Janssen-Cilag International NV

Non-interventional Study – Final Study Report

Survey to Assess the Effectiveness of SPRAVATO® Educational Materials for Additional Risk Minimization Measures in the European Union

Protocol PCSNSP002812

SPRAVATO® (esketamine)

EU PAS Register Number: EUPAS38144

SPONSOR'S RESPONSIBLE PARTY: Christian von Holt, MD

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PASS INFORMATION

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Name of Marketing Authorization Holder(s)	Janssen-Cilag International NV
Joint PASS	No
Research question and objectives	To determine the effectiveness of the medical educational materials aimed at HCPs related to the understanding and management of SPRAVATO important identified risks of drug abuse, transient dissociative states and perception disorders, disturbances in consciousness, and increased blood pressure in Europe
Countries of study	Austria, Belgium, Germany, France, Italy, the Netherlands, Spain, Sweden
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MARKETING AUTHORIZATION HOLDER

Name of Marketing Authorization Holder:	Janssen-Cilag International NV
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1. SYNOPSIS

Name of Sponsor/Company	Janssen-Cilag International NV
Name of Finished Product	SPRAVATO®
Name of Active Ingredient(s)	(esketamine)

Protocol No.: PCSNSP002812

Title of Study: Survey to Assess the Effectiveness of SPRAVATO Educational Materials for Additional Risk Minimization Measures in the European Union

Sponsor's Responsible Party: Christian von Holt, MD **(Main Author).**

Keywords: Education, Survey, PASS, esketamine, Major Depressive Disorder.

EU PAS Register Number: EUPAS38144.

Clinical Registry No.: Not Applicable.

Marketing Authorization Holder(s): Janssen-Cilag International NV.

Names and Affiliations of Principal Investigator(s): Not Applicable.

Study Center(s): Not Applicable.

Publication (Reference): None.

Study Period: Wave 1: 4 October 2023 to 31 October 2023

Wave 2: 12 July 2024 to 07 August 2024

Background and Rationale: Major Depressive Disorder is a common and serious psychiatric disorder affecting over 30 million individuals in the EU. Major Depressive Disorder is the leading cause of disability (measured as years lived with disability) worldwide and is associated with elevated mortality and suicide risk. SPRAVATO nasal spray, in combination with a SSRI or SNRI, is indicated for adults with treatment-resistant MDD, who have not responded to at least 2 different treatments with antidepressants in the current moderate to severe depressive episode, for the treatment of patients with TRD, and for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency.

Risk minimization measures related to understanding and management of the important identified risks of drug abuse, transient dissociative states and perception disorders, disturbances in consciousness, and increased blood pressure associated with SPRAVATO are essential to increase awareness of its safety profile and risks. Therefore, the MAH developed educational materials consisting of a Healthcare Professional Guide, Patient Guide (for patients), and Checklist for readiness to leave for use by all HCPs potentially involved in the prescribing, administration and management of SPRAVATO nasal spray.

Research Question and Objectives: The objective of this survey was to determine the effectiveness of the educational materials aimed at HCPs practicing in the EU, at increasing awareness about the important identified risks related to SPRAVATO treatment such as drug abuse, transient dissociative states and perception disorders, disturbances in consciousness, and increased blood pressure.

1. The effectiveness of the Healthcare Professional Guide (also referred to as “SPRAVATO materials for Healthcare Professionals”) was assessed via a survey. The survey responses from HCPs involved in prescribing, administration, or management of patients with SPRAVATO was evaluated to assess their knowledge and understanding for the management of SPRAVATO risks with regards to:

a. The appropriate patient selection for the approved indication (age and severity of MDD)

b. The important identified risks with SPRAVATO treatment

c. Monitoring before and after SPRAVATO administration

d. Healthcare facility requirements for patient monitoring

2. The effectiveness of the Patient Guide (also referred to as "SPRAVATO Patient Risk Minimization Guide") was assessed by surveying HCPs and evaluating their perception of patients' knowledge and understanding of the following:

   a. The 4 important identified risks of SPRAVATO: drug abuse, transient dissociative states and perception disorders, disturbances in consciousness, and increased blood pressure

   b. Monitoring considerations, when being treated with SPRAVATO

   c. Post-treatment restrictions

3. A Checklist for readiness to leave is also available to the HCPs as part of the educational materials (in addition to the Healthcare Professional Guide and Patient Guide). This checklist together with clinical judgment is used to evaluate when a patient is deemed stable and can safely be allowed to leave following SPRAVATO nasal spray administration.

Study Design: A survey of HCPs was conducted to measure the effectiveness of the educational materials (including the Patient Guide), to address the important identified risks associated with SPRAVATO treatment. Health care professionals involved in the prescribing, administration and management of SPRAVATO treatment were asked to participate in the survey to assess knowledge and understanding of the important identified risks.

The survey was administered in 2 waves in selected countries of the EU where SPRAVATO is commercially available and where there is an adequate projected number of HCPs (and thus potential number of respondents). Waves 1 and 2 were conducted within 4 years and within 5 years, respectively, of the availability of the approved educational materials in selected countries. This Final report reflects data collected for both Wave 1 and Wave 2.

The survey implementation was managed by an external third-party vendor (Adelphi Research), and all HCP respondents were independently recruited by a sub-contracted recruitment partner (M3 Global) which maintains panels of verified healthcare professionals. Questionnaires were distributed by M3 Global, following local Health Authority notification of this study where required per country legislation. Questionnaire distribution was done via a web-based platform.

Setting: The survey was conducted in selected EU countries in which SPRAVATO had been approved and was commercially available.

Study Population and Study Size: The survey population consisted of HCPs (prescribers, nurses, other) involved in the prescribing, administration and management of SPRAVATO treatment. Participation in the survey was entirely voluntary. No patients participated in the survey.

The goal for survey completion was to obtain a target of 270 completed surveys as a combined output from Wave 1 (n=130) and Wave 2 (n=140).

Variables and Data Sources: A questionnaire was designed, tested, and validated through pilot testing to evaluate the clarity and understanding of the questions. Careful consideration was required to design appropriate survey questions that allowed assessment of HCP awareness and understanding of the **Key Messages** included in the SPRAVATO educational materials. Patients' knowledge and understanding of the **Key Messages** included in the Patient Guide were assessed by surveying HCPs. These **Key Messages** feature in the SPRAVATO educational materials and were formulated to aid questionnaire development by directly addressing the objectives of the survey.

Statistical Methods: Participant answers to the online survey were collected using Confirmit Horizons software and the data exported via SPSS (.save) and analyzed using Q-research software. Responses from the survey were summarized using descriptive statistics ie, frequencies with proportions for all answer options. Categorical variables were summarized in terms of the number of participants in the analysis set, the number of participants providing data at the relevant time point, frequency counts, and percentages.

A sample size of 270 produces a 2-sided 95% confidence interval (CI) with a width equal to 0.100 (ie, a precision of 5%) when the sample proportion of correct response rate is 80%.

Participant Information:

The expected sample size was 270 participants. A total of 270 participants (ie, 217 psychiatrists and 43 nurses, and 10 other healthcare professionals) were enrolled in this web-based survey. A total of 130 and 140 respondents completed surveys from Wave 1 and Wave 2 period, respectively.

Demographics And Baseline Information:

The majority of respondents (80.4%) were psychiatrists, with most (49.3%) spending their time in a treatment setting described as in-patient secondary care (ie, university, teaching or general and specialized psychiatric hospitals). A significant portion (76.3%) were involved in prescribing SPRAVATO, with 73.0% monitoring patients during treatment. Regarding educational materials, 80.7% of healthcare professionals had read the "Risk minimization measures in patients treated with SPRAVATO spray" (Healthcare Professional Guide) material.

Outcomes of Interest:

Data from both waves have been combined for all questions, except for Question 5 as the question was re-phrased per the request from EMA PRAC, and following interim analysis on completion of Wave 1.

The HCP survey to measure the effectiveness of the educational materials for SPRAVATO showed that:

- A total of 270 complete surveys were suitable for analysis.
- A majority of the HCPs (80.4%) self-reported a primary medical role of psychiatrist.
- With regard to the HCP educational materials:
  - This HCP survey showed the level of familiarity and understanding of key messages from the SPRAVATO educational materials amongst the HCPs surveyed at this time.
- With regard to patient educational materials
  - HCPs considered the SPRAVATO Patient Guide to be effective in communicating to patients and caregivers the risks of dissociation, sedation, and blood pressure increase (75.9%).
  - HCPs also considered that, after reviewing the SPRAVATO Patient Guide, patients were aware of their monitoring needs before, during, and after SPRAVATO administration (≥96.7%), as well as the need to self-administer SPRAVATO under the direct supervision of a HCP.
- The average score for correct responses was 71.7%
  - A modification of Question 5 in Wave 2 related to the MDD-PE indication increased the percentage of correct answers from 23% in Wave 1 to 83% in Wave 2.

Overall Score for Both Wave 1 and Wave 2

- The average score for correct responses was 71.7%
- For questions relating to the HCP materials, the average score was 66.5%

- For questions relating to the patient materials, the average score was 87.2%
- For questions relating to both HCP materials and patient materials, 30% of participants achieved an overall score of 80% for correct responses

Other Analyses:

Five sub-group analyses were performed in this study.

1. Subgroup analysis for questions related to a) Healthcare Professional Guide and Checklist for readiness to leave, as well as for the subgroup of questions related to b) Patient Guide showed that the average score for questions relating to the patient materials was 87.2% and the average score for questions relating to the HCP materials was 66.5%.
2. Subgroup analysis by country separately compared 4 main countries, Germany, France, Italy, and Spain. Due to the small sample sizes (<30), the analyses for Austria, Belgium, the Netherlands, and Sweden were combined. The results are consistent across countries.
3. Additionally, subgroups analyses by specialty, treatment setting, and receipt of materials were also completed. The average score of correct responses per question was mostly consistent across all subgroups.

Adverse Events/Adverse Reactions:

No AEs were reported from the survey due to no patients participating in the study, no presence of any open text in the survey, and no questions directly soliciting AEs in the questionnaire.

