2.0 SYNOPSIS

Name of Customer/Company: H. Lundbeck A/S
Name of Finished Product (optional): Vortioxetine
Name of Active Ingredient: 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine

Title of Study: Open-label, flexible-dose study of vortioxetine in patients with Major Depressive Disorder in India

Investigators:
28 Principal Investigators

Study Sites:
28 study sites

Publication (Reference):
None

Study Period:	**Phase of Development:**
26 February 2020 (first patient first visit) – 12 March 2022 (last patient completed)	Phase IV

Background and Rationale for the Study:

Major Depressive Disorder (MDD) is a severe, recurrent, and disabling medical illness characterized by the presence of one or more Major Depressive Episodes (MDEs) that presents with depressed mood, loss of interest or pleasure, disturbed sleep or appetite, low energy, feelings of guilt or low self-worth, and poor concentration. Vortioxetine is approved for the treatment of major depression globally in more than 80 countries, including the United States and Europe at a dose range of 5 to 20 mg/day. Overall short- and long-term treatment with vortioxetine at the therapeutic doses (5 to 20 mg/day) was safe and well-tolerated in adults and in the elderly. This Phase IV study was a post-marketing commitment with the aim of further supporting the safety, tolerability, and therapeutic effectiveness of vortioxetine (5 to 20 mg/day) in patients diagnosed with MDD in a real-life clinical setting in India. The patients were treated in accordance with the approved local label for vortioxetine.

Objectives

Primary Objective:

- To evaluate the safety and tolerability of flexible doses of vortioxetine (5 to 20 mg/day) over a period of 12 weeks in patients with MDD in India.

Secondary Objective:

- To evaluate the effectiveness of flexible doses of vortioxetine (5 to 20 mg/day) over a period of 12 weeks in patients with MDD in India.

Study Design:

This was a Phase IV interventional, multi-site, open-label, flexible-dose study in patients with MDD in India to evaluate the safety, tolerability, and effectiveness of vortioxetine treatment in a real-life clinical setting.

The study consisted of a 2-week Screening period followed by a 12-week open-label treatment period with vortioxetine, and a 4-week safety follow-up period. The total study duration per patient from baseline to the end of follow-up was approximately 16 weeks. There was a total of 7 scheduled visits: Screening (Visit 1), Baseline (Visit 2), Week 1 (Visit 3), Week 4 (Visit 4), Week 8 (Visit 5), Week 12 (Visit 6), and a Safety Follow-up contact/visit (Visit 7).

All enrolled patients received open label 10 mg/day vortioxetine once daily by oral administration (tablets) for 1 week until Visit 3 (Week 1). Thereafter, the dose could be increased to a maximum of 20 mg/day or decreased to 5 mg/day, according to the patient's response and the Investigator's judgment from Visit 3 to Visit 6. The

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vortioxetine was dispensed at each scheduled visit starting from Visit 2 (Baseline visit) and the patients were instructed to take a daily dose, orally, at the same time of the day. The first dose of vortioxetine was taken on the day after vortioxetine was dispensed to a patient (Day 1). After the study, the patients were treated according to usual clinical practice.

Main Criteria for Inclusion:

Patients who met each of the inclusion criteria at the Screening and Baseline visits were eligible to participate in this study.

1. Patient had a MDE, was diagnosed with MDD according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5®), and would benefit from pharmacological treatment with vortioxetine. The current MDE was confirmed using the Mini International Neuropsychiatric Interview.
2. Patient had a Clinical Global Impression–Severity of Illness (CGI-S) score ≥4 at the Screening and Baseline visits.
3. Patient was a man or woman, aged ≥18 and ≤65 years.

Test Product, Dose, and Mode of Administration, Batch Numbers:

Vortioxetine – 5, 10, or 20 mg/day; tablets; orally

Batch numbers: 2580048, 2586274, 2586283, 2631946, 2635910, 2637546

Duration of Treatment:

The total duration of treatment was 12 weeks

Endpoints

Primary Endpoint

- Safety and tolerability assessed by adverse events (AEs).

