of esketamine in an elderly population was important as TRD in this population is more severe and less responsive to treatment. Furthermore, treatment of depression in the elderly is challenging as patients not only commonly suffer from disability, functional decline, and diminished quality of life from TRD, but also as a consequence of comorbid medical conditions.

Table M: Summary of clinical data in older subjects

Controlled Trial TRD3005	**Age 65-74 (Older subjects number /total number)**	**Age ≥75 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Number of patients	116/137	21/137	N/A
Total MADRS score at baseline	approximately 34 or 35 points	approximately 37 points	
Difference in the Change, baseline to Day 28 or endpoint between Esketamine (28, 56, or 84 mg) + Oral AD and Oral AD + intranasal Placebo MMRM	-4.9 (-8.96; -0.89)	-0.4 (-10.38; +9.50)	
Difference in the Change, baseline to endpoint between Esketamine (28, 56, or 84 mg) + Oral AD and Oral AD + intranasal Placebo ANCOVA LOCF	-5.2 (-9.13; -1.26)	+1.3 (-8.05; +10.62)	

According to the Applicant in the very elderly subjects (aged ≥75 years), the small sample size limited any meaningful conclusions.

With oral AD + intranasal placebo, improvements were approximately similar between elderly and very elderly subjects, with all showing approximately 5 to 7 points of improvement in mean MADRS total scores.

With esketamine + oral AD, the differences versus oral AD + intranasal placebo were clinically meaningful for the elderly group, but were not consistent for the very elderly group. For the difference in least-squares mean changes (95% CI):

- By MMRM at Day 28, results were -4.9 (-8.96; -0.89) for elderly subjects and -0.4 (-10.38; +9.50) for very elderly subjects.
- By ANCOVA LOCF at study endpoint, results were -5.2 (-9.13; -1.26) for elderly subjects and +1.3 (-8.05; +10.62) for very elderly subjects.

Table 15: MADRS Total Score for Elderly (Aged 65 to 74 years) and Very Elderly (Aged ≥75 years) Subpopulations: Change From Baseline to Day 28 by MMRM or to Endpoint by ANCOVA LOCF in the Double-blind Induction Phase of Study TRD3005 (Full Analysis Set)

	To Day 28, by MMRM		**To Endpoint, by ANCOVA LOCF**	
	Esketamine (28, 56, or 84 mg) + Oral AD (N=72)	**Oral AD + intranasal Placebo (N=65)**	**Esketamine (28, 56, or 84 mg) + Oral AD (N=72)**	**Oral AD + intranasal Placebo (N=65)**
Elderly, aged 65 to 74 years				
Baseline				
N	59	57	59	57
Mean (standard deviation)	35.1 (6.13)	34.4 (5.88)	35.1 (6.13)	34.4 (5.88)
Day 28 or endpoint				

N	53	53	58	56
Mean (standard deviation)	24.1 (12.68)	28.3 (9.52)	25.0 (12.48)	28.8 (9.68)
Change, baseline to Day 28 or endpoint				
N	53	53	58	56
Mean (standard deviation)	-10.9 (12.90)	-6.2 (9.06)	-10.2 (12.64)	-5.6 (9.24)
Statistical analysis [a]				
Difference (standard error)	-4.9 (2.04)		-5.2 (1.99)	
95% confidence interval on difference	-8.96; -0.89		-9.13; -1.26	
Very elderly, aged ≥75 years				
Baseline				
N	13	8	13	8
Mean (standard deviation)	37.3 (4.61)	37.1 (9.75)	37.3 (4.61)	37.1 (9.75)
Day 28 or endpoint				
N	10	7	13	8
Mean (standard deviation)	32.2 (11.01)	31.6 (14.46)	32.2 (9.80)	31.9 (12.81)
Change, baseline to Day 28 or endpoint				
N	10	7	13	8
Mean (standard deviation)	-5.1 (11.14)	-7.0 (7.72)	-5.1 (9.91)	-5.3 (8.78)
Statistical analysis [a]				
Difference (standard error)	-0.4 (5.02)		+1.3 (4.72)	
95% confidence interval on difference	-10.38; 9.50		-8.05; 10.62	

Key: AD = antidepressant; ANCOVA = analysis of covariance; LOCF = last observation carried forward; MADRS = Montgomery-Asberg Depression Rating Scale; MMRM = mixed model using repeated measures.

[a] **Statistical analyses:** The difference is the result of the least-squares means for esketamine + AD minus AD + intranasal placebo.

- The MMRM is based on change from baseline as the response variable and the fixed effect model terms for treatment (esketamine + oral AD or oral AD + intranasal placebo), day, region, class of oral AD (serotonin and norepinephrine reuptake inhibitor [SNRI] or selective serotonin reuptake inhibitor [SSRI]), age group, treatment-by-day, treatment-by-age group, treatment-by-age group, and treatment-by-day-by-age group, and baseline value as a covariate.
- The ANCOVA is based on change from baseline as the response variable and factors for treatment (esketamine + oral AD or oral AD + intranasal placebo), region, class of oral AD (SNRI or SSRI), age group, and treatment-by-age group, and baseline value as a covariate.
- For both MMRM and ANCOVA analyses, a negative difference favors esketamine, and the results were not adjusted for sample size re-estimation.

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. The age categories apply to study entry.
Sources: The data are adapted from the TEFMADSG02 table series presented in (or attached to) the sections about subgroup analyses in the Clinical Study Report (Mod5.3.5.1/TRD3005/Sec6.2.3.2 and Sec6.2.4.1).

The results for the subgroup 65-74 years of age are supportive of the effect of esketamine as add-on therapy for TRD. However, the impact from the very elderly aged ≥ 75 years did not allow the primary endpoint results to reach statistical significance. The difference in the change of MADRS total score from Baseline to Day 28 MMRM, double induction phase, Full analysis set was -3.6 (-7.20; 0.07) with a 1-sided p-value=0.029 which was greater than the predefined 1-sided p-value of 0.025 [ANCOVA LOCF -3.6 (-7.16; -0.03) 1-sided p-value=0.026]. In addition, as already pointed out by the Applicant, the number of patients for 75 years and older is very small (n=17) to draw any conclusions.

2.5.3. Discussion on clinical efficacy

The initially proposed indication for this application was:

- Spravato is indicated for treatment-resistant depression (Major Depressive Disorder in adults who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode).

The data submitted from phase 2 and phase 3 studies could not support such a broad indication, since esketamine has been administered only as an add-on therapy, concomitantly with a SSRI or SNRI.

The Applicant agreed to modify the proposed indication for SPRAVATO to better describe the patient population evaluated in the clinical development program:

- *SPRAVATO, **in combination with a SSRI or SNRI**, is indicated for adults with treatment-resistant Major Depressive Disorder, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode.*

The latest proposed indication was considered acceptable by the CHMP.

Clinical Development program

The current European Guideline on clinical investigation of medicinal products in the treatment of depression (EMA/CHMP/185423/2010 Rev. 2 previously, London 30 May 2013) outlines the clinical requirements for the development of a medicinal product for the treatment of major depressive disorder. The minimum requirements according to this guideline are short term randomised, double-blind, parallel group, placebo controlled studies for demonstration of the antidepressant effect and a relapse prevention study for the demonstration of the maintenance of effect for at least 6 months. For the latter a randomised withdrawal study, allowing to study relapse prevention is probably the best design. Prevention of the next episode(s) or recurrence prevention is not a mandatory part of a registration package for treatment of MDD episodes. The requirement for additional long term data beyond 6 months can be fulfilled post approval. For treatment-resistant depression at least one failure to previous treatments should be demonstrated prospectively.

The Applicant has received scientific advice for its development program from EMA, FDA and National Authorities.

The Applicant performed a clinical program which consisted of data from four phase 2 studies and five completed Phase 3 studies investigating efficacy and safety of esketamine as an adjunctive treatment together with a newly initiated oral AD for the treatment of adults with TRD, including those 65 years and older.

In order to support the short term antidepressant effect, the Applicant has performed two short term (4-week) double blind randomised parallel group phase 3 studies comparing esketamine plus a newly initiated oral antidepressant with a newly initiated oral antidepressant plus intranasal placebo. For the maintenance of effect a double blind active controlled relapse prevention study was conducted. In addition, a double blind active controlled study in elderly and very elderly and an open label long term safety and efficacy study, without a comparator have been submitted.

As such the clinical development program can be considered as comprehensive and conforming to the requirements of the EU Guideline.

However, the objectives of the studies to demonstrate the efficacy and safety of esketamine in the treatment of TRD can be misinterpreted, since the data submitted only support the adjunctive use of esketamine as add-on therapy administered concomitantly with a newly initiated oral AD for the treatment of TRD. The phase 3 clinical program does not include data from the use of esketamine as monotherapy in the treatment of TRD. In the dose response phase 2 study TRD2003, although the presentation of the study and its results was focused on a comparison of various groups taking different doses of esketamine versus placebo, concomitant medication with other antidepressants was also

allowed. Hence, the administration of esketamine in this phase 2 study TRD2003 was in an adjunctive setting, as in the case of the phase 3 studies.

Design and conduct of clinical studies

With respect to the design of the studies, several points can be considered innovative compared to the studies performed up to now in the field of depression. It should be noted that the field of major depressive disorder and its treatment is a dynamic field with several interesting discussions taking place in various fora.

First of all, the clinical program of intranasal esketamine is aiming for the indication of treatment-resistant depression when no other product has been approved in this indication in Europe [the combination of olanzapine-fluoxetine (Symbyax) has been approved only in USA].

Secondly, it was considered important to show that the population included in the studies belonged to the treatment-resistant depressed patients according to the definitions of contemporary guidelines. According to the current EU Guideline on depression, patients who have not responded to at least 2 different AD treatments, at an adequate dose for an adequate duration, in the current depressive episode are considered to have TRD. The intended target population for the proposed therapeutic indication should be suffering from treatment-resistant depression. As such it was attempted to make clear that the study participants belong to this patient group and had certain characteristics with special focus on treatment failures. To this purpose, the Applicant has used the conservative definition of Treatment-resistant depression with at least two treatment failures and made a considerable effort to recruit treatment-resistant depressed patients in line with recommendations of the current EU Depression Guideline. Eligibilty criteria demanded both retrospective assessment of prior AD nonresponse and prospective assessment of AD nonresponse. However, it should be noted that the EU Depression Guideline is currently under revision and these discussions, especially those which reflect a less restrictive approach for the definition of TRD, could be taken on board.

It is noted that a high percentage of patients in the short term studies (~89.4% and 89.5% in TRD3001 and ~92.1% in TRD3002 in the Esketamine + Oral AD group) had treatment failures with 2 or more specific antidepressant medications and a high percentage (~74% and 78% in TRD3001 and ~80% in TRD3002 in the Esketamine + Oral AD group) had treatment failures with 2 or more classes of antidepressant medications. For the prior oral antidepressants in the pooled studies TRD3002 and TRD3001, it is noted that a small percentage ~10% (9.7% for the esketamine + oral AD and 11.3% for oral AD + intranasal placebo) had only one treatment failure. For the esketamine + oral AD group (N=343) 53.7% had 2 treatment failures, 25.2% had 3 treatment failures, 8.5% had 4 treatment failures and 2.9% had 5 treatment failures or more. The various analyses provided for the population selected to be included in the studies are further reassuring that these patients belonged to the TRD spectrum.

The amendments in studies TRD3001 and TRD3002 revising the inclusion criteria to change the required number of antidepressant treatment failures could have had an impact on the patient population. However, the definition for TRD resistant depression is being discussed for quite some time among experts in the field. It should also be noted that nonresponse to at least 1 antidepressant was assessed prospectively during the screening/prospective observational phase. It could be argued that 1 treatment failure assessed prospectively can be considered sufficient to define a treatment-resistant depressed patient, since TRD develops in a continuum with progressively higher resistance depending on the number and nature of interventions failed. Taking this under consideration the amendments for the demonstration of non-response in TRD3001 and TRD3002 are not expected to have influenced the target population. It can hence be considered that the population studied with esketamine belonged in the treatment-resistant depressed patients' spectrum.

With respect to the amendment 4 in study TRD3003, changing the definitions of stable remission and stable response, it is acknowledged that a post-hoc sensitivity analysis was performed to determine whether the change in definition changed the result. Of the 176 stable remitters, 167 subjects met the stable remission definition per pre-Amendment 4, 8 subjects met the definition in Amendment 4 (2 with missing MADRS at Week 13, 6 with one excursion of a MADRS >12 at Week 13 or 14), and 1 stable responder was incorrectly randomized as a stable remitter. It is considered that amendment 4 in the protocol of TRD3003 did not affect the conclusions of the study. In addition to the subgroup analysis of pre/post Amendment 4, the Cox proportional hazards model and unweighted log-rank test was performed post-hoc on the 167 subjects who met the more stringent definition per pre-Amendment 4 to evaluate the robustness of the results. The HR (95% CI) for the 167 subjects was 0.44 (0.26; 0.74) with a 2-sided p-value of 0.002. It is considered that amendment 4 in the protocol of TRD3003 did not affect the outcome of the study.

As mentioned above, the requirement of prospectively demonstrating a treatment failure in depression was fulfilled by the Applicant during a screening/prospective observational phase. Following this screening phase the third innovative key feature in the design of the short term DB studies was the initiation of a new oral antidepressant. The newly initiated oral antidepressant was restricted to four agents: escitalopram, sertraline, duloxetine and venlafaxine extended release. The newly initiated antidepressant can be justified from the ethical point that patients with TRD should not be left without any treatment during the studies, as well as from the contemporary clinical practice which dictates that after 4 weeks prospective observation with one antidepressant these patients cannot continue receiving the same AD that did not show response and improvement in their condition.

Another key design feature in the short term DB phase 3 studies was the flexible dosing. The amount of esketamine and the dosing frequency used in the phase 3 trials is supported by data from the phase 2 studies. The use of a flexible dosing scheme is considered part of the everyday clinical practice, with which the depressed patient is being evaluated by the physician for its response and tolerability to treatment and modifications to the treatment are expected to occur. It is not considered uncommon to increase the amount of antidepressants or decrease them to the minimum effective dose or modify the dosing frequency in order to achieve the best possible effect for the patient. The flexibility in the dosing regimen is within the general approach for treatment of depression depending on the observed efficacy and the undesirable effects. In addition, the population studied in the clinical program of esketamine is considered to be moderate to severe depressed patients since they are suffering from treatment-resistant depression and have already experienced treatment failures with antidepressants. The setting for esketamine administration is as add-on therapy. These factors contribute to the recommendation of a flexible dosing scheme based on efficacy and tolerability and the Applicant has provided adequate data from phase 2 and phase 3 studies supporting such a flexible dosing scheme.

The design of the elderly study (TRD3005) was comparable to the adult study TRD3002 with flexible dosing, apart from adding a 28 mg esketamine dose in the elderly study. Introducing the lower dose of 28 mg as a cautionary approach is endorsed due to the immediate adverse events of esketamine i.e. dissociation and blood pressure increase, which may be more detrimental in the elderly. However, there is no clear dose-response relationship with respect to adverse events. The available PK data indicates that exposure is larger in elderly as compared to younger adults.

Apart from these key design features the remaining parts of the design of the clinical studies were in accordance with contemporary guidelines and clinical practice. There are, however, some comments for the statistical methods and analysis of the results and clarifications are requested.

Due to the absence of data, extrapolation to other oral ADs apart from SSRIs and SNRIs, which were used in the clinical trials, is not possible.

Study participants

The subjects were 67.1% women and 32.9% men; were white in 83.2% of cases; were enrolled in North America for 43.2% of subjects, in Europe for 38.8% of subjects, and in Central or South America for 18.1% of subjects; and had a mean (SD) age of 46.1 (11.46) years. Population from EU was sufficiently represented in the studies (conforming to CHMP Scientific Advice). The Applicant also attempted to fulfil the commitment to CHMP to include as many subjects ≥75 years of age as possible to evaluate efficacy in an elderly population in the study TRD3005 (please see also section on outcomes).

The number of patients included in the studies is considered sufficient.

In studies TRD3001, TRD3003 and TRD3005 there were subjects with protocol deviations regarding data related to previous non-response to antidepressant treatment. None of these subjects were withdrawn from the study in contrast to study TRD3002. The Applicant presented a per protocol analysis excluding patient with major protocol deviations for the studies 3001, 3002, 3003 and 3005 and the results of these analyses are consistent with the conclusions from the primary endpoint analysis.

Endpoints

The selection of the endpoints and the measurement of MADRS change from baseline to endpoint (after 4 weeks in double-blind induction phase) is considered appropriate and in accordance with the current treatment and development guidelines, literature and clinical practice. The duration of 4 weeks is within the recommendations of the EU Depression Guideline. The randomised withdrawal design to evaluate relapse prevention is also according to the current EU Depression Guideline. The long term study was not aiming to investigate recurrence prevention of the next episode, but this is not mandatory for marketing authorisation. The efficacy data collected together with the safety data in this open-label long term study have provided useful supportive information.

The endpoints (primary and secondary) used for the evaluation of efficacy of esketamine in TRD (as adjunctive treatment) are considered reliable, validated, referenced in treatment and development guidelines and used throughout many years in the clinical practice and hence appropriate.

The Applicant confirmed that efficacy evaluations were performed prior to administration of intranasal study medication (esketamine or placebo) at each study visit

Sample size

Sample size re-calculations and interim analysis as well as implementation of several measures to protect the integrity of the study, are considered acceptable.

Randomisation was considered appropriate.

Blinding

With respect to blinding, the use of independent remote (by phone) blinded raters is considered appropriate. The use of a bittering agent in the intranasal placebo and the use of 3 devices (for doses up to 84mg) in each treatment session were additional precautionary measures to ensure that blinding was maintained. For study TRD3003, despite the fact that patients who were used to the effects of esketamine were re-randomised, post-hoc analyses and assessment did not reveal any major concerns.

MADRS assessment was performed by a blinded remote rater due to clear acute but transient (adverse) effects of esketamine, which may have made the investigator aware of the treatment assignment, which is accepted. However, considering these effects it is presumed that many patients on esketamine could correctly guess whether they were on the active treatment arm and the score by the blinded evaluator is based on the interview with the patient. The dissociative effects of esketamine leading to unblinding probably had an effect on the effect size, however not to a significant extent. It is also acknowledged that

a higher than expected response in the oral AD + intranasal placebo arm is an opposite effect than is expected in case of unblinding.

Baseline values

No major imbalances that could affect the outcome of the studies have been observed in the baseline data between the esketamine plus oral antidepressant group and the oral antidepressant plus nasal placebo group.

Statistical methods

For the short-term induction studies, the target of estimation (estimand) according to the Applicant was the hypothetical treatment effect when the drug was taken as intended in the protocol. However, the treatment effect that is of primary interest from a regulatory point of view is the effect regardless of treatment discontinuations, and if patients changing treatment to an alternative AD therapy had simply discontinued corresponding treatment(s) instead. Actually, it is somewhat unclear what treatment effect is targeted by the primary analysis ANCOVA (LOCF). Furthermore, handling of missing data by LOCF is considered problematic as it assumes patients will not deteriorate when they have missing data after treatment failure and loss to follow up. This is a strong assumption, and the analyses based on this are likely overoptimistic. However, ANCOVA (BOCF) that was provided as sensitivity analysis, which was already recommended in the CHMP scientific advice as a possibility for missing data imputation, could be considered as a conservative analysis in accordance with the target of estimation of primary regulatory interest because BOCF assumes that all benefits potentially achieved from treatment are lost.

Different statistical methods were used for EU (ANCOVA (LOCF)) and non-EU countries (MMRM), which is acceptable. Interim analysis with sample size re-calculation were performed for studies 3001 and 3005. Adequate procedures to ensure confidentiality of interim results and integrity of the study were implemented. The interim analysis was appropriately taken into account in the statistical analysis.

In the relapse prevention study, the target of estimation (estimand) according to the Applicant was the effect 'while on initially randomised treatment'. However, this is not the treatment effect of primary interest for assessment of maintenance of effect from a regulatory point of view because this effect is only related to the subset of the population that is on treatment, which changes with time because of treatment drop-outs. The treatment effect that is actually of primary interest is the effect regardless of treatment discontinuations and if patients changing treatment to an alternative AD therapy had simply discontinued corresponding treatment(s) instead. However, as the proportion of patients who discontinued treatment during the maintenance phase was relatively small (~10%), the strategy how intercurrent events are addressed is not of critical importance for the conclusions from the study. Furthermore, the pre-sensitivity analysis which was originally intended to serve another purpose can also be considered as sensitivity analysis for the effect of primary regulatory interest.