DISCUSSION AND CONCLUSION:

The results of this study demonstrated the effectiveness of the educational materials aimed at HCPs practicing in Europe, to increase their awareness about the important identified risks related to SPRAVATO treatment, ie, drug abuse, transient dissociative states and perception disorders, disturbances in consciousness, and increased blood pressure. Although the mean percentage of correct responses (71.7%) to the question did not meet the per-protocol predefined threshold of >80%, it was apparent that most survey respondents correctly answered the **Key Messages** questions, indicating that all educational materials provided by Janssen on the minimization of risks with esketamine were effective. The results of the survey

a) indicated awareness among surveyed HCPs about requirements for management of patients whilst being treated with SPRAVATO and the recommended post-dose monitoring (including supervision); and

b) reflected that patient educational materials create awareness among patients of their monitoring needs before, during, and after SPRAVATO administration.

2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

AE	adverse event
AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
CADSS	clinician administered dissociative states scale
CI	confidence interval
CHMP	Committee for Medicinal Products for Human Use
COVID-19	coronavirus disease-2019
CV	confidence interval
EU	European Union
HCP	healthcare professional
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MADRS	Montgomery-Asberg Depression Rating Scale
MAH	marketing authorization holder
MDD	major depressive disorder
MDD-PE	major depressive disorder in a psychiatric emergency
PE	psychiatric emergency
PRAC	Pharmacovigilance Risk Assessment Committee
RMP	risk management plan
SmPC	summary of product characteristics
SNRI	serotonin and norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TEAE	treatment-emergent adverse event
TRD	treatment-resistant depression

Definition of Terms

Study	The term "study" indicates the collection of data for research purposes only. The use of this term in no way implies that any interventional treatments or procedures, planned or otherwise, have been provided or performed.
Related Research Activity (RRA)	A non-interventional clinical activity that may be conducted by any group in the company where patient level data may be systematically collected and/or analyzed for medically important results/outcomes.
Prospective study	A study in which the outcome of interest occurs after the research begins.
Post Authorization Safety Study (PASS)	Any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.

3. INVESTIGATORS AND SPONSOR'S RESPONSIBLE PARTY

Not applicable.

4. OTHER RESPONSIBLE PARTIES

Sponsor's Responsible:	
Medical Officer:	Christian von Holt, MD
Lead Medical Writer:	PPD
Contract Research Organization and level of involvement:	PPD

5. MILESTONES

The dates for key milestones in this study are outlined below.

Milestone:	Planned Date:	Actual Date:
Conduct of survey (Wave 1)[a]	No earlier than the date of Committee for Medicinal Products for Human Use (CHMP) opinion for this PASS	4 October 2023
End of survey (Wave 1)[a]	No later than 31 October 2023	31 October 2023
Wave 1 report submission	No later than 31 December 2023[b]	11 December 2023
Conduct of survey (Wave 2)[c]	No later than 31 July 2024	12 July 2024
End of survey (Wave 2)	No later than 30 September 2024	07 August 2024
Final report of study results[d]	Q4 2024	

a Survey was conducted within 4 years of the availability of the approved educational materials.
b Based on the first launch in European Union, 1 February 2020.
c Survey was conducted within 4 to 5 years of the availability of the approved educational materials.
d A report on the educational measures undertaken and the results of the survey will be submitted within 4 years and no later than 5 years after launch.

6. BACKGROUND AND RATIONALE

6.1. Treatment-resistant Depression

Major depressive disorder is a common and serious psychiatric disorder affecting over 30 million individuals in the EU (Wittchen 2011). MDD is the leading cause of disability (measured as years lived with disability) worldwide and is associated with elevated mortality and suicide risk (Global Burden of Disease Study 2017; Walker 2015; World Health Organization 2023). About 30% of patients with MDD fail to achieve remission from their depressive symptoms despite treatment with multiple medications (Fava 2003; Rush 2006); these patients are identified as suffering from TRD. A globally accepted definition for TRD does not yet exist. The EMA defines TRD as lack of clinically meaningful improvement despite the use of adequate doses of at least two antidepressant agents, derived from the group(s) of commonly used first-line treatment, prescribed for adequate duration with adequate affirmation of treatment adherence (EMA 2013). However, a variety of

definitions have been used in studies ranging from nonresponse to 1 antidepressant for ≤4 weeks to a failure to respond to multiple adequate (duration and dosage) trials of different classes of antidepressants and electroconvulsive therapy (Schosser 2012). This variation in definitions makes it difficult to compare rates of TRD presented in the medical literature which also means there are no agreed upon estimates of incidence or prevalence of the disorder.

Patients with TRD have a lower likelihood to respond to available oral antidepressants; these patients are more likely to have pronounced functional impairment, substantially lower quality of life, and incur higher medical and mental healthcare costs compared with patients who respond to treatment (Mathew 2012; Mrazek 2014).

6.2. Major Depressive Disorder in a Psychiatric Emergency

Patients with a PE due to MDD are an acutely ill population that requires immediate intervention (Wasserman 2012). Only limited information is available to guide clinical decisions, since this population has typically been excluded from antidepressant drug trials. Current standard practice includes initiation or optimization of oral antidepressants and, frequently, hospitalization (American Psychiatric Association 2003; Wasserman 2012). Standard antidepressants may take several weeks to exert their full effect (Machado-Vieira 2010) limiting their utility in crisis situations.

Antidepressants are the treatment of choice for the relief of depressive symptoms and suicidal ideation, which often accompanies depression, with SSRIs considered first-line therapy in primary care settings (Schwartz-Lifshitz 2012). Electroconvulsive therapy has also been used as treatment for acute suicidality among severely depressed patients (Schwartz-Lifshitz 2012).

6.3. SPRAVATO

SPRAVATO, the active ingredient of which is esketamine, the S-enantiomer of racemic ketamine, has been developed as a nasal spray formulation for the treatment of patients with TRD and MDD-PE. Esketamine is a non-selective, non-competitive, antagonist of the NMDA receptor, an ionotropic glutamate receptor.

Through NMDA receptor antagonism, esketamine produces a transient increase in glutamate release, leading to increases in AMPAR stimulation and subsequently to increases in neurotrophic signaling, which may contribute to the restoration of the synaptic function in brain regions involved with the regulation of mood and emotional behavior.

SPRAVATO nasal spray, in combination with a SSRI or SNRI, is indicated for adults with treatment-resistant MDD, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode. SPRAVATO, co-administered with oral antidepressant therapy, is also indicated in adults with a moderate to severe episode of MDD, as acute short-term treatment, for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a PE(SPRAVATO SmPC 2024).

The nasal spray device is a single-use device that delivers a total of 28 mg of esketamine, in 2 sprays (one spray per nostril). SPRAVATO nasal spray is administered by the patient under the direct supervision of a HCP (SPRAVATO SmPC 2024).

6.4. Important Identified Risks with SPRAVATO

6.4.1. Drug Abuse

As an antagonist of NMDA receptors, ketamine and SPRAVATO induce psychoactive effects. Ketamine is well known for its abuse potential in both humans and animals (Liu 2016). The exact mechanism underlying ketamine's abuse potential is unknown.

Evidence from a SPRAVATO abuse potential trial (Trial 54135419TRD1015) suggests that the potential for drug abuse is similar to that of ketamine, a known drug of abuse recreationally. No evidence of drug-seeking behavior was observed, and no confirmed cases of diversion were reported in pivotal clinical trials of SPRAVATO nasal spray.

6.4.2. Transient Dissociative States and Perception Disorders

The perceptual side effects attenuate with repeated administration and intensify with higher doses (within the subanesthetic dose range), while the antidepressant action is maintained or improves over repeated treatments and appears to reach maximum antidepressant effects at an intravenous ketamine dose of 0.5 mg/kg (Fava 2017), and an SPRAVATO 84 mg dose administered nasally (Fedgchin 2019 [TRD3001]; Chen 2022 [TRD3001, TRD3002, TRD3003]). Moreover, the perceptual/dissociative side effects do not correlate with improvement of depression symptoms (Fava 2017; Fedgchin 2019 [TRD3001] and Popova 2019 [TRD3002]; Chen 2022 [TRD3001, TRD3002, TRD3003]). Additionally, there was insufficient evidence from mediation analyses on data collected in Trial TRD3002 that the antidepressant effect of SPRAVATO nasal spray (assessed by change in the MADRS after initiation of the first nasal spray and after the last nasal spray) was mediated by the perceptual/dissociative effects (assessed by change in CADSS total scores 40 minutes post-dose).

Transient dissociative states and perception disorders are expected effects of SPRAVATO nasal spray based on SPRAVATO mechanism of action, and have been observed in all phases of the clinical development program (ie, Phase 1 trials and controlled, randomized and open-label Phase 2 and Phase 3 trials that included patients with TRD and MDD-PE).

6.4.3. Disturbances in Consciousness

At antidepressant doses, the side effects that follow administration of SPRAVATO nasal spray, including sedation, and these symptoms diminish rapidly with the decline in SPRAVATO plasma levels.

Disturbances in consciousness such as sedation and somnolence are expected effects of SPRAVATO nasal spray based on SPRAVATO mechanism of action and have been observed in all phases of the clinical development program (ie, Phase 1 trials and controlled, randomized and open-label Phase 2 and Phase 3 trials that included patients with TRD and MDD-PE).

6.4.4. Increased Blood Pressure

Cardiovascular effects of ketamine and SPRAVATO at subanesthetic doses include transient increases in blood pressure in some subjects

Cardiovascular effects due to increased blood pressure are expected for SPRAVATO nasal spray based on SPRAVATO mechanism of action (sympathomimetic effect; direct stimulation of the central nervous system that leads to increased sympathetic nervous system outflow). Transient increases in blood pressure, as well as cardiovascular and blood pressure-related events, in association with SPRAVATO nasal spray have been reported in the Applicant's completed randomized, double-blind, controlled and open-label clinical trials. In clinical trials, elevations of blood pressure were transient, generally self-limiting, and did not require intervention.

