Janssen-Cilag International NV

Non-interventional Postauthorization Safety Study - Protocol

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

Protocol PCSNSP002812
AMENDMENT 3

SPRAVATO® (esketamine) nasal spray

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Compliance: This study will be conducted in compliance with the protocol and applicable regulatory requirements.

1. PASS INFORMATION

Title:	Survey to Assess the Effectiveness of SPRAVATO® Educational Materials for Additional Risk Minimization Measures in the European Union
Protocol version:	5.0
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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 education materials related to the understanding and management of SPRAVATO important identified risks of Drug abuse, Transient dissociative states and perception disorders, Disturbances in consciousness, and Blood pressure increased in Europe.
Country(-ies) of study	The survey is proposed to be conducted in European Union (EU) countries where SPRAVATO has been approved and is commercially available and where there will be an adequate projected number of healthcare professionals (HCPs) (and thus the potential number of respondents)
Author	PPD

2. MARKETING AUTHORIZATION HOLDER(S)

Name of Marketing Authorization Holder:	Janssen-Cilag International NV
Address:	Turnhoutseweg 30 2340 Beerse Belgium
Contact Details:	PPD
Qualified Person Pharmacovigilance:	
Name:	PPD
Signature:	[e-signature appended at the end of this document]
Date:	[e-signature appended at the end of this document]

3. RESPONSIBLE PARTIES

Principal Participating Physician:	Not applicable
Coordinating Physician:	Not applicable
Contact person for this protocol:	PPD
E-mail address of contact person:	PPD

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LIST OF IN-TEXT TABLES

AMENDMENTS AND UPDATES

The sponsor will not modify this protocol without a formal amendment. All protocol amendments must be issued by the sponsor, and will follow the review and approval process in accordance with local regulations.

This is the second amendment for this protocol.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Version Date**
Amendment 3	18 March 2022
Amendnent 2	10 May 2021
Amendment 1	17 March 2021
Original Protocol	17 September 2020

Amendment 3 (18 March 2022)

Overall Rationale for the Amendment: A second extension to the final study report (wave 2) and corresponding milestone dates including for wave 1, to allow the use of SPRAVATO to reach the levels reasonably needed to conduct the survey. This reflects the delay in the uptake of SPRAVATO usage resulting in an insufficient number of HCPs with experience of prescribing or managing SPRAVATO patients to ensure conduct of the survey in accordance with the originally agreed timelines.

Section number and Name	Description of Change	Brief Rationale
4 Abstract; 5 Milestones; 6.5 Overall Rationale for the Study; 8.1 Study Design	Changed the date of conduct of wave 1 and wave 2 of the survey and corresponding milestone dates.	To allow the use of SPRAVATO to reach the levels reasonably needed to conduct the wave 1 survey, given the delay in the uptake of SPRAVATO usage by HCPs. This also impacts on the timing of the conduct of the subsequent wave 2 survey.
1 PASS Information; 3 Responsible Parties; 4 Abstract	Changed the main author for this protocol amendment.	Change in sponsor personnel.

Amendment 2 (10 May 2021)

Overall Rationale for the Amendment: To revise the adverse event reporting procedure to better reflect the manner of interactions with respondents during the conduct of the survey (ie, reporting of adverse events to the sponsor through the third party vendor overseeing and administering the survey rather than directly).

Section number and Name	Description of Change	Brief Rationale
10 Management and Reporting of Adverse Events/Adverse Reactions.	Clarified that if any adverse event(s) is/are reported by the participating HCP to the third party vendor overseeing and administering the survey, the vendor is obliged to report the event(s) to the sponsor in accordance with the agreed timelines.	To better reflect the manner of interactions with survey respondents and potential routes of adverse event reporting.

Amendment 1 (17 March 2021)

Overall Rationale for the Amendment: 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. This reflects the delay in the uptake of SPRAVATO usage, principally due to the COVID-19 pandemic, resulting in an insufficient number of HCPs with experience of prescribing or managing SPRAVATO patients to ensure conduct of the survey in accordance with the originally agreed timelines is feasible. This extension also results in an extension of wave 2 and its corresponding milestone dates.