The two- stage design with sample size estimation at interim was adequately taken into account for statistical testing by using the weighted log-rank statistic and for estimation by a method proposed by Wassmer.

Efficacy data and additional analyses

As already pointed out, monotherapy data comparing esketamine alone versus placebo or active comparator have not been collected in phase 3 studies.

Outcomes – Primary endpoints

Short term DB phase 3 studies in adults

In Study TRD3002, a statistically significant effect for esketamine (56 or 84 mg) + oral AD was obtained, where the estimated difference (95% CI) compared to oral AD + intranasal placebo treatment was -4.0 (-7.31; -0.64) points by MMRM, -3.5 (-6.67; -0.26) points by ANCOVA LOCF and -3.5 (-6.70; -0.27) by ANCOVA BOCF analysis methods. In this study, which is considered pivotal, and a specific study site did not dominate the results.

In Study TRD3001, the treatment effect (difference in MADRS change form baseline to Day 28) for esketamine 84mg + oral AD group compared with oral AD + intranasal placebo was not statistically significant at the 2-sided 0.05 level. As a result, the treatment effect for esketamine 56mg + oral AD group compared with oral AD + intranasal placebo could not be formally tested. The estimated differences (95% CI) for the 56 mg dose were -4.1 (-7.67; -0.49) (p=0.027) points by MMRM, -4.1 (-7.53; -0.60) (p=0.022) by ANCOVA LOCF and -4.3 (-7.79; -0.80) (p=0.017) by ANCOVA BOCF analysis methods. In the case of the 84 mg dose the estimated differences were: -3.2 (-6.88; +0.45) (p=0.088) points by MMRM, -2.0 (-5.52; +1.42) (p=0.250) points by ANCOVA LOCF and -1.2 (-4.66; +2.32) (p=0.513) by ANCOVA BOCF analysis methods. However, the results for 56 mg cannot be formally evaluated and the p-value should not be referenced.

Despite the fact that the results in study TRD3001 were statistically non-significant (BOCF analysis for the 84mg fixed dose, p-value=0.513), a very consistent treatment effect (-4.1 and -4.3) favouring esketamine +oral AD was observed for the 56 mg fixed dose across various analysis methods. In contrast a variable treatment effect (from -1.2 to -3.2) was observed for the 84 mg fixed dose. The same magnitude of treatment effect that was observed for the 56 mg dose in study TRD3001 (difference of change in MADRS using BOCF analysis: -4.3) was also recorded in study TRD3002 (difference of change in MADRS using BOCF analysis: -3.5).

The effect size of -3.5 or -4.3, which was observed in the esketamine short term DB studies, is considered clinically relevant, since a difference of 2 between the test and the reference treatment or placebo has been previously considered sufficient to demonstrate efficacy in the regulatory setting for monotherapy. However, in a number of publications provided by the Applicant there was a range in the treatment effect sizes for MADRS total score reported in individual published studies of approved antidepressant drugs either as monotherapy or add-on treatment, i.e. the MADRS difference of treatment from placebo was for quetiapine (add-on) from -1.19 to -3.05, aripiprazole (add-on) from -2.80 to -3.70, for brexpiprazole (add-on) from -1.19 to -3.12 and for vortioxetine from -0.5 to -7.1. Hence, the treatment effect observed with esketamine in TRD population is considered clinically relevant and meaningful.

In studies 3001 and 3005 with interim analysis, larger treatment effects were observed after interim analysis. Regarding a potential concern on confidentiality of interim results, it is reassuring that study 3002 without interim analysis showed a larger treatment group difference for subjects who were enrolled later in the analysis mimicking a by stage evaluation, which was performed with setting cut-off for stage 1 according to the same rules as for studies 3001 and 3005 (although it is noted that the difference between stage 1 and stage 2 was smaller than for studies 3001 and 3005). However, the consistent finding of a larger treatment effect for subjects who were enrolled later in three studies, which may be explained by changes in study conduct, raises concerns on a heterogeneous treatment effect. However, as there were only slight differences in patient characteristics between stage 1 and stage 2, it cannot be concluded that there is a difference in patient populations between stage 1 and 2. Therefore a patient population in which esketamine on top of an oral AD would have a greater efficacy cannot be defined and it is considered that the observed effect estimates in the short-term studies can be generalized to the target patient population.

The Applicant is also requested to clarify the most common reasons for screening failures, to give perspective in the difficulty of identifying TRD population and the possibility of including patients without

treatment resistance in the study, taking into account the higher than expected response in the control arm, as presented later. The Applicant described the specific reasons for withdrawal by subject (Studies TRD3001/3002/3005). The most common reason was inability to follow the study visit schedule.

It should be noted however, that similar effect sizes to those observed in the short term DB phase 3 studies have been also observed in the phase 2 clinical studies for esketamine indicating a consistency of the antidepressant effect.

MMRM was primary analysis only for non-EU countries; for EU, ANCOVA (LOCF) was primary. ANCOVA (BOCF) is considered the most relevant method of analysis which is presented in the SmPC.

Besides the differences observed in the change of MADRS from baseline to day28/endpoint between esketamine + oral AD and oral AD + intranasal placebo, responder and remitter rates are also important to demonstrate efficacy in depression. In study TRD3001, the response and remission rates at Day 28 in the esketamine + oral AD groups were 54.1% and 36.0% (for the esketamine 56-mg group), 53.1% and 38.8% (for the esketamine 84-mg group) and were 38.9% and 30.6% in the oral AD + intranasal placebo group. In study TRD3002 the response and remission rates at Day 28 were 69.3% and 52.5% of the esketamine + oral AD group and 52.0% and 31.0% of the oral AD + intranasal placebo. The differences in response and remission rates can be considered at least comparable or even higher than those previously observed in studies with approved antidepressants. The statement by the Applicant that "a treatment difference of the magnitude observed in the end point (DB LOCF) response rates between esketamine + oral AD and oral AD + intranasal placebo in the Phase 3 short-term studies (i.e., 11% to 16%) has been considered clinically meaningful for approval of other Ads" is considered valid.

In the esketamine + oral AD groups, remission rates (MADRS total score ≤12) at end point (DB LOCF) among adult subjects were 48.2% in TRD3002 and 34.8% and 35.4% in the 56 mg and 84 mg dose groups of TRD3001 (vs 30.3% and 29.2% for oral AD + intranasal placebo groups of both studies), and were 15.5% in the elderly population in TRD3005 (vs 6.3% in elderly oral AD + intranasal placebo group).

In the pooled adult population of studies TRD3001 and TRD3002 no major differences in the results could be observed in the various subgroups. Only two subgroups in country and one in functional impairment functions did not favour esketamine + oral AD. Analyses has been provided for efficacy in select subpopulations using data pooled for adults in Studies TRD3002 and TRD3001. These analyses of pooled data were performed to increase the precision of efficacy estimates in adult subpopulations.

With respect to the higher than expected response for oral AD +placebo in the TRD3002 and TRD3001 studies, this can be attributed to the initiation of a new oral AD, the increased interaction with healthcare professionals, the novelty with the nasal administration and the expectation for benefit by the patients. The argumentation provided by the Applicant on this issue is considered valid, reflecting the current situation in the major depressive disorder field. The Applicant provided an analysis with the number of previous treatment failures in the patients who showed response in studies TRD3002 and TRD3001 and belonged to the oral AD+ intranasal placebo group. In TRD3001, the majority of oral AD + intranasal placebo responder subjects at endpoint had 2 failures (57.1%), followed by 3 (28.6%), and ≥4 (14.3%). In TRD3002, the majority of oral AD + intranasal placebo responder at endpoint subjects had 2 failures (77.8%), followed by 3 (11.1%), and ≥4 (11.1%).

Based on these results, a statistically significant and clinically relevant antidepressant effect of esketamine as adjunctive treatment in TRD has been demonstrated in at least one short term randomised, controlled, double blind study and is supported by trends favouring esketamine + oral AD in two more short term DB studies.

Secondary endpoints

Three prespecified key secondary endpoints for study TRD3002 were tested in the following sequence: onset of clinical response by Day 2 (24 hours), change in SDS total score, and change in PHQ-9 total score. It would have been a clearer demonstration of efficacy if the hierarchical testing showed results in the prespecified prioritised way for the most important key secondary efficacy endpoint followed by the next two. Since the onset of clinical response by Day 2 in TRD3002 (2-sided p=0.321) was not statistically significant, the results for the other two key secondary efficacy endpoints cannot be used in a confirmatory way. Similarly, in the case of TRD3001, since the primary endpoint for esketamine 84mg+oral AD was not statistically significant (2-sided p=0.513), consequently, the primary endpoint for esketamine 56mg as well as the key secondary endpoints could not provide confirmation. However, the results from the key secondary endpoints in both studies cannot be disregarded and they did show a trend favouring esketamine + oral AD versus oral AD + intranasal placebo. The other secondary endpoints (changes in CGI-S, EQ-VAS and GAD-7 scores) also showed a trend in favour of esketamine + oral AD versus oral AD+ intranasal placebo, further supporting the antidepressant primary efficacy results.

The nominal p-value suggests separation from oral AD + intranasal placebo in SDS and PHQ-9. As in study TRD3001, the numerical improvement in SDS as well as PHQ-9 can be considered large. At Day 28, the RR vs. control is higher for remission as compared to response, while in study TRD3001 the opposite was seen, which is more of the expected pattern. The Applicant calculated the relative risks for response and remission and to discuss the observations. It is acknowledged that the RR vs. control for response was comparable in studies TRD3001 and TRD3002 and the difference in remission rates between the studies is noted.

It should be noted that for the onset of clinical response at Day 2 (24 hours) in TRD3001 showed higher numerical values for esketamine 56mg + oral AD (10.4%, 1-sided p=0.010) and esketamine 84mg + oral AD (8.8%, 1-sided p=0.041>p=0.025) vs oral AD + intranasal placebo (1.8%). Similarly, in TRD3002 the percentage that showed onset of clinical response by Day 2 (24 hours) was 7.9% for esketamine + oral AD and 4.6% for oral AD + intranasal placebo (p=0.321). Despite the fact that statistical significance was not achieved, it is obvious that a rapid onset of effect by Day 2 for esketamine + oral AD was observed in both double blind phase 3 studies TRD3001 and TD3002.

However, it is also noted that there is a considerable change in MADRS total score from Day 0 (BL) to Day 2 (24hrs) (please see below Table with results from TRD3002 from TEFMAD03A: Montgomery-Asberg Depression Rating Scale (MADRS) Total Score: Means and Mean Changes From Baseline Over Time; Double-blind Induction Phase (Study ESKETINTRD3002: Full Analysis Set). Furthermore, this decrease does not follow the same rate of decline between Day 2 (24hrs) and Day 8. From day 8 onwards MADRS total score continue to decline considerably (Figure 6a with Least-squares Mean Changes (±SE) Over Time by ANCOVA LOCF for the Double-blind Induction Phases in Studies TRD3002, TRD3001). The Applicant discussed this "plateau" phase in the change of MADRS total score between Day 2 (24hrs) and Day 8, which was probably due to the overlapping recall periods of these 2 assessments.

For the first time it is noticed that efficacy starts earlier with a medicinal product in comparison to already approved conventional ADs (which usually requires a start of the effect at 2 weeks). This can be considered an important advantage, although a claim cannot be made due to the lack of statistical significance and a direct comparison.

Subgroup analyses were supportive of the results for the primary analysis of the primary endpoint.

For the 3 short-term studies, the subpopulations of the 223 subjects in Study TRD3002, the 342 subjects in Study TRD3001, and the 137 subjects in Study TRD3005 were compared for the primary efficacy outcomes. Efficacy results were generally consistent in favouring esketamine for both younger adult subjects (ages 18 to 44 years) and older adult subjects (aged 45 to 64 years). Comparisons for patients >75 years of age could not be meaningful due to the small sample size of this age group.

Study in elderly and very elderly patients TRD3005

In TRD3005, similarly to the studies TRD3001 and TD3002, the estimated treatment difference (95% CI) of -3.6 (-7.20; +0.07) by MMRM and -3.6 (-7.16; -0.03) by ANCOVA LOCF analysis methods for esketamine + oral AD over oral AD + intranasal placebo suggests a clinically meaningful benefit, without reaching statistical significance (LOCF 1-sided p=0.026) due to the outcome in the very elderly patients ≥75 years of age (+1.3 difference in the change of MADRSThe results for study TRD3005 were analysed by ANCOVA BOCF.

Baseline scores indicate that, on average, patients had severe depression with long duration (over 20 years) in most cases. Data regarding the number of classes of antidepressants with prior non-response was similar to younger adults.

The results for the subgroup 65-74 years of age are supportive of the effect of esketamine as add-on therapy for TRD. However, the outcome for the very elderly aged ≥ 75 years had an impact which did not allow the primary endpoint results to reach statistical significance. The difference in the change of MADRS total score from Baseline to Day 28 MMRM, double induction phase, Full analysis set was -3.6 (-7.20; 0.07) with a 1-sided p-value=0.029, which was greater than the predefined 1-sided p-value of 0.025 [ANCOVA LOCF -3.6 (-7.16; -0.03) 1-sided p-value=0.026]. In addition, as already pointed out by the Applicant, the number of patients for 75 years and older is very small (n=17) to draw any conclusions. it is acknowledged that the obtained MADRS effect size and the effect sizes of CGI-S, PHQ-9, and SDS scales in the elderly study are consistent with the adult studies, and add-on treatment with esketamine may provide an additional benefit to elderly patients with TRD. It is considered appropriate that the decision to continue or stop treatment, based on the individual status of the patient regarding efficacy and safety, is left to the discretion of the prescriber.

The same clear difference between the stages in observed treatment difference between esketamine and the control group as in the adult studies is seen in the elderly study. The protocol amendments introduced during the study modified the inclusion criteria for example with respect to non-response to previous treatment. Based on the slight differences in baseline psychiatric history it cannot be concluded that there is a difference in patient populations between stage 1 and 2.

Relapse prevention study TRD3003

As already mentioned above, a relapse prevention study is required for a MAA in order to demonstrate the maintenance of the antidepressant effect. Study TRD3003 served as a relapse prevention study with statistically significant results in favour of esketamine + oral AD. The results showed a statistically significantly longer time to relapse in patients randomized to continue esketamine compared with those randomized to discontinue esketamine. This was also true for those patients who were in stable remission after 16 weeks of treatment with esketamine + oral AD (2-sided p=0.003). The secondary efficacy results for the time to relapse by stable responders (but who were not in remission) showed a statistically significantly longer time to relapse in subjects randomized to continue esketamine compared to those randomized to discontinue esketamine (2-sided p<0.001). Overall, 24 (26.7%) subjects in the intranasal esketamine + oral antidepressant group and 39 (45.3%) subjects in the oral antidepressant + intranasal placebo group experienced a relapse event during the maintenance phase. Due to non-proportional hazards, relapse proportion differences at fixed time points provide a better description of the treatment effect than hazard ratio. After 12 weeks, the relapse proportions (Kaplan-Meier estimates) were 13% in the esketamine + oral AD arm and 37% in the oral AD + intranasal placebo arm, corresponding to a difference of −24.0% (95% CI: −35.2%; −10.7%). After 24 weeks, the relapse proportions were 32% in the esketamine + oral AD arm and 46% in the oral AD + intranasal placebo arm, corresponding to a difference of −14.0% (95% CI: −28.1%; 2.7%). Subgroup analyses and secondary efficacy endpoints were supportive of the results of the primary and key secondary endpoints.

Certain points in the short term DB phase 3 studies and the relapse prevention study were clarified i.e.:

– details on 14 subjects relapsed during the optimization phase were provided

- Dosing frequency allocation during the maintenance phase was based on a MADRS algorithm which allowed patients to switch frequency up to 3 times during the maintenance phase. This resulted in a rather complex overall administration of esketamine. Patients could switch back and forth between dosing frequency. For the purpose of further examination of efficacy between dosing frequencies, some additional analyses was requested and provided and no apparent differences between the subpopulations were identified.

- The majority of the subjects who relapsed during the first month after discontinuation of esketamine were subjects who required a weekly dosing frequency to sustain remission. For a comparison of patient characteristics between the subpopulations, the Applicant provided a comparison of demographic characteristics and psychiatric history in these subpopulations (i.e. weekly vs. once in two weeks administration).

- It is considered that due to transient effects that esketamine has, patients switched from esketamine to placebo in the re-randomization could have perceived that they no longer received esketamine. The Applicant's analysis regarding dissociation and sedation pre-post randomization is appreciated, however it is questioned whether assessment of these two aspects can capture all symptoms which patients associate with esketamine. The Applicant has no other means to examine the impact of transient effects of esketamine on unblinding than the CADSS and MOAA/S scores. Unfortunately, there are no data on whether patients were indeed correctly aware of their assigned treatment.

– Other key secondary endpoints included change from baseline (of maintenance phase) to endpoint in MADRS, PHQ-9, CGI-S, GAD-7, SDS and EQ-5D-5L. For these endpoints the change from baseline was calculated to endpoint, which could be the maximum of the date of last visit in the maintenance phase, date of completion of the maintenance phase due to relapse or study termination, or date of early withdrawal in the maintenance phase. Observation time differs by patient and could be defined by relapse; therefore, it is questioned whether any conclusions can be drawn based on these data. It is acknowledged that the collected data on supporting endpoints could provide valuable insight in the patient's wellbeing on an individual level. On a group level the data however is difficult to interpret due to differences of follow-up time and possible relapse. The data on these secondary endpoint are not presented in the SmPC, which is endorsed in view of the uncertainties mentioned above.

<u>OL long term safety study TRD3004</u>

It appears that there were improvements in measurements of depression in the induction phase, which were consistent across multiple assessments of depressive symptoms over the 4-week induction phase and these improvements appeared to be maintained in subjects who continued treatment up to the 1-year exposure. The graph presentation analysis for the 150 subjects who completed the optimisation/maintenance phase from the baseline of the induction phase was similar and consistent with the overall study results.

The study included both direct-entry subjects and patients from the elderly study TRD3005. Non-responders from study TRD3005 could enter the induction phase of this study. The applicant has clarified that this was done to allow patients on the oral AD + intranasal placebo the opportunity for treatment benefit with esketamine add-on treatment or allow patients on the oral AD + esketamine to gain further benefit from longer induction phase.

2.5.4. Conclusions on the clinical efficacy

In summary, although statistical significant results were only obtained in one of the short term randomised DB study (TRD3002), clear favourable trends were observed in the two other short-term studies (TRD3001, TRD3005) with the effect size being of similar magnitude. Taken together, the results demonstrate the antidepressant efficacy of esketamine vs. placebo, both on top of an oral antidepressant, in an appropriately defined treatment-resistant population. The results of the key secondary endpoints were supportive of those of the primary endpoint, i.e. change in MADRS. In study TRD3001, the hierarchical testing sequence did not formally allow testing for all the endpoints since the primary endpoint was non-significant. In study TRD3005 in patients over 65 years of age, the treatment response in the very elderly (≥75 years) patients did not allow any meaningful conclusions. The requirement to demonstrate maintenance of the antidepressant effect was achieved via a relapse prevention study of adequate duration (TRD3003). Furthermore, supportive efficacy data were generated in an open-label long term mainly safety study (TRD3004). Overall, the clinical program can be considered comprehensive and supports the use of esketamine as an adjunctive treatment administered concomitantly with a newly initiated oral SSRI or SNRI. The clinical program and the data submitted could not support a broad TRD indication since pivotal data on esketamine monotherapy are not available. Treatment with intranasal esketamine should be initiated by a psychiatrist.

The following latest proposal from the Applicant best reflects the patient population studied and can be considered acceptable:

- *SPRAVATO, in combination with a SSRI or SNRI, is indicated for adults with treatment-resistant Major Depressive Disorder, who have not responded to at least two different* ***treatments with*** *antidepressants in the current moderate to severe depressive episode (see section 5.1).*

2.6. Clinical safety

The experience with the use of the active substance is broad, given the fact that esketamine, the S-enantiomer of racemic ketamine, is a well-known active substance already approved as solution for injection in induction and maintenance of anaesthesia in some EU countries. The racemic ketamine has been in widespread use worldwide for the same indications since the 1970s and is on the World Health Organization's List of Essential Medicines.

The presented clinical development program aimed at collecting sufficient information on the safety profile of nasal esketamine spray in the target population with TRD over the intended therapeutic dose range of 56 to 84 mg up to twice applications weekly. Achieved plasma levels are below those required for induction and maintenance of anaesthesia.

