Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Esketamine hydrochloride

Proprietary Product Name: Spravato

Sponsor: Janssen-Cilag Pty Ltd

May 2021

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse event
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
ANCOVA	Analysis of covariance
ARTG	Australian Register of Therapeutic Goods
ASA	Australian specific Annex
AUC	Area under the plasma concentration time curve
$AUC_{0-\infty}$	Area under the plasma concentration time curve from time 0 to infinity
BCRP	Breast cancer resistance protein
CGI-S	Clinical Global Impressions-Severity scale
CHMP	Committee for Medicinal Products for Human Use (European Medicines Agency)
CI	Confidence interval
C_{max}	Maximum plasma concentration
CMI	Consumer Medicines Information
CNS	Central nervous system
CSR	Clinical study report
CYP	Cytochrome P450
DLP	Data lock point
ECT	Electroconvulsive therapy
EMA	European Medicines Agency (European Union)
EQ-5D-5L	5-level EuroQol 5 dimensions questionnaire
EU	European Union
FDA	Food and Drug Administration (United States of America)
GAD-7	General Anxiety Disorder-7 scale

Abbreviation	Meaning
GCP	Good Clinical Practice
HCP	Healthcare professional
ICH	International Council for Harmonisation
IV	Intravenous
LOCF	Last observation carried forward
LS	Least squares
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	Major depressive disorder
MDSI	Major depressive disorder with suicidal ideation
MGH-ATRQ	Massachusetts General Hospital Antidepressant Treatment Response Questionnaire
M*X*	Esketamine-derived metabolites (for example: M4, M9, M10 and M19)
NMDA	N-methyl-D-aspartate
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
PD	Pharmacodynamic(s)
P-gp	P-glycoprotein
PHQ-9	Patient Health Questionnaire, 9-item
PI	Product Information
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetics
REMS	Risk Evaluation and Mitigation Strategy (United States Food and Drug Administration)
RMP	Risk management plan
SAE	Serious adverse event

Abbreviation	Meaning
SDS	Sheehan Disability Scale
SNRI	Serotonin and noradrenaline reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
t½	Terminal half life
TEAE	Treatment emergent adverse event
T_{max}	Time to maximum plasma concentration
TRD	Treatment resistant depression
UGT	Uridine 5'-diphospho-glucuronosyltransferase
US(A)	United States of America
WHO	World Health Organization

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Product name:	Spravato
Active ingredient:	Esketamine hydrochloride
Decision:	Approved
Date of decision:	5 March 2021
Date of entry onto ARTG:	9 March 2021
ARTG number:	311827
, *Black Triangle Scheme:*[1]	Yes. This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
Sponsor's name and address:	Janssen-Cilag Pty Ltd 1-5 Khartoum Road, Macquarie Park, NSW, 2113
Dose form:	Nasal spray solution
Strength:	32.3 mg esketamine hydrochloride (equivalent to 28 mg of esketamine) per 2 actuations
Container:	Vial assembled in nasal spray device
Pack sizes:	1, 2 or 3 single-use nasal spray devices
Approved therapeutic use:	*Spravato is indicated for treatment resistant depression (Major Depressive Disorder in adults who have not responded adequately to at least two different antidepressants of adequate dose and duration to treat the current moderate to severe depressive episode).* *Spravato is to be initiated in conjunction with a newly initiated oral antidepressant.*
Route of administration:	Nasal
Dosage:	Spravato should be administered in conjunction with a newly initiated oral antidepressant. During the Phase III clinical

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

program patients were assigned a serotonin and noradrenaline reuptake inhibitor (SNRI) or selective serotonin reuptake inhibitor (SSRI) as the new oral antidepressant (see Section 5.1 Pharmacodynamic properties, clinical trials, in the Product Information).

Spravato will be provided by the supervising healthcare professional for the patient to self-administer under their direct supervision. A treatment session consists of nasal administration of Spravato and post administration observation under the supervision of a healthcare professional (see Section 4.4 Special warnings and precautions for use, in the Product Information).

Dosage – adults

The dosage recommendations for Spravato are shown in Table 1 of the Product Information. Recommended dosing consists of an induction phase (Weeks 1 to 4), followed by a maintenance phase (Week 5 onwards). Dose adjustments should be made based on efficacy and tolerability to the previous dose.

For further information refer to the Product Information.

Pregnancy category: B3

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Janssen-Cilag Pty Ltd (the sponsor) to register Spravato (esketamine hydrochloride) 28 mg of esketamine per 2 actuations, nasal spray solution for the following proposed indication:

> *Spravato is indicated for treatment resistant depression (Major Depressive Disorder in adults who have not responded adequately to at least two different antidepressants of adequate dose and duration to treat the current depressive episode).*

Major depressive disorder (MDD) is a common, serious, severely debilitating and recurrent psychiatric disorder. It is the leading cause of disability (years lived with

disability) worldwide according to the World Health Organization (WHO).[2] Severe mental illness is associated with a reduction in life expectancy by 10 to 20 years compared to the general population.[3] 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.[2] Based on a 2007 Australian survey, depressive episode (that is, a period of depression lasting at least 2 weeks) was the most common type of affective disorder with a prevalence of 4.1% in the population, with an estimated 1 million Australians having had depression in their lifetime.[4]

Treatment-resistant depression (TRD) is considered to be a subset of MDD and is defined as lack of clinically meaningful improvement to at least two different antidepressant agents prescribed in adequate dosages for adequate duration. TRD is a principal contributor to the morbidity and mortality associated with depression. Patients with TRD are more likely to have lower remission rates, pronounced functional impairment, substantially lower quality of life, higher suicide rates, and incur higher medical and mental healthcare costs compared to patients with MDD who respond to antidepressant treatment.

At the time the submission described in this AusPAR was under consideration, no medication was currently indicated for TRD in Australia. Quetiapine, an atypical antipsychotic agent, is approved in Australia for treatment of recurrent MDD in patients who are intolerant of, or who have an inadequate response to alternative therapies.[5] However, atypical antipsychotic usage has been limited by significant adverse reactions, including metabolic disturbances, weight gain and neuroleptic malignant syndrome. In the United States of America (USA), an olanzapine-fluoxetine combination product has been approved for TRD.[6] Non-pharmacological treatment options for TRD have limited efficacy or patient acceptability. These include electroconvulsive therapy (ECT), transcranial direct current stimulation, repetitive transcranial magnetic stimulation, vagus nerve stimulation and deep brain stimulation. Most options require anaesthesia and are associated with significant adverse events.

The sponsor has applied to register a new chemical entity, Spravato (esketamine hydrochloride), an N-methyl-D-aspartate (NMDA) receptor antagonist for use in TRD (MDD in adults who have not responded adequately to a least two different antidepressants). Esketamine belongs to the same pharmacological class as ketamine (a racemic mixture containing 50% esketamine and 50% arketamine). While, the exact mechanism of action for esketamine as an antidepressant is not completely understood, evidence within the literature suggests that through NMDA receptor antagonism, esketamine produces a transient increase in glutamate release leading to increases in AMPA receptor stimulation,[7] and subsequently to increases in neurotrophic signalling that restore synaptic function in these brain regions.[8] Spravato is to be self-administered intranasally using a single-use device under the supervision of a healthcare professional.

[2] Depression and Other Common Mental Disorders: Global Health Estimates. Geneva: World Health Organization; 2017. Available from the WHO website.
[3] Manger, A, Lifestyle interventions for mental health, *AJGP*, 2019; 48: doi: 10.31128/AJGP-06-19-4964.
[4] Australian Bureau of Statistics (ABS), National Survey of Mental Health and Wellbeing: Summary of Results, Reference period: 2007, Released 23 October 2008. Available from the ABS website.
[5] Product Information (PI) for Seroquel XR (quetiapine fumarate) modified release tablets, Date of revision 7 December 2020. Available from the TGA PI repository at: https://www.ebs.tga.gov.au/.
[6] Center for Drug Evaluation and Research, FDA, Approval Package for application number NDA 21-520/S-012, Symbyax (olanzapine and fluoxetine hydrochloride), Approval date 19 March 2009. Available from the FDA website.
[7] AMPA receptors are glutamate receptors activated by and named after the artificial glutamate analogue α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA).
[8] Abdallah, C. et al, Ketamine and rapid-acting antidepressants: a window into a new neurobiology for mood disorder therapeutics, *Annual Reviews in Medicine*, 2015; 66: 509-523.

Regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

At the time the TGA considered this application, similar applications had been approved in the USA, European Union (EU), Switzerland and New Zealand, and were under consideration in Canada and Singapore (see Table 1).

Table 1: International regulatory status as of March 2020

Region	Submission date	Status	Approved indications
USA	4 September 2018	Approved on 5 March 2019	*Spravato is indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adults (see Clinical Studies (14.1))*
EU (Centralised Procedure)	10 October 2018	Approved on 18 December 2019	*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 antidepressants in the current moderate to severe depressive episode (see section 5.1).*
Switzerland	20 December 2018	25 February 2020	*Spravato in combination with an oral antidepressant is indicated for the treatment of treatment resistant episodes of major depression in adults who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode.* *Spravato must only be administered in a treatment setting in which the necessary safety measures (including cardiopulmonary resuscitation measures) can be ensured before, during and after administration of the medicinal product (see Dosage/Administration and Warnings and precautions).*

Region	Submission date	Status	Approved indications
New Zealand	17 December 2018	19 December 2019	*Spravato is indicated for treatment resistant depression (Major Depressive Disorder in adults who have not responded adequately to at least two different antidepressants of adequate dose and duration to treat the current depressive episode).*
Canada	7 December 2018	Under consideration	Under consideration
Singapore	12 April 2019	Under consideration	Under consideration

SNRI = serotonin and noradrenaline reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2018-04814-1-1

Description	Date
Submission dossier accepted and first round evaluation commenced	2 January 2019
First round evaluation completed	11 July 2019
Sponsor provides responses on questions raised in first round evaluation	6 August 2019
Second round evaluation completed	12 September 2019
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	2 March 2020
Sponsor's pre-Advisory Committee response	13 March 2020
Advisory Committee meetings	2 and 3 April 2020 4 and 5 June 2020
Registration decision (initial rejection)	10 September 2020

Description	Date
Number of working days from submission dossier acceptance to initial registration decision*	188
Section 60 appeal decision (initial decision revoked)	27 January 2021
Registration decision (Section 60 approval)	5 March 2021
Completion of administrative activities and registration on ARTG	9 March 2021

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

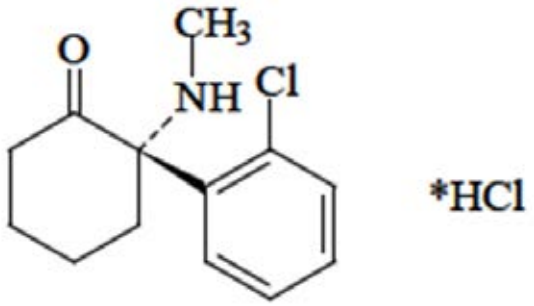
The submission was summarised in the following Delegate's overview and recommendations.

The Delegate referred to the TGA-adopted European Medicines Agency (EMA) Guideline on the clinical investigation of medicinal products in the treatment of depression.[9]

Quality

The drug substance esketamine hydrochloride (see Figure 1) is the (S)-enantiomer of ketamine hydrochloride.

Figure 1: Chemical structure of esketamine hydrochloride



Esketamine hydrochloride is freely soluble in methanol, sparingly soluble in ethanol. It appears as a white to almost white crystalline powder, and is non-hygroscopic.

The drug product is a clear, colourless to slightly yellowish aqueous nasal solution containing esketamine hydrochloride 32.3 mg /0.2 mL, corresponding to esketamine 28 mg/0.2 mL as the active ingredient. The solution is supplied as a nominal fill of 0.2 mL in a glass vial and closed with a rubber stopper.

The stoppered filled vial is assembled in a manually activated single-use nasal spray device. Each assembled product (also referred to as 'combination product' of 'vial and device') contains 2 actuations totalling 28 mg esketamine.

Each combination product is individually packaged in a blister and placed in a carton containing 1, 2 or 3 units.

[9] EMA, Committee for Medicinal Products for Human Use (CHMP), Guideline on clinical investigation of medicinal products in the treatment of depression: EMA/CHMP/185423/2010 Rev. 2. 30 May 2013.

The formulation of esketamine (as hydrochloride) nasal solution includes commonly used excipients for this dosage form, including citric acid (to combat any potential pH fluctuations) and disodium edetate (to chelate any potential metal ions).

There is no difference between esketamine (as hydrochloride) nasal solution formulation used in pivotal Phase III clinical studies and the formulation proposed for registration.