6.5. Overall Rationale for the Study

6.5.1. Risk Minimization Measures

Prescribers and patients are referred to the European SmPC for detailed information on the safety and known risks of SPRAVATO (SPRAVATO® SmPC 2024). Nevertheless, additional risk minimization measures related to understanding and management of the important identified risks of drug abuse, transient dissociative states and perception disorders, disturbances in consciousness, and increased blood pressure associated with SPRAVATO are essential to increase awareness of its safety profile and risks.

Therefore, the MAH developed educational materials consisting of a Healthcare Professional Guide, Patient Guide (for patients), and Checklist for readiness to leave for use by all HCPs potentially involved in the prescribing, administration and management of SPRAVATO treatment.

The educational materials are aimed at increasing awareness about the important identified risks of drug abuse, transient dissociative states and perception disorders, disturbances in consciousness, and increased blood pressure, and provide guidance on ways to minimize the risks, as described in Part V.1, 'Routine Risk Minimisation Measures', of the EU RMP. Prior to the launch of SPRAVATO in each Member State, the MAH must agree with the Member State the overall content and format of the educational materials which provide guidance on how to manage the risks.

In order to evaluate the effectiveness of these educational materials, a survey of HCPs involved in the prescribing, administration, and management of SPRAVATO treatment was conducted to assess knowledge and understanding of:

(a) the appropriate patient selection for the approved indication (age and severity of MDD)

(b) the important identified risks with SPRAVATO treatment

(c) monitoring before and after SPRAVATO administration

(d) healthcare facility requirements for patient monitoring

6.5.2. Educational Materials

The MAH ensured that all HCPs expected to prescribe, dispense, and manage patients using SPRAVATO nasal spray, as well as all patients who receive this product, are given the necessary educational materials listed below, in all participating EU countries where SPRAVATO is commercially available:

- Healthcare Professional Guide (for prescribers, nurses, other)
- Patient Guide (for patients)
- Checklist for readiness to leave

1. The specific objectives of the Healthcare Professional Guide are to increase awareness of appropriate product administration (ie, under the direct supervision of a healthcare professional), to increase awareness of the need for monitoring of blood pressure before and after dosing under the supervision of a healthcare professional, and to educate HCPs about the following:
    a. Whether or not a patient is eligible to take SPRAVATO nasal spray;
    b. The risk for drug abuse, including risk factors/groups, signs of abuse and dependence, and the need to assess and monitor for this risk;
    c. Expected transient dissociative states/perception disorders and disturbances in consciousness and how to minimize potential adverse outcome from such effects;
    d. Blood pressure values may trigger additional measures;
    e. Expected cardiovascular adverse effects;
    f. The need for patient observation under the supervision of a healthcare professional during and after dosing until the patient is stable based on clinical judgement and following the criteria on “Checklist for readiness to leave” after treatment;
    g. The need for post-dose monitoring by HCPs with training in blood pressure monitoring;
    h. Only to initiate treatment with SPRAVATO nasal spray in patients with clinically significant or unstable cardiovascular or respiratory conditions if the benefit outweighs the risk. In these patients, SPRAVATO nasal spray should be administered in a setting where appropriate resuscitation equipment and HCPs with training in cardiopulmonary resuscitation are available;
    i. The influence of SPRAVATO nasal spray on the patient’s ability to drive or operate machinery and related instructions;
    j. Minimum equipment for monitoring blood pressure to be available at the site.
2. The proposed Patient Guide addresses the following important identified risks: drug abuse, transient dissociative states and perception disorders, disturbances in consciousness, and increased blood pressure for patients. The objective of the Patient Guide is to:
    a. Provide education about what adverse effects to expect and how to minimize those effects;
    b. Provide education about the risk for drug abuse and dependence, including risk factors/groups, signs of drug abuse and dependence, and the need to assess and monitor for this risk;

c. Describe the drug administration procedure, including preparation (fasting for 2 hours, no drinking for 30 minutes) and monitoring during the visit;

d. Increase awareness of:

1) Proper product administration (ie, under the direct supervision of a healthcare professional);

2) The need for monitoring of blood pressure before and after dosing under the supervision of a healthcare professional, and the need for post-dose observation until the healthcare professional decides that the patient is stable and can safely be allowed to leave following SPRAVATO nasal spray administration, based on the use of a checklist and clinical judgement;

3) The influence of SPRAVATO nasal spray on the patient's ability to drive or operate machinery and related instructions.

3. The proposed Checklist for readiness to leave addresses the following important identified risks: drug abuse, transient dissociative states and perception disorders, disturbances in consciousness, and increased blood pressure. The objective of this checklist is to aid HCPs in evaluating when a patient is deemed stable and can safely be allowed to leave following SPRAVATO nasal spray administration.

7. RESEARCH QUESTION AND OBJECTIVES

The objective of this survey was to determine the effectiveness of the educational materials aimed at HCPs practicing in the EU, at increasing awareness about the important identified risks (related to SPRAVATO treatment) of drug abuse, transient dissociative states and perception disorders, disturbances in consciousness, and increased blood pressure.

1. The responses from HCPs involved in prescribing, administration, or management of patients with SPRAVATO was evaluated to assess their knowledge and understanding for the management of SPRAVATO risks with regards to:

e. The appropriate patient selection for the approved indication (age and severity of MDD)

f. The important identified risks with SPRAVATO treatment

g. Monitoring before and after SPRAVATO administration

h. Healthcare facility requirements for patient monitoring

2. The effectiveness of the Patient Guide was assessed by surveying HCPs and evaluating their perception of patients' knowledge and understanding of the following:

a. The 4 important identified risks of SPRAVATO: dissociation, sedation, increased blood pressure, and drug abuse

b. Monitoring considerations, when being treated with SPRAVATO

c. Post-treatment restrictions

8. AMENDMENTS AND UPDATES

Number	Date	Overall reason
Amendment 1	17 March 2021	To extend the timelines of Wave 1 and its corresponding milestone dates, to allow the use of SPRAVATO to reach the levels reasonably needed to conduct the Wave 1 survey, reflecting the delay in the uptake of SPRAVATO usage, principally due to the COVID-19 pandemic.
Amendment 2	10 May 2021	To revise the adverse event reporting procedure to better reflect the manner of interactions with respondents during the conduct of the survey.
Amendment 3	18 March 2022	To extend the timelines of the final study report and both Waves 1 and 2, and their corresponding milestone dates, to ensure sufficient number of HCPs with experience of prescribing or managing SPRAVATO patients to ensure conduct of the survey in accordance with the originally agreed timelines.

Changes in the conduct of the study are further described in Section 9.1.5.

9. RESEARCH METHODS

9.1. Study Design

A survey of HCPs was conducted to measure the effectiveness of the educational materials (including the Patient Guide), to address the important identified risks associated with SPRAVATO treatment.

Health care professionals (practicing in the EU) involved in the prescribing, administration and management of SPRAVATO treatment were asked to participate in the survey to assess knowledge and understanding of the important identified risks.

The survey was administered in 2 waves in selected countries of the EU where SPRAVATO is commercially available and where there is an adequate projected number of HCPs (and thus potential number of respondents). Waves 1 and 2 were conducted within 4 years and within 5 years, respectively, of the availability of the approved educational materials in selected countries. This Final report reflects data collected for both Wave 1 and Wave 2.

9.1.1. Suitable Methodology

An external third-party vendor experienced in conducting multi-country effectiveness surveys was contracted by the sponsor to conduct the survey.

The most effective design for this survey involved an online quantitative approach to provide representative numbers of HCPs who prescribe, administer or monitor patients treated with SPRAVATO. A quantitative online survey is considered the most suitable methodology over a qualitative method, as the latter would not allow for robust sample sizes and therefore results would only be of an indicative/directional nature. Furthermore, an online methodology has a number of

associated advantages, including a wide geographical spread, a number of SPRAVATO sites of care, and flexibility for survey respondents to complete the survey at a convenient time without feeling pressure of being questioned or judged by an interviewer. Prior to commencing the Wave 1 survey phase described below, a pilot testing of the questionnaire was performed to validate the questionnaire. The feedback received from the pilot testing was incorporated into the final quantitative questionnaire design. This strategy helped to ensure that the final questionnaire provided data relevant to meeting the objectives of this effectiveness survey.

9.1.2. Target Respondent Group Identification

The survey included HCPs involved in prescribing, administration, and monitoring of SPRAVATO treatment, and who had received SPRAVATO educational materials (Healthcare Professional Guide, Patient Guide), Checklist for readiness to leave, ie, largely prescribing psychiatrists, but also nurses, and other healthcare personnel involved in administration and monitoring of SPRAVATO treatment.

All respondents were independently recruited through a third party, remained anonymous and were required to meet screening criteria before participating in the survey.

9.1.3. Questionnaire Design

The HCP Survey Questionnaire (Appendix 12) was developed to assess HCPs' knowledge and understanding of the important identified risks of SPRAVATO treatment. Patients' knowledge and understanding of the important identified risks of SPRAVATO treatment was assessed by surveying treating physicians and/or nurses. To assess the effectiveness of the Patient Guide, the survey included targeted questions to obtain HCPs' perception of patients' knowledge and understanding of the 4 important identified risks, the need for HCP monitoring during treatment, and post-treatment restrictions (ie, not driving or operating machinery until the next day).

The questionnaire was scripted for all target respondents and exceptionally for France routed in such a way that respondents did not answer Questions 4 and Question 5 as the MDD-PE indication is not actively marketed in France. The Questionnaire consisted of closed and/or multiple-choice questions. The survey was programmed so that the respondent could only progress forward through the questions and was not allowed to go back to return to previously given answers. The respondent was therefore unable to alter answers once responses had been given. Every question must have been answered for the respondent to progress forward through the survey. The survey was presented in the local language. Questions were translated from English to the local language and then translated back from the local language to English to ensure the translator correctly understood the questions.

The survey was comprised of 4 screening questions; followed by the in-depth questionnaire on educational materials, of which 12 were related to HCP materials and 4 were related to patient materials. Two questions, Question 4 and Question 5 related to MDD-PE indication, which is not actively marketed in France, were not asked in France, therefore there were only 14 questions in total in that country. For each question answered correctly, the HCP scored 1 point, giving a maximum score of 16 (14 in France) for each HCP. The number of scores was converted to a

percentage, indicating the percentage of correct responses across all questions for each HCP. For questions with multiple correct responses to be considered correct and scoring a point, the HCP had to select all correct responses, and no incorrect responses.