Section number and Name	Description of Change	Brief Rationale
4 Abstract; 5 Milestones; 6.5 Overall Rationale for the Study; 8.1 Study Design	Changed the term 'initiation' of survey to 'conduct' of survey. Changed the date of conduct of wave 1 and wave 2 of the survey and corresponding milestone dates.	To allow the use of SPRAVATO to reach the levels reasonably needed to conduct the wave 1 survey, given the delay in the uptake of SPRAVATO usage by HCPs, principally due to the COVID-19 pandemic. This also impacts on the timing of the conduct of the subsequent wave 2 survey.
4 Abstract; 6.2 Background, Major Depressive Disorder in a Psychiatric Emergency (MDD-PE); 6.3 Background, SPRAVATO; 6.4 Background, Important Identified Risks with SPRAVATO; 8.3 Variables	Added indication for SPRAVATO in the MDD-PE population to the survey protocol.	To include the new indication (Major Depressive Disorder in a psychiatric emergency [MDD-PE]) as approved in procedure EMEA/H/C/ 004535/II/0001/G (EC decision, 04 Feb 2021).
1 PASS Information; 3 Responsible Parties; 4 Abstract	Changed the main author for this protocol amendment.	Change in sponsor personnel.

4. ABSTRACT

Protocol Title: Survey to Assess the Effectiveness of SPRAVATO® Educational Materials for Additional Risk Minimization Measures in the European Union, Version 5.0 (18 March 2022).

Sponsor's Responsible Medical Officer: PPD (Main Author).

Background and Rationale

SPRAVATO, the S-enantiomer of racemic ketamine, has been developed as a nasal spray formulation for the treatment of patients with treatment-resistant depression (TRD) and for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency (MDD-PE). SPRAVATO is a non-selective, non-competitive, antagonist of the N-methyl-D-aspartate (NMDA)-receptor (NMDAR), an ionotropic glutamate receptor.

SPRAVATO induces psychoactive effects, similar to ketamine, which include:

- Potential for abuse, based on results of a SPRAVATO abuse potential study
- Transient dissociative states and perception disorders, and Disturbances in consciousness are expected effects of SPRAVATO nasals spray, based on its mechanism of action on NMDARs
- Cardiovascular effects of SPRAVATO, including transient increases in blood pressure mediated by the sympathomimetic effect of esketamine

As risk minimization measures, the Marketing Authorization Holder (MAH) has developed educational materials consisting of a Healthcare Professional Guide, Patient Guide (for patients), and Checklist for readiness to leave for use by all healthcare professionals (HCPs) potentially involved in the prescribing, administration and management of SPRAVATO nasal spray. These educational materials are aimed at increasing awareness about these important identified risks, and provide guidance for risk management.

In order to evaluate the effectiveness of these risk minimization measures, a survey of HCPs will be conducted to assess knowledge and understanding for these risks.

Research Question and Objectives

The objective of this survey is to determine the effectiveness of the educational materials 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 Blood pressure increased. The responses from HCPs involved in prescribing, administration or management of patients with SPRAVATO will be 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 major depressive disorder [MDD])

(b) the important identified risks

(c) monitoring before and after SPRAVATO administration

(d) healthcare facility requirements for patient monitoring

The effectiveness of the Patient Guide will be 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, blood pressure increased, and abuse

(b) Monitoring considerations, when being treated with SPRAVATO

(c) Post-treatment restrictions

Study Design

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

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

Prior to commencing the main survey phase described below, a small pilot testing of the questionnaire will be performed to validate the questionnaire and ensure that the main quantitative survey will provide data relevant to meeting the objectives of this survey.

The main online quantitative phase, referred to as the survey, will be administered in 2 waves in selected countries of the European Union (EU) where SPRAVATO is commercially available and where there will be an adequate projected number of HCPs (and thus potential number of respondents). Waves 1 and 2 will be conducted within 4 years and within 5 years, respectively, of the availability of the approved educational materials in selected countries.

Setting and Study Population

Healthcare professionals involved in the prescribing, administration and management of SPRAVATO treatment will be invited to participate in the survey to assess their knowledge and understanding of the important identified risks, in accordance with the educational materials. All respondents will be independently recruited through a third party vendor.

Variables

Awareness and understanding of the following SPRAVATO Key Messages are proposed to be tested by the effectiveness survey:

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 MDD, who have not responded to at least 2 different treatments with antidepressants in the current moderate to severe depressive episode (for testing of the 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 psychiatric emergency (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 (for testing of the HCP Guide and 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 (for testing of the HCP Guide, Patient Guide, and 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 HCPs with training in cardiopulmonary resuscitation are available (for testing of the HCP Guide).

