ADDITIONAL DISCLOSURE DATA FOR SWITZERLAND

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Date: 30 March 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.: ESKETINTRD3001

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

Study Name: TRANSFORM-1

EudraCT Number: 2014-004584-20

NCT No.: NCT02417064

2. Protocol change history

Protocol and Amendments:

Original Protocol, 10 March 2015

Amendment-1, 07 January 2016 – substantial

Amendment-2, 31 May 2016 – substantial

Amendment-2 / France-1, 08 June 2016 – substantial

3. Clinical trial investigators and study centres

Principal Investigator*:* Pierre Blier, MD, PhD

Study Centres: The study was conducted in 42 sites in the United States, 9 sites each in France, Belgium, and Mexico, 8 sites in Brazil, 5 sites each in Canada and Slovakia, 3 sites in Hungary, and 2 sites in Estonia.

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, 502228, 501298, 501487, 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, M23709, M32758, and N37062.

5. Study population

Number of participants – planned: 348

Number of participants – analysed: 346

6. Summary and conclusion

- Results from the primary efficacy analysis using both MMRM and ANCOVA LOCF showed that treatment with intranasal esketamine (84 mg) plus a newly initiated oral antidepressant did not demonstrate statistical superiority for improvement 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 TRD. However, the data showed a clinically meaningful treatment benefit in adults with TRD who were treated with intranasal esketamine + oral antidepressant. The improvement in the MADRS total score achieved after 4 weeks of treatment numerically favored the intranasal esketamine + oral antidepressant treatment group over the oral antidepressant + placebo treatment group. The difference in the LS means was at least that of the average difference of 2 points in the change in MADRS total score for approved antidepressants when compared to placebo alone.
- In accordance with the predefined testing sequence to account for multiple comparisons, the intranasal esketamine 56 mg + oral antidepressant treatment group could not be formally evaluated. Importantly however, the 56-mg dose demonstrated a clinically meaningful treatment benefit compared to an oral antidepressant + intranasal placebo in subjects with TRD on the primary efficacy endpoint using both MMRM and ANCOVA LOCF. The improvement in the MADRS total score after 4 weeks showed a larger difference in the LS means than the average difference of 2 points in the change in MADRS total score for approved antidepressants when compared with placebo alone.
- In accordance with the predefined testing sequence of key secondary endpoints, onset of clinical response by Day 2 (24 hours), SDS total score, and PHQ-9 total score could also not be formally evaluated. The proportion of subjects with onset of clinical response by Day 2 was numerically higher in the two intranasal esketamine + oral antidepressant treatment groups than it was in the oral antidepressant + intranasal placebo treatment group. The change in SDS and PHQ-9 total scores at Day 28 of the double-blind induction phase in the MMRM and ANCOVA LOCF analyses numerically favored both intranasal esketamine + oral antidepressant treatment groups compared to oral antidepressant + intranasal placebo treatment group.
- Evaluation of the other secondary efficacy endpoints showed greater improvement in depression response based on MADRS total score (response rates and onset of clinical response by Day 8) and remission rates (based on MADRS total score), and overall severity of depressive illness (also based on CGI-S score) for subjects treated with both doses of intranasal esketamine + oral antidepressant compared to those treated with oral antidepressant + intranasal placebo.
- Plasma esketamine concentrations exhibited expected dose-dependent differences between the 56- and 84-mg doses. Mean esketamine and noresketamine concentrations were similar on Days 4 and 22.

- The 56- and 84-mg doses of intranasal esketamine (administered twice a week for 4 weeks) appeared to be safe and tolerated in adult subjects with TRD from a multiregional population. There were no meaningful differences in safety and tolerability between doses. While there was a higher rate of discontinuations due to AE observed in the intranasal esketamine 84 mg + oral antidepressant treatment group, this was not due to any new dose-related safety finding, and the majority of these subjects (ie, 5 of 7 subjects) discontinued after receiving only 1 dose on Day 1 (per study design, the Day 1 dose was to be 56 mg). Most AEs were mild or moderate in severity and were typically observed on intranasal dosing days, and generally resolved on the same day. Evaluation of transient dissociative and perceptual change symptoms observed (measured by the CADSS) and increases in BP suggested the onset of these effects in subjects treated with intranasal esketamine occurred shortly after dose administration and returned to or close to predose values by 1.5 hours after dose administration. Overall, there were no new or clear dose-related differences in the safety and tolerability. A slightly higher incidence of dissociation and nausea was observed in the esketamine 84 mg + oral antidepressant treatment group as compared to the esketamine 56 mg + oral antidepressant treatment group, based on the CADSS and severe AEs.

7. Results reporting

Date of Clinical Trial Report: 26 July 2018

Prepared by: Janssen Research & Development, LLC

Publication(s) Reference(s): Maggie Fedgchin, Madhukar Trivedi, Ella J. Daly, Rama Melkote, Rosanne Lane, Pilar Lim, Dawn Vitagliano, Pierre Blier, Maurizio Fava, Michael Liebowitz, Arun Ravindran, Raphael Gaillard, Hans van den Ameele, Sheldon Preskorn, Husseini Manji, David Hough, Wayne C. Drevets, Jaskaran B. Singh. Efficacy and Safety of Fixed-Dose Esketamine Nasal Spray Combined With a New Oral Antidepressant in Treatment-Resistant Depression: Results of a Randomized, Double-Blind, Active-Controlled Study (TRANSFORM-1). International Journal of Neuropsychopharmacology (2019); 22(10): 616–630.

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