Secondary Endpoints

- Depressive symptoms assessed by:
  - Change from baseline to Week 12 in patient health questionnaire (PHQ-9) total score
- Global Clinical Status assessed by:
  - Change from baseline to Week 12 in CGI-S score
  - Clinical Global Impression-Global Improvement (CGI-I) score at Week 12

Statistical Methods:

Adverse events were coded using Medical Dictionary for Regulatory Activities central coding dictionary Version 24.0. Adverse events were classified according to the time of onset of the AE: pre-treatment AE and treatment-emergent AE (TEAE).

The clinical safety laboratory tests and electrocardiogram (ECG) parameters were summarized using descriptive statistics. Potentially clinically significant values were flagged and summarized. The summary of baseline, actual values, and change from baseline by visit were presented for the following vital signs parameters: systolic and diastolic blood pressure, pulse rate, height, weight, and body mass index (BMI). Neurological examination was summarized.

Effectiveness Analysis:

The effectiveness analyses were performed for the full analysis set (FAS). For PHQ-9 and CGI-S scores, descriptive statistics of both actual values and change from baseline were presented based on observed cases (OC) and Last Observation Carried Forward (LOCF) imputed cases. The change from baseline to Weeks 1, 4, and 12 (based on OC) in PHQ-9 total score and CGI-S score was analysed using a mixed model for repeated measurements (MMRM) with site and week as fixed factors, baseline total score as covariate, and baseline score by week interaction. The adjusted mean changes from baseline for PHQ-9 total score and CGI-S score were presented with 2-sided 95% confidence intervals (CIs) and p-values. The number and proportion of remitters at

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each post-baseline visit based on CGI-S (defined as a CGI-S score of 1 or 2) was presented.

For CGI-I, descriptive statistics were presented for the actual values based on OC and values imputed using LOCF Method. The CGI-I score at Weeks 1, 4, and 12 (based on OC) was analysed using MMRM with site and week as fixed factors, baseline CGI-S score as covariate and baseline CGI-S score by week interaction. The adjusted mean for the CGI-I score was presented with 2-sided 95% CIs, and p-values of the hypothesis CGI-I score=4, ie, no change. The number and proportion of responders at Weeks 1, 4, and 12 based on CGI-I (defined as a CGI-I score of 1 or 2) was presented.

No interim analysis was planned for the study.

Subgroup analyses were performed based on sex (male and female), age groups (≤median age and >median age), and baseline severity (PHQ-9 total score: ≤14 and >14).

Summary – Conclusions:

Disposition and Demography:

Out of the 497 patients in the all patients enrolled set, 395 (79.5%) patients took at least 1 dose of vortioxetine (all patients treated set [APTS]) where 392 (78.9%) patients had a valid baseline and at least one valid post-baseline assessment of the PHQ-9 total score (FAS). Most (322/497; 64.8%) of the patients completed this study. A total of 78 (15.7%) patients were withdrawn from the study; withdrawal of consent (62.8%) was the most common reason for withdrawal followed by lost to follow-up (11.5%), AEs (10.3%), and other reasons (10.3%).

Out of 395 patients in the APTS, 228 (57.7%) were males and 167 (42.3%) were females. The mean (standard deviation [SD]) age, height, weight, and BMI of the overall population was 38.9 (11.39) years, 162.3 (8.96) cm, 63.2 (11.18) kg, and 24.0 (3.68) kg/m^2, respectively. The mean (SD) PHQ-9 total score and CGI-S score at baseline was 15.4 (3.37) and 4.5 (0.69), respectively.

Protocol Deviations:

A total of 217 (43.7%) patients had any protocol deviations, where 163 (32.8%) patients had any major protocol deviations, and 103 (20.7%) patients had any minor protocol deviations. The most common major protocol deviation was related to visit schedule criteria (102 [20.5%] patients) followed by informed consent (29 [5.8%] patients). None of the important protocol deviations were considered to have affected the interpretation or conclusions of the study.