In Phase 3 trials esketamine treatment was initiated concomitantly with a new oral antidepressant.

Patient exposure

Safety data have been derived from a total of 25 completed clinical studies (Phases 1 to 3) with additional limited data coming from 4 ongoing trials. As of the clinical cutoff date of 4 March 2018, 1861 unique patients were treated with esketamine corresponding to 1045 patient-years of exposure and 486 unique patients were treated with oral AD + intranasal placebo corresponding to 100 patient-years of exposure.The primary safety assessment was based on a total of 1,708 patients with TRD, who received at least 1 dose of esketamine in six completed Phase 2 and 3 studies (TRD 3001, TRD 3002, TRD 3005, TRD 3003, TRD 3003, TRD 2003) with a combined cumulative exposure to esketamine of 611 patient-years and 108 patient-years to placebo. Five of the six studies were completed Phase 3

studies with 479 subjects exposed to esketamine for at least 6 months and 178 for at least 12 months (in total 1,601 subjects included in Phase 3).

Supportive data was derived from the Phase 1 trials as well as from ongoing Phase 2 and 3 trials and one completed Phase 2 trial in subjects with MDSI.

Table 16: Extent of Cumulative Exposure to Intranasal Study Medication Across Phase 3 TRD Studies (Studies TRD3001, TRD3002, TRD3003, TRD3004, TRD3005: Safety/Full Analysis Sets)

	Intranasal Esk 56 mg + Oral AD (N=115)	Intranasal Esk 84 mg + Oral AD (N=116)	Flex-dose Esketamine (N=1371)	Total Esketamine (a) (N=1602)	Oral AD + Intranasal Placebo (N=432)
Total Cumulative Duration, Days					
N	115	116	1370	1601	432
Category, n (%)					
≤ 28	54 (47.0%)	63 (54.3%)	411 (30.0%)	528 (33.0%)	238 (55.1%)
29-56	55 (47.8%)	69 (59.5%)	469 (34.2%)	593 (37.0%)	268 (62.0%)
57-84	57 (49.6%)	70 (60.3%)	518 (37.8%)	645 (40.3%)	290 (67.1%)
85-112	94 (81.7%)	96 (82.8%)	758 (55.3%)	948 (59.2%)	325 (75.2%)
113-140	94 (81.7%)	99 (85.3%)	814 (59.4%)	1007 (62.9%)	341 (78.9%)
141-168	102 (88.7%)	106 (91.4%)	879 (64.2%)	1087 (67.9%)	357 (82.6%)
169-196	104 (90.4%)	106 (91.4%)	955 (69.7%)	1165 (72.8%)	370 (85.6%)
197-224	107 (93.0%)	109 (94.0%)	995 (72.6%)	1211 (75.6%)	382 (88.4%)
225-252	107 (93.0%)	109 (94.0%)	1038 (75.8%)	1254 (78.3%)	386 (89.4%)
253-280	109 (94.8%)	110 (94.8%)	1081 (78.9%)	1300 (81.2%)	392 (90.7%)
281-308	109 (94.8%)	111 (95.7%)	1134 (82.8%)	1354 (84.6%)	403 (93.3%)
309-336	110 (95.7%)	113 (97.4%)	1181 (86.2%)	1404 (87.7%)	409 (94.7%)
337-364	111 (96.5%)	113 (97.4%)	1334 (97.4%)	1558 (97.3%)	415 (96.1%)
365-392	111 (96.5%)	114 (98.3%)	1352 (98.7%)	1577 (98.5%)	416 (96.3%)
393-420	112 (97.4%)	115 (99.1%)	1358 (99.1%)	1585 (99.0%)	416 (96.3%)
421-448	112 (97.4%)	115 (99.1%)	1361 (99.3%)	1588 (99.2%)	418 (96.8%)
449-476	114 (99.1%)	115 (99.1%)	1361 (99.3%)	1590 (99.3%)	421 (97.5%)
>476	115 (100.0%)	116 (100.0%)	1370 (100.0%)	1601 (100.0%)	432 (100.0%)
Mean (SD)	93.2 (108.73)	75.5 (92.19)	146.1 (127.87)	137.2 (126.20)	90.1 (117.31)
Median	92.0	26.0	103.0	101.0	26.0
Range	(4; 743)	(1; 542)	(1; 692)	(1; 743)	(1; 655)
≥ 6 months (180 days) exposure	13 (11.3%)	10 (8.6%)	456 (33.3%)	479 (29.9%)	68 (15.7%)
≥ 12 months (350 days) exposure	5 (4.3%)	3 (2.6%)	170 (12.4%)	178 (11.1%)	18 (4.2%)
Total exposure (subject years)	29	24	548	601	107

Note: Flex-dose Esketamine = 56 or 84 mg esketamine + oral AD.

Note: The duration of exposure is defined as the duration between the date of the first exposure and the date of the last exposure to intranasal study medication. Due to the intermittent dosing frequency, it includes days on which subjects did not actually take intranasal study medication.

(a) Total esketamine column includes both the fixed-dose and flexible dose esketamine treatment groups. In the safety analysis set, one placebo-treated subject from TRD3005 who transferred to TRD3004 was treated with an oral AD, but did not receive esketamine.

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Most patients received the 28 mg or 56 mg dose only for a few dosing days (≤ 8), while patients receiving the higher dose of 84 mg were more frequently treated for more dosing days, as outlined in the table below.

Table 17 a: Number of days dosed with Study Medication

Q150_EX_POOL_T094: Number of Days Dosed with Intranasal Study Medication Across All Studies and Treatment Phases; (Studies ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, ESKETINTRD3005): Safety/Full Analysis Sets			
	Intranasal Esk 28 mg + Oral AD (N=236)	Intranasal Esk 56 mg + Oral AD (N=1564)	Intranasal Esk 84 mg + Oral AD (N=977)
Number of days dosed			
N	236	1564	977
Category, n (%)			
≤ 8	212 (89.8%)	1123 (71.8%)	396 (40.5%)
9-16	4 (1.7%)	96 (6.1%)	202 (20.7%)
17-24	6 (2.5%)	131 (8.4%)	151 (15.5%)
25-32	6 (2.5%)	81 (5.2%)	99 (10.1%)
33-40	5 (2.1%)	79 (5.1%)	58 (5.9%)
41-48	0	26 (1.7%)	41 (4.2%)
49-56	3 (1.3%)	25 (1.6%)	27 (2.8%)
>56	0	3 (0.2%)	3 (0.3%)
Mean (SD)	4.6 (8.92)	9.3 (12.76)	16.3 (13.59)
Median	2.0	2.0	14.0
Range	(1; 56)	(1; 104)	(1; 89)

Since the first submission new long term data from 1140 subjects included in TRD3008 (interim report of an open-label extension study in subjects previously participating in TRD3001, TRD3002, TRD3003, TRD3004, TRD3005 and TRD3006) have become available:

Table 17 b: Frequency Distribution of Cumulative Subject Exposure to Intranasal Esketamine (Study TRD3008: All Enrolled Analysis Set)

	Intranasal Esketamine (N=1140)
Subjects with 6 months of exposure	1039 (91.1%)
Subjects with 12 months of exposure	927 (81.3%)
Subjects with 18 months of exposure	592 (51.9%)
Subjects with 24 months of exposure	228 (20.0%)
Subjects with 30 months of exposure	54 (4.7%)

Note: 6 months is defined as >=180 days; 12 months is defined as >=360 days; 18 months is defined as >=540 days; 24 months is defined as >=720 days and 30 months is defined as >=900 days.
Source: Sequ0002/Mod5.3.5.3/TRD3008_interim/Table 13

Regarding the overall length of treatment on different doses the median duration of exposure to intranasal esketamine was 0.3 months (range: 0–33 months) for the 28-mg dose, 0.5 months (range: 0–39 months) for the 56-mg dose, and 11.0 months (range: 0–37 months) for the 84-mg dose.

Adverse events

Overall summary of adverse events

Adverse events (verbatim terms) were coded using the Medical Dictionary for Regulatory Activities Terminology (MedDRA).

Across the studies in TRD included in the primary safety assessment, esketamine had a consistent and tolerable safety profile, in accordance with ADRs already known for the active substance.

Most of the subjects receiving esketamine + oral AD experienced one or more TEAEs, which were judged to be possibly related to the intranasal drug at a high rate. The frequency of TEAEs was lower in the placebo + oral AD groups.

	TEAEs		TEAEs possibly related to esketamine
	Esketamine + oral AD	placebo + oral AD	Esketamine + oral AD
pooled TRD3001/TRD3002	87%	64%	78.3%
TRD3005	70.8%	60.0%	58.3%
TRD3003 (db MA-Phase)	82.2%%	45.5%	69.7%

The frequencies of TEAEs and TEAEs possibly related to esketamine was similar in TRD2003, the OL phases of TRD3003, the OL long-term study TRD3004 (90.1%) as well as in the interim-analysis of the long-term extension study TRD3008.

Most TEAEs were reported post-dose on the day of dosing and resolved the same day. A large number of TEAEs (psychiatric, gastro-intestinal or cardiovascular disorders) are in accordance with ADRs already known for the active substance or can be derived from its anaesthetic potential (e.g. sedation, somnolence, feeling drunk).

Most TEAEs were mild to moderate, only a minority were assessed as severe. There were no new TEAEs considered by the Sponsor as associated with long-term treatment up to 30 months. Dose effects were described only for the TEAE of dissociation.

Common adverse events

Short term studies 3001/3002

Table 18: Treatment-emergent Adverse Events in at Least 5% of Subjects in Any Treatment Group; Double-blind Induction Phase (Pooled Studies ESKETINTRD3001, ESKETINTRD3002: Safety Analysis Set)

	Intranasal Esk 56 mg + Oral AD (N=115)	Intranasal Esk 84 mg + Oral AD (N=116)	Flex-dose Esketamine (N=115)	Total Esketamine (a) (N=346)	Oral AD + Intranasal Placebo (N=222)
Total no. subjects with TEAE	100 (87.0%)	103 (88.8%)	98 (85.2%)	301 (87.0%)	143 (64.4%)
Nervous system disorders	74 (64.3%)	74 (63.8%)	72 (62.6%)	220 (63.6%)	86 (38.7%)
Dizziness	32 (27.8%)	26 (22.4%)	24 (20.9%)	82 (23.7%)	15 (6.8%)
Headache	23 (20.0%)	24 (20.7%)	23 (20.0%)	70 (20.2%)	38 (17.1%)
Dysgeusia	17 (14.8%)	20 (17.2%)	28 (24.3%)	65 (18.8%)	30 (13.5%)
Somnolence	24 (20.9%)	21 (18.1%)	15 (13.0%)	60 (17.3%)	20 (9.0%)
Paraesthesia	19 (16.5%)	11 (9.5%)	13 (11.3%)	43 (12.4%)	4 (1.8%)
Hypoaesthesia	14 (12.2%)	16 (13.8%)	8 (7.0%)	38 (11.0%)	3 (1.4%)
Dizziness postural	7 (6.1%)	7 (6.0%)	8 (7.0%)	22 (6.4%)	1 (0.5%)
Sedation	6 (5.2%)	8 (6.9%)	5 (4.3%)	19 (5.5%)	2 (0.9%)
Lethargy	7 (6.1%)	5 (4.3%)	1 (0.9%)	13 (3.8%)	1 (0.5%)
Tremor	4 (3.5%)	6 (5.2%)	2 (1.7%)	12 (3.5%)	2 (0.9%)
Mental impairment	6 (5.2%)	3 (2.6%)	2 (1.7%)	11 (3.2%)	2 (0.9%)
Gastrointestinal disorders	57 (49.6%)	58 (50.0%)	52 (45.2%)	167 (48.3%)	52 (23.4%)
Nausea	31 (27.0%)	37 (31.9%)	30 (26.1%)	98 (28.3%)	19 (8.6%)
Hypoaesthesia oral	16 (13.9%)	12 (10.3%)	9 (7.8%)	37 (10.7%)	3 (1.4%)
Vomiting	7 (6.1%)	14 (12.1%)	11 (9.6%)	32 (9.2%)	4 (1.8%)
Diarrhoea	8 (7.0%)	5 (4.3%)	10 (8.7%)	23 (6.6%)	13 (5.9%)
Dry mouth	5 (4.3%)	5 (4.3%)	9 (7.8%)	19 (5.5%)	7 (3.2%)
Paraesthesia oral	9 (7.8%)	1 (0.9%)	9 (7.8%)	19 (5.5%)	3 (1.4%)
Psychiatric disorders	49 (42.6%)	56 (48.3%)	55 (47.8%)	160 (46.2%)	43 (19.4%)
Dissociation	30 (26.1%)	32 (27.6%)	30 (26.1%)	92 (26.6%)	8 (3.6%)
Anxiety	10 (8.7%)	9 (7.8%)	12 (10.4%)	31 (9.0%)	12 (5.4%)
Insomnia	10 (8.7%)	8 (6.9%)	11 (9.6%)	29 (8.4%)	16 (7.2%)
Euphoric mood	8 (7.0%)	2 (1.7%)	5 (4.3%)	15 (4.3%)	2 (0.9%)
Ear and labyrinth disorders	30 (26.1%)	27 (23.3%)	34 (29.6%)	91 (26.3%)	10 (4.5%)
Vertigo	24 (20.9%)	24 (20.7%)	30 (26.1%)	78 (22.5%)	5 (2.3%)
General disorders and administration site conditions	30 (26.1%)	20 (17.2%)	30 (26.1%)	80 (23.1%)	31 (14.0%)
Fatigue	12 (10.4%)	8 (6.9%)	5 (4.3%)	25 (7.2%)	11 (5.0%)
Feeling drunk	7 (6.1%)	3 (2.6%)	9 (7.8%)	19 (5.5%)	1 (0.5%)
Respiratory, thoracic and mediastinal disorders	20 (17.4%)	20 (17.2%)	24 (20.9%)	64 (18.5%)	33 (14.9%)
Throat irritation	5 (4.3%)	9 (7.8%)	9 (7.8%)	23 (6.6%)	9 (4.1%)
Nasal discomfort	4 (3.5%)	5 (4.3%)	8 (7.0%)	17 (4.9%)	9 (4.1%)
Eye disorders	17 (14.8%)	14 (12.1%)	18 (15.7%)	49 (14.2%)	4 (1.8%)
Vision blurred	8 (7.0%)	9 (7.8%)	14 (12.2%)	31 (9.0%)	3 (1.4%)
Investigations	12 (10.4%)	18 (15.5%)	14 (12.2%)	44 (12.7%)	9 (4.1%)
Blood pressure increased	8 (7.0%)	11 (9.5%)	11 (9.6%)	30 (8.7%)	5 (2.3%)
Renal and urinary disorders	7 (6.1%)	5 (4.3%)	9 (7.8%)	21 (6.1%)	3 (1.4%)
Pollakiuria	6 (5.2%)	2 (1.7%)	3 (2.6%)	11 (3.2%)	1 (0.5%)

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In subjects treated with esketamine, the most common TEAEs were:

Relapse prevention study TRD3003

- during the IND phase (≥10% subjects): vertigo, dizziness, nausea, dysgeusia, dissociation, somnolence, headache, paraesthesia, vision blurred, and sedation.
- during the OP phase (≥10% subjects): vertigo, dysgeusia, dissociation, somnolence, dizziness, headache, and nausea.
- In the DB MA phase (≥10% subjects) dysgeusia, vertigo, dissociation, somnolence, dizziness, headache, nausea, vision blurred, and hypoaesthesia oral. No TEAEs were reported at this rate in the oral AD + intranasal placebo group

OL extension study TRD3004

- during the IND phase: dizziness (29.3%), diassociation (23.4%), nausea (20.2%), headache (17.6%), somnolence (12.1%), hypoaesthesia (10.1%).
- during the OP/MA phase: dizziness (22.4%), headache (18.9%), dissociation (18.7%), somnolence (14.1%), nausea (13.9%), viral upper respiratory tract infection (11.6%).

OL extension study TRD3008 (interim-results)

- during the IND phase (≥10% subjects): dissociation, dizziness, vertigo, nausea, dysgeusia, and headache.
- during the OP/MA phase (≥10% of subjects): dizziness, nausea, headache, dissociation, somnolence, dysgeusia, vertigo, nasopharyngitis, vomiting, and blood pressure (BP) increase.

Severe adverse events

Pooled short-term studies TRD3001/3002

Severe TEAEs were reported in 14.7% of subjects in the total esketamine + oral AD group, compared to 5.0% of subjects in the oral AD + intranasal placebo group. The most common severe TEAEs in the total esketamine + oral AD group included dissociation (3.8% of subjects), vertigo (2.9%), and dizziness, dysgeusia, headache, fatigue, nausea, and vomiting (each reported in <2% subjects). In the oral AD + intranasal placebo group, no severe TEAEs were reported at the rate of 1% or higher. The majority of severe TEAEs reported on intranasal dosing days resolved the same day (88.9% in the total esketamine + oral AD group and 83.3% events in the oral AD + intranasal placebo group).

Relapse prevention study TRD3003

Severe TEAEs were reported in esketamine-treated subjects at the rate of 10.1% in the IND phase and 7.5% in the OP phase. Most common severe TEAEs during the IND phase included somnolence (1.6%), dysgeusia (1.4%), sedation, dissociation, vertigo, and nausea (1.1% each); and during the OP phase, headache (1.8%), vertigo (1.3%), and dissociation (1.1%). In the DB MA phase, severe TEAEs were reported at the rate of 7.9% in the esketamine + oral AD group and 4.1% in the oral AD + intranasal placebo group. Most common severe TEAEs in the esketamine + oral AD group included somnolence, dysgeusia, nasal congestion, nasal discomfort, upper-airway cough syndrome, anxiety, and vertigo (each reported in 1.3%), and in the oral AD + intranasal placebo group, depression and headache (2.1% and 1.4%, respectively) In the IND phase, 91.2% of the severe TEAEs reported on intranasal dosing days resolved the same day. In the OP and MA phases, 100% of the severe TEAEs reported on intranasal dosing days resolved the same day.

Long-term safety study TRD3004

In this study 14.7% of subjects reported TEAEs of severe intensity during the combined IND and OP/MA phases. Most common severe TEAEs (reported in at least 1% of subjects) included dissociation (1.9%), anxiety (1.6%), dizziness (1.6%), and nausea (1.2%). The overall rates of severe TEAEs in the IND and OP/MA phases were 8.2% and 10.3%, respectively. During the IND and OP/MA phases, most of the severe TEAEs reported on intranasal dosing days resolved the same day (75%).

Long-term safety study TRD3008

TEAEs classified as severe in the induction phase most commonly (ie, reported for ≥2% of subjects) included dysgeusia (2.6%), dissociation (2.2%), and dizziness (2.0%), and those in the optimization/maintenance phase most commonly (ie, reported for ≥1% of subjects) included dysgeusia (1.8%), dissociation (1.4%), anxiety and nausea (1.3%), headache (1.2%), and dizziness (1.0%).

Adverse events by causality

TEAEs were judged to be possibly related to intranasal esketamine at a high rate.

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.

Table 19: Adverse Drug Reactions Reported with Esketamine Nasal Spray by Frequency Category Estimated from Phase 2 and Phase 3 Studies (Studies TRD2003, TRD3001, TRD3002, TRD3003, TRD3004, TRD3005; Safety Analysis Sets)

	Adverse Drug Reaction Frequency		
System Organ Class	Very Common	Common	Uncommon
Psychiatric disorders	Dissociation*, Anxiety*	Euphoric mood	
Nervous system disorders	Dysgeusia*, Dizziness*, Sedation*, Headache*, Hypoaesthesia*	Mental impairment, Tremor*, Lethargy*, Dysarthria*	
Ear and labyrinth disorders	Vertigo*		
Cardiac disorders		Tachycardia*	
Respiratory, thoracic and mediastinal disorders		Nasal discomfort*	
Gastrointestinal disorders	Vomiting, Nausea	Dry mouth	Salivary hypersecretion
Skin and subcutaneous tissue disorders		Hyperhidrosis	
Renal and urinary disorders		Pollakiuria*	
General disorders and administration site conditions		Feeling abnormal, Feeling drunk	
Investigations	Blood pressure increased*		

The adverse reactions are coded using the MedDRA version 20.0.
* Represents grouped terms.

Modified from: Mod2.7.4/AppADR/Att4

The highest incidences were attributed to Nervous system disorders (64.1%), Psychiatric disorders (46.1%) and Gastrointestinal disorders (32.2%).

