Synopsis – Study 18314A

Study Title
Interventional, open-label effectiveness study of flexible doses of vortioxetine on depressive symptoms in patients with major depressive disorder comorbid with generalized anxiety disorder

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

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

Publications
None (as of the date of this report)

Study Period
First patient first visit – 27 December 2019 (the date when the first *Informed Consent Form* was signed)
Last patient last visit – 9 March 2021 (the date of the last protocol-specified contact with any patient)

Objectives and Endpoints

Objectives	Endpoints
Primary Objective • to assess the effectiveness of 8-week acute treatment with 10 to 20 mg/day vortioxetine on depressive symptoms in patients with major depressive disorder comorbid with generalized anxiety disorder (GAD)	**Depressive Symptoms** • Primary endpoint: – change from baseline in Montgomery and Åsberg Depression Rating Scale (MADRS) total score at Week 8 • Secondary endpoints: – response (defined as a ≥50% decrease from baseline in MADRS total score) at Week 8 – remission (defined as a MADRS total score ≤10) at Week 8
Secondary Objectives • to assess the effectiveness of vortioxetine on: – anxiety symptoms – functioning – global clinical impression – health-related quality of life	**Anxiety Symptoms** • Secondary endpoints: – change from baseline to Week 8 in Hamilton Anxiety Rating Scale (HAM-A) total score – change from baseline to Week 8 in Hospital Anxiety and Depression Scale (HADS) total score (HADS A- and D-subscales are presented) • Exploratory endpoints: – HAM-A response defined as a ≥50% decrease from baseline in HAM-A total score at Week 8 – HAM-A remission defined as a HAM-A total score ≤10 at Week 8 **Functioning** • Secondary endpoint: – change from baseline to Week 8 in Functioning Assessment Short Test (FAST) total score and the domain scores

Objectives and Endpoints (continued)

Objectives	Endpoints
	Clinical Global Impression • Secondary endpoints: – change from baseline to Week 8 in Clinical Global Impression - Severity of Illness (CGI-S) score – Clinical Global Impression - Global Improvement (CGI-I) score at Week 8 • Exploratory endpoints: – CGI-I response defined as a CGI-I score ≤2 at Week 8 – CGI-S remission defined as a CGI-S score ≤2 at Week 8 **Health-related Quality of life** • Secondary endpoint: – change from baseline to Week 8 in Quality of Life Enjoyment and Satisfaction Questionnaire Long Form (Q-LES-Q LF) domain scores **Composite Response and Composite Remission** • Exploratory endpoints: – MADRS response and HAM-A response at Week 8 – MADRS remission and HAM-A remission at Week 8
Safety Objectives • to evaluate the safety and tolerability of 10 to 20 mg flexible-dose vortioxetine	**Safety Endpoints** • adverse events • withdrawals due to adverse events

Study Methodology

- This was an interventional, prospective, multi-national, multi-site, open-label, flexible-dose study.
- The study consisted of:
  - Screening Period – a period of up to 14 days from screening to before the Baseline Visit
  - Treatment Period – 8-week, open-label, flexible-dose treatment period with vortioxetine
  - Safety Follow-up Period – 4-week period after the end of the Treatment Period
- Of the 100 patients planned to be enrolled, approximately 50 patients were planned to receive vortioxetine as a first-treatment for the current Major Depressive Episode (MDE) (First-Treatment Group) and the remaining 50 patients were planned to be switched to vortioxetine due to inadequate response to the current antidepressant medication treatment (Switch Group).
- The starting dose was 10 mg/day vortioxetine at Visit 2 (Week 0). At Visit 3 (Week 1), the dose was to be increased to 20 mg/day for all patients. The dose could be adjusted to 10 or 20 mg/day at scheduled or unscheduled visits depending on the patients' response as per investigator judgement.
- Effectiveness data were collected at baseline, throughout the Treatment Period (Visits 3, 4, and 5), and at withdrawal; safety assessments were performed throughout the study.

Number of Patients Planned

100 patients were planned for enrolment.