Effectiveness Results:

- There was a statistically significant improvement in LS mean (standard error [SE]) PHQ-9 total score from baseline to Week 12 (−9.36 [0.276], p<0.0001). Statistically significant improvement was also observed in other visits (Week 1 [Visit 3] and Week 4 [Visit 4]).
- PHQ-9 subgroup analyses based on sex (male and female), age (age ≤ median age of 39 years and age > median age of 39 years), and baseline severity (PHQ-9 total score: ≤14 and >14) showed statistically significant improvement from baseline to Week 12 (p<0.0001).
- There was a statistically significant improvement in LS mean (SE) CGI-S score from baseline to Week 12 (−2.14 [0.065], p<0.0001).
- There was an increase in the proportion of patients with CGI-S score 1 (normal, not at all ill)/score 2 (borderline mentally ill) from Week 1 (0.3%/1.8%) to Week 12 (19.1%/27.8%), respectively (Remission rate is defined as CGI-S score of 1 and/or 2). The remission rate based on CGI-S improved from 2.0% at Week 1 to 46.9% at Week 12.
- The LS mean (SE) CGI-I score was statistically significant at Week 12 (1.93 [0.067], p<0.0001) compared to CGI-I score=4 (CGI-I score = 4 means 'no change' compared to the reference point, ie, the baseline [where CGI-I is not measured]).
- There was an increase in the proportion of patients with CGI-I score 1 (very much improved)/score 2 (much improved) from Week 1 (0.5%/6.6%) to Week 12 (26.0%/41.1%), respectively (Response rate is defined as CGI-S score of 1 and/or 2). The response rate based on CGI-I improved from 7.1% at Week 1 to 67.1% at Week 12.

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- Overall, statistically significant improvement in effectiveness was observed from Week 1 to Week 12 compared to baseline for PHQ-9 and CGI-S, and at Week 1 to Week 12 for CGI-I after administration of vortioxetine.

Safety Results:

- A total of 140 (35.4%) patients and 4 (1%) patients experienced at least 1 TEAE during the 12-week treatment period and the 4-week Safety Follow-up period, respectively.
- Incidence of TEAEs, by preferred term, occurring in >2% of the patients were nausea and pruritus (6.6% each), headache (4.8%), insomnia (2.8%), and abdominal discomfort and vomiting (2.3% each).
- Most of the TEAEs were mild (25.6%) or moderate (12.9%) in intensity. Only 2 TEAEs (hypothyroidism and depression) were reported to be severe in intensity, which were nonserious and were resolved.
- A total of 93 (23.5%) patients experienced at least one TEAE that was probably/possibly related to vortioxetine.
- Two serious adverse events (SAEs) (Corona Virus Disease-2019 [COVID-19] pneumonia and myocardial infarction) were reported during the treatment period. Both SAEs were moderate in intensity, not related to vortioxetine, and the patients recovered. The event of myocardial infarction led to patient withdrawal from the study.
- No deaths were reported in the study.
- Eight (2%) patients experienced TEAEs (depression; myocardial infarction; insomnia and restlessness; sleep disorder; mania; COVID-19; pruritus; and rash maculopapular) that led to permanent discontinuation of vortioxetine and patient withdrawal.
- There were no clinically meaningful changes from baseline to Weeks 4, 8, or 12 for hematology, liver, urine, electrolytes, kidney, endocrine and metabolic, lipids, or C-reactive protein (infection). All the potentially clinically significant abnormalities were considered TEAEs as per Investigator's discretion.
- No major changes in vital signs and ECG parameters were reported from baseline to Week 4, Week 8, or Week 12.
  - Potentially clinically significant weight abnormalities were reported in 6 patients at Week 4 and in 11 patients at Week 12
  - Potentially clinically significant high QTcB interval of 462 msec at Week 8 and ECG mean heart rate of 134 beats/min at Week 12 were reported in 1 patient.

Conclusion:

Patients treated with vortioxetine 5 to 20 mg/day showed a statistically significant improvement in PHQ-9 total score, and CGI-S, and CGI-I scores over the period of 12 weeks. Additionally, vortioxetine 5 to 20 mg/day was safe and well-tolerated; only 2 SAEs were reported in the study, which were moderate in intensity, not related to vortioxetine, and were resolved. No death was reported in the study. There were no clinically meaningful changes for laboratory, vitals, or ECG parameters during the 12-week treatment period. Overall, flexible doses of vortioxetine (5 to 20 mg/day) were considered safe and well-tolerated and effective in the treatment of patients with MDD in a real-life clinical setting in India over a period of 12 weeks.

Date and Version of Report:

Final, 03 October 2022