ADDITIONAL DISCLOSURE DATA FOR SWITZERLAND

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Date: *27 April 2020*

Swiss marketing authorisation data

Swiss Marketing Authorisation number: 67103

Swiss Marketing Authorisation date: 25 February 2020

Name of the preparation: Spravato – 28 mg – nasal spray

Name of active pharmaceutical ingredient: Esketamine (JNJ-54135419-AAC)

Clinical trial data

1. **Clinical trial identification**

Protocol No.: ESKETINTRD3002

Title of Study: A Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Flexible Doses of Intranasal Esketamine Plus an Oral Antidepressant in Adult Subjects with Treatment-resistant Depression

Study Name: TRANSFORM-2

EudraCT Number: 2014-004585-22

NCT No.: NCT02418585

2. **Protocol change history**

Protocol and Amendments:

Original Protocol, 10 March 2015

Amendment-1, 15 January 2016 – substantial

Amendment-2, 03 June 2016 – substantial

3. Clinical trial investigators and study centres

Principal Investigator*:* Madhukar Trivedi, MD

Study Centres: Countries and number of sites in each country in which the study was conducted: Czech Republic (6), Germany (9), Poland (7), Spain (7), and United States (10)

4. Medication used

Test Product, Dose and Mode of Administration, Batch No.: Intranasal Esketamine was supplied as a solution of esketamine hydrochloride (16.14% weight/volume [w/v]; equivalent to 14% w/v esketamine base) in a nasal spray pump (device), which delivered 16.14 mg esketamine hydrochloride (14 mg esketamine base) per 100-µL spray. Each nasal spray device contained a total of 28 mg (ie, 2 sprays). Intranasal esketamine batch numbers were: 500122, 500491, 502169, 501298, 501698, and 501908.

Reference Therapy, Dose and Mode of Administration, Batch No.: Intranasal placebo was supplied as a solution of water for injection with a bittering agent (0.001 mg/mL denatonium benzoate). The placebo solution was provided in matching nasal spray devices, each containing 2 sprays. Intranasal placebo batch numbers were: 500116, 500472, 502264, 500472, 501738, 501901, and 501577.Oral antidepressant medications were obtained from commercial stock and remained in their commercial packaging; duloxetine 30 mg batch numbers: C413520, C464905, C488361, and C517829; escitalopram 10 mg batch numbers: 2403193, 2417821, and 2438864; sertraline 50 mg batch numbers: H79697, L87615, L72845, and N00893; venlafaxine XR 75 mg batch numbers: L25831, H03571, L13316, and M32758.

5. Study population

Number of participants – planned: 196

Number of participants – analysed: 227

6. Summary and conclusion

- Results from the primary efficacy analysis in this study showed that treatment with intranasal esketamine (either 56 or 84 mg) plus a newly initiated oral antidepressant demonstrated a clinically meaningful and statistically significant treatment benefit in depressive symptoms compared to treatment with a newly initiated oral antidepressant treatment plus intranasal placebo as assessed by change in MADRS total score after 28 days in adult subjects with

treatment-resistant depression. The majority of subjects were titrated up to a dose of 84 mg intranasal esketamine.

- The 3 key secondary analyses were performed sequentially. Analysis of the onset of clinical response by Day 2 (24 hours) that was maintained to Day 28 did not show a statistically significant difference between treatment groups; however, the difference between treatment groups for improving depressive symptoms as assessed by change in MADRS total score was clinically meaningful at all assessment days. The subject-reported changes in functioning and associated disability (measured by the SDS) and changes in depressive symptoms (measured by the PHQ-9) could not be formally evaluated following the results from analysis of the onset of clinical response at Day 2 (24 hours). However, results from the SDS and PHQ-9 assessments were consistent with the results from the primary efficacy analysis.
- Evaluation of the other secondary efficacy endpoints including: response and remission rates (based on MADRS total score), overall severity of depressive illness (based on CGI-S score), and health-related quality of life (based on the EQ 5D-5L) showed greater improvement for subjects treated with intranasal esketamine in addition to oral antidepressant compared to those treated with oral antidepressant in addition to intranasal placebo.
- The 56- and 84-mg doses of intranasal esketamine (administered twice a week for 4 weeks) evaluated in this flexible-dose study appeared to be safe and tolerated in adult subjects with treatment-resistant depression from a multiregional population. Most adverse events were mild or moderate in severity. Evaluation of transient dissociative and perceptual change symptoms (measured by the CADSS) and increases in mean BP suggested the onset of these effects in subjects treated with intranasal esketamine occurred shortly after dose administration and subsequently returned close to predose values by 1.5 hours after dose administration. Overall, there were no new or unexpected safety concerns noted with the administration of intranasal esketamine during this study.
- Plasma esketamine concentrations exhibited expected dose-dependent differences between the 56- and 84-mg doses. The pharmacokinetics of esketamine was consistent during the double-blind induction phase.

7. Results reporting

Date of Clinical Trial Report: 3 August 2018

Prepared by: Janssen Research & Development, LLC

Publication(s) Reference(s):

Popova, V; et al. Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study (TRANSFORM-2). Am. J. Psychiatry. 2019 Jun;176(6)428-438. DOI:10.1176/appi.ajp.2019.19020172

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