All quality issues have been resolved. Approval is recommended for the registration of the proposed product from a quality perspective.

Nonclinical

The nonclinical evaluator summarised the following in regard to the nonclinical evaluation:

- The submitted nonclinical dossier was in accordance with the relevant ICH guideline for the nonclinical assessment of pharmaceuticals.[10,11] The overall quality of the nonclinical dossier was high. All pivotal safety-related studies were Good Laboratory Practice compliant.
- Esketamine, ketamine and the metabolite M10 are non-competitive, subtype nonselective, activity-dependent NMDA receptor antagonists. Esketamine is more potent at the NMDA receptor than either ketamine or M10. Other esketamine metabolites (M4, M5, M9 and M19) were inactive as NMDA receptor antagonists. Esketamine at 10 μM inhibited radioligand binding to the μ-opioid receptor, κ-opioid receptor and 5-HT (serotonin) transporter. No relevant interactions were noted for esketamine-derived metabolites M4, M9, M10 and M19 when tested against a panel of receptors, ion channels and transporters *in vitro*. Esketamine, arketamine and the tested metabolites (M10, M4, and M19) were inactive against the human α7 nicotinic acetylcholine receptor *in vitro*, while metabolite M9 produced weak inhibition at this receptor.
- Safety pharmacology studies assessed effects on the cardiovascular, respiratory and central nervous system (CNS). In dogs, transient dose-related increases in heart rate, blood pressure, and shortening of the QT-interval[12] and the PQ-interval[13] were observed following treatment with esketamine from 0.3 mg/kg intravenous (IV). Transient increases in respiration rate were also noted in dogs at a dose of 3 mg/kg IV and increased heart rate was also observed at doses of ≥ 24 mg/day intranasal. These effects occurred at clinically relevant doses and therefore effects on the cardiovascular and respiratory systems may be observed in patients. No adverse effects were seen on cardiovascular or respiratory function in rats or on CNS function in rats and dogs following intranasal dosing. No significant inhibition of human ether-à-go-go-related gene potassium ion channel tail current was observed at clinically-relevant concentrations.

[10] ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.
[11] ICH, Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, M3 (R2), Current Step 4 version, 11 June 2009.
[12] The **QT interval** is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.
[13] The **PQ interval** is the time taken from the start of the P wave to the start of at QRS wave complex. It indicates the speed at which the action potential is being transmitted through the atrioventricular node from the atria to the ventricles. The PQ interval approximates to the period of time from the start of atrial contraction and ending at the start of ventricular contraction.

- Overall, the pharmacokinetic (PK) profile in animals was qualitatively similar to that of humans. Esketamine was readily and rapidly absorbed with a similar time to maximum plasma concentration (T_{max}) in all species following intranasal dosing. The maximum plasma concentration (C_{max}) levels of the active metabolite M10 were reached slightly later than those of the parent drug, esketamine. Following intranasal dosing in mice and rats, area under the plasma concentration time curve (AUC) values were higher for M10 than for the parent drug, esketamine. In dogs, exposure to M10 was lower than the exposure to esketamine. The bioavailability of esketamine is moderate in dogs and humans following intranasal dosing (54% and 48%, respectively), and low following oral dosing (1.3% and 14%, respectively), indicating high first pass metabolism in these species. Plasma protein binding of esketamine and M10 was moderate in humans. Esketamine and its metabolites were found in the brain and plasma of rats after oral administration, with brain concentrations higher than plasma for esketamine, M4 and M19. The main human metabolite, M10, was a significant metabolite in animals. Drug-related material was excreted via urine in humans and animal species.
- The main cytochrome P450 (CYP) enzymes responsible for esketamine metabolism are CYP2B6 (approximately 60%) and CYP3A4 (35 to 40%).[14]
- N-nitroso compounds were not formed under simulated gastric conditions, indicating that any orally absorbed esketamine is unlikely to react in the stomach to form the potentially genotoxic compound, N-nitroso-esketamine.
- Esketamine and its major circulating metabolites had no clinically relevant inducing or inhibiting effects on CYPs and uridine 5'-diphospho-glucuronosyltransferases (UGTs). Esketamine and M10 were not substrates of transporters (P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP)1B1, OATP1B3 for esketamine, and P-gp, BCRP, OATP1B1, OATP1B3, organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)1, OCT2 for M10) and were not inhibitors of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, multidrug and toxin extrusion 1 and multidrug and toxin extrusion 2-K transporters.
- Esketamine had a moderate order of acute toxicity in rats and dogs.
- Repeat-dose toxicity studies were conducted in rats (up to 6 months) and dogs (up to 9 months). Maximum exposures (AUC) were subclinical. Treatment-related effects were minimal. Local reactions within the nasal cavity and clinical signs consistent with the pharmacological actions of esketamine were observed including locomotor and postural changes (ataxia, abnormal gait, lying on side, prostrate, tremors, uncoordinated, low carriage, hunch posture), behavioural changes (decreased activity, subdued, fixed stare), appearance changes (ungroomed, skin discoloration, fur staining), and salivation and abnormal respiration (hyperpnoea or bradypnoea).
- The weight of evidence suggests that esketamine is not genotoxic. No treatment related increase in tumour incidence was observed in a 6 month carcinogenicity study in mice or in a 2 year carcinogenicity study in rats.

[14] **Cytochrome P450** (**CYP**) **enzymes**: CYPs are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds.
Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

- Reproductive toxicity studies with either esketamine or ketamine examined effects on fertility, embryofetal development toxicity and pre-/post-natal development in rats and rabbits. Fertility and reproductive parameters were unaffected in male and female rats treated with esketamine at clinically relevant doses. Increased post-implantation loss due to an increase in the number of early resorptions was observed in rabbits at 100 mg/kg/day ketamine (31% plasma esketamine; relative exposure 2.9). This was correlated to a decrease in the mean number of live fetuses at this dose level. Decreased bodyweight (8 to 9%) was observed in female offspring at 30 mg/kg/day intranasal and in males and females combined at 100 mg/kg day intranasal (31% plasma esketamine; relative exposure 2.9). In a pre/postnatal development study in rats, first filial generation offspring derived from females given esketamine showed a delay in the age of attainment of the Preyer response reflex,[15] from doses of ≥ 0.9 mg/day intranasal (relative exposure 0.12 to 2.6). All offspring attained this reflex by Day 19 and no other CNS effects were noted. Studies in the literature have shown developmental neurotoxic findings in the fetus and offspring following maternal treatment with ketamine in rodents and non-human primates.[16,17,18,19]
- Esketamine was well tolerated in a 14 day juvenile neurotoxicity study in rats at doses up to 150 mg/kg subcutaneous (relative exposure 40). Treatment-related effects were limited to clinical signs consistent with the pharmacological actions of esketamine. No histopathological brain lesions were observed after single or repeat dosing.
- In neurotoxicity studies in adult rats, no histopathological brain lesions were observed at esketamine doses up to 72 mg/day intranasal (relative exposure 89) in single dose studies and 54 mg/day intranasal in repeat-dose studies (relative exposure 12).
- Pregnancy Category B3 is considered appropriate.[20] Use during pregnancy and breastfeeding is not recommended based on developmental neurotoxicity observed in rodents and monkeys following treatment with ketamine.
- Overall, there are no nonclinical objections to the registration of esketamine (Spravato).

Clinical

The clinical evaluator identified the following clinical studies and summaries in the submitted dossier:

- Nineteen Phase I clinical pharmacology studies;
  - Fourteen PK studies (all completed);
  - Five pharmacodynamic (PD) studies (all completed by the second round of evaluation).

[15] **Preyer response reflex** is the elicitation of a startle response to auditory stimuli, used for the evaluation of hearing in rodents and other animals.
[16] Zhao, T. et al. Prenatal ketamine exposure causes abnormal development of prefrontal cortex in rats. *Nature Scientific Reports*. 2016; 6: 26865, 1-12.
[17] Zhao, T. et al. Ketamine administered to pregnant rats in the second trimester causes long-lasting behavioural disorders in their offspring, *Neurobiology of Disease*, 2014; 68: 145-155.
[18] Brambrink, A.M. et al. Ketamine-induced neuroapoptosis in the fetal and neonatal rhesus macaque brain. *Anesthesiology.*, 2012; 116: 372-384
[19] Slikker, W. et al. Ketamine-induced neuronal cell death in the perinatal rhesus monkey. *Toxicological Sciences*, 2007; 98: 145-158.
[20] **Australian Pregnancy Category B3**: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

- One Phase II dose-ranging study in TRD;
- One population PK (PopPK) study;
- Four pivotal efficacy/safety Phase III studies (3 short-term; 1 maintenance/ withdrawal) in TRD;
- One long-term Phase III safety study in TRD;
- Four other Phase II efficacy/safety studies in TRD (two intranasal, two IV);
- Two ongoing TRD studies (interim safety data only available for evaluation);
- One Phase II study in MDD with suicidal ideation (MDSI);
- One integrated summary of safety;
- Literature references;
- Clinical overview, summary of clinical efficacy, summary of clinical safety, summary of clinical pharmacology and synopses of pivotal studies.

The submitted studies were stated to have been conducted in compliance with the ethical principles originating in the Declaration of Helsinki and, in accordance with the ICH guideline for Good Clinical Practice (GCP) and applicable regulatory requirements, including the archival of essential documents.

Pharmacology

Pharmacokinetics

Table 3 (shown below) provides a summary of the submitted studies that were considered to provide evaluable PK data.

Table 3: Pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK (single dose)	TRD1001	*
	General PK (multi-dose)	TRD1010	*
	Nasal guide effect	TRD1004	*
	Mass balance	TRD1016	*
	Absolute bioavailability	TRD1009	
	Relative bioavailability	TRD1003	
PK in special populations	Target population - Single / multi-dose	TRD2001	*
	Hepatic impairment	TRD1011	*
	Renal impairment	TRD1014	*
	Elderly	TRD1003 TRD1012 TRD1018	* * *

PK topic	Subtopic	Study ID	*
	Race effect (Asian versus White)	TRD1002 TRD1008	* *
	Allergic rhinitis	TRD1007	*
PK interactions	Induction potential (CYP3A4 and CYP2B6)	TRD1010	*
	Rifampicin	TRD1008	*
	Mometasone / oxymetazoline	TRD1007	*
	Clarithromycin	TRD1009	*
	Ticlopidine	TRD1020	*
Population PK analyses	Healthy subjects/target population	PopPK Report	*

CYP = cytochrome P450; PK = pharmacokinetic(s); PopPK = population pharmacokinetics.

* Indicates primary PK aim of the study.

Generally, the PK data provided in the application dossier was sufficiently comprehensive to support the proposed indication of intranasal esketamine in adults with TRD. The clinical evaluator and Delegate highlighted the following points, including some gaps in PK data that may impact on the overall benefit-risk balance for approval and influence post-market risk management:

- The PK of esketamine in pregnant or lactating subjects were not specifically studied. Given the physico-chemical and known PK characteristics of the esketamine molecule, it would be expected to cross the placenta and be excreted into breast milk.
- Concomitant ingestion of ethanol on PK of esketamine has not been evaluated.
- Studies of the PK of esketamine administered once-a-week and on alternate weeks, as used in the long-term safety studies, were not undertaken.
- Since 28 mg esketamine is a sub-therapeutic dose in adults, the effect of higher dosing and exposure to esketamine and noresketamine remains unknown in mild and moderate hepatic impairment.
- The esketamine PK in dialysis patients remains unknown. The PK of esketamine in subjects with mild, moderate or severe (not on dialysis) renal impairment was compared to that in subjects with normal renal function, post self-administered 28 mg of esketamine nasal spray (Study TRD1014). It indicated that the:
  - mean C_{max} and area under the plasma concentration time curve from time 0 to infinity ($AUC_{0-\infty}$) values were 20 to 26% and 13 to 36% higher in subjects with any degree of renal impairment relative to healthy subjects, respectively.
  - plasma PK of esketamine and renal function (that is, creatinine clearance) were poorly correlated.
  - mean percentage of esketamine dose excreted unchanged in urine and mean esketamine renal clearance were ≤ 1.34% and ≤ 1.97 L/h, respectively, across renal function groups.

  - mean fraction of unbound esketamine was similar across cohorts: 57.4 to 60.0% in subjects with renal impairment versus 54.7% in healthy subjects.

  The Delegate commented that the PI should include:

  - a statement to the effect that it appears renal function does not significantly affect the PK and clearance of intranasal esketamine. The latter might indicate that no dose adjustment is required in renal impairment;
  - the statement that the use of intranasal esketamine in patients on dialysis has not been studied.