After completion of Wave 1, Question 5 (MDD-PE indication) of the Questionnaire was revised, following a request (dated 21 March 2024) from EMA PRAC in procedure EMEA/H/C/004535/MEA-003.1 to re-phrase the original question as it may have biased the HCPs answers.

The survey implementation was managed by an external third-party vendor (Adelphi Research), and all HCP respondents were independently recruited by a sub-contracted recruitment partner (M3 Global) which maintains panels of verified healthcare professionals. Questionnaires were distributed by M3 Global, following local Health Authority notification of this study where required per country legislation. Questionnaire distribution was done via a web-based platform. The survey was conducted in accordance with the EU GVP VIII guidelines.

9.1.4. Recruitment and Screening Criteria

The HCPs were contacted by the external third-party vendor and invited to participate in this survey. Relevant consents were sought prior to commencing the survey.

A screening questionnaire assessed whether a HCP (prescribers, nurses, other) met the participation criteria and could proceed to the main questionnaire.

The survey was stratified by the following criteria:

- Type of HCP (prescribers, nurses, other)
- Country
- Site of care (inpatient, outpatient, community/office based)

Data from internal market research studies were utilized to help shape the degree of stratification, such as the percentage of prescribers per country.

9.1.5. Changes in Conduct

There were 3 amendments to the protocol (see Section 8).

Amendments to the protocol were adopted before the start of data collection.

9.2. Setting

The survey was conducted in the EU countries in which SPRAVATO had been approved and was commercially available.

The survey was conducted during the period of 4 October 2023 to 31 October 2023 (Wave 1) and 12 July 2024 to 07 August 2024 (Wave 2). Waves 1 and 2 were conducted within 4 years and within 5 years, respectively, of the availability of the approved educational materials in selected countries.

9.3. Study Population

The survey population consisted of HCPs involved in the prescribing, administration and management of SPRAVATO treatment. Participation in the survey was entirely voluntary. No patients participated in the survey.

9.4. Variables

A questionnaire was designed, tested and validated through pilot testing to evaluate the clarity and understanding of the questions. Careful consideration was required to design appropriate survey questions that allowed assessment of HCP awareness and understanding of the **Key Messages** included in the SPRAVATO educational materials. Patients' knowledge and understanding of the **Key Messages** included in the Patient Guide were assessed by surveying HCPs.

SPRAVATO **Key Messages** to be assessed are provided in Table 1. These **Key Messages** feature in the SPRAVATO educational materials and were formulated to aid questionnaire development by directly addressing the objectives of the survey as outlined in Section 7.

Table 1: List of SPRAVATO Key Messages To Be Tested Through The Questionnaire

Number	SPRAVATO® Key Message To Be Assessed	Educational Material Tested
1.	SPRAVATO, in combination with a selective serotonin reuptake inhibitor (SSRI) or serotonin and norepinephrine reuptake inhibitors (SNRI), is indicated for adults with treatment-resistant major depressive disorder (MDD), who have not responded to at least 2 different treatments with antidepressants in the current moderate to severe depressive episode.	HCP Guide
2.	SPRAVATO, co-administered with oral antidepressant therapy, is indicated in adults with a moderate to severe episode of Major Depressive Disorder, as acute short-term treatment, for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a PE(only in countries where at the time the survey is conducted the MDD-PE indication is included within the SPRAVATO educational materials).	HCP Guide (only in countries where at the time the survey is conducted the MDD-PE indication is included within the SPRAVATO® educational materials)
3.	SPRAVATO may induce transient sedation, dissociative and perception disorders and/or blood pressure increase, and it has potential for abuse.	HCP Guide, Patient Guide
4.	SPRAVATO is intended to be self-administered by the patient under the direct supervision of a healthcare professional. Patient's blood pressure should be assessed prior to dosing with SPRAVATO, at 40 minutes post-dose and subsequently as often as clinically warranted. Because of the possibility of sedation, dissociation and elevated blood pressure, patients must be monitored by a healthcare professional until the patient is considered clinically stable and ready to leave the healthcare setting. Patients should be instructed not to drive a vehicle or operate heavy machinery, until the next day following a restful sleep.	HCP Guide, Patient Guide, Readiness to Leave Checklist
5.	Both administration and post-administration observation of SPRAVATO should be carried out in an appropriate clinical setting, where blood pressure monitoring equipment is available. In patients with clinically significant or unstable cardiovascular or respiratory conditions, SPRAVATO should be administered in a setting where appropriate resuscitation equipment and healthcare professionals with training in cardiopulmonary resuscitation are available.	HCP Guide

9.4.1. Evaluation of Safety

No adverse events were to be collected or reported within this study. No patients participated in the study and no open text responses were available to respondents for reporting other information.

If any adverse event(s) related to any Janssen product is/are reported (to the third-party vendor overseeing and administering the survey) by the HCP participating in this survey, the third-party vendor was obliged to report the event(s) directly to the sponsor in accordance with the agreed reporting timelines.

9.5. Data Sources and Measurement

The data source for this survey is the online questionnaire used to survey HCPs involved in prescribing, administration or management of SPRAVATO treatment.

9.6. Bias

The potential for selection bias of participating respondents in a survey is an inherent bias/limitation to any study based on voluntary participation. In order to quantify any selection bias of participating HCP, the distribution of each stratification criterion of respondents (as described in Section 9.1.4) was described for participants. Data input was not completed for "missing value".

9.7. Study Size

The sample size calculation was based on the survey objective, to determine the effectiveness of the educational materials related to the management of the important identified risks of SPRAVATO through evaluation of responses from HCPs involved in prescribing, administration or management of patients with SPRAVATO. The proposed sample was designed to be a representative sample of SPRAVATO prescribers in the EU.

The target number of total completed surveys was determined based on both practical and statistical considerations, the potentially limited population of HCPs, and/or the width of the exact binomial 2-sided 95% CIs was provided.

Table 2 shows the precision of the estimated level of correct response rate for the Key Messages identified using an exact binomial 2-sided 95% CIs for a sample size (based on an estimated precision of 5%). Exact binomial 2-sided CIs (Clopper 1934) were used to indicate that for an estimated comprehension level (ie, correct response rate), the true population level of comprehension was at least as high as the lower limit of the 95% CI and may be as high as the upper limit of the 95% CI.

Table 2: Sample Size Needed[a] To Achieve A Precision Of 5% For Various Assumed Correct Response Rates (2-sided 95% Confidence Interval)

Estimated Correct Response Rate	Exact 95% Confidence Interval	Sample Size
50%	45.0%, 55.0%	400
60%	54.9%, 64.9%	390
70%	64.9%, 74.8%	340
80%	74.7%, 84.7%	**270**

[a] Obtained using PASS 15 (2017)

Thus, the goal for the survey was to obtain a target of 270 completed surveys (in both Wave 1 and Wave 2 combined).

A sample size of 270 produces a 2-sided 95% CI with a width equal to 0.100 (ie, a precision of 5%) when the sample proportion of correct response rate is 80% (Table 2).

Countries with market penetration (HCPs who have used SPRAVATO at least once) of approximately 30% or more were considered for inclusion in the survey study. Market penetration figures were based on internal market research data provided by the sponsor. The proportion of HCPs that had used SPRAVATO at least once (by country) at the time of the conduct of the survey are presented (Table 3).

Table 3: Information for SPRAVATO in the Planned Countries/Regions

Market	Number of completed surveys	SPRAVATO launch date	Proportion used SPRAVATO once or more*	Date for approval of educational materials
Austria	10	February 2020	N/A†	December 2019
Belgium	16	June 2021	70 %	July 2020
France	39	March 2020	61%	February 2020
Germany	64	March 2021	69%	December 2020
Italy	58	October 2020	75%	March 2020
Netherlands	6	September 2021	61%	November 2020
Spain	65	November 2022	85%	February 2021
Sweden	12	August 2020	N/A†	June 2020

* Predicted market penetration figures are based on internal market research data provided by the sponsor
† Data not available for alpine and Nordic regions

9.8. Data Management

An external third-party vendor performed rigorous 'real time' checks to ensure that the data collected were valid and of a high quality. These checks involved:

- Reviewing the length of time respondents took to complete sections of the survey, as well as total survey length
- Looking at patterned responses to questions

9.9. Statistical Methods

Statistical analyses were performed by or under the authority of the sponsor.

9.9.1. Main Summary Measures

Participant answers to the online survey were collected using Confirmit Horizons software and the data exported via SPSS (.save) and analyzed using Q-research software. Responses from the survey were summarized using descriptive statistics ie, frequencies with proportions for all answer options.

Data were summarized for country, site of care, and type of HCP separately, by question. Categorical variables were summarized in terms of the number of participants in the analysis set,

the number of participants providing data at the relevant time point, frequency counts, and percentages. Subgroup analyses (Section 10.5) are presented separately for

- Questions related to a) Healthcare Professional Guide and Checklist for readiness to leave, as well as for the subgroup of questions related to b) Patient Guide.
- Correct responses by country

The survey consisted of 4 screening questions; followed by an in-depth questionnaire on educational materials, of which 12 were related to HCP materials and 4 were related to patient materials. For more detail, refer to Section 9.1.3 and Section 9.4.

9.9.2. Main Statistical Methods

To consider the educational materials related to SPRAVATO as effective, a minimum total score of ≥80% of correct responses on all survey questions was considered indicative of satisfactory effectiveness. This threshold represents the 'vast majority' of respondents and is consistent with the threshold in previous surveys of risk minimization measures conducted by the MAH in the EU

Upon completion of the survey (Wave 1 and Wave 2) by the required number of respondents, data collected during the course of the survey was aggregated and tabulated. All questions were analyzed individually.

Summary results for the overall response rate were presented. In addition, subgroup analyses were presented separately for questions related to a) Healthcare Professional Guide and Checklist for readiness to leave, as well as for the subgroup of questions related to b) Patient Guide.