Adverse events of special interest

Selected safety topics of interest were comprehensively examined. The following broadly defined safety categories of interest for the esketamine development program included:

- Psychiatric and nervous system disorders (comprised of suicidal ideation and behaviour; dissociative/perceptual changes; psychotic-like symptoms, anxiety, hypomania and mania; transient dizziness/vertigo, and sedation/somnolence)
- Potential effects on cognition
- Interstitial cystitis and Lower Urinary Tract Symptoms
- Post-dose gastrointestinal symptoms (nausea, vomiting)
- AEs potentially suggestive of abuse potential
- Withdrawal symptoms
- Cardiovascular safety (including changes in BP and pulse rates)
- Nasal tolerability and impact on sense of smell

Suicidal Ideation and Behavior

Suicidal ideation was assessed using the C-SSRS (Columbia-Suicide Severity Rating Scale) throughout Phase 2 and 3 trials.

Suicidal ideation at baseline was reported for 17.1% to 25.3% of subjects in the esketamine + oral AD group and 16.9% to 27.0% of subjects in the oral AD + intranasal placebo group in the short-term studies.

For subjects with no suicidal ideation or behaviour at baseline, the rates of reported suicidal ideation (based on C-SSRS) at least once during the treatment phase were similar for the esketamine + oral AD groups and the oral AD + intranasal placebo groups in the short term DB studies (TRD3001/3002: 10.2% vs 12.3%, respectively; TRD3005: 13.8% vs 16.7%) and in the DB MA phase of the relapse prevention study TRD3003 (2.4% vs 4.5%). Across all Phase 3 studies, the 10 subjects who reported suicidal behaviour based on the C-SSRS (score of 6-10) had a lifetime history of suicidal ideation or suicidal behaviour.

Worsening of suicidal ideation/behaviour in the subgroup of subjects with no suicidal ideation or behaviour at baseline, the proportion of subjects reporting suicidal ideation at any time post-baseline was similar in the esketamine + oral AD group and in the oral AD + intranasal placebo group during the DB IND phase of the pooled short-term studies (TRD3001/3002: 10.2% vs. 12.3%) and short-term elderly study (TRD3005: 13.8% vs. 16.7%), and in the DB MA phase of the relapse-prevention study (TRD3003: 2.4% vs. 4.5%). Only a small number of subjects in this subgroup, all of whom had esketamine exposure, had suicidal behavior at any time post-baseline (1 [0.3%] subject in the IND phase of TRD3003; 2 [0.3%] subjects in IND phase of TRD3004, and 2 [0.4%] in the OP/MA Phase of TRD3004). In the subgroup of subjects with suicidal ideation at baseline across all Phase 3 studies, a total of 5 subjects, all of whom received esketamine, reported suicidal behaviour at any time post-baseline: 1 (1.2%) subject in the esketamine + oral AD group in the pooled short-term studies TRD3001/3002 and 4 subjects in TRD3004 (2 [1.6%] during the IND phase and 2 [2.2%] in the OP/MA Phase).

Overall, across the Phase 2 and 3 studies in TRD, suicidality-related TEAEs were uncommon (~1% to 5%), and most of the reported cases were those of suicidal ideation. In the controlled Phase 3 studies, the incidence of these events was overall consistent for the esketamine + oral AD and oral AD + intranasal placebo groups (pooled TRD3001/TRD3002: 0.9% vs 0.9%, respectively; TRD3005: 1.4% vs 0%; DB MA phase of TRD3003: 2.0% vs 0.7%). In the uncontrolled, OL long term safety study, 5.2% of subjects reported a suicidality-related TEAE across the entire study (Mod2.7.4/Tab28). Severe suicidality-related TEAEs were reported at a low incidence (<1% for individual preferred terms) in each of the Phase 2 and 3 studies.

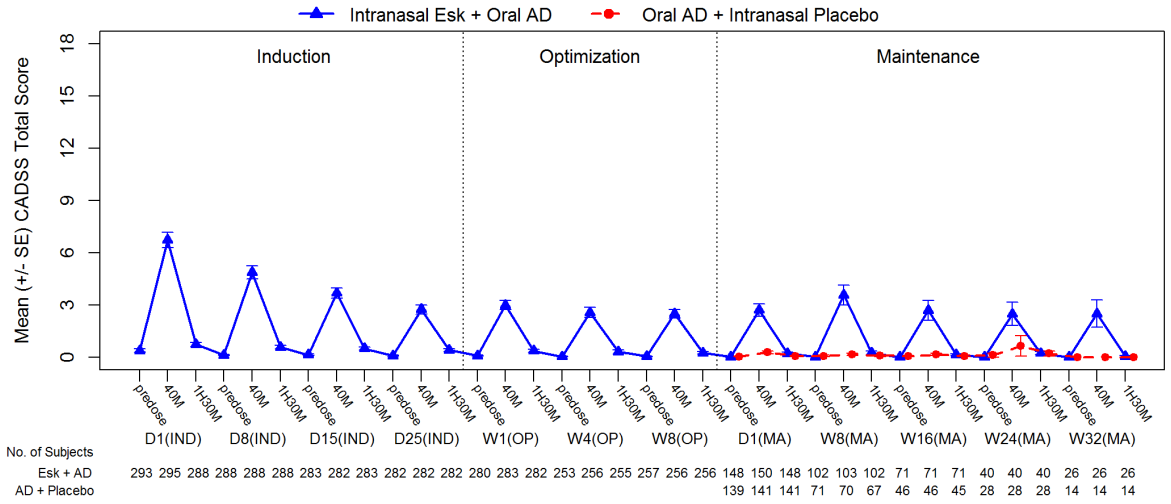
Dissociation/perceptual changes

Across completed Phase 2 and 3 studies, the most common psychological effects of esketamine have been dissociative/ perceptual changes (including distortion of time and space and illusions), derealization and depersonalization and were measured using CADSS (Clinician Administered Dissociative States Scale).

Across the Phase 2 and 3 studies, the following similar pattern of change was observed in the mean CADSS score in esketamine dosing sessions: dissociative/perceptual changes had an onset shortly after the start of dosing, peaked by 40 minutes post-dose, and typically returned to post-dose levels at the 1.5-hour post-dose assessment. The maximum mean values did not exceed 10 (scale range of 0 to 92, with higher scores representing a more severe condition).

Over the course of each Phase 3 study, the peak mean CADSS total score at the 40-minute post-dose time-point in the esketamine + oral AD groups generally decreased with consecutive doses. This attenuation was apparent both in the short-term studies as well as with prolonged exposure in the long-term studies (see Figure 13 for study TRD3003).

Figure 12: Arithmetic Mean (+/- SE) Clinician-administered Dissociative States Scale (CADSS) Total Score Over Time; Induction, Optimization, and Maintenance Phases (Study ESKETINTRD3003)



Dissociative/perceptual changes were reported as adverse events at a rate of 12.5-27.6% across trials, primarily mild or moderate in severity, transient and self-limited. Dissociation was reported as severe in intensity at the incidence of less than 4% across studies, was not considered serious for any subjects and rarely led to discontinuation of study drug. Transient dissociative/perceptual changes were more pronounced in subjects receiving higher doses of esketamine.

Psychotic-like symptoms

To capture the extent of treatment-emergent psychotic-like symptoms potentially associated with esketamine administration, the Phase 3 clinical trials included the 4 item Brief Psychiatric Rating Scale (BPRS) + subscale, which assessed suspiciousness, hallucinations, unusual thought content, and conceptual disorganization.

Across all studies, a small mean increase in BPRS+ total score from baseline was observed at 40-minute post-dose assessment in esketamine + oral AD treatment groups (mean maximum values of <1, indicating symptoms were 'very mild'). After this transient, minimal worsening, mean scores generally returned to pre-dose values at the 1.5-hour post-dose assessment. In the short-term studies (TRD3001, TRD3002, and TRD3005), the mean BPRS+ score (possible range: 0 - 24) remained below 1.2 at all post-dose time-points. Although mean values suggest only a minimal increase in BPRS+ score, percentages of patients with a total score of 3 or more were substantially higher in each of the phase III trials in the esketamine treated patients vs placebo patients (up to 28.1% versus 1.8% in TRD3002).

No TEAEs of psychosis were reported across the Phase 2 and 3 studies in TRD.

Anxiety

TEAE grouped terms related to anxiety (preferred terms of anxiety, anticipatory anxiety, and anxiety disorder) were reported at higher rates in the esketamine + oral AD groups than in the oral AD + intranasal placebo group in the controlled Phase 3 studies/study phases in adults (TRD3001/TRD3002: 9.0% vs 5.4%, respectively; DB MA phase of TRD3003: 7.9% vs 3.4%), but was reported less often in the esketamine + oral AD group for elderly subjects in TRD3005 (4.2% vs 7.7%). There was no apparent increase in the overall incidence of anxiety TEAEs with longer-term esketamine treatment, with anxiety preferred terms reported for 9.0% of subjects receiving esketamine + oral AD across both phases of the OL safety study TRD3004. Anxiety (grouped term) is identified as an ADR for esketamine.

In the Phase 3 studies in TRD, severe anxiety TEAEs (individual preferred term) were uncommon in the esketamine + oral AD treatment groups (incidence rates of 0.3% to 1.4% across studies/study phases). The TEAE of anxiety only infrequently required rescue treatment (<4% in esketamine + oral AD groups for each study) or resulted in esketamine discontinuation (<2% across Phase 3 studies/study phases). Moreover, extreme levels of anxiety manifested as TEAEs of panic attacks was reported at low rates (<2% across studies/study phases).

The reported frequency of anxiety TEAEs on each dosing day generally decreased after the first week of dosing in the pooled short-term studies TRD3001/3002 and the induction phase in TRD3003 and TRD3004 (compared with the remainder of the study).

Hypomania and mania

Across the Phase 2 and 3 studies in TRD, the TEAE of mania was reported in only 2 esketamine-treated subjects (1 report after first dose of esketamine and oral AD [duloxetine] and second report during follow-up phase), while hypomania was not reported in any subject. Both events of mania resolved without sequelae.

Transient dizziness or vertigo

Examination of TEAEs related to dizziness and vertigo revealed higher rates for the esketamine + oral AD groups compared with the oral AD + intranasal placebo groups (pooled TRD3001/TRD3002: 46.5% vs 9.9%, respectively; TRD3005: 27.8% vs 10.8%; DB MA phase of TRD3003: 43.4% vs 11.7%). Across the uncontrolled, OL long term safety study, dizziness and vertigo-related TEAEs were reported for 46.5% of subjects treated with esketamine + oral AD.

Dizziness and vertigo (individual preferred terms) were generally mild or moderate in intensity, non-serious, and not treatment limiting. Across the Phase 3 studies/study phases, both of these individual TEAEs were reported as severe in intensity at incidences of <3% and resulted in discontinuation of esketamine in <1% of subjects. No serious individual TEAEs of dizziness or vertigo were reported in esketamine-treated subjects.

Reported TEAEs of dizziness and vertigo following esketamine dosing in the Phase 3 studies were generally transient and self-limiting. Most of these events occurred on the day of dosing, and of those events reported on the day of dosing, almost all (>95%) resolved spontaneously the same day. Decreases in the reporting frequencies of dizziness and vertigo were observed early in treatment (i.e., on Days 1 through 8) compared with subsequent nasal spray dosing sessions in the short-term studies TRD3001/3002 and the long-term studies TRD3003 and TRD3004.

Sedation/Somnolence

Across all Phase 2 and 3 studies, sedation was one of the most common effects associated with esketamine treatment. Sedation was measured using the MOAA/S (Modified Observer's Assessment of Alertness/Sedation) scale. Based on the MOAA/S, sedative effects were generally mild, had an onset shortly after the start of the dose and typically resolved by 1 to 1.5 hours post-dose.

TEAEs of somnolence (12.1-21.1%) and sedation (4.2-10.1%) were primarily mild or moderate in severity, occurred on the day of intranasal dosing and resolved spontaneously the same day, with the median duration under 2 hours across dosing sessions. These TEAEs led to treatment discontinuation in isolated cases and reported as a SAE in only 1 subject across all Phase 2 and 3 studies. Rates of TEAEs of somnolence were relatively stable over time during longer-term treatment.

Effects on cognition

In the Phase 3 studies in TRD, the potential effect of esketamine on cognition was evaluated using 2 standardized tests: (1) the CogState, shown to provide a rapid and reliable assessment of subtle changes in multiple cognitive domains, including attention/processing speed, visual learning and memory, working memory, and executive function, and (2) the HVLT-R test, a brief measure of verbal learning and memory.

In the Phase 3 short-term studies, performance on each of the cognitive tests demonstrated either an improvement from baseline or appeared stable relative to baseline both at the end of the DB induction phase and at the 2-week follow-up assessment.

One of the primary safety objectives of the OL safety study TRD3004 was to examine the potential effects of long-term esketamine treatment on cognitive function. Overall, results of group mean performance on tests of attention/reaction time and higher level cognitive domains either remained stable or showed slight improvement from baseline in all enrolled subjects as well as among subgroups of subjects aged <65 years and those aged ≥65 years.

- The exception was for tests assessing simple and choice reaction time which showed a slowing starting at Week 20 of the OP/MA phase in the elderly subgroup, with the greatest slowing seen at Week 44. As there was a substantial decrease in the number of elderly subjects at the latter time-points in this study due, in part, to the early study termination upon achieving the required exposure to esketamine, post hoc analyses were conducted for the elderly subjects who completed the study. In elderly completers, the mean slowing in reaction time at the Week 52 endpoint was of a magnitude representing an effect size of 0.52 for simple reaction test and 0.47 for choice reaction test (Cohen's d), and there was considerable intra-individual variability in reaction time among elderly subjects. No elderly subject demonstrated impaired reaction time performance at endpoint that persisted into the follow up phase. In the absence of a comparator group in TRD3004 or published longitudinal studies of reaction time in elderly MDD/TRD patients, firm conclusions cannot be made as to whether the high intra-individual variability in reaction time observed in TRD3004 is characteristic of the elderly MDD/TRD population. Therefore, Cognitive disorders and memory impairment (long-term use) have been included in the risk management plan (RMP) as important potential risk, to be further investigated via the category 3 study 54135419TRD3008, an open-label long-term extension safety study of intranasal esketamine in TRD (currently ongoing; the clinical study report is awaited by Q1 2023; annual analyses of safety results should also be provided until study completion).
- Results of the elderly completer analyses showed that the performance on tests of other, more complex cognitive domains was not affected, which was consistent with results of analyses involving the all enrolled analysis set (and by-age subgroup analyses).

No TEAEs related to cognitive impairment (i.e., preferred terms, cognitive disorder, cognitive motor disorder) were reported in the Phase 3 studies in TRD.

Interstitial cystitis and lower urinary tract symptoms

The Phase 2 and 3 studies with esketamine included monitoring for symptoms of cystitis or lower urinary tract symptoms using the BPIC-SS (Bladder Pain/ Interstitial Cystitis Symptom Score). Subjects with a score > 18 on the scale were further evaluated for interstitial cystitis and urinary tract infection. Virtually all cases with complaints could be related to bacterial infections. Urinary tract symptoms in general were reversible. There were no cases of interstitial cystitis (including ulcerative cystitis) in any of the clinical trials with esketamine, which involved treatment for up to 30 months. Pollakiuria (also prolonged), dysuria, micturition urgency, nocturia and cystitis were reported more often compared to placebo. Interstitial cystitis is a serious adverse reaction that may result in persistent or significant disability or incapacity. Given that no cases of esketamine nasal spray-related interstitial cystitis were observed in any of the Phase 2 and Phase 3 trials, which involved treatment for up to 1 year, the impact on the risk-benefit balance of the product is expected to be low. With intermittent exposure at the doses of 28 mg, 56 mg, and 84 mg recommended in the SmPC for treatment of patients with TRD, the bladder has sufficient time between dosing sessions for self-repair from any potential irritation. However, in clinical trials with esketamine nasal spray, there was a higher rate of lower urinary tract symptoms (pollakiuria, dysuria, micturition urgency, nocturia, and cystitis) in esketamine nasal spray-treated patients than in placebo-treated patients. Therefore, Interstitial cystitis (long-term use) was included in the RMP as Important potential risk, requiring further evaluation via the category 3 study 54135419TRD3008 above outlined.

Post-dose Gastrointestinal Symptoms of Nausea and Vomiting

Study protocols restricted food consumption for at least 2 hours before dosing and fluids for at least 30 min before dosing with intranasal study drug.

Across the Phase 2 and 3 studies in TRD, nausea and vomiting were the most frequent gastrointestinal TEAEs in esketamine-treated subjects In the controlled Phase 3 studies, nausea and vomiting were reported at higher rates for the esketamine + oral AD groups than for the oral AD + intranasal placebo group (pooled TRD3001/TRD3002: 28.3% vs 8.6%, respectively, for nausea; 9.2% vs 1.8%, respectively, for vomiting; TRD3005: 18.1% vs 4.6% for nausea; 6.9% vs 1.5% for vomiting; DB MA phase of TRD3003: 16.4% vs 0.7% for nausea; 6.6% vs 0.7% for vomiting). In the OL long-term safety study TRD3004, nausea and vomiting were reported for 25.1% and 10.8%, of subjects, respectively, across both study phases.

In the pooled TRD3001/TRD3002 studies, ~85% of TEAEs of nausea and vomiting were reported on the day of dosing for esketamine treated subjects, with 81% of reports of nausea and 98% of reports of vomiting resolving the same day. The same pattern was seen in elderly subjects and for each phase of the relapse prevention study TRD3003. Over the up to 1-year treatment period for TRD3004, ~80% of reports of nausea and vomiting occurred on the day of dosing (83% and 81%, respectively), and of these postdose events, approximately 89% resolved the same day.

TEAEs of nausea and vomiting were primarily mild or moderate in severity, transient, and self limited with the median duration not exceeding 1 hour in most subjects across dosing sessions. Nausea and vomiting were reported as severe in intensity at incidences under 2% across studies/study phases. No SAEs of nausea and vomiting were reported in esketamine-treated subjects. Discontinuation of study drug due to nausea and vomiting was reported in less than 1% of subjects. Rates of reported nausea and vomiting decreased over time.

Abuse potential

An abuse potential for ketamine is well-known and recognized by the WHO. The results of TRD1015 indicate that the abuse potential of intranasal administration of esketamine is similar to IV administration of ketamine.

The exact mechanism underlying esketamine's abuse potential is unknown. Esketamine is active within the central nervous system (CNS) and has a mechanism of action similar to that of racemic ketamine. As antagonists of NMDA receptors, both ketamine and esketamine induce psychoactive effects. Ketamine is a known drug of abuse recreationally and induces psychological effects, including dissociation and other perceptual distortions; alterations in cognition; and changes in mood. The most common way that ketamine is used recreationally is insufflation.

Data from all clinical studies with esketamine nasal spray were examined for the occurrence of CNS-related AEs suggestive that the drug might be sought out by patients for abuse purposes in accordance with FDA's guidance on assessment of a drug's abuse potential.

Across all clinical studies, there were no reported TEAEs (individual preferred terms) of overdose or drug abuse. Approximately one-half of adult subjects treated with esketamine in the Phase 2 and 3 studies reported at least 1 TEAE suggestive of abuse potential, with post-dose events of dizziness, somnolence, and dissociation being the most common. these symptoms are predominantly reported shortly after dosing on the day of esketamine administration, are transient and self-limiting, and mild or moderate in intensity. Other events, such as euphoric mood, feeling drunk, or feeling abnormal, were also observed but occurred at considerably lower incidences. These additional events were also transient in nature and resolved the same day of dosing in almost all cases. After up to 1 year of repeated intermittent dosing with esketamine in the OL long-term safety study, the reporting frequencies of TEAEs of euphoric mood, feeling drunk, and feeling abnormal were 1.9% to 3.4%.

There were no reports of drug seeking behaviour made during the studies (i.e., calls to the sites requesting more frequent treatment sessions or increase in dose above that allowed in study).

Drug abuse is considered an important identified risk for esketamine nasal spray. The following routine and additional risk minimisation measures (RMMs)

The abuse potential of esketamine nasal spray and its mitigation are addressed in the EU product information (EU PI) (ie, Summary of Product Characteristics [SmPC] and Package Leaflet [PL]) and include the following concepts:

Esketamine nasal spray is administered under the direct supervision of a healthcare professional.

The recommended dosing of esketamine nasal spray is twice weekly for 4 weeks, followed by weekly or every-other-week dosing for patients with a favorable clinical response. During longer-term treatment, physicians are recommended to individualize the dosing frequency to the lowest frequency needed to maintain the patient's clinical response and to perform periodic re-evaluation of patients to determine the need for continued treatment.