- Given the mean esketamine C_{max} and AUC values were approximately 25 to 48% higher across the three intranasal esketamine regimens in Japanese subjects versus White race subjects, dose adjustment is recommended in Japanese subjects.
- The results from the PopPK analysis were generally consistent with PK from individual Phase I studies. Generally, PK in healthy subjects was similar to subjects with TRD for plasma concentrations of esketamine and noresketamine over the proposed therapeutic dose range.
- While metabolism of esketamine did not appear to be influenced by CYP2B6 status, there were only 19 (5.2%) poor metabolisers carrying 2 variant *6 alleles in the pooled PopPK analysis. Since, in all populations studied to date CYP2B6*6 has been detected in 15 to 40% Asian subjects and > 50% African-American subjects, and these population sub-groups were under-represented across the esketamine clinical development program (approximately 10% of each group), the sponsor's conclusion that CYP2B6*6 polymorphism does not adversely affect metabolism of intranasal esketamine should be interpreted with caution. The Delegate commented that the sponsor's statement is probably in relation to dose adjustment requirement.
- In the PopPK analysis, the fraction of dose absorbed through the nasal cavity was reduced by 38% for subsequent 28 mg doses. Therefore, for the 56, 84 and 112 mg doses, approximately 44%, 40% and 38% of esketamine dose was absorbed directly through the nasal cavity, respectively. The explanation for the reduction in bioavailability in higher dose regimens remains unknown. The therapeutic implication is that while higher dose adjustment can be expected to result in higher plasma concentrations of esketamine, this will not occur in a linear dose-proportional manner. Hence, there may be an adverse impact on the expected esketamine efficacy with higher dosing for example, possible lack of reduction in relapse potential, consequent to the above bioavailability issue.
- It remains unclear, whether nasal conditions other than allergic rhinitis will adversely affect esketamine absorption/bioavailability and, hence efficacy. Such conditions include rhinorrhoea for example, during viral illness or other allergic conditions and dry mucous membranes during adverse temperature from the external environment or significant dehydration. A precautionary statement regarding intranasal esketamine use in patients with allergic rhinitis, especially if chronic, may be warranted.
- There is potential risk for mucosa sensitisation and other local topical reactions, which may limit the usefulness of intranasal esketamine in some patient groups.
- Regarding PK interactions, the Delegate commented that it appears that the AUCs for esketamine post drug interactions do not always correlate with predicted terminal half life ($t_{½}$) estimations.
- Based on the results for mometasone and oxymetazoline nasal sprays, the sponsor recommends in the draft PI and draft Consumer Medicines Information (CMI) that patients should wait for ≥ 1 hour after using a nasal decongestant or corticosteroid before self-administering esketamine nasal spray. This is considered to be reasonable.

- Generally, the PK information in the draft PI is satisfactory.

Pharmacodynamics

The following studies were considered to provide evaluable PD data (see Table 4).

Table 4: Pharmacodynamic studies

PD topic	Subtopic	Study ID	*
Primary Pharmacology	Effect on depression	No PD studies	
Secondary Pharmacology	Effect on thorough QT-interval	TRD1013	*
	Haemodynamic parameters (blood pressure and heart rate)	TRD1013	
	Effect on cognitive function	TRD1005	*
	Effect on road safety	TRD1006	*
		TRD1019**	*
	Effect on abuse potential	TRD1015	*

PD = pharmacodynamic(s).

* Indicates primary PD aim of the study; **study ongoing – only interim analysis available

The clinical evaluator's conclusions on the PD studies were:

- *In vitro* ketamine acts as a selective antagonist of the NMDA receptor, an ionotropic glutamate receptor. It binds specifically to the dizocilpine (MK-801) site of the NMDA receptor, near the channel pore, and is an uncompetitive antagonist. The *S* (+) and *R* (–) stereoisomers of ketamine bind to the dizocilpine site of the NMDA receptor with different affinities, the former showing greater receptor affinity.
- Generally, PD data provided in the application dossier was sufficiently comprehensive to support the proposed indication of intranasal esketamine in adults with TRD.
- Secondary PD effects were generally consistent with C_{max} and total exposure (AUC). Plasma concentration-effect relationships were not defined for the primary PD but were for many important secondary PD effects, including dose-related effects on systolic and diastolic blood pressures. The therapeutic window was generally defined by plasma drug concentrations.
- Major anticipated clinical safety concerns based on the claimed mechanism of action include:
  - hypertension (elevated systolic blood pressure and/or diastolic blood pressure);
  - associated cardiovascular events (for example, tachycardia and palpitation);
  - cerebrovascular events (for example, haemorrhagic stroke);
  - potential drug of abuse/misuse;
  - disturbance of perception; and
  - driving impairment.

Dose finding

The dosing regimens used in the pivotal efficacy studies were based on a combination of the PK, efficacy and safety data derived from the Phase II clinical program (particularly from the dose-finding study, Study TRD2003), as well as additional safety and PK data from the Phase I clinical program. This was considered to be an acceptable approach.

The sponsor did not provide adequate rationale for selection of flexibly dosed regimens in 3 out of 4 studies (Studies TRD3002, TRD3003 and TRD3005) of its pivotal Phase III efficacy studies, in preference to a more traditional, fixed-dose regimen (Study TRD3001).

The use of flexibly dosed regimens, while perhaps being more representative of the real-world clinical setting, does not allow for extensive evaluation of dose-response trends in both efficacy and safety aspects of the clinical evaluation.

Efficacy

There were four pivotal/ main efficacy studies (all Phase III):

- Study ESKETINTRD3001 (pivotal, induction), also known as the TRANSFORM-1 trial, and referred here to as Study TRD3001.
- ESKETINTRD3002 (pivotal, induction) also known as the TRANSFORM-2 trial, and referred here referred to as Study TRD3002.
- ESKETINTRD3005 (pivotal, induction, elderly) also known as the TRANSFORM-3 trial, and referred here referred to as Study TRD3005.
- ESKETINTRD3003 (pivotal, maintenance/relapse prevention), also known as the SUSTAIN-1 trial, and referred to here as Study TRD3003.

There was one open label study which contributed efficacy data:

- ESKETINTRD3004 (Phase III, long-term open label safety/tolerability/efficacy), also known as the SUSTAIN-2 trial, and referred to here as Study TRD3004.

Pivotal/main induction studies

Study TRD3001; a randomised, double blind, multicentre, 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 TRD3002; a randomised, double blind, multicentre, 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 TRD3005; a randomised, double blind, multicentre, 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.

The Delegate commented that none of the studies were actually active-controlled as there was no active comparator to the tested drug (that is, intranasal esketamine).

Due to similarities in study design and methodology, the above listed three short-term pivotal efficacy induction studies were evaluated together.

For each study, there was:

- a screening/prospective observational phase (4 weeks);
- an optional period to taper the current antidepressant medication (3 weeks);
- a double blind induction phase (4 weeks);

- a follow-up phase (24 weeks for both Studies TRD3001 and TRD3002 and, 2 weeks for Study TRD3005).

Responders to double blind induction treatment in both Studies TRD3001 and TRD3002 were eligible to participate in Study TRD3003 (see '*Maintenance of effect/relapse prevention study*' section, below), while regardless of response status, subjects in Study TRD3005 were eligible to participate in Study TRD3004 (see '*Open label study*' section, below).

Study treatments

Subjects received twice-weekly self-administered intranasal spray (esketamine or placebo) under supervision at the study site.

Each intranasal device contained 28 mg esketamine. When multiple devices were required to achieve a scheduled dose, there was a 5 minute period between device administrations.

Food was not allowed for ≥ 2 hours before each administration and subjects remained at the clinical site until study procedures were completed.

Study TRD3001 used a fixed dose regimen (56 mg or 84 mg). Subjects only received 84 mg esketamine from Day 4 after titration from 56 mg on Day 1.

Study TRD3002 used a two dose flexible dose regimen (56 mg to 84 mg). All subjects randomised to esketamine treatment received 56 mg on Day 1 of the double blind treatment period. Upward titration to 84 mg was permitted on Day 4, downward titration permitted on Days 8 and upward titration on Day 11, no dose increase was permitted on Day 15 and the dose remained unchanged on Days 18, 22 and 25.

Study TRD3005 used a three dose flexible dose regimen of 28 mg to 56 mg or 84 mg. Elderly subjects were randomised to receive placebo nasal spray or esketamine nasal spray 28 mg on Day 1 then flexibly-dosed to remain on 28 or increased to 56 or 84 mg on Days 4, 8, 11 and 15, and the dose was scheduled to remain unchanged from Days 18, 22 and 25. Dose reduction was however permitted if there was poor tolerance.

Regarding the oral medication, subjects simultaneously initiated on Day 1, a new oral antidepressant (the 'active comparator') in an open label fashion, from duloxetine, escitalopram, sertraline or venlafaxine XR (venlafaxine extended release formulation). The new oral antidepressant was taken daily (most doses self-administered off-site) for at least the duration of the double blind treatment phase. The new antidepressant medication was assigned by the investigator based on MGH-ATRQ;[21] review and the relevant information regarding prior antidepressant treatments.

Main objectives and endpoints

The primary objective (for all trials) was to evaluate the efficacy of switching adult subjects with TRD from a prior antidepressant treatment (to which they had not responded) to intranasal esketamine (56 mg or 84 mg) + a newly initiated oral antidepressant, compared with switching to a newly initiated oral antidepressant (active comparator) + intranasal placebo, in improving depressive symptoms.

The primary efficacy endpoint was the change in the MADRS total score, as measured by the change from Baseline (Day 1 prior to randomisation) to the end of the 4 week double blind induction phase.[22]

[21] **The Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ)** is a self-rated scale used to determine treatment resistance in major depressive disorder (MDD). The ATRQ examines a patient's antidepressant treatment history and electroconvulsive therapy history in the current episode of depression and determines the adequacy of treatment response.
[22] **Montgomery-Åsberg Depression Rating Scale (MADRS)** is a clinician-rated scale designed to measure depression severity and detect changes due to antidepressant treatment. The scale consists of 10 items, each

The key secondary objective (for both Studies TRD3001 and TRD3002 but not for Study TRD3005) was to assess the effect of intranasal esketamine + a newly initiated oral antidepressant versus a newly initiated oral antidepressant (active comparator) + intranasal placebo:

- on the onset of clinical response by Day 2 (24 hours);
- functioning and associated disability;
- depressive symptoms (subject reported) in adult subjects with TRD.

The key secondary endpoints were:

- the proportion of subjects showing onset of clinical response by Day 2 (24 hours) that was maintained through to the end of the 4 week double blind induction phase;[23]
- the change in Sheehan Disability Scale (SDS) total score measured by the change from baseline to the end of the 4 week double blind induction phase. Scores ≤ 4 for each item on the subject- reported 5-item questionnaire and ≤ 12 for the total score were considered response.[24] Scores ≤ 2 for each item and ≤ 6 for the total score were considered remission.
- the subject-reported change from Baseline to end of double blind induction in depressive symptoms, using the Patient Health Questionnaire, 9-item (PHQ-9) total score from the subject-reported 9-item questionnaire: none to minimal (0 to 4), mild (5 to 9), moderate (10 to 14), moderately severe (15 to 19) and severe (20 to 27).[25]

Results

Baseline demographics were generally similar across treatment groups and across the double blind induction studies: most subjects were female (61.9 to 70.5%) and White race (76.6 to 94.9%), except for Study TRD3002 with more diversity in race and ethnicity.

As per study design, subjects in Studies TRD3001 and TRD3002 were all adults (aged < 65 years), with mean subject age 45.7 to 46.3 years, while subjects in Study TRD3005 were all elderly (aged ≥ 65 years), with mean subject age 70.0 years (range: 65 to 86). Most subjects were enrolled in North America (40 to 50%) followed by Europe (39.6%).

Primary efficacy outcome

The treatment differences in least squares (LS) means for MADRS total scores (with 7 day recall) demonstrated a clinically meaningful difference of at least 2.0 units between all intranasal esketamine + oral antidepressant treatments versus intranasal placebo + oral antidepressant treatments, across the three pivotal induction studies, at the end of double blind treatment (see Table 5).

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scored from 0 (item not present or normal) to 6 (severe or continuous presence of symptoms), for a possible score of 60. Higher scores represent a more severe condition; total scores of 0 to 6 are considered normal (or in clinical remission), 7 to 19 suggestive of mild depression, 20 to 34 of moderate depression and scores over 34 are indicative of severe depression. The test exhibits high inter-rater reliability. The typical recall period for the MADRS is 7 days, and the 7 day recall period was used for the primary efficacy evaluation.

[23] Onset of clinical response was defined as ≥ 50% reduction in MADRS total score by the day after taking the first dose of double blind medication (Day 2, 24 hours) that continued through to the end of the 4 week double blind induction phase, with one excursion (non-response) allowed on Days 8, 15 or 22 (but with ≥ 25% improvement).