These outputs show data based on absolute numbers of respondents and percentages of the total sample. For each question, the total number of individuals answering is presented. All correct results include a 95% CI.

9.9.3. Missing Values

The survey was administered in a way that did not allow incomplete questionnaires, ie, HCPs had to answer all questions on the electronic form. As a result, no missing values were found in this study.

9.9.4. Sensitivity Analyses

Not applicable.

9.9.5. Amendments to the Statistical Analysis Plan

There have not been any amendments to the statistical analysis plan (Appendix 9 - Statistical Analysis Plan).

9.10. Quality Control

A unique online survey link was generated when each participant was invited to take part in the survey. This link could only be accessed and completed once by the respondent, preventing multiple survey completions from one respondent.

To accurately assess participants' knowledge, care was taken in drafting survey questions to avoid raising any implication that affirmative guesses would probably be 'correct', which is sometimes observed when a series of yes/no agreement questions are posed to survey respondents. The most practical and least intrusive method for achieving this was to provide multiple-choice questions where the respondent may choose one or more answers from a list. In addition, participants were offered the opportunity to select 'I don't know' as a response.

As an additional quality control measure, where multiple answers are offered, the order of presentation will be rotated. Routing and logic checks within the questionnaires ensured that answers were logical and correct, thereby enhancing data accuracy.

10. RESULTS

10.1. Participant Information

A total of 7,918 HCPs were contacted to participate in the Wave 1 and Wave 2 period of the study. There were 1,051 (13.3%) respondents to this invitation to participate. The most common reason for respondents failing eligibility was "not working in an appropriate setting" (67.6%). A total of 13.3% of participants failed to complete the survey. A total of 270 participants (ie, 217 psychiatrists and 43 nurses, and 10 other healthcare professionals) were enrolled in this web-based survey. The survey respondents were identified through the M3 global database. A total of 130 and 140 completed surveys from Wave 1 and Wave 2 period, respectively, were suitable for analysis. For more detail, refer to Table 4.

Table 4: Survey Participation Information

	Total
N	1,051 13.3(%)
Refused consent	22 (2.1%)
Failed eligibility check	490 (46.6%)
Not working in appropriate setting (S2)	331 (67.6%)
Not involved in prescribing, supervising, or monitoring patients on Spravato (S3)	126 (25.7%)
Have not read educational materials (S4)	33 (6.7%)
Exceeded country quota[1]	129 (12.3%)
Incomplete survey	140 (13.3%)
Completed survey	270 (25.7%)

[1] These HCPs were unable to enter the survey as the required number of completed surveys had already been completed in their country for Wave 1 or Wave 2.

10.2. Demographics and Baseline Information

The majority of respondents (80.4%) were psychiatrists, with most (49.3%) spending their time in a treatment setting described as in-patient secondary care (ie, university, teaching or general and specialized psychiatric hospitals). A significant portion (76.3%) were involved in prescribing SPRAVATO, with 73.0% monitoring patients during treatment. Regarding educational materials, 80.7% of healthcare professionals had read the "Risk minimization measures in patients treated with SPRAVATO spray" (Healthcare Professional Guide) material. For more detail, refer to Table 5.

Table 5: Health Care Professionals Profile

	Total
N	270 (%)
S1. Primary medical role	
Psychiatrist	217 (80.4%)
Psychiatric/ mental health nurse	43 (15.9%)
Other healthcare professional	10 (3.7%)
S2. Primary treatment setting	
In-patient secondary care (eg, University/Teaching, General and Specialized Psychiatric Hospitals)	138 (51.1%)
Outpatients attached to a hospital/ Day clinic	100 (37.0%)
Office based practice in the community (single or joint practices)	32 (11.9%)
S3. Involvement with Spravato	
Prescribing SPRAVATO® (esketamine)	206 (76.3%)
Supervising patients when self-administering SPRAVATO® (esketamine)	169 (62.6%)
Monitoring patients during SPRAVATO® (esketamine) treatment sessions	197 (73.0%)
S4. Educational materials read[1]	
SPRAVATO® materials for Healthcare Professionals: “Risk minimization measures in patients treated with Spravato (esketamine) nasal spray”	218 (80.7%)
SPRAVATO® materials for Healthcare Professionals: “Checklist for healthcare professionals”	174 (64.4%)
SPRAVATO® Patient Risk Minimisation Guide: “Spravato (esketamine) nasal spray: what are the risks? A guide for patients.”	167 (61.9%)

[1] Titles shown aligned with country specific materials, with a thumbnail view of the cover page shown to aid identification

10.3. Treatment Information

Not applicable.

10.4. Outcomes of Interest

Data from both waves (Wave 1 sample n=130, Wave 2 sample n=140) have been combined for all questions, except for Question 5, as the question was re-phrased for clarity following interim analysis on completion of Wave 1. All apparent differences seen in the survey for Question 5 are noted under the Question 5 analysis. There are no major differences seen between Wave 1 and Wave 2 in the percentage of HCPs giving the correct response for other questions.

10.4.1. Assessing the Effectiveness of the SPRAVATO HCP Guide

All questions concerning the HCP guide (Questions 1 to 12) had multiple answer options "multiple choice". For most questions there is one correct answer and respondents could only choose one option (ie, combination of answers were not considered). However, for Question 1 and Question 4 respondents were requested to select "all that apply". Partial responses for both these questions were discussed in the report for completeness.

QUESTION 1

For Question 1 (Table 6, TRD indication), respondents were requested to select "all that apply" with 37.4% of HCPs correctly identified that SPRAVATO is indicated for treatment in both adults and elderly. However 2 responses could be considered correct (adults and adults and elderly) from the possible 4 response options. Only 12 (4.4%) HCPs incorrectly selected adolescents, that could be considered that 95.6% gave an answer in Question 1 that would not put patients at risk as they selected adults, elderly, or both of these options. Nearly all respondents (98.1%) correctly selected adults, with a high degree of certainty (95% CI: 96.48-99.72%). By excluding treatment of the elderly, this represents a more clinically conservative response. A significant portion (41.9%) correctly selected the elderly. For more detail, refer to Table 6.

Table 6: Question 1: Based On Your Understanding of The Prescribing Information For TR-MDD, In Which of The Following Age Groups Can SPRAVATO Be Used?

	Total	95% CI	
N	270 (%)	Lower limit	Upper limit
Adolescents (12– 17 years)	12 (4.4%)		
Adults (18 – 64 years)	265 (98.1%)	96.48%	99.72%
Elderly (65 years and over)	113 (41.9%)	36.02%	47.78%
I don't know	0 (0%)		
Selecting Adults and Elderly, but not Adolescents[1]	101 (37.4%)	31.63%	43.17%

[1]The row shaded in grey indicates the correct answers to the question

QUESTION 2

For Question 2 (Table 7, TRD indication), 55.6% of HCPs correctly selected that SPRAVATO is indicated in the current "moderate to severe depressive episode". A substantial proportion (43.0%) of surveyed HCPs selected that SPRAVATO is indicated in "severe depressive disorder" which represents a more clinically conservative response. For more detail, refer to Table 7.

Table 7: Question 2: SPRAVATO, in Combination With A SSRI Or SNRI, Is Indicated For Adults With TR-MDD In The Current:

	Total	95% CI	
N	270 (%)	Lower limit	Upper limit
Moderate depressive episode	4 (1.5%)		
Severe depressive episode	116 (43.0%)		
Moderate to severe depressive episode[1]	150 (55.6%)	49.68%	61.52%
I don't know	0 (0%)		

[1]The row shaded in grey indicates the correct answer to the question

QUESTION 3

For Question 3 (Table 8, TRD indication), 91.5% of HCPs correctly identified that use of SPRAVATO is indicated in those who have not responded to "at least 2 different treatments with antidepressants". For more detail, refer to Table 8.

Table 8: Question 3: Please Complete The Following Sentence: SPRAVATO, In Combination With An SSRI Or SNRI, Is Indicated For Adults With TR-MDD In The Current Moderate To Severe Episode Who Have Not Responded To

	Total	95% CI	
N	270 (%)	Lower limit	Upper limit
at least 1 treatment with an antidepressant	20 (7.4%)		
at least 2 different treatments with antidepressants[1]	247 (91.5%)	88.18%	94.82%
I don't know	3 (1.1%)		

[1]The row shaded in grey indicates the correct answer to the question

QUESTION 4

For Question 4 (Table 9, MDD-PE indication) respondents were requested to select "all that apply". There was 1 correct response regarding the age group for the MDD-PE indication (adults). Nearly all respondents (98.7%) correctly selected adults, with a high degree of certainty (95% CI: 97.24%–100.00%). There were 94 HCPs (40.7% based on a sample of 231, excluding France) who selected the incorrect response of "elderly". For more detail, refer to Table 9.

Table 9: Question 4: Based On Your Understanding Of The Prescribing Information For A PE Due To MDD, In Which Of The Following Age Groups Can SPRAVATO Be Used?

	Total	95% CI	
N	231[2] (%)	Lower limit	Upper limit
Adolescents (12– 17 years)	9 (3.9%)		
Adults (18 – 64 years)	228 (98.7%)	97.24%	100.00%
Elderly (65 years and over)	94 (40.7%)		
I don't know	0 (0%)		
Selecting Adults only[1] (not Adolescents or Elderly)	135 (50.0%)	43.56%	56.44%

[1] The row shaded in grey indicates the correct answer to the question
[2] Question not asked in France

QUESTION 5

For Question 5 (Table 10, Table 11, MDD-PE indication), Wave 1 and Wave 2 results are reported separately, as the wording of this question was updated following the EMA feedback on the interim CSR (Sequ0055/Mod5.3.5.4/CSR 2023). The update was triggered by a high percentage of incorrect responses. The tables for this question are provided separately for each wave. In Wave 1, only 22.7% of HCPs correctly selected "depressive symptoms". The most selected answer (76.4%) was that SPRAVATO was indicated for the treatment of suicidal ideation or behavior including prevention of suicide. This response may be due to the phrasing of the question which may have biased the HCPs answers (as indicated by the EMEA PRAC in EMEA/H/C/004535/MEA003).