Data Sources

The data source for this survey will be the questionnaire used to survey HCPs involved in prescribing, administration and management of SPRAVATO treatment.

Study Size

The sample size calculation is 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 is designed to be a representative sample of SPRAVATO prescribers in the EU. The selection of countries participating in Wave 1 or Wave 2 of the survey will be made based on SPRAVATO commercial availability.

The goal for the survey is to obtain a target of 270 completed surveys. Based on the exact binomial distribution, 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%. The maximum sample size would be 400 with an assumed correct response rate of 50%.

Data Analysis

In order to consider the educational materials related to SPRAVATO as effective, a minimum total score of ≥80% of correct responses on all survey questions will be 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 for STELARA® and DARZALEX®.

Summary results for the overall response rate and 95% CI will be presented. In addition, subgroup analyses will be 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. Country-specific analyses may be performed, where appropriate and where adequate responses are obtained.

Milestones

Milestone	Planned 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
End of survey (wave 1)[a]	No later than 31 October 2023
Wave 1 report submission	No later than 31 December 2023[b]
Conduct of survey (wave 2)[c]	No later than 31 July 2024
End of survey (wave 2)	No later than 30 September 2024
Final report of survey results[d]	4Q2024

a Survey should be conducted within 4 years of the availability of the approved educational materials.
b Based on the first launch in European Union, 1st February 2020.
c Survey should be conducted within 4 to 5 years of the availability of the approved educational materials. Timeline provided here is at the 4.5 year timepoint.
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.

5. MILESTONES

The planned dates for key milestones in this survey are outlined below.

Milestone:	Planned 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
End of survey (wave 1)[a]	No later than 31 October 2023
Wave 1 Report submission	No later than 31 December 2023[b]
Conduct of survey (wave 2)[c]	No later than 31 July 2024
End of survey(wave 2)	No later than 30 September 2024
Final report of survey results[d]	4Q2024[d]

[a] Survey should be conducted within 4 years of the availability of the approved educational materials.
[b] Based on the first launch in Europe, 1st February 2020.
[c] Survey should be conducted within 4 to 5 years of the availability of the approved educational materials. Timeline provided here is at the 4.5 year timepoint.
[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.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

CI	confidence interval
EMA	European Medicines Agency
HCN	hyperpolarization-activated cyclic nucleotide-gated
HCP	healthcare professionals
MAH	marketing authorization holder
MDD	major depressive disorder
MDD-PE	major depressive disorder in a psychiatric emergency
NMDA	N-methyl-D-aspartate
NMDAR	N-methyl-D-aspartate (NMDA)-receptor
SNRI	serotonin and norepinephrine reuptake inhibitors
SSRI	selective serotonin reuptake inhibitor
TRD	treatment-resistant depression

Definition of Term(s)

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.

6. BACKGROUND AND RATIONALE

6.1. Treatment-resistant Depression (TRD)

Major depressive disorder (MDD) is a common and serious psychiatric disorder affecting over 30 million individuals in the European Union (EU) (Wittchen 2011). 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 (Global Burden of Disease Study 2017; Walker 2015; World Health Organization 2018). 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 treatment-resistant depression (TRD). A globally accepted definition for TRD does not yet exist. The European Medicines Agency (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 (European Medicines Agency 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 (MDD-PE)

Patients with a psychiatric emergency due to MDD (MDD-PE) 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. SPRAVATO is a non-selective, non-competitive, antagonist of the N-methyl-D-aspartate (NMDA)-receptor, an ionotropic glutamate receptor.

Through NMDA receptor antagonism, SPRAVATO produces a transient increase in glutamate release, leading to increases in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (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. Restoration of dopaminergic neurotransmission in brain regions involved in reward and motivation, and decreased stimulation of brain regions involved in anhedonia, may contribute to the rapid response.

SPRAVATO nasal spray, in combination with a selective serotonin reuptake inhibitor (SSRI) or serotonin and norepinephrine reuptake inhibitors (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 Major Depressive Disorder, as acute short-term treatment, for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency.