Individuals with a history of drug abuse or dependence may be at greater risk for abuse and misuse of esketamine nasal spray. Physicians are advised to assess individuals prior to treatment for a history of substance use disorder and to monitor for signs of abuse or dependence.

Esketamine nasal spray is designed with the following features to deter abuse (and misuse):

1. The product is supplied in limited pack sizes.

The drug product is contained in a Type I glass vial sealed with a chlorobutyl rubber stopper. The filled and stoppered vial is seated into a container holder assembled into a manually activated nasal spray device. The device is difficult to disassemble due to interlocking design features of the actuator subassembly. Attempts to break open the device damage the vial and the contents are lost. The force required to pull the device apart is at least 60 Newtons (~13 pounds). If the device is taken apart, the stoppered vial provides an additional challenge to disassembly, as it is very difficult to pull the stopper out. Breaking the vial instead results in loss of the contents.

2. The product is supplied as a single-use device containing a total of 32.3 mg of esketamine HCl (equivalent to 28 mg of esketamine). When manually actuated, the device dispenses 2 individual sprays; no sprays remain after the second spray is actuated.
3. The nasal spray device has a nominal fill volume of 230 µL and a delivery volume of 200 µL. The average measured residual volume left in the nasal spray device after actuation is ~30µL (4 mg base).

Legal controls (e.g., restrictions on storage and prescribing including special and restricted medical prescription with categorization at the Member State level) will be in place according to local legal requirements in the majority of Member States (MS) where esketamine is currently scheduled, either directly or indirectly due to its chemical relationship to ketamine. In these Member States (MS), it is proposed that the scheduling class should be the same as that which applies already to any ketamine- or esketamine-containing medicinal product. The following recommendations minimize the risk of abuse, diversion and misuse. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. All treatment should be administered under the direct supervision of a healthcare professional (HCP) and signs of abuse or dependence should be carefully monitored.

No unsupervised administration of the product is allowed. Furthermore, a controlled access program should be implemented, as key element to ensure esketamine nasal spray is dispensed to the healthcare settings where administration takes place, as agreed at the Member State level, based on local legal requirements and/or local healthcare systems.

A HCP Guide and a Patient Guide containing key messages regarding product administration and the potential for abuse and dependence are also agreed as additional RMMs.

Withdrawal

All Phase 3 studies included the PWC 20 to systematically assess the risk of dependence with short- and long-term use of esketamine nasal spray. The PWC-20 was measured at the 1- and 2-week follow-up visits in Studies TRD3001, TRD3002, TRD3005, and TRD3003 and at the 1-, 2- and 4-week follow-up visits in the long-term OL Study TRD3004. Given the short half-life of esketamine, a 2-week follow-up was expected to be sufficient to assess potential symptoms of withdrawal.

Across studies, the changes in withdrawal symptoms assessed by the PWC 20 after cessation of esketamine + oral AD treatment were consistent with observed changes in symptoms of depression and anxiety. Reported symptoms were primarily mild to moderate in severity. New worsening of depression symptoms was observed mostly in subjects who discontinued treatment due to lack of therapeutic response. Based on the PWC-20 results, there was no evidence suggestive of a distinct withdrawal syndrome at 1 or 2 weeks after cessation of esketamine treatment in TRD3003 or at 1, 2, or 4 weeks after cessation of esketamine treatment in TRD3004.

Cardiovascular safety

Heart rate, blood pressure and ECG

The impact of esketamine on BP and heart rate was evaluated in the Phase 2 and 3 studies through vital sign measurements performed pre- and post-dosing with the nasal spray study drug

Transient, primarily asymptomatic, increases in systolic and diastolic BP were observed following esketamine administration in all Phase 2 and 3 studies in TRD, with maximum mean changes typically

observed within 40 minutes of dosing and mean BP values subsequently returning to, or close to, pre-dose values within the 1.5-hour post-dose time-point

Across the Phase 3 studies/study phases, treatment-emergent markedly abnormal elevations of SBP to ≥ 180 mm Hg or DBP to ≥110 mm Hg (i.e., acute hypertension) were reported at rates of <5% among the esketamine treatment groups for the pooled studies TRD3001/TRD3002 (0.9% for total oral AD + intranasal placebo group) and all study phases of TRD3003 and TRD3004; the exception was for study TRD3005 in elderly subjects where the percentage was 11.1% (6.2% for oral AD + intranasal placebo). These elevations primarily occurred within 1.5 hours after dosing, and the rates for subjects meeting these acute hypertension criteria were higher among subjects with a history of hypertension than in those without such a history.

Exposure-response PK/PD models were developed to describe the relationship between SBP and DBP and esketamine plasma concentration.

Observed mean increases in pulse rate following esketamine administration were not clinically meaningful in any of the Phase 3 studies. In the controlled Phase 3 studies/study phases, the proportion of subjects with a treatment-emergent abnormal increase in pulse rate (≥15 bpm relative to baseline to a value ≥100 bpm) was less than 9% and similar for the esketamine + oral AD and oral AD + intranasal placebo groups.

Esketamine administration did not produce any meaningful changes in ECG parameters and had no effect on cardiac repolarization in a thorough QT study TRD1013).

AEs related to cardiovascular safety

Adverse events in this category included an examination of TEAEs grouped terms related to increased BP and increased heart rate (preferred terms included for type of event listed in Mod2.7.4/Tab4). TEAEs related to increased heart rate occurred at low incidence rates (<2%) across the Phase 3 studies/study phases. By comparison, TEAEs related to increased BP were reported at higher frequencies following treatment with esketamine + oral AD compared to oral AD + intranasal placebo in the controlled Phase 3 studies/study phases (pooled TRD3001/TRD3002 studies: 10.1% vs 2.7%, respectively; TRD3005: 13.9% vs 6.2%: DB MA phase of TRD3003: 8.6% vs 3.4%). Across the OL long-term safety study TRD3004, TEAEs related to increased BP were reported for 12.8% of subjects receiving esketamine + oral AD (Mod2.7.4/Tab37). In the DB phases of Phase 2 study TRD2003, the reporting rate for TEAEs related to increased BP was 13.1% across all esketamine groups and 7.4% for the placebo group; no TEAEs related to increased heart rate were reported in the DB phases of this study.

Among esketamine-treated subjects in the Phase 3 studies, very few of the TEAEs (individual preferred terms) of BP increased or tachycardia were severe (≤0.2% in all study/study phases except TRD3005 where incidence of severe increased BP TEAEs was 1.4% [representing 1 subject]). Further, TEAEs of increased BP or tachycardia were reported as serious in only isolated cases, and discontinuation of esketamine treatment for these events occurred in <2% of subjects across studies/study phases .

Between 90% and 100% of the reported TEAE preferred term of increased BP occurred on the day of dosing in the Phase 3 studies/study phases and of these, >93% resolved spontaneously the same day.

A subgroup analyses revealed that patients with cardiovascular risk factors (BMI ≥ 30 kg/m2, diabetes mellitus, hypertension, or hypercholesterolemia) who are taking esketamine experience cardiovascular-related adverse events more frequently than those without.

Keeping in mind that Spravato will be prescribed by psychiatrists, who might not be very familiar with cardiovascular diseases, it might be helpful to keep the examples as an orientation for them.

Overall, Due to the transient and self-limiting nature of the cardiovascular effects observed in clinical trials, the overall impact on the risk-benefit balance of the product is considered low; however, the impact

on an individual patient may be significant. The SmPC and PL, as well as the Healthcare Professional Guide and Patient Guide, provide information to the prescriber and the patient on how to manage the risk. A checklist for readiness to leave will be provided to aid HCP in determining when a patient is deemed stable and should safely be allowed to return home following esketamine nasal spray administration.

Nasal Tolerability and Sense of Smell

Across Phase 2 and 3 studies there were no nasal exam findings or Nasal Symptom Questionnaire evidence to support an impact on nasal anatomy or function including the sense of smell assessed by the UPSIT (University of Pennsylvania Smell Identification Test) and the Smell Threshold Test scores.

Most esketamine-treated subjects had no findings upon nasal examination, detected abnormalities were mostly of mild severity (consisting mainly of nasal erythema, nasal discharge, nasal crust), with the exception of a few moderate findings and no findings that were severe. The frequency of these symptoms did not increase with continued administration.

Nasal tolerability of esketamine nasal spray was good, also after long term treatment.

Interim data on AESIs from TRD3008 appear to be similar to what has been observed before.

Serious adverse event/deaths/other significant events

Serious adverse events

Table 20: Overall Incidence of Treatment-emergent Adverse Events and Serious Adverse Events in Completed Phase 3 TRD studies Esketamine *(Module 2.7.4. Summary of Clinical Safety, Table 24)*

Study Phase	Treatment (+ Oral AD)	N	TEAE	SAE	SAE Considered as at Least Possibly Related
TRD3001 (Fixed-Dose)					
Induction Phase	Esk 56 mg:	115	100 (87.0%)	2 (1.7%)	2 (1.7%)
	Esk 84 mg:	116	103 (88.8%)	0	0
	Placebo:	113	77 (68.1%)	0	0
TRD3002 (Flex-Dose)					
Induction Phase	Esk 56-84 mg:	115	98 (85.2%)	1 (0.9%)	0
	Placebo:	109	66 (60.6%)	1 (0.9%)	0
Pooled TRD3001/3002					
Induction Phase	Total Esketamine[a]:	346	301 (87.0%)	3 (0.9%)	2 (0.6%)
	Total Placebo:	222	143 (64.4%)	1 (0.5%)	0
TRD3005					
Induction Phase	Esk 28-84 mg:	72	51 (70.8%)	3 (4.2%)	2 (2.8%)
	Placebo:	65	39 (60.0%)	2 (3.1%)	1 (1.5%)
TRD3003					
Induction Phase	Esk 56-84 mg:	437	336 (76.9%)	13 (3.0%)	6 (1.4%)
Optimization (OP) Phase	Esk 56-84 mg:	455	335 (73.6%)	11 (2.4%)	0
Maintenance (MA) Phase	Esk 56-84 mg:	152	125 (82.2%)	4 (2.6%)	0
	Placebo:	145	66 (45.5%)	1 (0.7%)	0
TRD3004					
Induction Phase	Esk 28-84 mg:	779	653 (83.8%)	17 (2.2%)	1 (0.1%)
OP/MA Phase	Esk 28-84 mg:	603	516 (85.6%)	38 (6.3%)	3 (0.5%)
IND and OP/MA Phases	Esk 28-84 mg:	802	723 (90.1%)	55 (6.9%)	4 (0.5%)

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Note: Serious AEs with onset during the FU phase are not included.
[a] Total esketamine row includes both the fixed-dose and flexible dose esketamine groups.

In the controlled Phase 3 studies, serious TEAEs were reported in subjects receiving esketamine + oral AD at rates that were low and generally similar to those in subjects receiving oral AD + intranasal placebo. Across all studies, the most frequently reported SAEs were in the psychiatric disorders category and were associated with the underlying disease state.

The SAEs assessed as related to study treatment in the Phase 3 short-term studies by the investigator included 1 subject each with depression, headache, increased blood pressure, and anxiety disorder.

In the long-term studies most SAEs were considered to be not associated with esketamine. Events at least possibly related to study treatment included 1 subject each with disorientation, suicidal ideation, sedation, autonomic nervous system imbalance and simple partial seizures, lacunar stroke, and hypothermia (TRD3003) and 1 subject each with delirium, anxiety and delusion, suicidal ideation, and suicidal attempt (TRD3004).

During the ongoing TRD3008 one patient had a hypertensive emergency 2 min after esketamine 28 mg application, which was regarded as possibly related to study treatment. During the ongoing and still blinded Study SUI3001/2 one patient had to be discontinued due to a hypertransaminasaemia.

No dose-relationship of SAEs could be observed.

Deaths

Until cut-off date of 31 December 2018, a total of 7 deaths were reported.

In the primary safety analysis set across the completed Phase 2 and 3 studies in TRD, there were 4 deaths (0.2%) among the 1,708 subjects treated with esketamine + oral AD. No deaths occurred in the oral AD + intranasal placebo groups (486 subjects).

Subject Number (Study)	Age Sex	Dictionary-derived Term (Reported Term)	Study Day of Onset	Protocol Phase	Onset Dose[a]	Investigator's assessment of Relationship
COMPLETED STUDIES						
Phase 3 TRD Studies (esketamine + newly initiated oral AD), n=1601						
24201706/TRD3002	41 Male	Multiple injuries (Multiple injuries following a road traffic accident)	16[b]	DB	<84>	Not related
43590610/TRD3004	60 Male	Acute Respiratory Failure (Acute Respiratory Failure)	113	Optimization/ Maintenance	<56>	Doubtful
		Cardiac Failure Acute (Acute Heart Failure)	113	Optimization/ Maintenance	<56>	Doubtful
40260116/TRD3004	55 Female	Completed Suicide (Completed Suicide)	188	Optimization/ Maintenance	<84>	Not related
Phase 2 TRD Study (adjunctive design), n=107						
30007206/TRD2003	41 Male	Completed suicide (suicide)	45	FU	<56>	Not related

In addition, in the ongoing uncontrolled long-term study TRD3008, a total of 3 deaths were reported in the interim-report, one completed suicide and one accidental polytrauma were regarded as not related and one myocardial infarction was regarded as doubtfully related to study treatment.

A total of 3 completed suicides were reported among the total of 7 deaths. All cases of completed suicide occurred in completed or ongoing open-label studies/study phases with no control group and had a latency of 20 (TRD2003), 12 (TRD3004) and 4 days (TRD3008) to the last dose of esketamine. None of the cases were considered to be related to esketamine treatment.

Laboratory findings

No clinically meaningful changes in mean laboratory analytes (hematology, chemistry, urinalysis parameters) from baseline were observed in any of the completed Phase 2 and 3 TRD studies.

Across Phase 2 and 3 TRD studies, there were isolated cases in which TEAEs were associated with abnormal laboratory results. There was no clinically important difference between oral AD placebo and esketamine plus oral AD groups in the incidence of these AEs. Only isolated laboratory-related AEs were recorded as serious and infrequently resulted in discontinuation.

Liver enzymes

Across the completed Phase 2 and 3 studies in TRD, increases in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) of greater than 3 x the upper limit of normal (ULN) occurred at low rates among the esketamine + oral AD treatment groups (ie, <2% in all studies/study phases).

The observed increases in ALT/AST in the Phase 3 studies in TRD were primarily asymptomatic, transient, and resolved spontaneously without worsening while treatment with esketamine + oral AD continued. No persistent increases in liver transaminases were observed.

Across all completed studies with esketamine, no subject met the criteria for severe drug-induced hepatocellular injury as defined by Hy's law. Further, no cases of treatment emergent elevated total serum bilirubin levels to >2x ULN were identified in esketamine-treated subjects.

Oxygen saturation and Respiratory Rate

At least 2 consecutive oxygen saturation levels below 93% within the same visit were reported only in isolated cases across Phase 3 studies. These cases were not associated with clinical symptoms of compromised respiratory function and resolved spontaneously in postdose period and prior to discharge. No clinically significant decreases in respiratory rate were observed in the Phase 3 studies.

Body weight

No clinically notable changes in mean body weight from baseline were observed in the short term Phase 2 and 3 studies.

Safety in special populations

Sex

In the main studies the majority of patients were female (~65%) and overall incidence of TEAEs were also higher in female subjects than in male subjects (approximately 5-10% higher). No clinically relevant differences between female and male patients were apparent.

Elderly

The population included in the short term phase 3 trials TRD3001 and 3002 and the relapse prevention study TRD3003 was between 18 and 65 years of age. The short-term study TRD3005 was performed in elderly patients aged > 65 years, of whom a number also entered the long-term trials TRD3004 and 3008. Due to the pharmacokinetic differences described for the elderly population as an increase of Cmax and AUC compared to younger adults, the starting dose was reduced to 28 mg in TRD3005. On Day 25, 64.5% of the subjects in the esketamine + oral AD group received the 84-mg dose, 25.8% received the 56-mg dose, and 9.7% received the 28-mg dose. Of the 194 subjects included in 25 were > 75 years of age.

The most common TEAEs (reported by ≥10% subjects) observed more frequently in the esketamine vs. the placebo group were: dizziness (20.8% versus 7.7%), nausea (18.1% versus 4.6%), headache (12.5% versus 3.1%), fatigue (12.5% versus 7.7%), BP increased (12.5% versus 4.6%), dissociation (12.5% versus 1.5%), and vertigo (11.1% versus 3.1%). The most common TEAE (reported by ≥5% subjects) observed more frequently in the oral AD + intranasal placebo group was anxiety (7.7% versus 2.8%).

Frequencies and pattern of TEAES revealed no clinically meaningful differences between patients <65 years and patients ≥ 65 years A dose relationship of TEAEs has not been observed.

Race

Throughout Phase 3 trials most patients were white (>80% in every trial), a small percentage was black (between 0 and 6.1%) and the rest was of other race. Drawing firm conclusions based on comparisons between the subsets was not regarded to be appropriate due to the large imbalances in sample sizes. The provided description of the TEAE patterns do not suggest a clinically meaningful difference between races.

Throughout Phase 1 trials differences in the PK in the Asian population were described. Please refer to the Pharmacology Assessment Report. Data from the ongoing study TRD2005 in Japanese subjects are outstanding.

Patients with Hepatic Impairment

Subjects with severe hepatic impairment were specifically excluded from Phase 3 studies. Esketamine is metabolized in the liver, and hepatic clearance is required for a termination of the clinical effects. There are preclinical findings suggestive of hepatotoxicity. A number of cases of liver damage (bile duct dilatation and hepatic enzymes elevation) have been reported in literature related to (off-label) long-term ketamine use.

Results of TRD1011 show increases in Cmax (8% higher) and AUC (114% higher) in subjects with moderate hepatic impairment. The reported rates of TEAEs were higher in patients with mild and moderate hepatic impairment in comparison with subjects with normal liver function (37.5% vs 25%).

Throughout Phase 2 and 3 trials there were no TEAEs of cholangiopathy, cholestasis, or biliary dilatation associated with esketamine treatment and no treatment emergent elevated total serum bilirubin levels >2x ULN. Transient asymptomatic increases of ALT and AST occurred at low rates.

Patients with Renal Impairment

Subjects with severe renal impairment were specifically excluded from Phase 3 studies. Esketamine metabolites are mainly excreted with urine. An increase in Cmax (20 to 26% higher) and AUC (13 to 36% higher) was observed in subjects with mild to severe renal impairment in TRD1014.

Pregnancy and lactation

Esketamine has not been studied in pregnant or breastfeeding women and these subjects were excluded from the clinical trials. Studies in animals have shown reproductive toxicity. The clinical significance of these nonclinical findings is not known.

18 pregnancies were reported in subjects exposed to esketamine throughout the clinical trial programme up to 27 March 2019:

Table 14: Status/Outcome of Pregnancies

Pregnancy outcome	Number of cases
Father case	4
Spontaneous abortion	4
Healthy baby	3
Unknown outcome	3
Elective abortion	2
Ectopic pregnancy	2

Outcomes included 2 ectopic pregnancies, 4 spontaneous abortions, 2 elective abortion, all assessed as not related to esketamine administration by the sponsor due to risk factors including advanced maternal age, obesity, previous history of spontaneous abortion, and sterilization procedure (for the cases of ectopic pregnancy). 3 pregnancies are described as unknown outcome.

The 3 healthy babies were reported in partners of male subjects who were exposed to esketamine No congenital anomalies were reported.

The possibility of foetal neurotoxicity cannot be excluded based on published findings in animals. As outlined in the product information, esketamine nasal spray is not recommended during pregnancy and in women of childbearing potential not using contraception. Use during pregnancy is included in esketamine nasal spray RMP as missing information. To further characterize the impact of this missing information on the safety profile of esketamine nasal spray periodic safety assessments of data will be conducted from a US-based pregnancy registry for psychiatric medications, including antidepressants. The aims of review of this registry data are as follows:

- To prospectively evaluate rates of congenital malformations among infants exposed in utero to psychiatric medications;
- To evaluate neonatal outcomes of infants with prenatal exposure to specific psychiatric medications alone or in combination with other psychotropics;
- To evaluate maternal health outcomes associated with use of psychiatric medications during pregnancy;

  To evaluate neurobehavioral development of children (1 month and older) with prenatal exposure to psychiatric medications.

Immunological events

No discussion has been provided by the Applicant, since it concerns a well-known small molecule.

Safety related to drug-drug interactions and other interactions

All subjects were treated with a SSRI/SNRI in addition to esketamine. No data on the combination with other oral antidepressants is available.