[24] The **Sheehan Disability Scale** (**SDS**) is a 5 item self-reported scale that assesses functional impairment in 3 subscales of work or school, social life, and family life. Each of the three subscales are scored from 0 (no disruption/unimpaired) to 10 (extreme disruption), with scores of ≥ 5 in any of the three subscales suggestive of impairment within that subscale area. Total scores range from 0, being unimpaired to a maximum of 30 indicating globally high impairment.

[25] The **Patient Health Questionnaire 9-item (PHQ-9)** is a 9 question tool validated to assess for the degree of depression present in an individual, but not as a screening tool for depression; the last question is not scored, but is useful functionally to help the clinician assess the impact of the patient's symptoms on his or her life.

Table 5: Studies TRD3001, TRD3002 and TRD3005 Montgomery-Åsberg Depression Rating Scale total score, change from Baseline to double blind endpoint in the induction phase (last observation carried forward analysis of covariance; full analysis set)

Study ID	MADRS Total Score			LOCF ANCOVA			
(Treatment)	Mean Baseline	Mean DB Endpoint	Mean change from baseline to DB endpoint	Diff in LS means	Lower 95% CI	Upper 95% CI	2-sided p value
TRD3001							
Esk 56 mg + oral AD (n = 115)	37.4	19.1	18.3	4.1	7.53	0.6	N/A
Esk 84 mg + oral AD (n = 114)	37.8	20.6	-17.4	-2	-5.52	1.42	0.25
Oral AD + placebo (n = 113)	37.5	23.1	-14.3				
TRD3002							
Esk + oral AD (n = 114)	37	17.4	-19.6	-3.5	-6.67	-0.26	0.034
Oral AD + placebo (n = 109)	37.3	21	16.3				
TRD3005							
Esk + oral AD (n = 72)	35.5	26.3	-9.3	-3.6	-7.16	-0.03	0.052
Oral AD + placebo (n = 65)	34.8	29.2	-5.6				

AD = antidepressant; ANCOVA = analysis of covariance; CI = confidence interval; DB = double blind; Esk = esketamine; LOCF = last observation carried forward; LS= least squares; MADRS = Montgomery-Asberg Depression Rating Scale; N/A = not applicable.

N/A: Esketamine 56 mg + oral AD versus oral AD + placebo was not evaluated in Study TRD3001 since the esketamine 84 mg + oral AD vs. oral AD + placebo comparison was not statistically significant, as pre-specified in the step-down sequence analysis in the statistical analysis plan.

The treatment differences in LS means for MADRS total scores (with 7 day recall) reached statistical significance in Study TRD3002 (2 sided; p = 0.034) and borderline statistical significance in the elderly population in Study TRD3005 (2 sided; p = 0.052). However, statistical separation between intranasal esketamine 84 mg + oral antidepressant versus intranasal placebo+ oral antidepressant was not achieved in Study TRD3001 (2 sided; p = 0.250).

The mean change in MADRS total scores from Baseline to the double blind endpoint for intranasal esketamine + oral antidepressant treatments in the elderly population (Study TRD3005) appeared numerically smaller versus those observed in the adult populations (Studies TRD3001 and TRD3002). However, the mean changes become comparable, ranging from approximately -3 to -4, when the observed intranasal placebo + oral antidepressant changes in all three clinical studies were factored out.

Key secondary outcomes (Studies TRD3001 and TRD3002 only)

None of the secondary efficacy endpoints could be formally tested in Study TRD3001.

Onset of clinical response by Day 2 (24 hours):

- In Study TRD3002, more subjects who were treated with intranasal esketamine + oral antidepressant versus intranasal placebo + oral antidepressant achieved this study endpoint, namely: 7.9% (n = 9) versus 4.6% (n = 5), respectively (2 sided p = 0.321; observed odds ratio (95% Cl) was 1.79 (0.6; 5.7)). While both classes of antidepressant (serotonin and noradrenaline reuptake inhibitor (SNRI) and selective serotonin reuptake inhibitor (SSRI)) resulted in numerically higher percentages of clinical response after esketamine compared with placebo (3.8% and 2.0%, respectively), these differences were small and based on small subject numbers (< 6 persons per treatment arm). These findings were supported in corresponding exploratory analyses in Study TRD3001.

SDS total score and PHQ-9 total score:

- Since there was no statistical separation between treatment groups, based on the pre-defined testing sequence of secondary endpoints, SDS total score and PHQ-9 total score could not be formally evaluated in Study TRD3001 or Study TRD3002. The following results are exploratory only.
- SDS total score: across studies, greater LS mean differences (95% confidence interval (CI)) in SDS total scores were achieved by esketamine treatments versus placebo treatments (last observation carried forward (LOCF) analysis):
  - Study TRD3001: -2.7 (-5.33, -0.01) and -1.7 (-4.35, 0.85) for intranasal esketamine 56 mg + oral antidepressant and intranasal esketamine 84 mg + oral antidepressant;
  - Study TRD3002: -3.5 (-5.85, -1.16) for intranasal esketamine + oral antidepressant;
  - Study TRD3005: -2.8 (-6.39, 0.75) for intranasal esketamine + oral antidepressant.
- PHQ-9 total score: across studies, greater LS mean differences (95% CI) in PHQ-9 total scores were achieved by esketamine treatments versus placebo treatments (LOCF analysis):
  - Study TRD3001: -2.5 (-4.53, -0.54) and -1.9 (-3.87, 0.08) for intranasal esketamine 56 mg + oral antidepressant and intranasal esketamine 84 mg + oral antidepressant;
  - Study TRD3002: -2.2 (-3.93, -0.40) for intranasal esketamine + oral antidepressant;
  - Study TRD3005: -2.7 (-5.02, -0.45) for intranasal esketamine + oral antidepressant.

Maintenance of effect/relapse prevention study

Study TRD3003; a randomised withdrawal design, double blind, multicentre, Phase III, active-controlled study of intranasal esketamine plus an oral antidepressant for relapse prevention in treatment-resistant depression.

The Delegate commented that, like the induction studies, the maintenance study is actually placebo controlled due to the lack of an active comparator to intranasal esketamine.

The study comprised of:

- a screening/prospective observational phase (direct-entry subjects only);
- a 4 week open label induction phase (direct-entry subjects only);
- a 12 week optimisation phase (direct entry and transferred entry subjects from Studies TRD3001 and TRD3002);
- a double blind maintenance phase (involving direct- and transfer- entry patients); and
- a 2 week follow-up phase.

The Delegate commented that it would have been a better designed maintenance study if the double blind studies, Studies TRD 3001 and TRD 3002, had adequate number of patients fulfilling both the stable remission response and stable non-remission response criteria for transferred entry into the maintenance study without contribution from the direct-entry route.

Study treatments

No intranasal study medication was administered during screening.

During open label induction (4 weeks), subjects self-administered intranasal study agent (esketamine 56 or 84 mg), twice per week for 4 weeks as a flexible-dose regimen at the

study site under direct supervision. In addition, direct-entry subjects simultaneously initiated a new open label oral antidepressant on Day 1. Dose adjustments were permitted as per titration schedule. Oral medication was assessed by pill counts and drug accountability.

During optimisation (12 weeks), transferred-entry subjects continued the same double blind intranasal study drug (at the same dose) from the double blind induction phase of Studies TRD3001 or TRD3002. Direct-entry subjects continued the same open label intranasal esketamine treatment (at the same dose) from the open label induction phase.

At the start of double blind maintenance phase, patients meeting the criteria for stable remitters (that is, stable remission response) or stable responders (that is, stable non-remission response) were identified and eligible for randomisation. Each group was then randomised (1:1) to continue either esketamine nasal spray + oral antidepressant or switch to placebo nasal spray + oral antidepressant.

Those subjects who initially received weekly intranasal treatment remained on this regimen for the first 4 weeks, to Week 16.

For those subjects who initially received alternate weekly intranasal treatment, the frequency of intranasal treatment was increased to weekly for the next 4 weeks, if the MADRS total score was > 12 at Week 16. If the MADRS total score was ≤ 12 at Week 16, the subject continued to receive alternate weekly intranasal dosing for the next 4 weeks.

Thereafter, changes to the intranasal dosing frequency occurred at 4weekly intervals based on the MADRS total score.

Main objectives and endpoints

The primary objective was to assess the efficacy of intranasal esketamine + oral antidepressant versus intranasal placebo + oral antidepressant in delaying relapse of depressive symptoms in subjects with TRD, who were in stable remission (that is, stable remission response) after an induction and optimisation course of intranasal esketamine + oral antidepressant.

The primary efficacy endpoint was the time from randomisation into the maintenance phase and the first documented relapse event,[26] in subjects in stable remission;[27] at the end of the optimisation phase, after treatment with intranasal esketamine + oral antidepressant.

The secondary objective was to assess the efficacy of intranasal esketamine + oral antidepressant versus intranasal placebo + oral antidepressant in delaying relapse of depressive symptoms in subjects with TRD who were in stable response (but not in stable remission, that is, stable non-remission response) after an induction and optimisation course of intranasal esketamine + oral antidepressant.

The key secondary efficacy endpoint was the time between subject randomisation and the first documented relapse in the maintenance phase for subjects with stable response;[28]

[26] Defined as MADRS total score ≥ 22 for 2 consecutive assessments separated by 5 to 15 days and/or hospitalisation for worsening depression or any other clinically relevant event judged to be suggestive of a relapse of depressive illness for example, suicide attempt, completed suicide or hospitalisation for suicide prevention. In the case of a clinically relevant event suggestive of relapse, based on the investigator's clinical judgment but, without hospitalisation and unmet MADRS criteria, a relapse adjudication committee (RAC) reviewed the case and determined if the event was a relapse.
[27] Defined as MADRS total score ≤ 12 for at least 3 of the last 4 weeks of the optimisation phase, with 1 excursion of a MADRS total score > 12 or one missing MADRS assessment permitted at optimisation Week 13 or 14 only. The subject's MADRS total score at Weeks 15 and 16 must have been ≤ 12 points. (Definition modified in Protocol Amendment 4 to allow for 1 excursion or missing assessment).
[28] Defined as ≥ 50% reduction in 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 optimisation phase, but without meeting the criteria for

(not in remission)[29] at the end of the optimisation phase, after treatment with intranasal esketamine + oral antidepressant.

Results

Generally, baseline demographic and disease characteristics were evenly distributed across treatment groups, and consistent with the populations from Studies TRD3002 and TRD3001.

Primary efficacy outcome (double blind maintenance phase)

As per hazard ratio, Kaplan-Meier, MADRS and hospitalisation findings, there were statistically significantly fewer stable remitters who relapsed in the intranasal esketamine + oral antidepressant group versus intranasal placebo + oral antidepressant group, that is, 26.7% (n = 24) versus 45.3% (n = 39): estimated hazard ratio (95% CI) was 0.49 (0.29, 0.84: 2 sided p = 0.003; based on the weighted combination log-rank test) and was less than 0.046, the threshold of statistical significance. This result indicated that relapse was, on average, 51% less likely for stable remitters who continued treatment with esketamine than for those switched to placebo.

Based on Kaplan-Meier estimates, the median time to relapse (time at which cumulative survival function = 0.5 or 50%) for the intranasal esketamine + oral antidepressant arm was not estimable, whereas the median time to relapse (95% CI) for the oral antidepressant+ intranasal placebo arm was 273.0 days (97.0 days; upper limit not estimable). Of note, 48.7% (n = 19) of relapses in subjects randomised to intranasal placebo +oral antidepressant occurred within the first 4 weeks.

The most common rating for relapse was MADRS total score ≥ 22 for 2 consecutive assessments, separated by 5 to 15 days was 75.0% (n = 18) in the intranasal esketamine + oral antidepressant group versus 97.4% (n = 38) in the oral antidepressant+ intranasal placebo group.

No subject in the intranasal esketamine + oral antidepressant group was hospitalised, whereas 12.5% (n = 3) were hospitalised for depression or major depression in the intranasal placebo +oral antidepressant group. The adjudication committee judged 3 (12.5%) additional cases of relapse (from depression or depressive symptoms) in the intranasal placebo + oral antidepressant group and 1 (2.6%) case of relapse in the intranasal esketamine + oral antidepressant group.

Key secondary outcome

Relapse events in stable responders occurred in 25.8% (n = 16) of the intranasal esketamine + oral antidepressant group versus 57.6% (n = 34) of the intranasal placebo + oral antidepressant group. The treatment group difference for time to relapse was statistically significant (2 sided p < 0.001), with an estimated hazard ratio (95% CI) of intranasal esketamine + oral antidepressant group relative to intranasal placebo + oral antidepressant group of 0.30 (0.16; 0.55). This result indicated that relapse was 70% less likely for stable responders who continued treatment with esketamine than for those who discontinued esketamine treatment.

