Synopsis – Study 18315A

Study Title
Interventional, open-label study of flexible doses of vortioxetine on depressive symptoms in patients with major depressive disorder and early dementia

Investigators
16 principal investigators at 16 sites in 5 countries
Signatory investigator – [redacted]

Study Sites
16 sites – 7 in Poland, 4 in Spain, 1 in Estonia, 3 in Italy, and 1 in France

Publications
None (as of the date of this report)

Study Period
First patient first visit – 19 February 2020 (the date when the first *Informed Consent Form* was signed)
Study terminated – 31 March 2022 (the date on which recruitment was terminated)
Last patient last visit – 20 July 2022 (the date of the last protocol-specified contact with any patient)

Objectives and Endpoints

Objectives	Endpoints
Primary Objective • to assess the effectiveness of 12-week acute treatment with flexible doses of 5-20 mg/day vortioxetine on depressive symptoms in patients with major depressive disorder (MDD) and early dementia	**Primary Endpoint** **Depressive Symptoms** – change from baseline to Week 12 in Montgomery and Åsberg Depression Rating Scale (MADRS) total score
Secondary Objectives • to assess the effectiveness of 12-week acute treatment with 5-20 mg/day vortioxetine on: – cognitive function – functioning – global clinical impression – depression – health-related quality of life	**Secondary Endpoints** **Cognitive Function** – change from baseline to Week 12 in Digit-Symbol Substitution Test (DSST) total score – change from baseline to Week 12 in Rey Auditory Verbal Learning Test (RAVLT) score **Functioning** – change from baseline to Week 12 in Instrumental Activities of Daily Living (IADL) total score **Global Clinical Impression** – change from baseline to Week 12 in Clinical Global Impression – Severity of Illness (CGI-S) score – Clinical Global Impression – Improvement (CGI-I) score at Week 12 **Depression** – response (defined as a ≥50% decrease from baseline in MADRS total score) at Week 12 – remission (defined as a MADRS total score ≤10) at Week 12 **Health-related Quality of Life** – change from baseline to Week 12 in Bath Assessment of Subjective Quality of Life in Dementia (BASQID) score

Exploratory Objective • to explore the effect of vortioxetine on cognitive function via self-administered cognitive tests in a remote environment (Self-test subset)	**Exploratory Endpoint** – change from baseline in Symbols, Grids and Prices test average performance scores up to 12 weeks (the Ambulatory Research in Cognition [ARC] mobile smartphone application)
Safety Objectives • to evaluate the safety and tolerability of 5-20 mg/day vortioxetine	**Safety Endpoints** • adverse events • withdrawals due to adverse events

Study Methodology

- This was an interventional, prospective, multi-national, multi-site, open-label, single-group, vortioxetine flexible-dose study in patients with MDD and early dementia.
- The study consisted of:
  - Screening Period – 14-day period from screening to the Baseline Visit
  - Treatment Period – 12-week open-label, flexible-dose Treatment Period with vortioxetine
  - Safety Follow-up Period – 4-week period after completion of the Treatment Period or after withdrawal from the study.
- All eligible patients were to receive 5 mg vortioxetine as a starting dose once daily for 1 week. At Visit 3 (Week 1), the dose was to be increased to 10 mg/day for all patients. Thereafter, the dose could be adjusted to 5, 10, or 20 mg/day at scheduled and unscheduled visits according to the patient's response and the investigator's judgement. Dosing continued for a further 11 weeks (12 weeks in total).
- Effectiveness data were collected at the Baseline Visit, throughout the Treatment Period (Visits 3, 4, 5 and 6), and at withdrawal (if applicable); safety assessments were performed throughout the study.
- The study was terminated due to slow recruitment. At the time of study termination, ongoing patients were allowed to complete the study.

Number of Patients Planned

100 patients were planned for enrolment.