Pharmacokinetic interactions

Changes in the activity of CYP enzymes (CYP2B6 and CYP3A4) are expected to influence the oral bioavailability of esketamine, however, due to nasal administration, where approximately half of the dose is absorbed via nasal mucosa avoiding the first-pass metabolism in the liver, nasal esketamine is expected to have a low propensity to pharmacokinetic interactions.

Pretreatment with oral ticlopidine or oral clarithromycin, inhibitors of hepatic CYP2B6 and CYP3A activity, respectively, produced small changes in the pharmacokinetics of nasally administered esketamine.

Pretreatment with oral rifampicin, a potent inducer of the activity of multiple hepatic CYP enzymes such as CYP3A4 and CYP2B6, decreased the mean C_{max} and AUC_{∞} values of nasally administered esketamine by approximately 17% and 28%, respectively.

Administration of 84 mg nasal esketamine twice a week for 2 weeks did not affect the activity of hepatic CYP2B6 activity, using oral bupropion as a probe substrate. The same regimen of esketamine reduced the mean plasma AUC of oral midazolam by approximately 16%.

The Applicant presented a post-hoc analysis of esketamine exposure under co-medication of oral antidepressant (ie, duloxetine, escitalopram, sertraline, and venlafaxine) based on a Pop PK model revealing a reduced Cmax by 1,5%, which is not likely to be clinically relevant.

Physiologically based PK modeling and simulation were performed to assess the potential drug-drug interaction of nasal esketamine towards ethinyl estradiol indicating that no effect of esketamine on ethinyl estradiol plasma concentrations is predicted.

Pharmacodynamic interactions

Pharmacodynamic interaction studies were not conducted by the Applicant. In line with other ketamine/esketamine products potential interactions with CNS depressants, psychostimulants or drugs that may increase blood pressure (e.g., xanthine derivatives, ergometrine, thyroid hormones, vasopressin or MAOI) are expected or cannot be excluded.

Discontinuation due to adverse events

TEAEs leading to discontinuation of esketamine were reported at low rates, which were higher in the esketamine groups compared to placebo groups:

	Esketamine + oral AD	placebo + oral AD
pooled TRD3001/TRD3002	4.6%	1.4%
TRD3005	5.6%	3.1%
TRD3003	2.6%	2.1%

After longer-term exposure to esketamine in TRD3003, discontinuation rates for nasal study drug during the DB MA phase were similar for the esketamine and placebo groups.

The overall discontinuation rate due to TEAEs observed in the Phase 3 uncontrolled, OL safety study (TRD3004) with esketamine treatment exposure of up to 1 year was 9.5%.

The rates of discontinuations of esketamine treatment due to TEAEs were generally highest immediately after treatment initiation. In the Phase 3 short-term studies in adults (TRD3001, TRD3002), nearly all discontinuations due to TEAEs in esketamine-treated subjects occurred within the first 2 weeks of the DB phase. In the Phase 3 relapse prevention (TRD3003) and OL long-term safety (TRD3004) studies, discontinuations due to TEAEs in esketamine-treated subjects occurred in higher rates in the IND phase compared to the OP and/or MA phases

Across the Phase 3 studies, TEAEs leading to esketamine discontinuation in more than 2 subjects (>0.1%) were (in order of frequency): anxiety, depression, blood pressure increased, dizziness, suicidal ideation, dissociation, nausea, vomiting, headache, muscular weakness, vertigo, hypertension, panic attack, and sedation.

The types of TEAES leading to discontinuation of esketamine in the Phase 2 studies in TRD (TRD2003) and MDSI (SUI2001) and in the Phase 1 studies were generally consistent with those observed in the Phase 3 studies in TRD. It was noted that a correlation between discontinuation and dose administered was not investigated.

Post marketing experience

N/A

2.6.1. Discussion on clinical safety

Esketamine, the S-enantiomer of racemic ketamine, is a well-known active substance approved as solution for injection in induction and maintenance of anaesthesia in some EU countries. The racemic ketamine is in widespread use worldwide for the same indications since the 1970s and is on the World

Health Organization's List of Essential Medicines. Hence, the experience with the use of the active substance is broad. Psychiatric (e.g. dissociation, dizziness, anxiety), cardiovascular (e.g. increased blood pressure and heart rate) or gastrointestinal (e.g. nausea, vomiting) ADRs are well known as well as the potential for drug abuse.

The presented clinical development program aimed at collecting sufficient information on the safety profile of nasal esketamine spray in the target population with TRD over the intended therapeutic dose range of 56 to 84 mg up to twice applications weekly. Achieved plasma levels are below those required for induction and maintenance of anaesthesia.

The Applicant chose to focus the primary safety analysis on phase 2 study TRD2003 and completed phase 3 studies including both short term studies (TRD3001/3002/3005) as well as long-term studies (TRD3003/3004) and a study evaluating esketamine in an elderly population (TRD3005).

In total 1708 subjects were included in the primary safety analysis, with 178 subjects receiving intranasal esketamine for at least 12 months. Interim Results (cutoff date 31st Dec 2018) are available from the ongoing study TRD3008 for the long-term treatment of 927 treated at least 12 months and up to 30 months (n=54). The overall long-term exposure is acceptable. So far, no trends over time could be observed for long-term effects on suicidality, cognition, interstitial cystitis/lower urinary tract symptoms as well as on hepatic disorders. Full data of the long-term ongoing study TRD3008 is, however, not yet available.

Across the clinical studies adverse events were reported more frequently in patients using esketamine than patients in the oral AD + intranasal placebo groups. Approximately 70-90% of patients in the esketamine groups experienced at least one adverse event compared to 45-60% in the oral AD + intranasal placebo groups. Most of the adverse events reported in the esketamine groups occurred on the same day as dosing (65~90%). Of these events almost all also were resolved that day (approximately 90%). Transient post-dose symptoms (e.g. dissociation, dizziness, nausea), were expected based on the pharmacological profile and the already known ADR profile of esketamine solution for injection and generally resolved without clinical sequelae in less than 2h. TEAEs that did not resolve the same day were mostly considered as associated either with the underlying (depression) or other co-occurring conditions. Cases of prolonged pollakuria were observed in the esketamine groups and this has been reflected in the SPC.

The Applicant provided sufficient information on the dose relationship on incidences and severity of TEAEs. Across trials no clear evidence for a dose response relationship could be seen for the incidence of TEAEs, for TEAEs leading to discontinuation of intranasal study medication, for SAEs or for TEAEs leading to dose interruptions.

For the TEAE dissociation, which is supposed to be dose related, only in TRD3005 and TRD3004 a clear dose relationship could be observed.

A PK/PD model revealed a correlation between blood pressure and plasma concentrations.

Most of the TEAEs were mild or moderate in severity. Overall, the results across Phase 2 and 3 studies including FU phases were consistent, no new adverse events were reported for elderly patients or with long-term repeated esketamine dosing (up to 1 year of exposure). Adverse events categorized as severe were reported infrequent and often self-limiting.

A Systematic evaluation of adverse event data from the completed Phase 2 and 3 studies identified 24 ADR terms for esketamine (15 grouped ADR terms and 9 individual ADR terms) with the following attributed frequencies:

Very common ADRs: Dissociation, Anxiety, Dysgeusia, Dizziness, Sedation, Headache, Hypoesthesia, Vertigo, Vomiting, Nausea, Blood Pressure Increased

Common ADRs: Euphoric mood, Mental impairment, Tremor, Lethargy, Dysarthria, Tachycardia, Nasal discomfort, Dry mouth, Hyperhidrosis, Pollakiuria, Feeling abnormal, Feeling drunk

Uncommon ADRs: Salivary hypersecretion

Overall, the described approach of the ADR analysis is regarded acceptable.

A total of 7 deaths have been reported throughout all trials and all were in the esketamine treatment groups. Three of the deaths were completed suicides. Given the severity of depression in the studied population and the high likelihood of suicide attempts, the latency to the last esketamine dose (4, 12 and 20 days), the imbalance in exposure between the esketamine group and control group (1045 vs 100 patient-years of exposure, respectively) and assessment of the individual cases, it appears unlikely that these were related to esketamine, but rather to the underlying severe condition. Furthermore, the suicides occurred during or after uncontrolled open-label treatment allowing no direct comparison with patients without esketamine treatment. However, the possibility cannot be excluded that there have been pharmacodynamic changes in the brain, which may have restored or facilitated the drive to commit suicide. Therefore, warnings regarding suicide risk have been included in the SmPC. Two deaths due to multiple injuries following a one-sided motorcycle accident and an accidental polytrauma were regarded as not related to esketamine. The relationship between esketamine and the acute respiratory/cardiac failure death or the myocardial infarction is deemed unlikely, due to the timeframe in which the event occurred and age/patient history.

Overall reporting of serious adverse events across the phase 3 studies was low (< 10%) and had similar incidences in both esketamine and oral AD + intranasal placebo groups. Most of the reported SAEs were in the psychiatric disorders category and associated to exacerbation of the underlying disease. However, there was also a hypertensive emergency 2 min after esketamine application, which seems plausibly be related to study medication. A dose-relationship of SAEs could not be observed TEAEs leading to study drug discontinuation, dose reduction or interruption of treatment were reported at low rates in the short-term studies in both adult and elderly subjects. Across all studies, most frequently reported TEAEs in these categories were related to the underlying disease state under study (e.g. depression, anxiety) or transient events (e.g. dissociation, dizziness, nausea), which occurred shortly after dosing and resolved the same day. The rates of discontinuation of esketamine treatment due to TEAEs were generally highest early in the course of treatment (range 4.6-6.8%). In the Phase 3 short-term studies in both adult and elderly subjects, TEAEs leading to discontinuation were reported at higher rates in the esketamine compared with the placebo group. After longer-term exposure discontinuation rates were similar in the esketamine and placebo groups.

Adverse events of special interest

Suicidal ideation and behaviour. Only patients with no or mild suicidal ideation (as assessed by C-SSRS and clinical judgment) were eligible for inclusion in the TRD studies since that level of suicidality is common for the disease severity of the studied population. All cases of completed suicide occurred in completed and ongoing open-label studies/study phases with no control group. The completed suicide rate of 0.29 per 100 patient years of treatment observed in the Phase 2/3 TRD studies does not appear higher than the completed suicide rate of 0.47 per 100 patient years of treatment reported in a meta-analysis of 30 TRD studies consisting of over 15,000 patients with TRD. Up to now, no trend could be observed that prolonged exposure to esketamine influences suicidality.

Worsening of suicidality and suicidality-related adverse events were reported infrequent. In the short-term studies there is a suggestion that, compared to oral AD + intranasal placebo, worsening of suicidality is lower in the esketamine groups. Interpretation is difficult as patients also initiated treatment with a new oral anti-depressant. The underlying disease may have also influenced events in some cases. A warning is included in the SmPC regarding suicide risk, which is supported.

Dissociation and perceptual changes.

Dissociation was reported more often in patients in the esketamine groups across the clinical development program. A distinctive pattern of dissociation was observed when monitoring the CADSS scores: onset shortly after dose administration, peak at 40 minutes post dose and resolvement at 1.5 hours post dose. This is in line with the PK profile of esketamine. In both long-term studies it can be seen that CADSS scores decreased over time.

Psychotic like symptoms & anxiety. Psychotic like symptoms were measured with the BRPS+. A small increase in score post baseline was more often reported in patients in the esketamine groups than in the oral AD + intranasal placebo groups. This transient increase follows the timing of the PK profile where it peaks at 40 minutes post dose and is mostly resolved at 1.5 hours post dose. Rescue antipsychotic medication was not needed. Based on additional analyses, there appears to be overlap between increases measured on the BRPS+ and the CADSS scales. Due to this overlap, it is more likely that any increase on the BRPS+ scale is related to dissociation, which may be transient, rather than psychosis. A warning has been included in the SmPC to be careful to treat patients with a history of psychosis, which is considered relevant.

Anxiety was reported infrequently across the treatment groups and rescue anti anxiety medication was rarely needed.

Hypomania and mania. Overall reporting of adverse events of mania was low during the study. Only two cases of mania were reported in the clinical development program. As there are uncertainties whether mania is to be attributed to esketamine treatment, to the newly initiated AD (duloxetine) treatment or to a so far undiagnosed bipolar disorder, a warning regarding "Presence or history of mania or bipolar disorder" has been included in the SmPC.

Dizziness and vertigo. Adverse events of this category were more commonly reported in any of the esketamine groups than in the oral AD + intranasal placebo group. Most of these events were mild or moderate in severity and occurred and resolved on the same day of dosing. It appears that patients developed tolerance to these effects over the course of treatment.

Somnolence and sedation Adverse events related to somnolence and sedation were more often reported in the esketamine groups than in the oral AD + intranasal placebo groups across the clinical development program. Most events were reported on the same day of dosing. Like other CNS symptoms, sedative effects were typically resolved at 1.5 hours post dose.

Cognition. Ketamine abuse has been associated with neurotoxicity and subsequent cognitive impairment. Effects on cognition seem to be negligible in Phase 3 observations. Across the studies, patients appeared to perform on cognitive tests either similar to baseline or improve. The observed improvement in some cases is in line with the antidepressant treatment in both oral AD + intranasal placebo and esketamine groups. These results of the Phase 1 TRD1005 study, where 40 min post esketamine administration a transient significant decline in cognition, an increase in mental effort required to complete the Cogstate computerized test and an increase in sleepiness was observed in healthy volunteers, are in line and to be plausibly explained with early post-dose sedation and resolved by 2h after dosing. Repeated dosing of esketamine does not appear to lead to cognitive impairment in the current data set with the exception of the observed slowing in reaction time only in elderly subjects in both TRD3005 (short term) and TRD3004 (long term safety). Slowing of RT was not reflected in any of the other cognitive tests. Due to the absence of a control arm in study TRD3004 the clinical relevance is not clear at present. Published longitudinal studies of RT in elderly patients with MDD also presented slowing of reaction time. The interim report of the long-term study TRD3008 outlines a decline in performance on tests designed to assess psychomotor function and attention in the elderly.

Cognitive disorders and memory impairment (long-term use) have been included in the risk management plan (RMP) as important potential risk, to be further investigated via the ongoing category 3 study 54135419TRD3008 (the clinical study report is awaited by Q1 2023; annual analyses of safety results should also be provided until study completion).

Interstitial cystitis and lower urinary tract symptoms. Most of the patients that experienced a post-baseline increase in BPIC-SS score only had it at one time-point during the studies. No cases of esketamine-related interstitial cystitis were observed in any of the studies, including long-term results. In esketamine treated patients, there was a higher rate of lower urinary tract symptoms (pollakiuria, dysuria, micturition urgency, nocturia, and cystitis) than in placebo-treated patients. These symptoms were typically mild to moderate in intensity and did not lead to discontinuation of treatment with esketamine. These findings are reflected in the SmPC. Furthermore, as in clinical trials, there was a higher rate of lower urinary tract symptoms in esketamine nasal spray-treated patients than in placebo-treated patients, Interstitial cystitis (long-term use) was included in the RMP as Important potential risk, requiring further evaluation via the category 3 (ongoing) study 54135419TRD3008.

Nausea and vomiting. Nausea/vomiting was more commonly reported in patients receiving esketamine than in patients receiving oral AD + intranasal placebo. Compared to the induction phase, the rates of nausea and vomiting in the esketamine groups decreased in the optimization/maintenance phase. Thus some tolerance appears to be developed at chronic esketamine use.

Abuse potential. The results of TRD1015 indicate that the abuse potential of intranasal administration of esketamine is similar to IV administration of ketamine. Furthermore, a number of TEAEs suggestive of Abuse Potential has been reported more commonly in the esketamine groups than in the placebo groups in the completed Studies. These were transient and self-limiting dizziness, somnolence, and dissociation and, reported at lower rates, euphoric mood, confusional state, feeling drunk or abnormal, and hallucinations. Throughout the trials, however, cases of drug abuse or drug seeking behaviour have not been observed. Given the chronic nature of the treatment more longitudinal data is needed to fully evaluate the abuse potential of esketamine.

Drug abuse is included in the RMP as an important identified risk for esketamine nasal spray. The following routine and additional risk minimisation measures (RMMs) are deemed necessary to prevent / minimise such safety concern.

The abuse potential of esketamine nasal spray and its mitigation are addressed, first of all, in the EU product information (EU PI) (ie, Summary of Product Characteristics [SmPC] and Package Leaflet [PL]) and include the following concepts:

- Esketamine nasal spray is administered under the direct supervision of a healthcare professional.
- The recommended dosing of esketamine nasal spray is twice weekly for 4 weeks, followed by weekly or every-other-week dosing for patients with a favorable clinical response. During longer-term treatment, physicians are recommended to individualize the dosing frequency to the lowest frequency needed to maintain the patient's clinical response and to perform periodic re-evaluation of patients to determine the need for continued treatment.
- Individuals with a history of drug abuse or dependence may be at greater risk for abuse and misuse of esketamine nasal spray. Physicians are advised to assess individuals prior to treatment for a history of substance use disorder and to monitor for signs of abuse or dependence.
- Esketamine nasal spray is designed with the following features to deter abuse (and misuse):
- The product is supplied in limited pack sizes.

- The drug product is contained in a Type I glass vial sealed with a chlorobutyl rubber stopper. The filled and stoppered vial is seated into a container holder assembled into a manually activated nasal spray device. The device is difficult to disassemble due to interlocking design features of the actuator subassembly. Attempts to break open the device damage the vial and the contents are lost. The force required to pull the device apart is at least 60 Newtons (~13 pounds). If the device is taken apart, the stoppered vial provides an additional challenge to disassembly, as it is very difficult to pull the stopper out. Breaking the vial instead results in loss of the contents.

- The product is supplied as a single-use device containing a total of 32.3 mg of esketamine HCl (equivalent to 28 mg of esketamine). When manually actuated, the device dispenses 2 individual sprays; no sprays remain after the second spray is actuated.
- The nasal spray device has a nominal fill volume of 230 µL and a delivery volume of 200 µL. The average measured residual volume left in the nasal spray device after actuation is ~30µL (4 mg base).

- Legal controls (e.g., restrictions on storage and prescribing including special and restricted medical prescription with categorization at the Member State level) will be in place according to local legal requirements in the majority of Member States (MS) where esketamine is currently scheduled, either directly or indirectly due to its chemical relationship to ketamine. In these Member States (MS), it is proposed that the scheduling class should be the same as that which applies already to any ketamine- or esketamine-containing medicinal product. The following recommendations minimize the risk of abuse, diversion and misuse. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. All treatment should be administered under the direct supervision of a healthcare professional (HCP) and signs of abuse or dependence should be carefully monitored.

- No unsupervised administration of the product is allowed.

Furthermore, a controlled access program should be implemented, as key element to ensure esketamine nasal spray is dispensed to the healthcare settings where administration takes place, as agreed at the Member State level, based on local legal requirements and/or local healthcare systems.

A HCP Guide and a Patient Guide containing key messages regarding product administration and the potential for abuse and dependence are also agreed as additional RMMs.

Withdrawal and rebound. There was no evidence suggestive of a distinct withdrawal syndrome after cessation of treatment with esketamine assessed by the PWC-20 (Physician Withdrawal Checklist). Taking into consideration the half-life of esketamine of 7 to 12 hours, with twice-a-week or lower dosing frequency, circulating levels of esketamine are not expected to accumulate and the occurrence of a withdrawal syndrome after discontinuation of nasal esketamine is unlikely.

Cardiovascular safety. TEAEs of increased blood pressure and increased heart rate were generally transient and mild or moderate in severity. Serious AEs were reported in isolated cases. Blood pressure increases occurred shortly after esketamine administration, reaching maximum within 40 minutes, at the time of peak plasma esketamine levels, and generally returning to values close to pre-treatment within 1.5 hours after administration. Increases of blood pressure were reported more frequently in patients with a history of hypertension and in elderly subjects. The presented findings are in accordance with the already known cardiovascular ADR-profile of esketamine. Exposure-response PK/PD models were developed to describe the relationship between SBP and DBP and esketamine plasma concentration.

Cardiovascular compromised individuals or those with poorly controlled hypertension were excluded from the clinical studies, however those with cardiovascular risk factors (obesity, hypertension, diabetes etc.) could participate in the studies Subgroup analyses revealed that cardiovascular-related adverse events occurred more frequently in patients with CV risk factors. It was agreed that for administration of esketamine in patients with unstable cardiovascular or respiratory conditions, as a precautionary

measure, resuscitation equipment and health care professionals trained in CPR should be available at the administration site.