Alternative reasons for this observed response rate could be due to respondents being most familiar with the TRD indication authorized in 2019 and less familiar with the MDD-PE indication authorized in 2021. Further, the MDD-PE indication is not reimbursed in most EU countries resulting in limited clinical experience; additionally, as acute suicidality constitutes the majority of the patients with psychiatric emergency, "suicidal ideation or behavior" may have been selected by most of the respondents. The lower sample size is due to this question not being asked in France. For more information, refer to Table 10.

Table 10: Question 5 Wave 1: SPRAVATO, Co-Administered With Oral Anti-Depressant Therapy, Is Indicated In A PE Due To Major Depressive Disorder Specifically For The Treatment of:

	Total	95% CI	
N	110[2] (%)	Lower limit	Upper limit
Depressive symptoms[1]	25 (22.7%)	14.88%	30.52%
Suicidal ideation or behavior including prevention of suicide	84 (76.4%)		
I don't know	1 (0.9%)		

[1] The row shaded in grey indicates the correct answer to the question
[2] Question not asked in France

In Wave 2, the update of the question led to a notable increase of the correct answer. A total of 82.6% of the HCPs selected the correct indication, with only 15.7% selecting "prophylaxis of suicide". For more detail, refer to Table 11.

Table 11: Question 5 Wave 2: SPRAVATO, Co-Administered With Oral Anti-Depressant Therapy, Is Also Indicated In Adults With A Moderate-Severe Episode Of Major Depressive Disorder Specifically As Acute Short-Term Treatment In Which Of The Following Circumstances?

	Total	95% CI	
N	121[2] (%)	Lower limit	Upper limit
For the rapid reduction of depressive symptoms which according to clinical judgement constitute a psychiatric emergency[1]	100 (82.6%)	75.85%	89.35%
Prophylaxis of suicide	19 (15.7%)		
I don't know	2 (1.7%)		

[1] The row shaded in grey indicates the correct answer to the question
[2] Question not asked in France

QUESTION 6

For Question 6 (Table 12, Identification of risks), 65.2% correctly identified "fever" as not being a risk associated with SPRAVATO. A small proportion (18.5%) of the HPCs incorrectly selected "abuse" and "misuse".

Only 2.2% participants selected "increases in blood pressure" option incorrectly. For more detail, refer to Table 12.

Table 12: Question 6: Which One Of The Following Is Not A Risk Associated With SPRAVATO Treatment?

	Total	95% CI	
N	270 (%)	Lower limit	Upper limit
Dissociation	12 (4.4%)		
Sedation	26 (9.6%)		
Increases in blood pressure	6 (2.2%)		
Abuse and misuse	50 (18.5%)		
Fever[1]	176 (65.2%)	59.52%	70.88%

[1] The row shaded in grey indicates the correct answer to the question

QUESTION 7

For Question 7 (Table 13, Blood pressure assessment), 95.9% of HCPs correctly selected "prior to administration and at around 40 minutes post dose and subsequently as often as clinically warranted", further reinforcing the high level of understanding of the risks associated with blood pressure. For more detail, refer to Table 13.

Table 13: Question 7: When, if At All, Should Patients Being Treated With SPRAVATO Have Their Blood Pressure Assessed?

	Total	95% CI	
N	270 (%)	Lower limit	Upper limit
Blood pressure assessment not required	1 (0.4%)		
Prior to administration	6 (2.2%)		
Prior to administration and at around 40 minutes post dose and subsequently as often as clinically warranted[1]	259 (95.9%)	93.54%	98.26%
I don't know	4 (1.5%)		

[1] The row shaded in grey indicates the correct answer to the question

QUESTION 8

For Question 8 (Table 14, Post dose monitoring), 48.5% of HCPs correctly selected "until the patient is considered clinically stable" with the majority of other HCPs (48.9%) incorrectly selecting "minimum of 1 hour".

As per the SPRAVATO SmPC, symptoms of sedation and dissociation typically resolve by 1.5 hours post-dose and the severity tends to reduce over time with repeated treatments. It is likely that HCPs familiar with esketamine use may have selected the "minimum of 1 hour" response as this may more closely reflect their clinical experience with SPRAVATO. For more detail, refer to Table 14.

Table 14: Question 8: Because of The Possibility Of Sedation, Dissociation And Elevated Blood Pressure, How Long, If At All, After Administration Of SPRAVATO Must Patients Be Monitored By A Healthcare Professional?

	Total	95% CI	
N	270 (%)	Lower limit	Upper limit
No monitoring is required	3 (1.1%)		
Minimum of 5 minutes	1 (0.4%)		
Minimum of 1 hour	132 (48.9%)		
Until the patient is considered clinically stable1	131 (48.5%)	42.54%	54.46%
I don't know	3 (1.1%)		

[1] The row shaded in grey indicates the correct answer to the question

QUESTION 9

For Question 9 (Table 15, Self-administration), 86.7% correctly identified that patients cannot self-administer SPRAVATO without direct supervision of an HCP. For more detail, refer to Table 15.

Table 15: Question 9: A Patient Can Self-Administer SPRAVATO Without Direct Supervision Of A Healthcare Professional

	Total	95% CI	
N	270 (%)	Lower limit	Upper limit
True	25 (9.3%)		
False[1]	234 (86.7%)	82.65%	90.75%
I don't know	11 (4.1%)		

[1] The row shaded in grey indicates the correct answer to the question

QUESTION 10

For Question 10 (Table 16, Driving machinery), the majority of HCPs (60.0%) correctly selected "the next day following a restful sleep" with 35.6% selecting "2-4 hours following treatment". The selection of this response may be based on clinical observation that most TEAEs (eg, blood pressure; dissociation; sedation) occurred and resolved on the same day and typically within 1.5 to 2 hours. For more detail, refer to Table 16.

Table 16: Question 10: When Is It Safe For A Patient To Drive A Vehicle Or Operate Heavy Machinery Following Treatment With SPRAVATO?

	Total	95% CI	
N	270 (%)	Lower limit	Upper limit
Immediately after treatment	2 (0.7%)		
2-4 hours following treatment	96 (35.6%)		
The next day following a restful sleep[1]	162 (60.0%)	54.16%	65.84%
I don't know	10 (3.7%)		

[1] The row shaded in grey indicates the correct answer to the question

QUESTION 11

For Question 11 (Table 17, Appropriate clinical setting), 97.4% of HCPs correctly identified that administration and observation must be carried out in a clinical facility where blood pressure monitoring equipment is available. For more detail, refer to Table 17.

Table 17: Question 11: Both Administration And Post-Administration Observation Of Persons Treated With SPRAVATO Should Be Carried Out In An Appropriate Clinical Setting, Where Blood Pressure Monitoring Equipment Is Available

	Total	95% CI	
N	270 (%)	Lower limit	Upper limit
True[1]	263 (97.4%)	95.51%	99.29%
False	5 (1.9%)		
I don't know	2 (0.7%)		

[1]The row shaded in grey indicates the correct answer to the question

QUESTION 12

For Question 12 (Table 18, Patients requiring resuscitation equipment), 43.7% of HCPs correctly selected "patients with clinically significant or unstable CV or respiratory conditions". The most selected answer was that the requirement for resuscitation equipment and training in cardiopulmonary resuscitation applies to all patients. This represents a more clinically conservative response than currently required in the SPRAVATO prescribing information. For more detail, refer to Table 18.

Table 18: Question 12: For Which Patients Should Resuscitation Equipment And Healthcare Professionals With Training In Cardiopulmonary Resuscitation Be Available When Administering SPRAVATO?

	Total	95% CI	
N	270 (%)	Lower limit	Upper limit
Patients aged 65 years and older	8 (3.0%)		
Patients with clinically significant or unstable cardiovascular or respiratory conditions[1]	118 (43.7%)	37.79%	49.61%
All patients	128 (47.4%)		
Never	7 (2.6%)		
I don't know	9 (3.3%)		

[1]The row shaded in grey indicates the correct answer to the question

10.4.2. Assessing the Effectiveness of the SPRAVATO Patient Guide

All questions concerning the Patient Guide (Questions 13 and 14) had multiple answer options "multiple choice". For Question 13 respondents were requested to select "all that apply". Question 14 included 3 sub questions. For Question 14 there is one correct answer per sub question and respondents could only choose one option.

QUESTION 13

For Question 13 (Table 19, Effectiveness of patient guide), 75.9% of HCPs correctly identified "all of the above" as the risks the patient guide is effective at communicating about risks. For those not selecting the correct response, most selected were "dissociation", "sedation", and "BP increase", but only a small number selected "potential abuse" indicating the lower HCP awareness of this as a risk associated with SPRAVATO. No HCPs considered "none of the above" risks were effectively communicated to patients and caregivers; ie, all HCPs considered at least one of the above risks was effectively communicated to patients and caregivers. For more detail, refer to Table 19.

Table 19: Question 13: Which of These Risks Do You Consider The SPRAVATO Patient Guide To Be Effective In Communicating To Patients And Caregivers?

	Total	95% CI	
N	270 (%)	Lower limit	Upper limit
Dissociation	49 (18.1%)		
Sedation	49 (18.1%)		
Blood pressure increase	51 (18.9%)		
Potential abuse	7 (2.6%)		
All of the above[1]	205 (75.9%)	70.80%	81.00%
None of the above	0 (0%)		
I don't know	1 (0.4%)		

[1] The row shaded in grey indicates the correct answer to the question

QUESTION 14

There were 3 elements to this question (Table 20, Effectiveness of patient guide), asking HCPs to evaluate whether the patient materials are effective at communicating to patients:

a. 96.7% of HCPs agreed that after reviewing the materials, patients understood they need to be monitored before, during, and after SPRAVATO administration.

b. 90.3% of HCPs agreed that after reviewing the materials, patients understood they will self-administer SPRAVATO under the direct supervision of an HCP.

c. 87.0% of HCPs agreed that after reviewing the materials, patients understood they should not drive or operate heavy machinery until the next day following a restful sleep.