Diagnosis and Main Selection Criteria

Outpatients with a primary diagnosis of MDD according to DSM-5® criteria, with onset before age of 55 years who:

- had a MADRS total score ≥26 at the Screening Visit and at the Baseline Visit
- were ≥55 and ≤85 years of age
- had a current MDE (confirmed using the Mini International Neuropsychiatric Interview [MINI]). The patient must have had the current MDE for <6 months
- had a diagnosis of current comorbid early dementia, that was not associated with vitamin B12 or folate deficiency, diagnosed at least 6 months prior to screening and after the patient had already been diagnosed with MDD
- had a Mini Mental State Examination, 2nd edition, standard version (MMSE-2:SV) total score of at least 20 and not greater than 24 at the Screening Visit

Investigational Medicinal Product (IMP), Doses and Mode of Administration, Batch Numbers

Vortioxetine – 5 to 20 mg/day, film-coated tablets, orally; batch Nos. 2615224 (5 mg), 2619119 (10 mg), and 2618143 (20 mg)

Duration of Treatment

The total treatment duration was 12 weeks.

Statistical Methodology

- The following analysis sets were used:
  - *all-patients-enrolled set* (APES) – all enrolled patients
  - *all-patients-treated set* (APTS) – all patients in the APES who took at least one dose of IMP
  - *full-analysis set* (FAS) – all patients in the APTS who had a valid baseline assessment and at least one valid post-baseline assessment of the MADRS total score
- Unless otherwise indicated, the effectiveness analyses were based on the FAS, and the safety analyses were based on the APTS.
- The estimates of change from baseline in MADRS total score, corresponding 95% confidence intervals (CIs) and p values were obtained using an MMRM model. The model included Week and Site as fixed factors, and baseline MADRS total score as a covariate on observed cases (OC). The interaction between Week and baseline MADRS total score was included in the model and an unstructured covariance matrix was applied. The Kenward Roger approximation was used to estimate denominator degrees of freedom. The analysis was performed using all available observations. The primary timepoint for change from baseline was Week 12.
- Change from baseline in MADRS total score at all visits was included in summary statistics using OC and last observation carried forward (LOCF). The results of the MMRM were also presented per visit.
- With 100 patients and an assumed SD of 10 points on the change in MADRS total score, a precision with a 95% CI width of 4 points on the MADRS total score was expected.
- The continuous secondary effectiveness endpoints were analysed using a similar MMRM model as for the primary endpoint.
- Response (defined as a ≥50% decrease from baseline in MADRS total score) and remission (defined as a MADRS total score ≤10) rates at Week 12 were summarized and a 95% binomial CI was provided.
- Frequency counts and percentages were presented for each visit for CGI-S and for each post baseline visit for CGI I. All other analyses were based on change from baseline.
- The RAVLT total score was calculated using the sum of the scores for Trials I to V. The short recall was the score from Trial VI, and the delayed recall was the score from Trial VII. Word recognition was also assessed. The statistical analyses were based on change from baseline to Week 12 using descriptive statistics and an MMRM similar to the one used for the primary endpoint.
- Health-related quality of life (QoL) was assessed using the BASQID scale, expressed as a percentage converted. The BASQID scale consists of 3 subscales; Subjective Global Impression of QoL, Life Satisfaction, and Feelings of Positive QoL. Frequency counts and percentages were presented per visit for each item of Subjective Global Impression of QoL. Descriptive statistics were presented for the percentage score per visit for the total score as well as the subscales (Life Satisfaction, and Feelings of Positive QoL). For the total score (based on the sum of Life Satisfaction and Feelings of Positive QoL), the change from baseline was calculated for each timepoint and was analysed using an MMRM analysis as described for the primary endpoint.
- The exploratory endpoint, assessed using the ARC smartphone app, was not analysed, due to low uptake. The endpoint was defined as the change from baseline at the end of the Treatment Period (Week 12) for each of the 3 tests.

Patient Disposition and Analysis Sets

- 83 patients were screened
- 83 patients were enrolled; 1 was subsequently found to be a screen failure, and was excluded from the APTS
- 82 patients were treated
- 69 patients completed the study
- 13 patients withdrew – primary reasons for withdrawal included adverse events (5 [6.0%] patients), other (3 [3.6%] patients), withdrawal of consent (2 [2.4%] patients), and lack of effectiveness, non-compliance with IMP, and protocol deviation (1 [1.2%] patient each)
- 82 patients were analysed – all 82 patients were included in the FAS and APTS