General results comments for Study TRD3003

The results supported both once-a-week and alternate week dosing frequency schedule in the maintenance phase, based on individual severity of symptoms, at previously optimised

stable remission. For transferred-entry subjects, Day 1 of the induction phase occurred in Study TRD3002 or Study TRD3001. (Definition modified in Protocol Amendment 4; before then, stability had been required for the last 4 weeks and had required at least 1 MADRS total score of > 12 points in those 4 weeks for differentiation versus stable remission.)

[29] Defined as MADRS total score ≤ 12, PHQ-9 total score ≤ 4 or SDS score ≤ 2 for each item and total score ≤ 6 at a given time point.

doses of either 56 or 84 mg of esketamine. Frequency of dosing in an elderly population in the maintenance phase of treatment effect/relapse prevention, would not be expected to be different from that of younger aged adults based on PK data and clinical response to treatment used in the once a week and alternate week dose regimens.

There was a tendency for greater efficacy in the 84 mg esketamine dose regimen in both stable remitters and stable responders, and more frequent dosing in stable responders compared with stable remitters, which may reflect a more treatment-resistant population in stable responders.

Also, while no antidepressant class difference was observed with stable remitter antidepressant comparisons, results suggest that responders may be less likely to relapse while on concomitant SNRI treatment rather than SSRI treatment. However, subject numbers were low and therefore caution should be exercised in the interpretation of these results and their generalisability.

While a high number of relapses occurred in the first month, it is unlikely that a withdrawal or rebound effect played a significant contribution due to the short half-life of esketamine (7 to 12 hours) and its lack of drug accumulation from PK studies. Of note, most subjects who relapsed during the first month after discontinuation of esketamine were subjects who required weekly dosing to sustain remission. This might reflect higher vulnerability in this subpopulation or a sub-optimal dose or maintenance dose duration before study drug discontinuation.

Open label study

Study TRD3004 was an open label, Phase III, long-term, safety and efficacy study of intranasal esketamine in, treatment-resistant depression over 1 year duration.

The study comprised of:

- a screening phase;
- a 4 week open label induction;
- 48 week optimisation/maintenance phase; and
- a 4 week follow-up.

Study treatments

Direct-entry patients initiated a new oral antidepressant; transferred-entry patients continued their oral antidepressant from Study TRD3005.

In the open label induction period, patients (direct-entry and Study TRD3005 non-responders) self-administered intranasal esketamine 28 mg (≥ 65 years), 56 mg or 84 mg flexible-dosing twice a week for 4 weeks, as in the double blind induction studies.

Open label optimisation/maintenance phase (direct and transferred entry patients): esketamine 28 mg, 56 mg or 84 mg was administered for 4 weeks, then weekly or every other week up to 48 weeks with option of down-titration as per treatment algorithm.

Main objectives and endpoints

The main objectives were to assess long-term safety, tolerability (primary objective) and efficacy (secondary objective) of intranasal esketamine + a newly initiated oral antidepressant in subjects with TRD.

The primary endpoint was about safety/tolerability (see '*Safety*' section, below).

The secondary endpoints (across phases) were:

- the change from Baseline of either phase for: MADRS, PHQ-9, Clinical Global Impressions-Severity scale (CGI-S), General Anxiety Disorder-7 (GAD-7), 5-level EuroQol 5 dimensions (EQ-5D-5L) and SDS; and
- the MADRS and PHQ-9 response and remission rates over time, from the open label induction baseline.

Results

MADRS optimisation/maintenance:

- for the total score, the mean change from Baseline to endpoint was -1.7 points at Week 48 (n = 139) and 0.3 points at endpoint (n = 603);
- regarding response, it was 89.2% (n = 124 out of 139) at Week 48 and 76.5% (n = 461 out of 603) at endpoint; and
- for remission, it was 55.7% (n = 325 out of 583) at Week 1 versus 68.3% (n = 95 out of 139) at Week 48 and 58.2% (n = 351 out of 603) at endpoint.

For other measures, similar patterns of improvement for CGI-S, PHQ-9, GAD-7, SDS and EQ-5D-5L were observed.

Sub-group analysis by age-group revealed low changes in mean MADRS total scores from maintenance Baseline to study endpoint across age-groups: 18 to 44 years = -0.2; 45 to 64 years = 0.1; 65 to 74 years = 1.6 and 75 years or older (n = 13) = 3.3.

Clinical evaluator's overall conclusions on clinical efficacy

- The clinical dossier included 5 Phase III trials in TRD. Four were pivotal (three induction (n = 720), one maintenance/relapse-prevention (n = 705)) and one was open label, with 1 year of safety data (n = 802).
- In the double blind induction studies, only Study TRD3002 demonstrated statistical superiority of flexible-dosing of intranasal esketamine + oral antidepressant over oral antidepressant + intranasal placebo treatment. The other two pivotal induction studies (including elderly subjects in Study TRD3005) were negative. No meta-analysis of the double blind induction studies was undertaken.
- In comparison, the maintenance/relapse prevention study (Study TRD3003) achieved a statistically significant and clinically meaningful reduction in relapse rate, when intranasal esketamine + oral antidepressant is compared with intranasal placebo + oral antidepressant.
- Furthermore, long-term sustained efficacy of intranasal esketamine + oral antidepressant was demonstrated in Study TRD3004, involving adults and elderly subjects at both once a week and, alternate week esketamine dosing regimens.
- The rationale for preferential selection of flexible-dose regimens in the double blind induction studies over conventional fixed-dose regimens appeared to be based on a pragmatic 'real-life' treatment approach, mainly based on concomitant ECT treatment of TRD with an oral antidepressant. Given that the pharmacological treatment options for TRD are extremely limited, the clinical evaluator considers it more important to clearly establish the efficacy (and safety) of the proposed individual esketamine dose regimens for TRD in a fixed-dose trial, before undertaking flexible-dose trials. In this application, efficacy was not adequately demonstrated in StudyTRD3001, the only fixed-dose study.
- The main issues of contention are in respect of the following:
  - The greatest impact on study validity and generalisability across the Phase III clinical studies, was related to the use of a new oral antidepressant as active comparator in the 2 treatment arms of the adjunctive design that is, intranasal

esketamine + oral antidepressant and intranasal placebo +oral antidepressant groups. An adjunctive design does not ordinarily allow for an estimation of background (placebo) effects, but may allow for an approximation of the contribution of the experimental drug (intranasal esketamine) versus the contribution of the active control (SSRI or SNRI) in MDD. However, this is only true provided the contribution of the oral antidepressant is established prior to randomised double blind treatment. Since 100% patients in the double blind induction studies received a newly initiated oral antidepressant at randomisation, their contribution towards treatment effect could not be established in these subjects during the double blind treatment phase, as the new oral antidepressant would be expected to have a major confounding effect on the study results, potentially adversely affecting both their internal and external validity. The planned Phase II study for the Japanese market (Study TRD2005), has a more acceptable design and is consistent with the design of an adjunctive aripiprazole-fluoxetine combination that led to registration of the combination in MDD in the US.[30]

- The role and treatment effect of intranasal esketamine treatment in acute episodes (as monotherapy or adjunctive treatment) are unknown, since the Phase II and Phase III clinical development programs for intranasal esketamine selected participants with chronic TRD. The sponsor claims in its justification to co-administer a new oral antidepressant at the same time as intranasal esketamine, that it would be unacceptable practice for participants to receive placebo treatment or an ineffective antidepressant treatment in acute episodes of MDD/TRD. That argument is not disputed. However, since the mean duration of the current episode for subjects in the double blind induction subjects ranged from 114.6 to 215.8 weeks, the double blind induction studies did not effectively investigate intranasal esketamine treatments in acute episodes of MDD/TRD *per se*. Hence, it would not have been unreasonable to have continued a prior open label oral AD into the double blind induction phase of treatment as per the dose-range study (Study TRD2003) and other Phase II studies, including Study TRD2005, which is planned for the Japanese market and allows for 6 weeks exposure to the newly initiated oral antidepressant prior to double blind randomised treatment.
- Interim analyses were undertaken in two double blind induction studies (Studies TRD3001 and TRD3005) and the maintenance-relapse prevention study (Study TRD3003). In the former two induction studies, a statistically significant treatment by stage effect for the primary efficacy analysis was demonstrated that is, pre-interim analysis (stage 1) versus post-interim analysis (stage 2). A *post hoc* analysis in Study TRD3002 revealed a similar apparent treatment effect. While the latter may lend support to the interim analysis process not adversely affecting the primary efficacy results, some other as yet ill-defined factor appears to have been introduced across the pivotal Phase III efficacy studies that has markedly increased the treatment difference that favours esketamine treatments over placebo treatments. In the absence of further explanation, the treatment effect by stage should be regarded with a high index of suspicion.
- The sponsor defined a clinically meaningful result as at least 2.0 units for the LS mean treatment differences in MADRS total scores between intranasal esketamine + oral antidepressant and intranasal placebo + oral antidepressant. This difference in treatment magnitude is generally consistent with approved antidepressants as monotherapy in short-term studies in MDD and, would be

[30] Pae, C-U. et al, Aripiprazole as Adjunctive Therapy for Patients with Major Depressive Disorder; Overview and Implications of Clinical Trial Data, *CNS Drugs*, 2011; 25 (2): 109-127

acceptable in a TRD population. Across the Phase III double blind induction studies in TRD, a clinically significant treatment effect of at least 2.0 units in LS means was observed for the primary and secondary efficacy endpoints, providing robust clinical evidence of a treatment effect of intranasal esketamine + oral antidepressant over intranasal placebo + oral antidepressant. However, these clinically meaningful differences were not in general supported by the corresponding statistical comparisons, since only 1 of 3 of the pivotal Phase III induction studies demonstrated statistical separation that favoured intranasal esketamine + oral antidepressant treatment over intranasal placebo treatment + oral antidepressant.

Safety

The safety studies consisted of:

- Two intranasal studies:
  - Study ESKETINTRD3004 (a Phase III, long-term open label safety, tolerability, and efficacy study) referred to as Study TRD3004 (described above in '*Open label study*');
  - Study ESKETINTRD2003 (a Phase II, dose-ranging study) referred to as Study TRD2003.
- Two intravenous studies:
  - Study ESKETIVTRD2001 (Phase II, with IV esketamine) referred to as Study TRD2001
  - KETIVTRD2002 (Phase II, with IV ketamine) referred to as Study TRD2002
- One intranasal study in MDSI:
  - Study ESKETINSUI2001 (a Phase II, proof-of-concept study) referred to as Study SUI2001

Safety data are available for 2,321 patients, who received at least one dose of esketamine nasal spray across completed Phase I, II and III clinical studies. In the six completed Phase II and III studies in subjects with TRD, 1708 subjects received at least one dose of esketamine, and 432 subjects received at least one dose of oral antidepressant + placebo (cumulative esketamine exposure 611 patient-years; cumulative exposure to oral antidepressant + placebo 108 patient-years). In the Phase III program, 479 subjects received esketamine for at least 6 months and 178 for at least 12 months. Subjects in the Phase II and III clinical programs in TRD were representative of patients commonly seen in psychiatric clinical practice and a population with MDD or TRD.

Across the Phase III studies in TRD, intranasal esketamine + oral antidepressant appeared to have a consistent and tolerable safety profile, with generally low reported numbers of deaths, serious adverse events (SAEs), severe treatment emergent adverse events (TEAEs) and TEAEs that led to discontinuation of study drug, with no major differences in incidence from the oral antidepressant + intranasal placebo comparison groups, with the exception of discontinuations. Rates of discontinuation of intranasal esketamine treatment due to TEAEs were generally highest early in the course of treatment and became more evenly distributed with long-term exposure, in both elderly and younger adult subpopulations. The relatively low rates of discontinuation due to TEAEs in the oral antidepressant + placebo groups of the Phase III studies may reflect a more tolerant population to oral antidepressant medications, given the prior antidepressant exposure in the current depression episode and > 1-year average duration of use of the last antidepressant prior to randomisation.

The pattern of TEAEs reported with longer-term repeated dosing of intranasal esketamine + oral antidepressant up to 1 year of exposure, was consistent with the experience in the short-term Phase III studies with respect to the types and relative incidence of common TEAEs, overall frequency of severe TEAEs, SAEs, discontinuations due to adverse events (AEs) and overall frequency of post-dose TEAEs that resolved the day of dosing.