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

6.4. Important Identified Risks with SPRAVATO

6.4.1. Drug Abuse

As an antagonist of NMDARs, 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. Given the known direct targets of ketamine and the effects of other NMDAR antagonists in the same class, the behavioral effects of ketamine at subanesthetic doses, including perceptual/dissociative symptoms, are thought to be primarily driven by its activity at the NMDAR, although indirect actions on dopaminergic neurotransmission may contribute as well (Broadbear 2004; De Luca 2012; Shram 2011; Winger 2002).

Evidence from an SPRAVATO abuse potential trial (Trial 54135419TRD1015) suggests that the potential for 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 clinical trials of SPRAVATO nasal spray.

6.4.2. Transient Dissociative States and Perception Disorders

Transient dissociative states reflect a type of sensory or proprioceptive perceptual disorder that are expected effects of SPRAVATO based on its mechanism of action as a non-competitive, non-selective, open-channel NMDAR antagonist. 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), an intravenous SPRAVATO dose of 0.2 mg/kg (TRD2001), and an SPRAVATO 84 mg dose administered nasally (TRD3001 data). Moreover, the perceptual/dissociative side effects do not correlate with improvement of depression symptoms (Fava 2017; TRD3001 and TRD3002 data). 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 Montgomery-Asberg Depression Rating Scale [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 Clinician Administered Dissociative States Scale [CADSS] total scores 40 minutes postdose). These findings together suggest that distinct mechanisms may underlie the antidepressant and perceptual actions. These mechanisms may depend on different subtypes of NMDARs.

Transient dissociative states and perception disorders are expected effects of SPRAVATO nasal spray based on SPRAVATO's 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, are induced by primary or secondary actions of NMDAR antagonism, which is why these symptoms diminish rapidly with the decline in SPRAVATO plasma levels.

However, unlike dissociation and antidepressant responses, the sedative responses are variable from time to time in the same individual, suggesting that there are confounding factors that are not fully understood. An important mechanism for some of the outlying sedation effects was concomitant benzodiazepine use; thus, the addition of concomitant medications needs to be considered in the mechanism for the observed sedation. From the pharmacological target point of view, sedation might require directly engaging potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channels (HCN) by ketamine or SPRAVATO and/or γ-amino butyric acid (GABA) stimulation from other sources. There is convincing evidence of the involvement of HCN in the sedation effects of ketamine and SPRAVATO at higher concentrations.

Disturbances in consciousness such as sedation and somnolence are expected effects of SPRAVATO nasal spray based on SPRAVATO's 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. Blood Pressure Increased

Cardiovascular effects of ketamine and SPRAVATO at subanesthetic doses include transient increases in blood pressure in some subjects. The primary target of both agents at this dose range are NMDARs. In addition to producing a transient increase in glutamate release in the brain, a single administration of ketamine at subanesthetic doses increases dopamine and norepinephrine in several brain regions. These effects can be explained by their direct inhibition of interneurons through NMDARs. One plausible explanation for their cardiovascular side effects is that, through inhibition of interneurons directly, these agents stimulate excitatory neurons and catecholaminergic neurons, resulting in increased sympathetic nervous system activity.

Cardiovascular effects due to increased blood pressure are expected for SPRAVATO nasal spray based on SPRAVATO's 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 Summary of Product Characteristics for detailed information on the safety and known risks of SPRAVATO. 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 Blood pressure increased associated with SPRAVATO are essential to increase awareness of its safety profile and risks.

Therefore, the Marketing Authorization Holder (MAH) has developed educational materials consisting of a Healthcare Professional Guide, Patient Guide (for patients), and Checklist for readiness to leave for use by all healthcare professionals (HCPs) potentially involved in the prescribing, administration and management of SPRAVATO nasal spray.

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 Blood pressure increased, and provide guidance on ways to minimize the risks, as described in Part V.1, 'Routine Risk Minimisation Measures', of the EU Risk Management Plan (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 nasal spray will be conducted to assess knowledge and understanding for the management 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

The survey will be administered in 2 waves based on the commercial availability of SPRAVATO and where there will be an adequate projected number of HCPs (and thus the potential number of respondents) in each country. Waves 1 and 2 will be conducted within 4 years and within 5 years, respectively, of the availability of the approved educational materials in selected countries.

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.

