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.: ESKETINTRD3003

Title of Study: A Randomized, Double-blind, Multicenter, Active-controlled Study of Intranasal Esketamine Plus an Oral Antidepressant for Relapse Prevention in Treatment-resistant Depression

Study Name: SUSTAIN-1

EudraCT Number: 2014-004586-24

NCT No.: NCT02493868

2. **Protocol change history**

Protocol and Amendments:

Original Protocol, 26 March 2015

Amendment-1, 21 April 2015 – non-substantial

Amendment-2, 13 January 2016 – substantial

Amendment-3, 09 June 2016 – substantial

Amendment-4, 04 April 2017 – 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: Belgium (4), Brazil (13), Canada (2), Czech Republic (11), Estonia (1), France (5), Germany (4), Hungary (12), Italy (4), Mexico (6), Poland (15), Slovakia (3), Spain (10), Sweden (4), Turkey (16), and United States (54)

4. Medication used

Test Product, Dose and Mode of Administration, Batch No.: Intranasal Esketamine was supplied as a solution containing 16.14% weight/volume (w/v) esketamine hydrochloride (equivalent to 14% w/v esketamine base), in a single-use nasal spray device. Each device delivered 28 mg of esketamine, delivered as 2 sprays (one spray per nostril). Intranasal esketamine batch numbers were: 160663, 161747, 170116, 500122, 500491, 500783, 501298, 501487, 501698, 501908, 502169, 502228, and 500122.

Reference Therapy, Dose and Mode of Administration, Batch No.: Intranasal placebo was supplied as a solution containing water with a bittering agent (0.001 mg/mL denatonium benzoate) added to simulate the taste of the intranasal esketamine solution. The placebo solution was provided in matching nasal spray devices; each individual nasal spray device contained 2 sprays. Intranasal placebo batch numbers were: 160665, 161165, 500116, 500472, 501577, 501738, 501901, and 502264. Oral antidepressant medications were obtained from commercial stock and remained in their commercial packaging; duloxetine 30 mg batch numbers: C413520, C464905, C488361, C517829, and C556088; escitalopram 10 mg batch numbers: 2403193, 2417821, and 2438864; sertraline 50 mg batch numbers: H79697, L72845, L87615, N00893, and N60294; venlafaxine XR 75 mg batch numbers: L13316, L25831, M23709, M32758, N37062, and N61186.

5. Study population

Number of participants – planned: 211 (Planned stable remitters)

Number of participants – analysed: 176 (Analysed stable remitters)

6. Summary and conclusion

- In this double-blind, randomized withdrawal study to assess the relative safety and efficacy of continuation vs. discontinuation of intranasal esketamine, results showed a statistically

significantly longer time to relapse in those randomized to continue esketamine compared with those randomized to discontinue esketamine, among patients who were in stable remission after 16 weeks of treatment with intranasal esketamine in addition to oral antidepressant. During the maintenance phase, the majority of stable remitters (68.9%) used an “every other week” dosing schedule for the majority of the time.

- In addition, the secondary efficacy results for the time to relapse in those who were in stable response (but not remission) after 16 weeks of treatment with esketamine in addition to oral antidepressant showed a statistically significantly longer time to relapse in those randomized to continue esketamine compared with those randomized to discontinue esketamine.
- No new safety signals confirmed as associated with esketamine with repeated dosing over time were observed in this study. No deaths were reported. Most AEs were mild to moderate in severity and were observed post dose on intranasal dosing days, generally resolving on the same day. Dissociative effects of esketamine attenuated during the IND phase with repeated dosing and appeared to remain of low magnitude over time with longer term dosing, as measured by the CADSS.
- This study provides support for a positive benefit-risk with continued long term intermittent dosing with intranasal esketamine, a novel, potentially transformational treatment for patients with TRD, after achieving stable remission or stable response following 16 weeks treatment with esketamine in addition to an oral antidepressant.

7. Results reporting

Date of Clinical Trial Report: 15 August 2018

Prepared by: Janssen Research & Development, LLC

Publication(s) Reference(s):

Daly EJ, Trivedi MH, Janik A, Li H, Zhang Y, Li X, Lane R, Lim P, Duca AR, Hough D, Thase ME, Zajecka J, Winokur A, Divacka I, Fagiolini A, Cubała WJ, Bitter I, Blier P, Shelton RC, Molero P, Manji H, Drevets WC, Singh JB. Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial (SUSTAIN-1). JAMA psychiatry. 903-893:(9)76;2019. Doi:10.1001/jamapsychiatry.

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