Generally, the safety data from the Phase I and II clinical studies were consistent with the results from the Phase III program, including ongoing studies in the related condition of MDSI. With the exception of dissociation and nausea, there was no conclusive evidence of a dose effect with regard to the incidence of commonly reported TEAEs. Other than somnolence, the incidence of most other TEAEs remained stable or reduced with long term intranasal esketamine exposure.

Most post-dose severe TEAEs were transient (median duration < 2 hours) and resolved without clinical sequelae on the same day as dosing. These severe TEAEs included dissociation, dizziness and nausea.

Each of the 5 deaths (including 3 completed suicides) in esketamine-treated subjects were assessed by the investigator as not associated with study treatment. The overall rate of death in the completed Phase II and III studies with esketamine was 0.2 (n = 4), which appears to be consistent with other published reports in MDD populations. Furthermore, higher rates of suicidality would be expected in the more functionally debilitating TRD population.

There was no evidence to suggest that esketamine is associated with increased risk of suicidal ideation and behaviour in the clinical dossier. Clinical review indicated, that most suicidality-related TEAEs events were likely to be associated with the underlying disease condition. Overall, incidence of suicidality-related TEAEs across the Phase III studies was low: 0.6% for the esketamine group versus 0.3% for the placebo group. Also, treatment with esketamine nasal spray did not appear to be associated with development of potential psychotic-like symptoms or a distinct withdrawal syndrome after cessation of treatment with esketamine + oral antidepressant.

Similar to the peak incidence of general TEAEs around 40 minutes post-dose (with resolution by 2 hours post-dose), AEs of special interest generally followed a similar pattern, including dissociative or perceptual changes, somnolence and sedation and effect on cognition.

Most TEAEs were mild or moderate in severity.

Reported AEs associated with dissociative or perceptual changes (captured by the Clinician-Administered Dissociative States rating scale) were more pronounced in subjects receiving higher doses of esketamine, with some degree of tolerance to esketamine effects over the initial 4 weeks of treatment. Of note, 28 to 40% subjects in the oral antidepressant + placebo groups of Phase III studies also experienced dissociative or perceptual changes. This is in contrast to no observed dissociative or perceptual changes in the dose-range study (Study TRD2003), in which subjects generally received open label antidepressant that had demonstrated non-response prior to double blind randomisation. The explanation for this discrepancy is unclear, but may in part have arisen if study subjects were allowed to interact on dosing days, or observed behaviours in other subjects who had been dosed with intranasal esketamine.

Cognitive data from completed Phase III studies suggested treatment with intranasal esketamine + oral antidepressant was not associated with negative cognitive effects and there was no deterioration in cognitive performance with repeated intermittent dosing, based on Cogstate battery and revised Hopkins Verbal Learning Test. While some elderly subjects appeared to exhibit slowing of reaction time after 20 weeks esketamine exposure, this finding should be interpreted with caution given the small number of elderly subjects

who completed later time-points in Study TRD3004, as well as the high intra-individual variability in reaction time and lack of comparator control.

Intranasal esketamine was demonstrated to have similar abuse potential to IV ketamine in Study TRD1015. Across all Phase I, II and III studies, TEAEs suggestive of abuse potential most commonly associated with esketamine were dizziness, somnolence and dissociation. These symptoms were predominantly reported shortly after dosing on the day of esketamine administration, transient, self-limiting and mild or moderate in severity. Other events, such as euphoric mood, confusional state, feeling drunk or abnormal, and hallucinations, occurred at lower rates and < 4% in up to 1 year esketamine exposure.

The overall clinical laboratory test results in the completed Phase I, II and III studies in TRD did not suggest any safety concerns associated with intranasal esketamine + oral antidepressant. There was no evidence of treatment emergent hepatotoxicity associated with esketamine nasal spray and no subject met the definition for a Hy's law case.[31] While there were some low rates of hepatic enzyme elevations across the completed Phase II and III studies in TRD, they were generally transient and resolved spontaneously without the need for study discontinuation. Since intranasal esketamine was co-administered with an oral antidepressant, the observed elevations in hepatic enzymes could, in part, be attributed to the oral antidepressant since many antidepressants (duloxetine, sertraline and escitalopram) have been associated with elevated hepatic enzymes.

Transient increases in systolic blood pressure, diastolic blood pressure and heart rate were observed across the Phase II and III studies, usually peaking to coincide with esketamine C_{max} around 40 minutes post intranasal esketamine dosing, and generally returned to pre-dose values by 1.5 hours post-dose. While the mean percent increase in systolic blood pressure or diastolic blood pressure values were relatively stable and proportional across the Phase III studies, elevations in diastolic blood pressure tended to occur earlier from intranasal esketamine + oral antidepressant exposure than corresponding elevations in systolic blood pressure, and in subjects without prior diagnosis of acute hypertension, diastolic hypertension tended to be the most common cause for the acute episode of hypertension. In contrast, subjects who had history of hypertension, while generally having overall higher rates of acute hypertension, tended to have an even number of subjects' who had primarily diastolic of systolic hypertension.

Elderly subjects also tended to have higher incidence of TEAEs of blood pressure elevation and this is reflected in the proportionally higher baseline of elderly subjects who reported hypertension compared with younger adults at study entry.

The major issue of contention that applies to the safety data is also directly applicable to the clinical efficacy data. In summary, the addition of a new oral antidepressant at the time of randomisation in the pivotal Phase III inductions studies, introduces a potentially major confounding effect of the new oral antidepressant on the study results (efficacy and safety). No direct assessment of the attributable contribution to TEAEs from each individual treatment (intranasal esketamine, intranasal placebo, oral antidepressant) could be made, with a high degree of precision and certainty. Even allowing for the fact the safety profiles of SSRIs and SNRIs are reasonably well characterised, the safety profiles of these agents cannot be assumed to be mutually exclusive from esketamine.

Further studies are recommended before approval is granted.

[31] **Hy's Law**: Evidence of hepatocellular injury with a rise in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 3 x the upper limit of normal (ULN) and total bilirubin > 2 x ULN, and no other reason to explain rise in aminotransferases and total bilirubin. Hy's law is a rule of thumb that a patient is at high risk of a fatal drug-induced liver injury if given a medication that causes hepatocellular injury with jaundice.

Clinical evaluator's recommendation

Unconditional approval of esketamine hydrochloride is not recommended for:

> *treatment resistant depression (Major Depressive Disorder in adults who have not responded adequately to at least two different antidepressants of adequate dose and duration to treat the current moderate to severe depressive episode).*

This recommendation is based on the available data at the time of the fourth round of the clinical evaluation, in particular due to the lack of efficacy data that supports the proposed indication.

However, since the sponsor has agreed to provide the TGA with the full clinical study report (CSR) for the Phase IIb Japanese study, Study TRD2005, as a post-approval commitment (estimated completion July 2020), it appears reasonable to the clinical evaluator that either of the following courses of action are acceptable:

- The application for Spravato in the treatment of TRD be deferred until the CSR for Study TRD2005 has been fully evaluated by the TGA, and if deemed acceptable, unconditional approval be granted; or
- The Delegate may consider granting a conditional approval for Spravato in the treatment of TRD, on the understanding that the full CSR for Study TRD2005 is provided as soon as practicably possible upon study completion and that the study findings, once they have been evaluated by the TGA, support ongoing registration of Spravato for the approved indication.

It is also noted in the sponsor's response to the TGA that the US Food and Drug Administration (FDA) requested the sponsor to provide a post-approval commitment to undertake a clinical study focused on the use of esketamine (56 mg or 84 mg) as monotherapy that is, intranasal esketamine versus placebo treatment (estimated start date: first quarter of 2020; estimated completion date: end of 2022). The sponsor has also agreed to commit to provide the full CSR for this clinical trial to the TGA, as part of its post-approval commitment. While the results of this latter study may be expected to provide a more accurate determination of the treatment effect, and safety profile, of intranasal esketamine, its results will not be critical for the determination of approval in the proposed indication in which intranasal esketamine is proposed to be used as adjunctive therapy with an oral antidepressant.

Risk management plan

The sponsor has submitted EU-risk management plan (RMP) version 1.0 (date 26 September 2018; data lock point (DLP) 4 March 2018) and Australian specific Annex (ASA) version 0.1 (date 25 October 2018) in support of this application.

In response to the first round of evaluation, the sponsor has provided an updated EU RMP version 1.0 Succession No. 2 (date 20 May 2019; DLP 4 March 2018) and ASA version 0.2 (date 27 June 2019).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 6.[32]

[32] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;

Table 6: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Drug abuse	ü	ü[3, 4]	ü[6]	ü[1]
	Transient dissociative states and perception disorders	ü	ü[3, 4]	ü[6]	ü[1, 2]
	Disturbances in consciousness	ü	ü[3]	ü[6]	ü[1, 2]
	Blood pressure increased	ü	ü[3]	ü[6]	ü[1, 2]
Important potential risks	Cognitive and memory impairment (long-term use)	ü	ü[5]	ü	–
	Interstitial cystitis	ü	ü[5]	ü	–
Missing information	Use during pregnancy	ü	–	ü	–

[1] Healthcare professional (HCP) Guide and Patient Guide to treatment; [2] Readiness to Leave Checklist for HCP, How to self-administer card for patient; [3] HCP Survey to assess effectiveness of additional risk minimisation; [4] Australian commitment (ASA only; not EU-RMP). Results of ongoing US Risk Evaluation and Mitigation Strategy (REMS) Registry; [5] Study 54135419TRD3008 (Final report estimated second quarter, 2022); [6] Boxed warning inclusion in PI and CMI.

- During the second round of evaluation, the sponsor has added *'disturbances in consciousness'* as an important identified risk in the RMP, and removed *'use in breast-feeding women'* and *'use in patients with severe hepatic impairment'* to align with changes to the EU-RMP. The removed items should have negligible impact on the risk management as the PI continues to convey that Spravato is not recommended for use during lactation and that there is no clinical experience when administered as a nasal spray in patients with severe hepatic impairment.
- Routine pharmacovigilance and risk minimisation activities are applicable for most safety concerns. There is an ongoing overseas long-term safety study for Spravato with Australian patient involvement to further address important potential risks of long term use including cognitive disorders, memory impairment, and interstitial cystitis. Study results will be relevant to the Australian use. During the second round of evaluation, the sponsor has agreed to include a US Spravato patient registry (US Risk Evaluation and Mitigation Strategy (REMS) Registry) in the ASA as an additional pharmacovigilance activity.
- Restrictive access controls for Spravato in Australia must be in accordance with its status as a Standard for the Uniform Scheduling of Medicines and Poisons Schedule 8 controlled drug.[33]

- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

[33] **The Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)**: is a record of decisions regarding the classification of medicines and chemicals into Schedules for inclusion in relevant legislation of the states and territories; includes model provisions about containers and labels, and recommendations about

- The sponsor proposes to apply strict eligibility criteria under the Spravato RMP to ensure that: access to Spravato is restricted to limited number of eligible health care sites and healthcare professionals (HCPs) to avoid drug diversion and dependence; the product and its use will be subject to direct oversight by certified HCPs following sponsor training of eligible HCP; patients will be appropriately monitored following treatment; stringent product disposal requirements are to be met by the HCP following use to ensure product cannot be taken away by patient or other personnel. During the second round of evaluation, the ASA's risk minimisation plan was considered deficient in key information concerning the restricted access provisions and patient support controls in Australia required to support safe use of Spravato. The sponsor provided further details, but on completion of the post-second round evaluation uncertainties remained on the adequacy of the plan, mainly on the patient monitoring and support controls required to address acute effects of Spravato that may lead to patient harm.
- The post-second round Advisory Committee advice (see '*Advisory Committee considerations*' section, below) is that the key risk communication documents including PI and additional risk minimisation materials must be further strengthened with additional safety-related messaging to HCPs, including the need for patient monitoring protocols to specify a minimum 2 hour duration of monitoring at the treatment site and that every patient must be discharged to the care of an accompanying support person or carer to help ensure compliance with patient's discharge instructions.[34] From an RMP perspective, the Advisory Committee advice is supported and further negotiations with sponsor on its risk minimisation plan are to ensue at the discretion of the Delegate.
- During the second round of evaluation, the sponsor agreed to include boxed warnings in the PI and CMI to highlight potential for acute effects of dissociation, sedation and elevated blood pressure following administration and specify key aspects of safe use. The sponsor commits to include these warnings on all HCP and patient educational materials as well as promotional materials.
- The ASA has been updated during the second round of evaluation to include additional risk minimisation materials and particulars of their implementation to support safe use of Spravato: '*HCP Guide* and *Patient Guide to Treatment*', HCP *'Readiness to Leave'* checklist to establish patient is clinically stable and safe to leave after dosing, and patient's instruction for self-administration ('*How to self-administer Card*'). Further particulars were sought during the post-second round evaluation on how sponsor will ensure that the key documents will be made available for HCP or patient's use during each treatment session. The sponsor has committed to conducting a physician survey for measuring effectiveness of the additional risk minimisation materials. The second round evaluation recommended, and the sponsor has now acknowledged, that an approved TGA protocol and questionnaire for use in the HCP survey be established prior to initial training of the HCP prescribers and that study timelines and submission to TGA be further agreed upon.

other controls on medicines and chemicals; and is registered on the Federal Register of Legislation as the Poisons Standard.