There were no clinically meaningful changes in ECG findings across the Phase 2 and 3 studies, including QTc interval or PR Interval, in agreement with the findings of the Phase 1 thorough QTc study in healthy subjects.

Overall, due to the transient and self-limiting nature of the cardiovascular effects observed in clinical trials, the overall impact on the risk-benefit balance of the product is considered low; however, the impact on an individual patient may be significant. The SmPC and PL, as well as the Healthcare Professional Guide and Patient Guide, provide information to the prescriber and the patient on how to manage the risk. A checklist for readiness to leave will be provided to aid HCP in determining when a patient is deemed stable and should safely be allowed to return home following esketamine nasal spray administration.

Nasal tolerability The active substance concentration of 140 mg/mL resulted in a high osmolality of the solution (appr. 1050 mOsm/kg). The effect of the osmotic pressure on the nasal irritation was investigated throughout clinical studies and considered acceptable. Although most subjects did not report any nasal tolerability symptoms or significant effects on the sense of smell, nasal discomfort was reported as a common and dysgeusia as a very common ADR. Reported symptoms were mild to moderate. Long term exposure had no impact on nasal tolerability or the sense of smell.

No clinically meaningful changes in mean laboratory analytes (hematology, chemistry, urinalysis parameters) from baseline were observed in any of the completed Phase 2 and 3 TRD studies, there were only isolated cases in which TEAEs were associated with abnormal laboratory results leading infrequently to discontinuation.

There were no cases of respiratory depression among esketamine-treated subjects across the studies, and no subject required cardiopulmonary resuscitation or other medical interventions.

No effect on body weight could be observed.

Esketamine is metabolized in the liver, and hepatic clearance is required for a termination of the clinical effects. There are preclinical findings suggestive of hepatotoxicity. A number of cases of liver damage (bile duct dilatation and hepatic enzymes elevation) have been reported in literature related to (off-label) long-term ketamine use. ALT/AST elevations observed in the Phase 3 studies were primarily asymptomatic, transient and resolved spontaneously without worsening while treatment with esketamine and oral AD continued, no persistent increases in liver transaminases were observed and no cases met the criteria for severe drug-induced hepatocellular injury. Results of TRD1011 show increases in Cmax and AUC in subjects with moderate hepatic impairment and the reported rates of TEAEs were higher in patients with mild and moderate hepatic impairment in comparison with subjects with normal liver function (37.5% vs 25%).

Although it is agreed that the differences to the placebo + AD group are minor and that the relationship to esketamine is difficult to determine due to the novel oral AD started at the same time, it is considered that the totality of the findings justify a warning in section 4.4 for patients with severe hepatic impairment unless there is new safety data generated in this patient group.

So far, the available long-term data from the interim-analysis of TRD3008 do not suggest a trend for hepatic events/liver function disturbances over time.

There have been no reported cases of overdose with esketamine in any of the clinical studies. The maximum single dose tested was 112 mg with a higher incidence of TEAEs compared to lower doses. The potential for overdosage by patients seems to be low, because esketamine has to be administered in the

presence of health care professionals. Nevertheless, it is reflected in the SmPC that above the 25-fold usual anaesthetic dose, life-threatening symptoms are expected. Clinical symptoms are described as convulsions, cardiac arrhythmias and respiratory arrest.

Pharmacokinetic differences have been described in the elderly population (increase of Cmax and AUC in comparison to younger adults). This was reflected by the lower starting dose (28 mg) of esketamine administered to the elderly subjects included in TRD3005. No clinically meaningful differences were described between any of the subgroups defined by age from the presented data from trial TRD3005 no clear dosing difference could be observed for TEAEs in the elderly. Data from the interim report of the ongoing trial TRD3008 show that the incidences of AEs overall and by SOC were generally similar for patients <65 years and for patients ≥ 65 years. However, it has to be taken into account that only a limited number of patients ≥ 65 years (n=14) has been included.

No clinical meaningful differences in frequencies or pattern of TEAEs could be observed for different sexes or different races in the Phase 3 trials. Subjects from Europe, North America and other regions were included in the trials at various frequencies. As pharmacokinetic observations revealed a higher exposure in Japanese subjects (Please refer also to the Pharmacology Assessment Report), a conservative dosing approach is recommended in this patient population unless data from the ongoing study TRD2005 in Japanese subjects provide further information on safety and dose-response (expected 2nd half 2020).

The use of esketamine is not recommended in pregnant women and these subjects were excluded from the clinical trials. There were 18 pregnancies during the clinical development program exposed to esketamine. Outcomes included 2 ectopic pregnancies, 4 spontaneous abortions, 2 elective abortions, all assessed as not related to esketamine administration by the sponsor due to risk factors including advanced maternal age, obesity, previous history of spontaneous abortion, and sterilization procedure (for the cases of ectopic pregnancy). 3 pregnancies are described as unknown outcome. 3 healthy babies were reported in partners of male subjects who were exposed to esketamine. No congenital anomalies were reported. Non-clinical studies have shown that racemic ketamine induced lower birth weight and can also induce neurotoxicity in juvenile animals. A similar risk with esketamine cannot be excluded.

Changes in the activity of CYP enzymes (CYP2B6 and CYP3A4) are expected to influence the oral bioavailability of esketamine, however, due to nasal administration, where approximately half of the dose is absorbed via nasal mucosa avoiding the first-pass metabolism in the liver, nasal esketamine is expected to have a low propensity to pharmacokinetic interactions.

A post-hoc analysis of esketamine exposure under co-medication of oral antidepressant (ie, duloxetine, escitalopram, sertraline, and venlafaxine) based on a Pop PK model revealed no clinically relevant interaction potential. PB PK modeling and simulation revealed that no effect of esketamine on ethinyl estradiol plasma concentrations is expected.

Pharmacodynamic interaction studies were not conducted by the Applicant. Since potential pharmacodynamic interactions (e.g. increasing cardiovascular ADRs like hypertension with psychostimulants and other substances) are described for other esketamine products, these are outlined also in the SPC for nasal esketamine.

Precautionary measures, such as food restriction up to 2 hours before drug administration and post-dose close observation under the supervision of a healthcare professional have to be ensured.

Taking into account that esketamine has the potential to cause sedation, dizziness and hypertension, patients have to be monitored adequately in the immediate post-dose period. Measures of post-dose observation, including concrete timelines, are specified in the product information (e.g. blood pressure, sedation). As PK considerations do not suggest an anaesthetic effect and no case of respiratory depression was detected throughout the trial programme in 78,244 dosing sessions or in the post-marketing experience with 11,260 dosing sessions in the USA, the CHMP considers that the

immediate availability of resuscitation equipment and supportive ventilation as well as the availability of adequately CPR trained staff at the administration site is not regarded as mandatory for all patients. However, based on the PRAC recommendation and further discussion within the Committee and with the company, it was deemed necessary to have this in place for at risk patients (i.e. patients with clinically significant or unstable cardiovascular or respiratory conditions).

Particular attention should be given to elderly patients, considering they are more prone to injury.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Over the proposed therapeutic dose range most TEAEs occur shortly after dosing when patients will be under the supervision of a HCP and are transient with same day resolution. Generally, TEAEs were expected based on the pharmacological profile and the already known ADR profile of esketamine solution for injection.

The most common ADRs for nasal esketamine in TRD patients were dissociation, dizziness, nausea, sedation, headache, vertigo, dysgeusia, hypoaesthesia, increased blood pressure, anxiety and vomiting. Esketamine has a potential for abuse.

The use of esketamine as a treatment for depression is novel. Treatment duration is expected to be at least over 6 months. Up to now long term data does not suggest a trend over time in how intranasal esketamine affects suicidality, cognition and interstitial cystitis/lower urinary tract symptoms as well as renal and hepatic adverse reactions in patients with TRD.

Because of the possibility of sedation, dissociative symptoms and hypertension, 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.

Taking into account the safety findings of the clinical trial program, intranasal administration of esketamine in the target population with TRD at doses of 56 or 84 mg up to twice weekly was deemed to have an acceptable safety profile under the supervision of a healthcare professional.

With regard to the general requirement of the presence of a specifically CPR-trained physician and resuscitation equipment at the administration site, the CHMP reviewed the available evidence and agreed that the applicant's justification for omitting the requirement of resuscitation equipment for all patients seemed sound as:

1. PK considerations do not suggest an anaesthetic effect (much lower plasma levels)
2. data throughout the trial program in 78,244 dosing sessions
3. Sedation levels MOAAS 0 (no response to painful stimulus) only in 4 cases, none of them associated with respiratory depression, 3 using additional other CNS depressants
4. US post-marketing data: no case of respiratory depression in 11,260 dosing sessions
5. Two anaesthesiological experts support the applicant's position
6. Labelling for other anaesthetics used at subanaesthetic doses (e.g. Xyrem, Clonazepam, Zubsolv) does not require resuscitation equipment

It was felt that the requirement for a full-time presence of a physician with CPR training during the Spravato administration sessions and availability of resuscitation equipment for all patients may be overly

strict, would restrict administration to a hospital setting and may prevent many TRD patients from receiving treatment with nasal esketamine.

Thereby a compromise was agreed to restrict the intensified monitoring/treatment conditions to patients at risk 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.

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.
Furthermore, the CHMP considers the following additional pharmacovigilance activities necessary to address issues related to safety:

- A survey to assess the effectiveness of the additional risk minimisations measures (category 3): To assess the effectiveness of the additional risk minimisation materials (i.e. HCP guide and checklist for readiness to leave, patient guide).
- An open-label long term extension safety study of intranasal esketamine in TRD (ongoing, category 3): 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; Potential effects on suicidal ideation/behaviour; interstitial cystitis
- A planned pregnancy registry for Psychiatric medications such as antidepressant, including esketamine. To further characterize the impact of the missing information of Use during pregnancy on the safety profile of esketamine nasal spray. Periodic safety assessments of data will be conducted from a US pregnancy registry for psychiatric medications, including antidepressants.

2.7. Risk Management Plan

Safety concerns

Summary of the safety concerns

Important identified risks	• Drug abuse • Transient dissociative states and perception disorders • Disturbances in consciousness • Blood pressure increased
Important potential risks	• Cognitive disorders and memory impairment (long-term use) • Interstitial cystitis (long-term use)
Missing information	• Use during pregnancy

Pharmacovigilance plan

Ongoing and Planned Additional Pharmacovigilance Activities

Study	Summary of objectives	Safety concerns addressed	Milestones	Due dates
54135419TRD3008 An open-label long term extension safety study of intranasal esketamine in TRD **(Category 3)** **Ongoing**	To assess the long-term safety (> 1 year) of esketamine nasal spray in subjects with TRD, with special attention to the following: Potential l 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; Potential effects on suicidal ideation/behavior.	Cognitive disorders and memory impairment (long-term use) Interstitial cystitis (long-term use)	Protocol submission (initial) Trial start date (first patient in) Interim report Final report	National submissions starting in 2Q 2016 21 Jun 2016 2Q 2019 1Q 2023 Annual analyses of safety results to be provided until the final study report becomes available
Pregnancy registry for Psychiatric medications such as antidepressants including esketamine **(Category 3)** **Planned**	To further characterize the impact of the missing information of Use during pregnancy on the safety profile of esketamine nasal spray. Periodic safety assessments of data will be conducted from a US pregnancy registry for psychiatric medications, including antidepressants.	Use during pregnancy	Protocol Submission (initial) Trial start date (first patient in) Periodic updates Final report	Within 6 months after approval of MAAa (by 30 June 2020) Relevant data being captured since US approval date of 05 March 2019 Periodic updates will be reported in the PBRER/PSUR. 4Q 2024
HCP and patient survey to assess the effectiveness of the additional risk minimization measures **(Category 3)** **Planned**	To assess the effectiveness of the additional risk Minimization measures (i.e. Healthcare Professional Guide, Patient Guide, Checklist for readiness to leave) related to understanding and management of the important identified risks with esketamine treatment	Drug abuse Transient dissociative states and perception disorders Disturbances in consciousness Blood pressure increased	Protocol Submission (initial) Trial start date (first patient in)	Within 6 months after approval of MAAa (by 30 June 2020) Initiation of the survey (wave 1): within 18 months of availability of the approved educational materials in the selected countries. Initiation of survey (wave 2): after 2.5-3 years of availability of the approved educational materials in the selected countries A report on the educational activities undertaken and the results of the survey will be submitted at

				18 months and 3 years after launch.
			Periodic updates	Updates will also be reported in the PBRER/PSUR.
			Final report	4Q2022

Risk minimisation measure

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: • SmPC Section 4.4; • PL Section 2. • Administration under the direct supervision of a healthcare professional (SmPC Sections 4.2 and 4.4, PL Section 3, and Instructions for Use); • Limited pack sizes; • Legal status: Special and restricted medical prescription with categorization at the Member State level. Additional risk minimization measures: • Healthcare Professional Guide; • Patient Guide; • Controlled access program.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Cumulative review of adverse events of interest including presentation and analysis of abuse-related serious adverse reactions in PBRER/PSUR. Additional pharmacovigilance activities: • Survey to assess the effectiveness of the additional risk minimization materials.

Summary Table of PV Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Transient dissociative states and perception disorders	Routine risk minimization measures: • SmPC Sections 4.4, 4.7, and 4.8; • PL Sections 2 and 4. • Recommendation for dose titration is included in SmPC Section 4.2; • Recommendation regarding driving a motor vehicle or operating machinery is included in SmPC Section 4.7 and PL Section 2; • Recommendation for post-administration observation is included in SmPC Section 4.2; • 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. Additional risk minimization measures: • Healthcare Professional Guide; • Patient Guide; • Checklist for readiness to leave.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Cumulative review of adverse events of transient dissociative states and perception disorders at an aggregate level; presentation and analysis of serious adverse reactions in PBRER/PSUR. Additional pharmacovigilance activities: • Survey to assess the effectiveness of the additional risk minimization materials.
Disturbances in consciousness	Routine risk minimization measures: • SmPC Sections 4.4, 4.7, and 4.8; • PL Sections 2 and 4. • Recommendation for dose titration is included in SmPC Section 4.2; • Recommendation regarding driving a motor vehicle or operating machinery is included in SmPC Section 4.7 and PL Section 2; • Recommendation for post-administration observation is included in SmPC Section 4.2; • 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. • Recommendation that administration and post-administration observation of esketamine should be carried out in an appropriate clinical setting (SmPC Section 4.2). Additional risk minimization measures: • Healthcare Professional Guide; • Patient Guide; • Checklist for readiness to leave.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Cumulative review of adverse events of disturbances in consciousness at an aggregate level; presentation and analysis of serious adverse reactions in PBRER/PSUR. Additional pharmacovigilance activities: • Survey to assess the effectiveness of the additional risk minimization materials.

Summary Table of PV Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Blood pressure increased)	Routine risk minimization measures: • SmPC Sections 4.2, 4.3, 4.4 and 4.8; • PL Sections 2 and 4. • 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; • Recommendation regarding treatment in patients whose blood pressure is elevated prior to administration is provided in SmPC Section 4.4; • Recommendation not to administer esketamine nasal spray 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. • As described in SmPC Section 4.2, administration and post-administration monitoring take place under the supervision of a healthcare professionals with training in blood pressure monitoring. Additional risk minimization measures: • Healthcare Professional Guide; • Patient Guide; • Checklist for readiness to leave.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Cumulative review of adverse events of Blood pressure increased) at an aggregate level; presentation and analysis of serious adverse reactions in PBRER/PSUR. Additional pharmacovigilance activities: • Survey to assess the effectiveness of the additional risk minimization materials.
Cognitive disorders and memory impairment (long-term use)	Routine risk minimization measures: • SmPC Section 4.8; • PL Section 2. Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • 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. Additional pharmacovigilance activities: • Long-term safety study 54135419TRD3008 (ongoing)
Interstitial cystitis (long-term use)	Routine risk minimization measures: • SmPC Sections 4.4 and 4.8; PL Section 2. Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • Long-term safety study 54135419TRD3008 (ongoing).

Summary Table of PV Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
• Use during pregnancy	Routine risk minimization measures: SmPC Sections 4.6 and 5.3; PL Section 2. Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Pregnancy registry for psychiatric medications such as antidepressants including esketamine.

PBRER = Periodic Benefit Risk Evaluation Report; PL = package leaflet; PSUR = Periodic Safety Update Report; SmPC = Summary of Product Characteristics.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.6 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

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 is of the opinion that a separate entry in the EURD list for Spravato is 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 applicant did not request the alignment of the new PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. 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

According to WHO, depression is the leading cause of ill health and disability worldwide. More than 300 million people are now living with depression, an increase of more than 18% between 2005 and 2015. According to facts and figures from WHO, each year, 25% of the population suffer from depression or anxiety and neuropsychiatric disorders account for 19.5% of the burden of disease in the European Region, and 26% in European Union (EU) countries. These disorders account for up to 40% of years lived with disability, with depression as the main cause and up to 50% of chronic sick leaves are due to depression/anxiety.

Major Depressive Disorder (MDD) is the fourth leading cause of global disease burden and affects about 15 % of the general population. MDD is not a benign disorder, it is associated with substantial psychosocial dysfunction and high individual mental strain as well as with excess morbidity and mortality - the risk of suicide is considerable.

3.1.2. Available therapies and unmet medical need

Although there are many oral antidepressant (AD) pharmacotherapies available for use worldwide, all of these agents act primarily by modulating the same pathway (monoaminergic system) and require several weeks before a full clinical effect on depression symptoms is evident. The conventional treatments over the past 50 years have targeted monoamine neurotransmitters, including selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors.

There are several publications discussing the definition and potential treatments of TRD. Quetiapine prolonged released tablets (e.g. Seroquel XR) are licensed as add-on treatment of major depressive episodes in patients with Major Depressive Disorder (MDD) who have had a sub-optimal response to antidepressant monotherapy; however, the population was differently defined in comparison to a treatment-resistant population.

While an olanzapine-fluoxetine combination (Symbyax®) has been approved only in the USA, there is currently no medicinal product specifically authorized for the treatment of TRD in Europe. In the European guideline on clinical investigation of medicinal products in the treatment of depression (EMA/CHMP/185423/2010 Rev. 2), the difficulties even in the conceptual elaboration and definition of clear criteria for incomplete response and TRD are acknowledged together with the unavailability of specifically approved treatments for this condition.

Despite the many treatment options currently available for MDD, a relevant proportion of patients, up to one third, do not adequately respond to treatment, and up to 20% are considered non-responders, even

if there is good compliance and the treatment has been taken long enough with an adequate dosage. Therefore, a high unmet medical need for treatment-resistant depression has been recognised.

Nasal esketamine may address this unmet medical need. The proposed therapeutic indication is:

SPRAVATO, in combination with a SSRI or SNRI, is indicated for adults with treatment-resistant Major Depressive Disorder, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode (see section 5.1).

3.1.3. Main clinical studies

A number of studies have been submitted to support the proposed indication for the treatment of TRD with the proposed flexible dosing regimen. This application includes results from (1) a comprehensive clinical pharmacology program in healthy volunteers and special populations to fully characterize the product's pharmacokinetic (PK) and pharmacodynamic (PD) activity, including Phase 2 studies with IV esketamine and ketamine; (2) a Phase 2 dose-response study in adults with TRD; (3) a Phase 2 proof-of-concept (PoC) study in the related condition of MDSI. The Applicant has also completed 5 Phase 3 studies: three short term (4-week) double-blind randomised parallel group studies (TRD3001, TRD3002) including one study in the elderly (TRD3005), comparing esketamine plus an oral antidepressant with an oral antidepressant plus nasal placebo, a double-blind relapse prevention study (3003), and an open-label long term safety and efficacy study (TRD3004). As such, the clinical development program can be considered as comprehensive and conforming to the requirements of the EU adopted Guideline on clinical investigation of medicinal products in the treatment of depression (EMA/CHMP/185423/2010 Rev. 2, 30 May 2013).

The Applicant has generally followed the recommendations of the Scientific Advices provided by EMA or National Agencies.

Inclusion criteria were adequate to define a treatment-resistant population. A high percentage of patients in the short term studies (~89.4% and 89.5% in TRD3001 and ~92.1% in TRD3002 in the Esketamine + Oral AD group) had treatment failures with 2 or more specific antidepressant medications and a high percentage (~74% and 78% in TRD3001 and ~80% in TRD3002 in the Esketamine + Oral AD group) had treatment failures with 2 or more classes of antidepressant medications. For the prior oral antidepressants in the pooled studies TRD3002 and TRD3001, it is noted that a small percentage ~10% (9.7% for the esketamine + oral AD and 11.3% for oral AD + intranasal placebo) had only one treatment failure. For the esketamine + oral AD group (N=343) 53.7% had 2 treatment failures, 25.2% had 3 treatment failures, 8.5% had 4 treatment failures and 2.9% had 5 treatment failures or more. In addition, one treatment failure was evaluated prospectively. The various analyses provided for the population selected to be included in the studies are further reassuring that these patients indeed belonged to the TRD spectrum.