For more detail, refer to Table 20.

Table 20: Question 14: After Patients Have Reviewed The Information Presented In The SPRAVATO Patient Guide, Do You Agree Or Disagree With The Following Statements

	Total	95% CI	
N	270 (%)	Lower limit	Upper limit
a. Patients understand that they need to be monitored before, during and after SPRAVATO administration			
I agree[1]	260 (96.7%)	94.57%	98.83%
I disagree	7 (2.6%)		
I don't know	2 (7.0%)		
b. Patients understand that they will self-administer SPRAVATO nasal spray under the direct supervision of a healthcare professional			
I agree[1]	243 (90.3%)	86.77%	93.83%
I disagree	21 (7.8%)		
I don't know	5 (1.9%)		
c. Patients understand that they should not drive or operate heavy machinery until the next day following a restful sleep.			
I agree[1]	234 (87.0%)	82.99%	91.01%
I disagree	18 (6.7%)		
I don't know	17 (6.3%)		

[1] The rows shaded in grey indicate the correct answers to the question

10.4.3. Overall Summary

Overall, 270 respondents (including 217 psychiatrists and 43 nurses, and 10 other healthcare professionals) completed the survey (Wave 1 and Wave 2, refer to Table 5):

- A total of 80.7% surveyed HCPs had read Healthcare Professional Guide, 64.4% had read "Checklist for healthcare professionals", and 61.9% had read the Patient Guide (Table 5).
- For the **Key Message** concerning treatment of TRD, more than 91.5% of surveyed HCPs responded correctly regarding the prior need for nonresponse to at least 2 different treatments with antidepressants (Table 8)
- For the **Key Message** concerning treatment in the second indication of MDD-PE 22.7% of surveyed HCPs in Wave 1 responded correctly that SPRAVATO is indicated for the treatment of depressive symptoms (Table 10). However, after the question was re-phrased to reduce bias following a recommendation from EMA PRAC, the number of correct responders in Wave 2 increased to 82.6% (Table 11).
- A total of 65.2% of surveyed HCPs correctly responded to the question concerning the 4 known risks of SPRAVATO (sedation, dissociation, increased blood pressure, drug abuse), identifying fever as a risk not associated with SPRAVATO (Table 12).

- Three of the 5 survey questions concerning post-dose monitoring (including supervision) requirements were correctly answered by >80% of the respondents.
  - For one question (Question 12; need for resuscitation equipment) the most selected answer (43.7%) was more clinically conservative than the correct answer (Table 18).
  - Approximately 48.5% correctly responded to the remaining post-dose monitoring question. However, the second most common response (48.9%) could also be clinically acceptable in those cases where dissociation and sedation are resolved within 1 hour (Table 14).
- Almost 60% of respondents correctly responded that it was safe for a patient to drive a vehicle or operate heavy machinery the next day following a restful sleep after treatment with SPRAVATO (Table 16).

10.4.3.1. Overall Score

- The overall scores for questions related to all materials are summarized below. The average score for correct responses was 71.7%
- For questions relating to the HCP materials, the average score was 66.5%
- For questions relating to the patient materials, the average score was 87.2%

The most frequent overall score was in the bracket of 60%-69% correct responses, which was achieved by 33.3% of participants; 81 of 270 HCPs (30.0%) scored 80% or more across all questions, and 6 of 270 HCPs (2.2%) scored less than 50% across all questions. For more detail, refer to Table 21.

Table 21: Summary of correct responses: percentage of HCPs achieving correct responses across all survey questions

	Total
N =	270 (%)
Less than 50% of questions correct	6 (2.2%)
50-59% of questions correct	32 (11.9%)
60-69% of questions correct	90 (33.3%)
70-79% of questions correct	61 (22.6%)
80% or more questions correct[1]	81 (30.0%)

[1] Shaded row indicates target for success
% correct responses calculated based on 16 survey questions (14 in France)

10.5. Other Analyses

There were 5 subgroup analyses performed in this study. See results in the sections below.

10.5.1. Subgroup Analysis of questions related to a) Healthcare Professional Guide and Checklist for readiness to leave, as well as for the subgroup of questions related to b) Patient Guide.

The average score for questions relating to the patient materials was higher (87.2%) than the average score (66.5%) for questions relating to the HCP materials. For more detail, refer to Table 22.

Table 22: Level of Correct Responses: HCP And Patient Materials

	Total (all questions)	Questions relating to HCP materials (Q1-Q12)	Questions relating to patient materials (Q13-Q14a/b/c)
N	270	270	270
Mean correct responses	71.7%	66.5%	87.2%
95% C.I.	66.35% - 77.09%	60.88% - 72.12%	83.22% - 91.18%
Minimum	18.8%	16.7%	0.0%
Maximum	100.0%	100.0%	100.0%
Standard Deviation	12.0%	14.1%	19.7%

10.5.2. Subgroup Analysis of Correct Responses by Country

Four main countries, Germany, France, Italy, and Spain have been compared separately. Due to the small sample sizes (<30), the analyses for Austria, Belgium, the Netherlands, and Sweden were combined. The scores for correct responses in Germany and Italy are slightly above those in France, Spain, and the combined group of countries, but the differences are statistically insignificant. The results of the analysis are consistent across countries. For more detail, refer to Table 23.

Table 23: Proportion of Correct Responses: By Country

	Total	Germany	France	Italy	Spain	Other markets[1]
N	270	64	39	58	65	44
Mean correct responses	71.7%	74.0%	71.1%	75.0%	68.8%	69.0%
95% C.I. (Lower)	66.4%	63.3%	56.9%	63.9%	57.5%	55.3%
95% C.I. (Upper)	77.1%	84.7%	85.3%	86.1%	80.1%	82.7%

[1] Includes Austria (n=10), Belgium (n=16), Netherlands (n=6), Sweden (n=12)
% correct responses calculated based on 16 survey questions (14 in France)

10.5.3. Subgroup Analysis of Correct Responses by Specialty

The average score of correct responses by psychiatrists was numerically higher (72.4%) than the average score (69.0%) of correct responses by mental health nurses but the difference is negligible. For more detail, refer to Table 24.

Table 24: Proportion of Correct Responses: By Specialty

	Total	Psychiatrists	Psychiatric/ mental health nurses/ other HCPs
N	270	217	53
Mean correct responses	71.7%	72.4%	69.0%
95% CI (Lower)	66.4%	66.5%	56.6%
95% CI (Upper)	77.1%	78.3%	81.5%

10.5.4. Subgroup Analysis by the Treatment Setting

A subgroup analysis was performed by treatment setting comparing correct response rates for HCPs in 3 settings.There was only one question where a difference between the 3 settings was observed, ie, those in office-based practice are more likely to select "all patients" at Question 12 (For which patients should resuscitation equipment and healthcare professionals with training in cardiopulmonary resuscitation be available when administering SPRAVATO® [esketamine]?). The analysis shows that those in office-based practice are more cautious about the need for resuscitation equipment during the management of patients being treated with SPRAVATO. For more detail, refer to Table 25.

There were no major differences in proportion of correct responses observed by treatment setting for 15 of the 16 questions (data not shown).

Table 25: Q12: For Which Patients Should Resuscitation Equipment And Healthcare Professionals With Training In Cardiopulmonary Resuscitation Be Available When Administering SPRAVATO® (Esketamine)?

	Primary practice setting			
	In patient secondary care	Outpatients attached to a hospital/ day clinic	Office based practice	p-value
N	138 (%)	100 (%)	32 (%)	
Patients aged 65 years and older	5 (3.6%)	3 (3.0%)	0 (0.0%)	0.55
Patients with clinically significant or unstable cardiovascular or respiratory conditions[1]	59 (42.8%)	50 (50.0%)	9 (28.1%)	0.09
All patients	67 (48.6%)	39 (39.0%)	22 (68.8%)	0.01
Never	3 (2.2%)	4 (4.0%)	0 (0.0%)	0.42
I don't know	4 (2.9%)	4 (4.0%)	1 (3.1%)	0.89

[a] The row shaded in grey indicates the correct answer to the question

10.5.5. Subgroup Analysis by the Receipt of Materials

For receipt of materials, there are no differences between those who have or have not received the HCP guide, or between those who have or have not received the Patient guide. However, there are differences between HCPs who have read the HCP Checklist and those that have not. Those who have read the Checklist are more likely to select a correct option. See details for Question 1, Question 8, Question 10, and Question 14 in the tables below.

Patient Age Eligibility – Question 1

Table 26: Q1: Based on Your Understanding Of The Prescribing Information For Treatment-Resistant Major Depressive Disorder, In Which Of The Following Age Groups Can SPRAVATO® (Esketamine) Be Used?

	SPRAVATO® Checklist for healthcare professionals		
	Have read	**Have not read**	**p-value**
N	174 (%)	96 (%)	
Adolescents (12-17 years)	12 (6.9%)	0 (0.0%)	0.01
Adults (18-64 years)	172 (98.9%)	93 (96.9%)	0.25
Elderly (65 years and over)	82 (47.1%)	31 (32.3%)	0.02
I don't know	0 (0.0%)	0 (0.0%)	-
Selecting Adults and Elderly, but not Adolescents[1]	**73 (42.0%)**	**28 (29.2%)**	0.04

[1] The row shaded in grey indicates the correct answer to the question

Monitoring Requirements – Question 8

Table 27: Q8:Because Of The Possibility Of Sedation, Dissociation And Elevated Blood Pressure, How Long, If At All, After Administration Of SPRAVATO® (Esketamine) Must Patients Be Monitored By A Healthcare Professional?

	SPRAVATO® Checklist for healthcare professionals		
	Have read	**Have not read**	**p-value**
N	174 (%)	96 (%)	
No monitoring is required	2 (1.1%)	1 (1.0%)	0.94
Minimum of 5 minutes	1 (0.6%)	0 (0.0%)	0.46
Minimum of 1 hour	75 (43.1%)	57 (59.4%)	0.01
Until the patient is considered clinically stable[1]	**93 (53.4%)**	**38 (39.6%)**	0.03
I don't know	3 (1.7%)	0 (0.0%)	0.20

[1] The row shaded in grey indicates the correct answer to the question

Requirements for Driving – Question 10

Table 28: Q10. When Is It Safe For A Patient To Drive A Vehicle Or Operate Heavy Machinery Following Treatment With SPRAVATO® (Esketamine)?