6.5.2. Educational Materials

The MAH shall ensure that in all countries in which SPRAVATO is commercially available, all HCPs and patients who are expected to prescribe, dispense and receive this product are provided with the appropriate educational materials below:

- Healthcare Professional Guide
- Patient Guide (for patients)
- Checklist for readiness to leave

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:

- Whether or not a patient is eligible to take SPRAVATO nasal spray;
- The risk for abuse, including risk factors/groups, signs of abuse and dependence, and the need to assess and monitor for this risk;
- Expected transient dissociative states/perception disorders and disturbances in consciousness and how to minimize potential adverse outcome from such effects;
- Blood pressure values may trigger additional measures;
- Expected cardiovascular adverse effects;
- 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;
- The need for post-dose monitoring by HCPs with training in blood pressure monitoring;

- 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;
- The influence of SPRAVATO nasal spray on the patient's ability to drive or operate machinery and related instructions;
- Minimum equipment for monitoring blood pressure to be available at the site.

The proposed Patient Guide addresses the following important identified risks: Drug abuse, Transient dissociative states and perception disorders, Disturbances in consciousness, and Blood pressure increased for patients. The objective of the Patient Guide is to:

- Provide education about what adverse effects to expect and how to minimize those effects;
- Provide education about the risk for abuse and dependence, including risk factors/groups, signs of abuse and dependence, and the need to assess and monitor for this risk;
- Describe the drug administration procedure, including preparation (fasting for 2 hours, no drinking for 30 minutes) and monitoring during the visit;
- Increase awareness of:
  - Proper product administration (ie, under the direct supervision of a healthcare professional);
  - 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;
  - The influence of SPRAVATO nasal spray on the patient's ability to drive or operate machinery and related instructions.

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 Blood pressure increased. 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 is to determine the effectiveness of the educational materials 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 Blood pressure increased. The responses from HCPs involved in prescribing, administration or management of patients with SPRAVATO will be 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

(c) monitoring before and after SPRAVATO administration

(d) healthcare facility requirements for patient monitoring

The effectiveness of the Patient Guide will be 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, blood pressure increased, and abuse

(b) Monitoring considerations, when being treated with SPRAVATO

(c) Post-treatment restrictions

8. RESEARCH METHODS

8.1. Study Design

A survey of HCPs will be 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 will be asked to participate in the survey to assess knowledge and understanding of the important identified risks.

The main survey will be administered in 2 waves in selected countries of the EU where SPRAVATO is commercially available and where there will be an adequate projected number of HCPs (and thus potential number of respondents). Waves 1 and 2 will be conducted within 4 years and within 5 years, respectively, of the availability of the approved educational materials in selected countries.

8.1.1. Suitable Methodology

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

The most effective design for this survey involves an online quantitative approach to provide representative numbers of HCPs who prescribe, administer or monitor patients treated with SPRAVATO. Prior to commencing the main survey phase described below, a small pilot testing of the questionnaire will be performed to validate the questionnaire. The feedback received from the pilot testing will be incorporated into the final quantitative questionnaire design. This strategy will help ensure that the final questionnaire will provide data relevant to meeting the objectives of this effectiveness survey.

An online methodology has a number of associated advantages including covering a wide geographical spread, SPRAVATO site of care, and flexibility for respondents to complete the survey at a convenient time in addition to allowing respondents to be completely honest without feeling like they are being questioned or judged by an interviewer. 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.

The survey will be conducted in accordance with the EU Good Pharmacovigilance Practices (GVP) VIII guidelines.

8.1.2. Target Respondent Group Identification

The survey will include HCPs involved in prescribing, administration and monitoring of SPRAVATO treatment, and who have received SPRAVATO educational materials (Healthcare Professional Guide, Patient Guide (for patients), Checklist for readiness to leave).

All respondents will be independently recruited through a third party. The respondents chosen will remain anonymous and will be checked for additional screening criteria. It is envisaged that the HCPs included in the survey will largely be prescribing psychiatrists, but also nurses and other healthcare personnel involved in administration and monitoring of SPRAVATO treatment.

8.1.3. Questionnaire Design

The questionnaire will be 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 will be assessed by surveying treating physicians and/or nurses. To assess the effectiveness of the Patient Guide, the survey will include 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 will be scripted and routed in such a way that a respondent will only answer questions that are relevant to them and will consist of open, closed and/or multiple choice questions. The survey will be programmed so that the respondent can only progress forward through the questions and is not allowed to go back to return to previously given answers. The

respondent is therefore unable to alter answers once responses have been given. Every question must be answered for the respondent to progress forward through the survey. The survey will be presented in the local language. Questions will be 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.