3.2. Favourable effects

The primary endpoint in all short-term studies was the difference for the change in the MADRS total score from Baseline to Day 28 or endpoint between esketamine + oral AD and oral AD + intranasal placebo, which is an acceptable endpoint and commonly used in studies in depression.

Study TRD3002 is considered a successful study since statistically significant and clinically relevant results in the primary endpoint were achieved (demonstrating a difference between groups greater than 2 points). The estimated treatment effect for esketamine flexible dosing (56 or 84 mg) + oral AD compared to oral AD + intranasal placebo treatment was -3.5 (-6.70; -0.27, 2-sided p=0.034) by ANCOVA BOCF analysis. In study TRD3001, the difference in the mean change in MADRS total score from

baseline to day 28, between esketamine 56mg + oral AD and oral AD + intranasal placebo was -4.3, without reaching statistical significance.

The onset of clinical response based on MADRS total score by Day 2 (24 hours) Fisher's Exact test did not achieve statistical significance, but provided some evidence for early, non-significant effect, which might be considered as an advantage for an antidepressant treatment.

A consistent effect in the primary endpoint was observed across pivotal studies and this was supported by responder and remitter rates. In study TRD3003, the mean change in MADRS total score from baseline (maintenance phase) to endpoint was 7.5 in the oral AD + esketamine group and 12.5 in the oral AD + intranasal placebo group in stable remitters and 4.4 versus 11.4 in stable responders. The differences in the LS means of the mean change in MADRS in Stable Remitters as well as in stable Responders between esketamine +Oral AD versus oral AD +intranasal placebo were statistically significant and provided reassurance for the maintenance of effect (-5.2; p=0.005 and -7.4; p <0.001 respectively).

Relapse proportion differences of −24.0% (95% CI: −35.2%; −10.7%) after 12 weeks and −14.0% (95% CI: −28.1%; 2.7%) after ~20 weeks were observed in favour of the oral AD + esketamine group.

The relapse proportion difference in stable responders after 12 weeks was -25.5% (95% CI: −44.3%; −12.5%) and −34.7% (−53.5%; −21.4%) after ~20 weeks in favour of the oral AD + esketamine group

Consistent findings with a trend in favour of esketamine + oral AD were also observed in an older population (>65 years of age) (TRD3005). In TRD3005, the estimated treatment difference in the change of MADRS (95% CI) of -3.6 (-7.20; +0.07) by MMRM and -3.6 (-7.16; -0.03) by ANCOVA LOCF analysis methods for esketamine + oral AD over oral AD + intranasal placebo showed a trend in favour of esketamine + oral AD without reaching statistical significance (LOCF 1-sided p=0.026).

In the open-label long term safety study TRD3004 non-responders assessed retrospectively or from study TRD3005 who completed the 4 weeks induction phase showed an improvement in MADRS of -16.4 and then proceeded to the optimisation/maintenance phase for another 48 weeks during which period the low MADRS total score was maintained (+0.3). Despite the fact that this study aimed to provide safety data, it also provided some degree of reassurance for the maintenance of the antidepressant effect of esketamine administered concomitantly with an oral antidepressant.

3.3. Uncertainties and limitations about favourable effects

The uncertainties about the favourable effects consist of the following:

In study TRD3001, the difference in the mean change (SD) in MADRS) total score from baseline to day 28, between esketamine 84mg + oral AD and oral AD + intranasal placebo did not reach statistical significance, despite showing a trend in favour of the active treatment. Furthermore, the estimated difference (95% CI) for the 56 mg dose could not be formally tested in the hierarchical testing procedure because the 84mg dose failed to reach statistical significance.

In all studies, esketamine was added on to an SSRI or an SNRI. The data on efficacy cannot simply be extrapolated to other antidepressants, e.g. tricyclic antidepressants or MAOIS, which were excluded in the phase 3 studies. The final proposed SmPC therefore specifies that esketamine can be added to an SSRI or SNRI.

MMRM was the predefined primary analysis but was not endorsed by CHMP. ANCOVA (BOCF) is considered the most relevant method of analysis and was recommended in the CHMP scientific advice as a possibility for missing data imputation. It can be considered as a conservative analysis in accordance with the estimand of primary regulatory interest because BOCF assumes that all benefits potentially achieved from treatment are lost upon drug discontinuation.

Despite a favourable trend for esketamine in older patients (≥65 years of age), it should be noted that the subgroup of patients ≥75 years did not show any treatment benefit. However, the latter group was too small to draw definite conclusions.

3.4. Unfavourable effects

Drug abuse potential

The potential for drug abuse is well known for ketamine and esketamine. Although cases of drug abuse have not been observed in the clinical studies, a number of TEAEs suggestive of Abuse Potential have been reported commonly throughout the trials with intranasal esketamine administration. These were transient and self-limiting such as dizziness, somnolence, and dissociation and, reported at lower rates, euphoric mood, confusional state, feeling drunk or abnormal, and hallucinations. Precautionary measures for the drug supply have to be taken to ensure that patients do not have the possibility to store the medicinal product.

Transient dissociative/perceptual changes

Across completed Phase 2 and 3 studies, the most common psychological effects of esketamine have been dissociative/ perceptual changes (including distortion of time and space and illusions), derealization and depersonalization, which is in accordance with the already known ADR-profile of esketamine. The dissociative/ perceptual changes had an onset shortly after the start of the dose, peaked by 40 minutes post-dose and typically resolved by 1.5 hours post-dose. Dissociative/perceptual changes were reported as adverse events at a rate of 12.5-27.6% across trials, primarily mild or moderate in severity, transient and self-limited. Dissociation was reported as severe in intensity at the incidence of less than 4% across studies, was not considered serious for any subjects and rarely led to discontinuation of study drug. Transient dissociative/perceptual changes were more pronounced in subjects receiving higher doses of esketamine. Patients have to be monitored for signs of dissociation after drug administration.

Cardiovascular effects (transient increase in blood pressure)

Transient mild to moderate increases in SBP and DBP were observed in Phase 2 and 3 studies shortly after esketamine administration, reaching a maximum within 40 minutes (at the time of peak plasma esketamine levels) and generally returning to values close to pretreatment within 1.5 hours after administration. In the oral AD + intranasal placebo group, mean BP pressure values remained fairly constant across predose and postdose timepoints. The proportion of subjects with markedly abnormal BP elevation (SBP to ≥180 mm Hg or DBP to ≥110 mm Hg, i.e. acute hypertension) ranged from 2.0% to 11.1% in the esketamine + oral AD treatment group across studies/phases. These elevations were reported at higher rates in subjects with a history of hypertension than those without and at a higher rate in elderly subjects vs. younger adults: 11.1% vs. 4.9% in the short-term studies.

Somnolence and Sedation

Across all Phase 2 and 3 studies, sedation was one of the most common effects associated with esketamine treatment and reported more often than in the oral AD+placebo group. TEAEs of somnolence (12.1-21.1%) and sedation (4.2-10.1%) were primarily mild or moderate in severity, occurred on the day of intranasal dosing and resolved spontaneously the same day, with the median duration under 2 hours across dosing sessions. These TEAEs led to treatment discontinuation in isolated cases and reported as a SAE in only 1 subject across all Phase 2 and 3 studies. Rates of TEAEs of somnolence were relatively stable over time during longer-term treatment.

For older patients, a careful monitoring statement should be introduced in the SmPC due to a greater risk of falling once mobilised.

Urinary tract adverse effects

Reports from the literature suggest that chronic recreational ketamine abuse may be associated with the emergence of a new bladder pain syndrome, ulcerative cystitis.

No cases of interstitial cystitis or ulcerative cystitis were reported in the clinical programme with nasal esketamine. However, pollakiuria was commonly reported. Urinary tract symptoms, in general, were reversible.

Hepatotoxicity

Esketamine is metabolized in the liver, and hepatic clearance is required for a termination of the clinical effects. There are preclinical findings suggestive of hepatotoxicity. A number of cases of liver damage (bile duct dilatation and hepatic enzymes elevation) have been reported in the literature related to (off-label) long-term ketamine use.

Elevations in ALT/AST >3 x ULN were reported at low rates across studies, were primarily asymptomatic, transient, and resolved spontaneously while treatment with esketamine and oral AD continued.

3.5. Uncertainties and limitations about unfavourable effects

Interstitial cystitis and hepatotoxicity have been reported in the literature in cases with long-term off-label use of ketamine, but not throughout the clinical trial programme for intranasal esketamine. With the limited sample size for long-term treatment, rare or very rare ADRs occurring after long-term treatment cannot be reliably detected.

In all studies, esketamine was added on to an SSRI or an SNRI. Safety in co-administration with TCAs is insufficiently characterized.

A total of 3 completed suicides were reported with esketamine compared to none with placebo. However, these suicides occurred in the in open-label studies/study phases with no control group allowing no direct comparison with patients without eseketmine treatment. Given the high likelihood of suicide attempts in the studied population, the latency to the last esketamine dose (20, 12 and 4 days), the imbalance in exposure between the esketamine group and control group (1045 vs 100 patient-years of exposure, respectively) and assessment of the individual cases, it appears unlikely that these were related to esketamine, but rather to the underlying severe condition.

3.6. Effects Table

Table X. **Effects Table for [SPRAVATO for treatment-resistant depression]**.

Effect	Short Description	Unit	Esketamine			PL	Uncertainties/ Strength of evidence	Ref
			Fixed 56 mg	Fixed 84 mg	Flexible dosing 28 -84mg			
Favourable Effects								
MADRS	Mean change (SD) in MADRS) total score from baseline to day 28		-18.4 (14.06)	-16.1 (14.63)		-14.2 (15.06)	**SoE:** Diff. LS mean (95%CI) E-F56 vs AD+PL -4.3 (-7.79; -0.80); p=.017 t.s.; Clinically relevant, consistent effect across pivotal studies, supported by responder rates and remitter rates. Comparable effects are demonstrated at the end of the maintenance phase in stable remitters and stable responders. Consistent findings in the elderly -10.1 vs -6.8, -3.2 (-6.85;0.36) p=.078 t.s.. Secondary effects in SDS (-3.5 (-5.85; -1.16); p=.002 t.s. ; and PHQ-9 (2.2 (-3.93; -0.40); p=.008 t.s) in line with primary findings. **UnC:** Diff.LS mean (95%CI) E-F84 vs AD+PL -1.2(-4.66; +2.32, p=.513 t.s.; Results cannot be extrapolated to e.g. tricyclic AD, MAOIS.	TRD3001 TRD3003
MADRS	Mean change (SD) in MADRS total score from BL to day 28				-19.0 (13.4)	-15.6 (14.10)	**SoE:** Diff.LS means (95%CI) -3.5 (-6.70; -0.27, p=.034 t.s ; effect size exceeds clinically relevant diff =2. **Unc:** results cannot be extrapolated to e.g. tricyclic AD, MAOIS.	TRD3002
MADRS	Onset of clinical response based on MADRS total score by Day 2 (24 hours) Fisher's Exact test, (n/N)	%			7.9 (9/114)	4.6 (5/109)	**Unc:** Odds ratio (95% CI) 1.79 (0.57; 5.67); p=.161 o.s. , Cochran-Mantel-Haenszel; early, non-significant, effect might be an important advantage.	TRD3002
Relapse	Percentage of subjects with relapses after 12 weeks; induction, and ~10 weeks AD+PL ~ 20 weeks Esk; maintenance, (n/N)	%			26.7 (24/90)	45.3 (39/86)	**SoE:** Diff. (95%CI) −24.0% (−35.2%; −10.7%), Diff.(95%CI) −14.0% (−28.1%; 2.7%); comparable effects are demonstrated in stable responders. Some reassurance of maintenance of effect.	TRD3003
Unfavourable Effects								
Transient dissociative/perceptual changes	Incidence of Derealisation, depersonalization, distortion of time and space and illusions (N)	%	12.5-27.6 (1708)			0-3.7	**Unc:** More pronounced with higher doses	Primary safety analysis
Transient increase BP	Incidence of abnormal BP elevation (SBP to ≥180 mm Hg or DBP to ≥110 mm Hg, i.e. acute hypertension (N)	%	2.0-11.1 (1708)			0-6.2	**Unc:** higher rates in subjects with a history of hypertension than those without and at a higher rate in elderly subjects	Primary safety analysis
Somnolence and Sedation	Incidence of Somnolence and Sedation (N)	%	12.1-21.1/ 4.2-10.1 (1708)			0.7-0.9	**Unc:** effect on the ability to drive or use machinery, risk of falls or dangerous behaviour in particular in case of early discharge.	Primary safety analysis
Hepatotoxicity	Cases described in chronic recreational abuse of ketamine	%	NR			NR	**Unc:** limited sample size for long-term treatment, rare or very rare ADRs cannot be reliably detected.	

Abbreviations: SoE=strength of evidence, Unc=Uncertainty

Notes:

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The study population is considered representative TRD patients. The careful selection of the appropriate population is of primary importance in order for depressed patients to be part of the definition of treatment-resistant depression. To this effect, the Applicant, in addition to the retrospective demonstration of antidepressant treatment failure, included a screening/prospective observational phase in the short term DB phase 3 studies where the treatment failure was shown prospectively prior to the patients entering the double induction phase. This is considered appropriate and, for some experts in the field of depression, could be sufficient as a unique demonstration of treatment resistance.

The endpoints (primary and secondary) used for the evaluation of the efficacy of esketamine in TRD are considered reliable, validated, referenced in treatment and development guidelines and used throughout many years in the clinical practice and hence appropriate.

In the pivotal study TRD3002 an effect size which exceeded the usually accepted clinically relevant difference of 2 points in MADRS total score was observed. The placebo-adjusted effect size of -3.5 or -4.3 difference in the change from baseline to 4 weeks/Endpoint in the MADRS total score observed in the short term DB phase 3 studies can therefore be considered as clearly clinically relevant. Similar supportive results were observed in study TRD3001.

In addition, similar effect sizes have been observed in the various phase 2 clinical studies for esketamine indicating consistency of the antidepressant effect across studies performed at various sites in various countries.

The relapse prevention study (as required by the EU Depression Guideline) showed that the antidepressant effect is maintained over time. Patients receiving esketamine on top of their oral AD treatment remained in remission for a longer period of time compared to patients receiving placebo on top of their oral AD.

Supportive evidence for the maintenance of effect has also been provided by the open-label long-term safety study.

Concerns regarding the concomitant initiation of two novel therapies (new oral AD + esketamine) in the clinical trials were expressed during the scientific advice procedures. In addition, esketamine has not been evaluated in monotherapy. However, it is considered unethical for patients with TRD to be left without any antidepressant treatment (which would have been the case in placebo-controlled monotherapy studies) or on a treatment that has not been sufficiently effective.

The safety profile derived from the clinical trial programme appears acceptable.

The most relevant safety issues are the immediate transient post-dose dissociative /perceptual changes, cardiovascular effects (transient increase in blood pressure) and somnolence and sedation, which require a close patient observation at least during the first two hours after intranasal esketamine application. Although these TEAEs were generally of mild to moderate severity, more severe cases may require immediate intervention (e.g. hypertensive emergency). Therefore, adequate monitoring has to be ensured. In patients with cardiovascular and cerebrovascular conditions not tolerating blood pressure increases, treatment is contraindicated. Somnolence /sedation could potentially have an influence on the ability to drive or use machinery and increase the risk of falls or dangerous behaviour in particular in case of early discharge.

Throughout the clinical trials, only rare cases led to treatment withdrawals. The fact that patients have to stay for at least 2 h under the observation of an HCP and are not allowed to drive or use machinery until the next day is clearly a burden of this new treatment option for TRD.

With regard to the initial general requirement of the presence of a specifically CPR-trained physician and resuscitation equipment at the administration site, the CHMP reviewed the available evidence and agreed that the applicant’s justification for omitting the requirement of resuscitation equipment seemed sound.

1. PK considerations do not suggest an anaesthetic effect (much lower plasma levels)

2. detected throughout the trial program in 78,244 dosing sessions

3. Sedation levels MOAAS 0 (no response to painful stimulus) only in 4 cases, none of them associated with respiratory depression, 3 using additional other CNS depressants

4. US post-marketing data: no case of respiratory depression in 11,260 dosing sessions

5. Two anaesthesiological experts (from NL and DE) support the applicant's position

6. Labelling for other anaesthetics used at subanaesthetic doses (e.g. Xyrem, Clonazepam, Zubsolv) does not require resuscitation equipment

It was felt that the requirement for a full-time presence of a physician with CPR training during the Spravato administration sessions and availability of resuscitation equipment for all patients may be overly strict, would restrict administration to a hospital setting and may prevent many TRD patients from receiving treatment with nasal esketamine. A compromise was agreed to restrict the intensified monitoring/treatment conditions to patients with unstable cardiovascular or respiratory conditions. However, all patients must be adequately monitored by a healthcare professional for possible development of sedation, dissociation symptoms and hypertension at each administration session.

3.7.2. Balance of benefits and risks

Short- and long-term efficacy of esketamine on top of an SSRI or SNRI in TRD patients has been established. The results from at least one short term randomised DB study confirmed the antidepressant efficacy of esketamine + oral AD compared to oral AD + intranasal placebo, despite innovative design features in the studies. Two more short-term studies showed trends in favour of esketamine + oral AD versus oral AD + intranasal placebo. Secondary endpoints and subgroup analysis were supportive of the positive results. Demonstration of maintenance of the antidepressant effect was achieved via a relapse prevention study of adequate duration. Furthermore, supportive efficacy data were observed in an open-label long term mainly safety study. As such, and further to clarifications provided, the clinical program can be considered comprehensive for intranasal esketamine as an adjunctive treatment administered concomitantly with a SSRI or SNRI. Based on the totality of the submitted data, including significant and clinically relevant differences from placebo and clear trends in line with the significant results, the product is considered efficacious.

The Applicant has agreed to modify the therapeutic indication in TRD to best reflect the population and treatments studied:

*SPRAVATO, **in combination with a SSRI or SNRI**, is indicated for adults with treatment-resistant Major Depressive Disorder, **who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode**.*

It should be pointed out that with the decision to prescribe Spravato should be determined by a psychiatrist and a specific protocol is required to inform prescribers about the drug distribution system across the various Member States, the minimum requirements available at the site, how the monitoring will take place, who will perform the monitoring and a checklist evaluating when a patient is deemed stable enough to be discharged should be also included.

Overall, the short-term safety profile of esketamine is sufficiently characterized. Nasal application has an acceptable tolerability with manageable risks when applied under the supervision of an HCP. An observation of the patient in the immediate post-application period is required, since transient dissociative disorders, sedation and elevated blood pressure, usually of mild to moderate severity, are described. The available long term safety data do not suggest a trend over time for effects on cognition, suicidality, and lower urinary tract symptoms, as well as renal and hepatic adverse reactions.

However, given that esketamine is a novel treatment for depression and the safety study TRD3008 is still ongoing, B/R should be further evaluated and subsequently updated when new data becomes available.

The so far generated safety data from the short-term studies indicate that most adverse events are transient in nature and could be managed by careful monitoring of the patient. Throughout treatment

with intranasal esketamine the potential for abuse has to be taken into consideration, especially in vulnerable subjects.

Although there was no signal of an increased risk of abuse in the clinical studies, emphasis was placed in the SmPC that esketamine should be initiated by a psychiatrist and can only be administered in a clinical setting under supervision. In addition, a controlled accesses programme must be implemented nationally.

Third party intervention during the evaluation of Spravato

On 31 October and 10 November 2019, the CHMP received, after the adoption of the CHMP positive opinion, correspondences from 2 groups of experts (hereinafter referred to as "third parties") which expressed concerns about the efficacy and safety profile of Spravato.

The CHMP considered those interventions and concluded that the arguments put forward by both third-parties did not impact the CHMP conclusions. However, a revised opinion was adopted by the CHMP on 21 November 2019 in order to provide further clarifications in relation to the clinical safety and the benefit-risk balance sections.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Spravato is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Spravato is favourable in the following indication:

Spravato, in combination with a SSRI or SNRI, is indicated for adults with treatment-resistant Major Depressive Disorder, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to special and restricted medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out

in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The 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.

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 hypertension. 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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.