[34] Sponsor clarification: following the Section 60 decision to register Spravato, the sponsor was notified by the RMP area that the sponsor was not required to address the recommendation for patient monitoring protocols to specify a minimum 2 hour duration of monitoring at the treatment site and that every patient must be discharged to the care of an accompanying support person or carer to help ensure compliance with patient's discharge instructions. This was not implemented in the final ASA at the discretion of the sponsor.

Risk-benefit analysis

Delegate's considerations

Major depressive disorder (MDD) is a severely debilitating and recurrent psychiatric disorder. Treatment resistant depression (TRD) is considered to be a subset of MDD and is defined, as MDD in adults who have not responded adequately, that is, lack of clinically meaningful improvement, to at least two different antidepressants, prescribed and used at adequate dose and for adequate duration, to treat the current depressive episode.

TRD is a principal contributor to the morbidity and mortality associated with depression. Patients with TRD are more likely to have lower remission rates, pronounced functional impairment, substantially lower quality of life, higher suicide rates, and incur higher medical and mental healthcare costs versus patients with MDD who respond to antidepressant treatment.

Although no medication is currently indicated specifically alone for TRD in Australia, antidepressants such as phenelzine (Nardil) and tranylcypromine (Parnate), both monoamine oxidase inhibitors, are indicated on the ARTG for '*MDD when other antidepressant therapy has failed*.'

Seroquel XR (quetiapine, extended release formulation), an atypical antipsychotic agent, is approved on the ARTG for:[5]

> *treatment of recurrent MDD in patients who are intolerant of, or who have an inadequate response to alternative therapies.*

However, atypical antipsychotic usage has been limited by significant adverse reactions, including metabolic disturbances, weight gain and neuroleptic malignant syndrome.

Non-pharmacological treatment options (ECT and transcranial direct current stimulation) for TRD have limited efficacy or patient acceptability.

Only about two-thirds of patients with MDD achieve remission after the first or second courses of treatment using currently approved drugs, mostly acting by modulating the monoaminergic system. Remission rates following subsequent steps of therapy are lower (approximately 13%), and relapse rates are higher and occur more quickly.

There is a need to develop innovative treatments, based upon relevant pathophysiologic pathways underlying MDD, for the rapid and sustained relief of depressive symptoms, especially in patients with TRD.

Esketamine, the S-enantiomer of racemic ketamine, is a first in class antidepressant with a novel mechanism of action as a glutamate receptor modulator, expected to address this unmet medical need.

The clinical evaluator found the evaluated PK data to be satisfactory overall. The Delegate believes that the observed variations in C_{max} and AUC with regard to the Japanese ethnicity are significant enough to warrant modifications to the proposed dosing regimen in that group.

Three pivotal short term (4 weeks) randomised double blind, multicentre, active-controlled induction studies (Studies TRD3001, TRD3002 and TRD3005), in adult subjects (> 18 years, including the elderly > 65 years) with TRD were evaluated. Study TRD3001 involved fixed esketamine doses (56 mg or 84 mg) while flexible doses of esketamine were utilised in Study TRD3002 (56 mg to 84 mg) and Study TRD 3005 (28 mg to 56 mg to 84 mg).

The primary objective for each trial was to assess the efficacy of switching adult subjects with TRD from a prior antidepressant treatment (to which they had not responded) to intranasal esketamine + a newly initiated oral antidepressant, compared with switching to

intranasal placebo + a newly initiated oral antidepressant (active comparator), in improving TRD symptoms.

The key secondary objective (for both Study TRD3001 and Study TRD3002 but not for Study TRD3005) was to assess the effect of intranasal esketamine + a newly initiated oral antidepressant versus intranasal placebo + a newly initiated oral antidepressant (active comparator) including (i) onset of clinical response by Day 2 (24 hours); (ii) functioning and associated disability; and (iii) depressive symptoms (subject reported) in adult subjects with TRD.

The clinical evaluator pointed out the limitations in the conduct of the pivotal double blind induction studies, such as:

- not having patients continued with baseline antidepressants that had demonstrated non-response in the current major depressive episode into the double blind treatment; and
- more so, that it cannot be assumed that each newly initiated oral antidepressant treatment will provide equal efficacy on a dose-for-dose basis.

Following the first round of evaluation, the clinical evaluator concluded in general that the:

- study objectives for the double blind induction studies were not completely achieved, namely:
  - while statistical separation was demonstrated in the primary efficacy analysis in Study TRD3002, for intranasal flexible-dose esketamine + oral antidepressant compared to intranasal placebo + oral antidepressant; statistical separation over intranasal placebo + oral antidepressant was not achieved for the pre-specified first key secondary endpoint (onset of clinical response by Day 2).
  - statistical significance was not achieved in the primary efficacy analysis in Study TRD3001 and only borderline statistical significance (p =0.052) was achieved in Study TRD3005.
- the differences in LS means of esketamine treatments versus the placebo treatments were consistently above 2 units across studies, for most primary and secondary efficacy endpoints. The latter provides support for a clinically meaningful difference of intranasal esketamine treatments *in the range 56 mg to 84 mg, at twice weekly dosing for adults and 28 mg to 84 mg in elderly persons.*

One randomised, withdrawal design, double blind, multicentre, Phase III, active-controlled relapse-prevention study (Study TRD 3003) was evaluated (known as a maintenance of effect/relapse study).

The primary objective was to assess the efficacy of intranasal esketamine + oral antidepressant versus intranasal placebo + oral antidepressant in delaying relapse of depressive symptoms in subjects with TRD, who were in stable remission (that is, stable remission response, also known as stable remitters) after an induction and optimisation course of intranasal esketamine + oral antidepressant.

The secondary objective was to assess the efficacy of intranasal esketamine + oral antidepressant versus intranasal placebo + oral antidepressant in delaying relapse of depressive symptoms in subjects with TRD, who were in stable response (but not in stable remission that is, stable non-remission response, also known as stable responders) after an induction and optimisation course of intranasal esketamine + oral antidepressant.

As part of the primary and secondary efficacy outcomes in the double blind maintenance phase, the clinical evaluator found that:

- There was statistically significantly fewer stable remitters who relapsed in the intranasal esketamine + oral antidepressant group versus intranasal placebo + oral antidepressant group that is, 26.7% (n = 24) versus 45.3% (n = 39): the estimated hazard ratio (95% CI) was 0.49 (0.29, 0.84: 2 sided p = 0.003; based on the weighted combination log-rank test) and was less than 0.046, the threshold of statistical significance. This result indicated that relapse was, on average, 51% less likely for stable remitters who continued treatment with esketamine than for those switched to placebo.
- Based on Kaplan-Meier estimates, median time to relapse (time at which cumulative survival function = 0.5 or 50%) in stable remitters for intranasal esketamine + oral antidepressant arm was not estimable, whereas median time to relapse (95% CI) for oral antidepressant + intranasal placebo was 273.0 days. Of note, 48.7% (n = 19) of relapses in subjects randomised to intranasal placebo + oral antidepressant occurred within the first 4 weeks.
- Relapse events in stable responders occurred in 25.8% (n = 16) of the intranasal esketamine + oral antidepressant group versus 57.6% (n = 34) of the intranasal placebo + oral antidepressant group.
- The treatment group difference for time to relapse in stable responders was statistically significant (2 sided p < 0.001), with an estimated hazard ratio (95% CI) of intranasal esketamine + oral antidepressant group relative to intranasal placebo + oral AD group of 0.30 (0.16; 0.55). This result indicated that relapse was 70% less likely for stable responders who continued treatment with esketamine than for those who discontinued esketamine treatment.

The clinical evaluator identified some issues with the submission that generated three rounds of questions from the TGA and associated sponsor responses, and four rounds of clinical evaluator's comments and authorisation recommendations. The clinical evaluator's fourth round recommendation is shown in the '*Clinical evaluator's overall conclusions on clinical efficacy*' section, above.

Despite the clinical evaluator's previously stated positive efficacy outcomes for both the primary and secondary objectives in both the induction and maintenance phases of the clinical trials (see above), the clinical evaluator's authorisation recommendation above is based on the perception of '*lack of efficacy data for the intranasal esketamine per se'*. The latter essentially relates to the clinical evaluator's impression, that initiation of both the new oral antidepressant and the test drug for TRD (intranasal esketamine) was simultaneous at the commencement of the double blind trial phase.

The Delegate's thought is that the clinical evaluator's perception may be superficial and the Delegate contends, that having a trial design of *intranasal esketamine + new oral antidepressant* compared to *intranasal placebo + new oral antidepressant* mitigates the clinical evaluator's view. The Delegate believes that the efficacy of the new oral antidepressant is also quantifiable in the main by such trial design. It is also plausible that in practice, clinicians may choose to change oral AD from time to time in conjunction with intranasal esketamine treatment for maximum efficacy.

It is worth mentioning, however, that the sponsor has provided the provisional negative outcome of a Phase IIb clinical study (Study TRD2005) for the Japanese market (completed September 2019). The study design in Study TRD2005 is very different from the Phase III double blind induction studies in that, subjects are stabilised on an oral antidepressant prior to randomisation to intranasal esketamine or placebo treatment. The sponsor stated that failure was most probably due to a high placebo response (the full CSR completion estimation date is July 2020, for submission to the TGA).

Of note is the US FDA request that the sponsor provides a post-approval commitment to undertake a clinical study focused on the use of esketamine (56 mg or 84 mg) as monotherapy, that is, intranasal esketamine versus placebo treatment (estimated start date: first quarter of 2020; estimated completion date: end of 2022). The sponsor has also agreed to provide the full CSR for this clinical trial to the TGA, as part of its post-approval commitment. In that regard, the clinical evaluator stated that the results of this latter study may be expected to provide a more accurate determination of the treatment effect and safety profile of intranasal esketamine. However, the study results will not be critical for the determination of approval, concerning the currently proposed indication in which intranasal esketamine is to be used as adjunctive therapy with an oral antidepressant. The Delegate agrees with the clinical evaluator, as a positive outcome will only be relevant if the sponsor is seeking a monotherapy TRD indication for intranasal esketamine.

Safety issues identified with the use of intranasal esketamine include elevated blood pressure, sedation, drug abuse /addiction potential and dissociation/perceptual changes. Those issues have led to suggested modifications to the draft PI and draft CMI, and to several recommendations in the RMP.

Indications

The proposed initial indication was:

> *Treatment resistant depression, defined as MDD in adults who have not responded adequately to at least two different antidepressants of adequate dose and duration, to treat the current depressive episode.*

This was later modified (post the final clinical evaluation report) to:

> *Treatment resistant depression, defined as MDD in adults who have not responded adequately to at least two different antidepressants of adequate dose and duration, to treat the current moderate to severe depressive episode.*

The proposed modified indication for intranasal esketamine (Spravato) as per the Delegate is:

> *Treatment resistant depression (defined as MDD in adults who have not responded adequately to at least two different antidepressants of adequate dose and duration, to treat the current moderate to severe depressive episode).Esketamine is to be initiated as adjuvant in conjunction with oral SSRI or SNRI antidepressant (preferably new) and, in the context of conjoint supportive psychotherapy combined with counselling and significant social assistance.*

This proposed indication is based on the following rationale:

- based on the evaluated data from the trial design;
- both the EMA and FDA did not particularly specify new SSRI or SNRI as followed in the clinical trials;
- contemporary clinical practice and therapeutic guidelines utilise psychotherapy, counselling and social support in the management of all forms of depression; and
- some patients received psychotherapy in the trials.

Proposed conditions of registration

- Fulfilment by the sponsor, prior to product launch, to adhere to the gamut of RMP recommendations as currently suggested by the RMP evaluator, the clinical evaluator and the Delegate. Any RMP recommendations by the Advisory Committee must also be complied with.
- Compliance with the Australian periodic safety report (PSUR) submission requirements.

- Resolution of all recommendations pertaining to the draft PI/draft CMI as per the clinical evaluator, Delegate, nonclinical and RMP evaluators, to the satisfaction of the TGA.
- Compliance with outcomes of the Advisory Committee deliberations.
- Provision of the US FDA requested clinical study, focused on the use of esketamine (56 mg or 84 mg) as monotherapy, that is, intranasal esketamine versus placebo treatment, when completed.
- Provision of the full CSR on Study TRD 2005 when completed.