Demographics and Baseline Characteristics of the Study Population

- Approximately two-thirds (66%) of the patients were women. The mean age of the patients was 70.3 years, ranging from 55 to 85 years. Most of the patients were white (95%).
- The number of previous MDEs ranged from 0 to 16 episodes. Amongst the 80 patients who had previous episodes, the average number of previous episodes was 3.7. The mean duration of the current episode was 12 weeks (ranging from 3 to 22 weeks). Sertraline was the most common antidepressant medication taken as previous treatment.
- Alzheimer's disease was the most common type of dementia experienced by patients in the study (35 [43%] patients), followed by mixed type dementia (22 [27%] patients), vascular dementia (12 [15%] patients) and 'other' types of dementia (11 [13%] patients).
- The mean baseline effectiveness scores are as follows:
  - MADRS total score of 30.4 points (corresponding to *moderate* depression)
  - DSST total score of 23.3 points
  - RAVLT total score of 28.7 words
    - short recall score of 4.5 words
    - delayed recall score of 4.1 words
    - recognition score of 8.9 words
  - IADL total score of 5.5 points
  - IADL polytomous score of 15.6 points
  - CGI-S score of 4.6 points
  - BASQID total score of 17.5 points
    - Life Satisfaction score of 9.4 points
    - Feelings of Positive QoL score of 8.1 points

Effectiveness Results

- In the primary analysis of the primary endpoint, change from baseline to Week 12 in the MADRS total score, the LS mean change from baseline to Week 12 was −12.4 points ($p < 0.0001$, MMRM). Overall, there was a statistically significant decrease in MADRS total score, indicating a reduction in depression symptoms in the study population.
- Overall, the results of the analyses of the secondary effectiveness endpoints were consistent with those of the primary effectiveness endpoint and showed significant improvement ($p < 0.0001$, MMRM) across the DSST, CGI-S, and BASQID total score at Week 12. There was a significant change from baseline in both the BASQID Life Satisfaction and QoL scores at Week 4 and Week 12, indicating a significant improvement in health-related QoL in the study population.
- The CGI-I score at both Week 4 (LS mean 3.4) and at Week 12 (LS mean 2.8) was lower than 4, indicating a patient's improvement on average in the study population.
- The LS mean change from baseline in the RAVLT total scores were statistically significant at Week 4 (2.1, $p = 0.0110$) and at Week 12 (2.1, $p = 0.0199$). Short recall (Trial VI) improved over time; the changes were statistically significant at both Week 4 (LS mean of 0.6, $p = 0.0361$) and Week 12 (LS mean of 0.7, $p = 0.0176$). Delayed recall improved from baseline to Week 4 ($p = 0.0047$), an effect which was maintained until Week 12. Recognition improved only at Week 4 (LS mean of 1.1, $p = 0.0005$), before returning to levels comparable with baseline at Week 12.
- There was no significant change in the level of functioning in the total population as assessed by the IADL total score, with minimal change from baseline at any timepoint, meaning that the baseline level of functioning was maintained throughout the study, however, a significant improvement was observed in women. At Week 12, the LS mean change from baseline in the IADL total score analysed using the MMRM in the total population was 0.1 points ($p = 0.2401$), indicating that the patients' ability to perform activities of daily living did not decline over the 12 weeks of the study. The corresponding mean change from baseline in women was 0.26 points ($p = 0.0308$), indicating a significant improvement. When using the IADL polytomous score, a significant improvement in the level of functioning was observed at Week 12 in the total population (−0.86 points [p=0.0094]), and in women, the improvement was observed already from Week 1 (−0.44 points [p=0.0436]).
- Response at Week 12, defined as at least a 50% decrease from baseline in the MADRS total score, was observed in 25 (36%) patients in the study population. Remission at Week 12, defined as a MADRS total score of 10 or less, was observed in 12 (17%) patients in the study population.