8.1.4. Recruitment and Screening Criteria

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

The survey will be stratified by the following criteria:

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

Other syndicated quantitative audits conducted by third parties will be utilized to help shape the degree of stratification, such as the percentage of prescribers per country. A screening questionnaire will assess whether a HCP meets the participation criteria and can proceed to main questionnaire.

8.2. Setting and Study Population

The survey will be conducted in EU countries in which SPRAVATO has been approved and is commercially available. The survey population consists of HCPs involved in the prescribing, administration and management of SPRAVATO nasal spray and will be recruited by an external third party vendor as described in Section 8.1. Participation in the survey will be entirely voluntary. No patients will participate in the survey.

8.3. Variables

A questionnaire will be designed, tested and validated through pilot testing to evaluate the clarity and understanding of the questions. Careful consideration is required to design appropriate survey questions that allow 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 will be assessed by surveying HCPs.

A list of draft suggested SPRAVATO Key Messages is provided in Table 1. These Key Messages feature in the SPRAVATO educational materials and have been 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 psychiatric emergency (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

8.4. Data Sources

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

8.5. Study Size

The sample size calculation is 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 is designed to be a representative sample of SPRAVATO prescribers in the EU. The selection of countries participating in Wave 1 or Wave 2 of the survey will be made based on SPRAVATO commercial availability.

The target number of total completed surveys is 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% confidence intervals (CIs) it will provide.

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) are used to indicate that for an estimated comprehension level (ie, correct response rate), the true population level of comprehension is 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 is to obtain a target of 270 completed surveys. 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%. The maximum sample size would be 400 with an assumed correct response rate of 50% (Table 2).

8.6. Data Management

An external third party vendor will perform rigorous 'real time' checks to ensure that the data collected are valid and of a high quality. These checks will involve:

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

8.7. Data Analysis

In order to consider the educational materials related to SPRAVATO as effective, a minimum total score of ≥80% of correct responses on all survey questions will be 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 for STELARA® and DARZALEX®.

Upon completion of the survey by the required number of sample respondents, data collected during the course of the survey will be aggregated and tabulated. All questions will be analysed individually as well as cross-tabulated with other survey questions to allow for more in-depth analysis.

Summary results for the overall response rate will be presented. In addition, subgroup analyses will be 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. Country-specific analyses may be performed, where appropriate and where adequate responses are obtained.

These outputs will show data based on absolute numbers of respondents and percentages of the total sample. For each question, the base of the respondents answering it will be presented. All results will include a 95% CI.

8.8. Quality Control

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

To accurately assess participants' knowledge, care will be 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 is to provide multiple choice questions where the respondent may choose one or more answers from a list. In addition, participants will be 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 will ensure that answers will be logical and correct, thereby enhancing data accuracy.

8.9. Limitations of the Research Methods

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 will not allow for in-depth probing of respondent answers in order to gain deeper understanding of HCP behaviour as the answers to the closed questions in the questionnaire are pre-defined.

The potential for selection bias of participating respondents in a survey is an inherent bias/limitation to any study based on volunteer participation. In order to quantify any selection bias, the distribution of each stratification criterion of respondents (as described in Section 8.1.4) will be compared between respondents and non-respondents. The collection of data on nonrespondents is not always possible due to absence of response; however, known characteristics will be compared.

9. PROTECTION OF HUMAN SUBJECTS

This survey will be provided to HCPs. No patients will participate in this survey.

The collection and processing of personal data from survey respondents will be limited to those data that are necessary to fulfill the objectives of the study. Respondents will be anonymized, retaining professional group (ie, psychiatrists, nurses and other HCPs), and country. The sponsor will consult with internal experts in data privacy/GDPR to ensure that all aspects of this research are compliant. The external third party vendor conducting the survey will at all times comply with the European Data Protection Directive.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of the survey will be summarised in a report generated by the sponsor with support from the external third party vendor that conducted the survey. The survey report will contain data collected from all HCPs that participated in the survey and will be submitted to EMA according to the agreed timelines.

All information, including but not limited to information regarding SPRAVATO or the sponsor's operations, and any data generated as a result of this survey are considered confidential and remain the sole property of the sponsor.

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ANNEX 1: STAND-ALONE DOCUMENTS AND ADDITIONAL INFORMATION

Annex 1.1: List of Standalone Documents

Title	Reference No	Date
Not applicable		

ANNEX 2: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.