	SPRAVATO® Checklist for healthcare professionals		
	Have read	**Have not read**	**p-value**
N	174 (%)	96 (%)	
Immediately after treatment	1 (0.6%)	1 (1.0%)	0.67
2-4 hours following treatment	52 (29.9%)	44 (45.8%)	0.01
The next day following a restful sleep[1]	**115 (66.1%)**	**47 (49.0%)**	0.01
I don't know	6 (3.4%)	4 (4.2%)	0.77

[1] The row shaded in grey indicates the correct answer to the question

Effectiveness at Communicating Messages – Question 14

Table 29: Q14C: After Patients Have Reviewed The Information Presented In The SPRAVATO® Patient Guide, Do You Agree Or Disagree With The Following Statements: Patients Understand That They Should Not Drive Or Operate Heavy Machinery Until The Next Day Following A Restful Sleep

	SPRAVATO® Checklist for healthcare professionals		
	Have read	**Have not read**	**p-value**
N	173 (%)	96 (%)	
I agree[1]	**158 (91.3%)**	**76 (79.2%)**	0.01
I disagree	8 (4.6%)	10 (10.4%)	0.07
I don't know	7 (4.0%)	10 (10.4%)	0.04

[1] The row shaded in grey indicates the correct answer to the question

10.6. Adverse Events/Adverse Reactions

No adverse events were reported from the survey due to no patients participating in the study, no presence of any open text in the survey, and no questions directly soliciting AEs in the questionnaire. However, as per protocol, if any adverse event related to Janssen products were reported directly to the third-party vendor by the HCPs participating in the study, those event(s) were required to be reported by the third-party vendor to the sponsor.

11. DISCUSSION

11.1. Key Results

The HCP survey to measure the effectiveness of the educational materials (including the Patient Guide) for SPRAVATO (both Wave 1 and Wave 2) showed that

- A total of 270 complete surveys were suitable for analysis.
- A majority of the HCPs (80.4%) self-reported a primary medical role of psychiatrist.
- With regard to the HCP educational materials:
  - This HCP survey shows the various level of familiarity and understanding of key messages from the SPRAVATO educational materials amongst the HCPs surveyed at this time and also reveals some areas of uncertainty.
  - Such information gaps (areas of uncertainty) may be associated with less familiarity with the later-approved MDD-PE indication (compared with the previously-approved TRD indication).
- With regard to patient educational materials
  - HCPs considered the SPRAVATO Patient Guide to be effective in communicating to patients and caregivers the risks of dissociation, sedation, and blood pressure increase (75.9%); only a small number (2.6%) selected "potential abuse, indicating the lower awareness of this as a risk associated with SPRAVATO.
  - HCPs also considered that, after reviewing the SPRAVATO Patient Guide, patients were aware of their monitoring needs before, during, and after SPRAVATO administration

(≥96.7%), as well as the need to self-administer SPRAVATO under the direct supervision of a HCP and that they should not drive or operate heavy machinery until the next day of SPRAVATO administration following a restful sleep (both ≥87%).

- The average score for correct responses was 71.7%
  - A modification of Question 5 in Wave 2 related to the MDD-PE indication increased the percentage of correct answers from 23% in Wave 1 to 83% in Wave 2.
- Subgroup analyses show the following:
  - **By questions related to Guides:** Patient materials (Patient Guide) were more effectively understood, as evidenced by their higher average score for correct responses compared to the HPC materials (Healthcare Professional Guide)
  - **By speciality:** The average score of correct responses by psychiatrists was numerically higher than the average score of correct responses by mental health nurses but the difference is negligible.
  - **By country:** The scores for correct responses in Germany and Italy are slightly above those in France, Spain, and the combined group of countries, but the differences are statistically insignificant.
  - **By treatment setting:** The analysis of correct responses observed by treatment setting shows that those in office-based practice are more cautious about the need for resuscitation equipment during the management of patients being treated with SPRAVATO.
  - **By the receipt of materials:** Those who have read the Checklist are more likely to select a correct option. This reinforces the importance for HCPs in referring to the Checklist and recognising it as an integral component of the educational materials, supporting the safe use of SPRAVATO, and a correct option of overall management of patients being treated with SPRAVATO.

11.2. Limitations

A quantitative limitation of the research methods is recognized within this study as the number of HCPs evaluated is considered representative of the whole - ie, it is not feasible to survey every single HCP involved in SPRAVATO management within any country.

Secondly, an online quantitative approach did not allow for in-depth probing of respondent answers in order to gain deeper understanding of HCP behavior as the answers to the closed questions in the questionnaire are pre-defined.

Inherent limitations associated with survey study design can also raise some within study result inconsistency. For example, when respondents were surveyed (Question 10, multiple choice of 4 responses) regarding driving a motor vehicle after SPRAVATO administration, 60.0% of respondents correctly responded that it was not safe to drive until the next day after a restful sleep. However, when the question was asked in the context of the Patient Guide (Question 14c, “agree” or “disagree” question format), 87.2% HCP considered that patient information material is sufficiently informative for patients with regard to the safety message/consideration about driving.

Online surveys may promote social desirability bias, which refers to the tendency of participants to give socially desirable/expected responses instead of choosing those reflecting their current knowledge or behavior.

11.3. Interpretation

- Participants were generally aware of key risks evaluated by the survey with the average score for correct responses of 71.7%. Although the percentage of correct responses to the question did not meet the per-protocol predefined threshold of ≥80%, it was apparent that most responders correctly answered the Key Messages questions indicating that the educational materials provided by Janssen on the minimization of risks with esketamine were effective.
- For some questions, where the percentage of correct answers was low, participants had selected a more conservative answer (ie, for Question 1 regarding age groups for indication, most participants selected Adults only rather than Adults and Elderly; for Question 2 regarding indication, participants selected Severe rather than Moderate to severe MDD), thus indicating a more conservative approach to prescribing, which presents a low risk of inappropriate use.

  HCPs in certain countries may be more familiar with the TRD indication authorized in 2019 and less familiar with the MDD-PE indication authorized more recently in 2021; additionally, the MDD-PE indication is not reimbursed in the EU countries that participated in the study (except Germany and Sweden) resulting in limited clinical experience; as acute suicidality constitutes the majority of the patients with psychiatric emergency, "suicidal ideation or behavior" was selected by most of the respondents possibly due to a study bias rather than reflecting current knowledge or clinical practice.
- Results for Question 1 and Question 4 indicate that there is some lack of clarity around the appropriate age ranges for each indication, with less familiarity with the MDD-PE indication.

11.4. Generalizability

Health Care Professionals recruitment extended across 8 EU countries (Austria, Belgium, France, Germany, Italy, the Netherlands, Spain, and Sweden). Health Care Professionals were recruited from the list of all prescribers, who have either prescribed or are involved in treatment of patients with SPRAVATO and who have received the educational materials. The participating countries provide a balance of different health care systems, enabling generalizability of study results at the EU level. Participating HCPs were also well balanced with regards to treatment setting in caring for patients with MDD (49.3% inpatient and 48.7% outpatient/community practice).

12. OTHER INFORMATION

Not applicable.

13. CONCLUSION

Results of the survey have demonstrated awareness among surveyed HCPs about important identified risks (related to SPRAVATO treatment) of drug abuse, transient dissociative states and perception disorders, disturbances in consciousness, and increased blood pressure. For items with lower scoring, such as the indication for age groups (Question 1) and the indication per severity of depressive episodes (Question 2), a more clinically conservative answer was selected by a substantial proportion of respondents. Although this reduced the percentage of correct responses,

respondents may have selected the most judicious response (such as incorrectly excluding treatment of the elderly and those with moderate MDD) which could reflect conservative prescribing practices or a survey study bias that the most conservative response is the correct response.

The results of the survey

a) indicated awareness among surveyed HCPs about requirements for management of patients whilst being treated with Spravato and the recommended post-dose monitoring (including supervision); and

b) reflected that patient educational materials create awareness among patients of their monitoring needs before, during, and after SPRAVATO administration.

It was apparent that most survey respondents correctly answered the **Key Messages** questions, indicating that all educational materials provided by Janssen on the minimization of risks with esketamine were effective.

Additionally, data highlighted a greater familiarity of surveyed HCPs with the earlier approved TRD indication (December 2019) rather than the later-approved MDD-PE indication (February 2021) for SPRAVATO.

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LIST OF APPENDICES

Some appendices may not be relevant to this study. The appendices that are relevant to this study will either be included with the report or will be available on request, based on regional requirements.

1	Protocol and Amendments
2	Sample Case Report Form(s)
3	List of IECs or IRBs and Sample Consent Forms
4	List and Description of Investigators and Sites
5	Signature of Sponsor's Responsible Party (located at the end of this document) Signature of Principal or Coordinating Investigator(s)
6	Listing of Patients Receiving Test Drug(s) from Specified Batch (Not Applicable)
7	Randomization Scheme (Not Applicable)
8	Audit Certificates
9	Documentation of Statistical Methods and Interim Analysis Plans
10	Documentation of Interlaboratory Standardization Methods and Quality Assurance Procedures if Used (Not Applicable)
11	Publications Based on the Study
12	Important Publications Referenced in the Report
13	Data Listings

SIGNATURE PAGE

STUDY TITLE:	**Survey to Assess the Effectiveness of SPRAVATO® Educational Materials for Additional Risk Minimization Measures in the European Union**
REPORT CONTRIBUTORS:	Sponsor's responsible physician: Christian von Holt, MD Sponsor's lead medical writer: PPD

SPONSOR'S RESPONSIBLE PARTY:

NAME:	Christian von Holt, MD
TITLE:	EMEA Medical Affairs Director

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

SIGNATURE:	eSignature has been applied on the next page.
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Signature

User	Date	Reason
von Holt Christian PPD	24-Oct-2024 11:53:09 (GMT)	Document Approval