Safety Results

The treatment-emergent adverse event (TEAE) incidence in the Treatment and Safety Follow-Up Periods are summarized below:

Overall Incidence	**Vortioxetine (N=82) n (%) [#events]**
Treatment Period	
Patients with TEAEs	38 (46.3) [56]
Patients with SAEs	1 (1.2) [1]
Patients with TEAEs leading to IMP withdrawal	6 (7.3) [8]
Patients with SAEs leading to IMP withdrawal	1 (1.2) [1]
Safety Follow-up Period	
Patients with TEAEs	1 (1.2) [2]
Patients with SAEs	1 (1.2) [1][a]

a 1 adverse event of cardiac failure, which was assessed as non-serious by the investigator, was subsequently upgraded to *serious* in Lundbeck's safety database, and is therefore not included in the count presented here

IMP = investigational medicinal product; N = number of patients in each group; n = number of observations; SAE = serious adverse event; TEAE = treatment-emergent adverse event

- In the Treatment Period, 38 (46%) patients had 1 or more TEAEs. One patient had 2 TEAEs during the Safety Follow up Period.
- There were 2 SAEs reported by the investigator in 1 patient; 1 event in the Treatment Period, and 1 event in the Safety Follow-up Period. Furthermore, an additional event of *cardiac failure* in the Safety Follow-up Period in the same patient was reported by the investigator as a non serious adverse event but was upgraded to an SAE by Lundbeck (based on the Important Medical Event criterion).
- The system organ classes (SOCs) with the highest incidences (>2%) of TEAEs were *gastrointestinal disorders* (27%), *nervous system disorders* (16%), *infections and infestations* (5%), *musculoskeletal and connective tissue disorders*, *psychiatric disorders*, *skin and subcutaneous tissue disorders* (4% each), and *metabolism and nutrition disorders* (2%).
- The TEAEs with an incidence >2% in the Treatment Period were *nausea* and *abdominal pain* (11% each), *headache* (7%), *diarrhoea*, *dizziness*, *nasopharyngitis*, *pruritus* (4% each) and *psychomotor hyperactivity*, *somnolence* and *spinal pain* (2% each).
- One patient had a *severe* TEAE of *COVID-19 pneumonia* within the SOC of *infections and infestations*, which resulted in 1 of the SAEs observed in the study. This event was deemed *not related* to IMP. The same patient also had the SAE of *bacterial pneumonia* and the TEAE *cardiac failure* (upgraded to SAE by Lundbeck). All remaining TEAEs were either *mild* or *moderate*.
- A total of 8 TEAEs in 6 patients led to withdrawal from the study. There were 2 TEAEs of *headache*, 2 TEAEs of *nausea*, and a single TEAE each of *anxiety*, *pruritus*, *psychomotor hyperactivity* and *COVID-19 pneumonia*.
- No deaths were reported.
- Overall, vortioxetine was safe and well tolerated in this study population.

Conclusions

The primary effectiveness analysis showed a significant reduction in depression symptoms after treatment with vortioxetine 5 to 20 mg/day for 12 weeks, based on the LS mean change from baseline in MADRS total score at Week 12 in patients with MDD with comorbid early dementia. Significant improvement was observed from Week 1 and increased to Week 12 of treatment.

Overall, the results of the analyses of the secondary effectiveness endpoints were consistent with those of the primary effectiveness endpoint and showed significant improvement across the DSST, RAVLT, CGI-S, and BASQID total score at Week 12. There was a significant change from baseline in both the BASQID Life Satisfaction and QoL scores at Week 4 and Week 12, indicating a significant improvement in health-related QoL in the study population. The LS mean change from baseline to Week 12 in CGI-S score analysed using the MMRM indicated a significant reduction in the illness severity of the study population.

The CGI-I score at both Week 4 and at Week 12 was lower than 4, indicating a patient's improvement on average in the study population.

The LS mean change from baseline in the RAVLT total scores were statistically significant at Week 4 and at Week 12. Short recall improved over time; the changes were statistically significant at both Week 4 and Week 12. Delayed recall improved from baseline to Week 4, an effect which was maintained until Week 12. Recognition improved only at Week 4, before returning to levels comparable with baseline at Week 12.

There was no significant change in the level of functioning in the total population as assessed by the IADL total score, with minimal change from baseline at any timepoint, meaning that the baseline level of functioning was maintained throughout the study, however, a significant improvement was observed in women. When using the IADL polytomous score, a significant improvement in the level of functioning was observed at Week 12 in the total population, and in women, the improvement was already observed from Week 1.

Overall, vortioxetine was safe and well tolerated in this population. The safety and tolerability profile was comparable to what has been observed in previous clinical studies of vortioxetine in adults with MDD, except for a higher incidence of *abdominal pain*.

Report Date

9 December 2022

This study was conducted in compliance with *Good Clinical Practice*.