Proposed action

The Delegate considers the submission to be approvable, provided all the stated RMP issues are complied with prior to product launch and the above stated conditions of registration are adhered to.

Advisory Committee considerations[35]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following at the April 2020 meeting.

Specific advice to the Delegate

The ACM advised the following in response to the Delegate's specific request for advice.

1. The ACM is requested to consider the approvability or not of the submission at this point in time and provide advice as appropriate, based on the gamut of available evidence and the stated conditions of registration.

There is significant and unacceptable uncertainty associated with the claims of the efficacy of esketamine in patients with TRD. The pivotal trials failed to achieve their primary outcomes. There were a number of irresolvable methodological issues with the pivotal trials. In addition, there is significant potential toxicity associated with use of this product, requiring the deployment of a complex and resource-intensive RMP, at both regulatory and clinical levels. There is also a high risk of misuse, diversion and abuse despite the proposed dangerous drug scheduling.[36] The ACM noted that ongoing studies which may address the efficacy uncertainties of esketamine in TRD, are due for reporting within the next 12 months.

The sponsor has undertaken to submit these data to the TGA once available. Given the magnitude of uncertainty regarding the efficacy of esketamine in treating TRD, the ACM advised against approval, conditional on access to these data. In light of the clearly negative benefit to risk balance, the ACM felt compelled to advise rejection of the request for registration.

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[35] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

[36] **Schedule 8 Controlled drug**: Medicines or chemicals which have special rules for producing, supplying, distributing, owning and using them. These medicines may only be prescribed by an authorised healthcare professional who may need a special prescribing permit.

2. The acceptability of the modified indication by the Delegate.

The ACM was of the view that it would be more appropriate for the indication to specify '*moderate to severe treatment resistant depression*', should the product be registered.

Conclusion

The proposed indication considered by the ACM was:

> *Spravato is indicated for treatment resistant depression, defined as MDD in adults who have not responded adequately to at least two different antidepressants of adequate dose and duration, to treat the current moderate to severe depressive episode.*

The ACM agreed that Spravato had an overall negative benefit-risk profile for the proposed indication. The data submitted did not satisfactorily establish adequate and unquestionable efficacy of the product, given the magnitude of the safety risk management issues to be associated with the use of the product. The ACM commented about the clinical trial design of the submission and the potential for misuse/diversion of the product.

Follow-up Advisory Committee considerations

Following the April 2020 ACM meeting, the sponsor was encouraged and given the opportunity by the TGA, to submit any new data it might hold on a properly designed clinical trial, in order to address the methodological issues identified with the pivotal efficacy induction trials (Studies TRD3001, TRD3002 and TRD3005), especially the trial requirement that, subjects simultaneously initiated on Day 1 of the double blind phase, a new oral antidepressant, the 'active comparator'. The sponsor has provided efficacy data from an ongoing, global, open-label trial (Study TRD3008),[37] new analysis of previously submitted data and recently published literature (a *post-hoc* study;[38] and a meta-analysis).[39,40]

The Delegate sought the Committee's advice at the June 2020 ACM meeting on whether the sponsor's response to the April 2020 ACM meeting outcome has addressed the Committee's concerns.

Specific advice to the Delegate

The ACM advised the following in response to the Delegate's specific request for advice.

The ACM remains concerned about lack of robust evidence to support the efficacy of intranasal esketamine for the proposed indication:

> *Spravato is indicated for treatment resistant depression (Major Depressive Disorder) in adults who have not responded adequately to at least two different antidepressants of adequate dose and duration to treat the current moderate to severe depressive episode). Spravato is to be initiated in conjunction with a newly initiated oral SSRI or SNRI antidepressant (AD).*

[37] Study TRD3008 is a Phase III, long-term open-label extension study that enrolled subjects who had previously participated in one of the Phase III TRD studies (Studies TRD3001, TRD3002, TRD3003, TRD3004, TRD3005, and TRD3006 (US sites only for Study TRD3006)).
[38] Citrome L, DiBernardo A, Singh J. Appraising esketamine nasal spray for the management of treatment-resistant depression in adults: Number needed to treat, number needed to harm, and likelihood to be helped or harmed. *J Affect Disord*. 2020; 271: 228-238.
[39] Dold, M, Bartova, L and Kasper, S. Treatment Response of Add-On Esketamine Nasal Spray in Resistant Major Depression in Relation to Add-On Second-Generation Antipsychotic Treatment, *International Journal of Neuropsychopharmacology*, 2020; 23 (7): 440–445
[40] Inclusion of the complete data/response is beyond the scope of this AusPAR.

The ACM noted that the response provided by the sponsor has not provided any new data from a properly designed trial of adequate duration that addresses the concerns previously communicated by the Committee. Due to the complexities associated with administering the product in a community setting, the ACM agreed that a more reliable RMP is required.

Conclusion

The ACM stated that Spravato has an overall negative benefit-risk profile for the proposed indication, as the evidence submitted did not satisfactorily establish the efficacy of the product with certainty. There is also doubt about the practicality of the RMP to support the management of significant safety and toxicity concerns.

Outcome

Initial outcome

Based on a review of quality, safety and efficacy, the TGA rejected the registration of Spravato (esketamine hydrochloride) 28 mg of esketamine per 2 actuations, nasal spray solution for the proposed therapeutic indication:

> *Treatment resistant depression, defined as MDD in adults who have not responded adequately to at least two different antidepressants of adequate dose and duration, to treat the current depressive episode.*

Reasons for the decision

The Delegate considers that there were a number of irresolvable methodological issues with the pivotal efficacy induction trials (Studies TRD3001, TRD3002 and TRD3005), especially the trial requirement that, subjects simultaneously initiated on Day 1 of the double blind phase, a new oral antidepressant, the 'active comparator'. The new oral AD was taken daily for at least the duration of the double blind treatment phase.

The Delegate gave a detailed account of their reasoning behind their decision to reject the registration of the product, including the following points of note:

- A new antidepressant was initiated at the same time as esketamine, leading to the possibility of confounding. The preference was for only one change to the treatment plan be made at any one time, as otherwise it was directly not straightforward to determine which agent was responsible for the clinical outcomes. An alternative trial design, allowing participants to remain on an existing antidepressant whilst initiating esketamine would have been more appropriate in assessing the efficacy of esketamine, thereby eliminating the current, significant and unacceptable uncertainty associated with the claims of the efficacy of esketamine in patients with TRD.
- Separate from the flawed clinical trial design and the failure of two out of the three pivotal studies to reach statistical significance in terms of the primary efficacy outcome, the magnitude of the safety risk management issues to be associated with the use of the product was of concern, in addition to the potential for misuse/diversion of the product.
- It is acknowledged, that (1) treatment resistant depression remains a challenging but treatable condition with the few effective pharmacological options currently available; and (2) Spravato has recently been approved in the United States, Europe, Switzerland and New Zealand for similar indications to those proposed for Australia.
- Based on the provided evidence to the TGA, the overall view was that the submission is not approvable at this time. In particular, there was lack of robust data demonstrating exemplary efficacy, probably embedded in the faulty clinical trial

design of the pivotal studies. Further deliberations on the approval of the submission should await the provision of the outcomes of (a) the US FDA-requested Study TRD4005, to which the sponsor has a post-approval commitment to undertake. Study TRD4005 is focused on the use of esketamine (56 mg or 84 mg) as monotherapy (that is, intranasal esketamine versus placebo treatment); and (b) the full CSR for the Phase IIb Japanese Study TRD2005 (the study design in Study TRD2005 is very different from the Phase III double-blind induction studies submitted in the clinical dossier. In Study TRD2005, subjects were stabilised on an oral antidepressant prior to randomisation to either intranasal esketamine or placebo treatment that is, recognised, proper adjunctive study design).

- In May 2020, the sponsor advised the TGA that (i) Study TRD2005 had failed to demonstrate efficacy of adjunctive esketmine nasal spray in Japanese adult patients with TRD; and (ii) initiation of Study TRD4005 (the sponsor's post marketing commitment of esketamine monotherapy study to the US FDA) has been delayed due to coronavirus disease 2019 (COVID-19) issues.
- Following the April 2020 ACM meeting, the sponsor was encouraged and given the opportunity by the TGA, to submit any new data it might hold on a properly designed clinical trial. The latter will counter the previously mentioned irresolvable methodological issues identified with the pivotal efficacy induction trials (Studies TRD3001, TRD3002 and TRD3005), especially the trial requirement that, subjects simultaneously initiated on Day 1 of the double blind phase, a new oral antidepressant, the 'active comparator'. As per the TGA's protocol, such new clinical trial data was to be formally evaluated. Rather than provide the required new data on properly designed clinical trial, the sponsor has provided efficacy data from an ongoing, global, open-label trial (Study TRD3008), new analysis of previously submitted data and recently published literature (on meta-analysis). In addition, the sponsor claimed that new data is provided in order to address the ACM's concern regarding the efficacy of esketamine potentially confounded by the initiation of a new oral antidepressant at the same time as intranasal esketamine.
- Following the ACM meeting, the Delegate provided a reply to each aspect of the sponsor's response, also taking into consideration the ACM's assessment. In summary, the ACM (see '*Follow-up Advisory Committee considerations*' section, above) and the Delegate did not consider the sponsor's response to be sufficient to resolve the previously outlined concerns regarding the submission.

Section 60 review

Following the initial decision described above, the sponsor sought a review under the provisions of Section 60 of the Therapeutics Goods Act. The Delegate of the Minister for the review noted that paragraph 25(1)(d) of the Therapeutic Goods Act, which requires the goods to be evaluated with regard to whether the quality, safety and efficacy of the goods for the purposes for which they are to be used have been satisfactorily established, is of particular relevance.

The Delegate of the Minister under Section 60 (hereafter referred to as the Section 60 Delegate) decided to revoke the initial decision and make a new decision in substitution for that decision. Their substituted decision is to register the product on the basis that the quality, safety and efficacy of the product for the purposes for which it is to be used have been satisfactorily established. The Section 60 Delegate decided to approve the product with the following indication:

> *Spravato is indicated for treatment resistant depression (Major Depressive Disorder in adults who have not responded adequately to at least two different*

antidepressants of adequate dose and duration to treat the current moderate to severe depressive episode).

Spravato is to be initiated in conjunction with a newly initiated oral antidepressant.

Reasons for the decision

The Section 60 Delegate has decided to revoke the initial decision and make a new decision in substitution for that decision. Their substituted decision is to register the product. Their reasons for that decision are as follows.

Although statistically significant results were achieved in only one of the pivotal induction studies (Study TRD3002), similar effect sizes were seen in the other two studies (Studies TRD3001 and TRD3005). In addition, maintenance of antidepressant effect was demonstrated in the relapse prevention study, Study TRD3003.

Adverse events were generally non-serious in nature. Important early adverse effects such as sedation, dissociation, and raised blood pressure can be managed by appropriate post-dose observation.

The clinical evaluator was concerned that the design of the pivotal induction efficacy studies did not allow estimation of the efficacy and safety attributable solely to Spravato. This concern was reflected in the initial decision letter. However, the study design was acceptable to comparable overseas regulators (including the FDA and EMA). Additionally, the sponsor provided expert opinion that commencing esketamine simultaneously with a new oral antidepressant likely reflected optimal clinical practice. Finally, the Section 60 Delegate accepted that it may be unethical for patients with treatment-resistant depression to be left without any antidepressant treatment (which would be the case in placebo-controlled esketamine monotherapy studies) or on a treatment that has not been sufficiently effective (which would be the case in studies of esketamine together with an existing oral antidepressant).

For the reasons outlined above, the Section 60 Delegate has decided to revoke the initial decision and make a new decision in substitution for that decision. Their substituted decision is to register the product on the basis that the quality, safety and efficacy of the product for the purposes for which it is to be used have been satisfactorily established.

Final outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Spravato (esketamine hydrochloride) 28 mg of esketamine per 2 actuations, nasal spray solution, indicated for:

Spravato is indicated for treatment resistant depression (Major Depressive Disorder in adults who have not responded adequately to at least two different antidepressants of adequate dose and duration to treat the current moderate to severe depressive episode).

Spravato is to be initiated in conjunction with a newly initiated oral antidepressant.

Specific conditions of registration applying to these goods

- Spravato (esketamine hydrochloride) is to be included in the Black Triangle Scheme. The PI and CMI for Spravato must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Spravato EU-RMP (version 1.0 Succession 2, date 20 May 2019; DLP 4 March 2018), with ASA (version 0.2; date 27 June 2019), included with submission PM-2018-04814-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of PSURs.

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter. The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Attachment 1. Product Information

The PI for Spravato approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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