Diagnosis and Main Selection Criteria

Outpatients with a primary diagnosis of recurrent MDE according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5®) criteria confirmed using the Mini International Neuropsychiatric Interview (MINI), who:

- had had the current MDE for <12 months

- had current comorbid GAD according to DSM-5® (diagnosed prior to the current MDE)
- had a MADRS total score ≥22 at the Screening and Baseline Visits
- had a HAM-A score ≥20 at the Screening and Baseline Visits
- were ≥18 and ≤65 years of age

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

Vortioxetine – 10 or 20 mg/day; tablets, orally; batch numbers: P1964 (10 mg) and P1965 (20 mg)

Duration of Treatment

8 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. All continuous endpoints are presented with descriptive statistics for both absolute values and changes from baseline based on observed cases data and if possible, on last observation carried forward data.
- The primary analysis of the primary endpoint, the change from baseline in MADRS total score, was analysed using a mixed model for repeated measurements (MMRM), and the model included Week and Site as fixed factors, and baseline MADRS total score as a covariate. 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 based on all available observations. The main time point for comparison was Week 8, which constituted the primary analysis.
- The same methodology as that described for the primary analysis was used for all secondary endpoints except for response and remission. All analyses were based on change from baseline, except for the analyses of CGI-I, response, and remission. Response and remission rates are presented using frequency counts and percentages and with a 95% binomial CI.
- The exploratory response and remission rates are presented using descriptive statistics and a 95% binomial CI. The response and remission rates were based on the actual number of patients at each visit.
- The associations between the change from baseline to Week 8 in the HAM-A total score and the change from baseline to Week 8 in FAST total score were described using standard Pearson correlation coefficients and the partial correlation coefficients conditional on the baseline HAM-A total score and the baseline FAST total score.
- With the sample size of 100 patients enrolled and an assumed equal standard deviation of 10 points on the change in MADRS total score in each of the patient groups, a precision with a 95% CI width of 4 points on the MADRS total score was expected.

Patient Disposition and Analysis Sets

- 104 patients were screened.
- Patient disposition is summarized below:

Disposition	First-Treatment Group n (%)	Switch Group n (%)	Total n (%)
Patients enrolled (APES)	23	79[a]	102
Patients treated (APTS)	23	77	100
Patients who completed study	20 (87.0)	77 (97.5)	97 (95.1)
Patients who withdrew from the study	3 (13.0)	0	3 (2.9)
Primary reason for withdrawal from study			
Adverse event	2 (8.7)	0	2 (2.0)
Withdrawal of consent	1 (4.3)[b]	0	1 (1.0)
FAS	23 (100)	77 (97.5)	100 (98.0)

a Two patients withdrew prior to the intake of the first dose of IMP.

b Additional reasons for withdrawal were *adverse event* and *lack of efficacy*.

Demographics and Baseline Characteristics of the Study Population

- Across both patient groups, nearly two-thirds (63%) of the patients were women. The mean age of the patients was 42 years, ranging from 20 to 65 years. Most of the patients were white (79%). The two patient groups were comparable and no notable differences were observed.
- The number of previous MDEs ranged from 1 to 20 episodes with a mean of 2. The average number of previous episodes in the First-Treatment Group and Switch Group was 3 and 2, respectively (median slightly lower in the First-Treatment group). The mean duration of the current episode was 15 weeks (ranging from 0 to 45 weeks). In the Switch Group, escitalopram was the most common antidepressant medication taken as previous treatment.
- With respect to baseline effectiveness scores, the patient groups were comparable. The mean effectiveness scores are as follows:
  - MADRS total score of 29.5 points (corresponding to *severe* depression)
  - HAM-A total score of 28.6 points (corresponding to *severe* anxiety)
  - HADS A-subscale score of 14.2 points
  - HADS D-subscale score of 14.7 points
  - FAST total score of 42.1 points
  - CGI-S score of 4.9 points
  - Q-LES-Q LF domain scores converted to percentage;
    - physical health/activities score of 30
    - feelings score of 37
    - work score of 36
    - household duties score of 40
    - school/course work score of 19
    - leisure time activities score of 26
    - social relations score of 35
    - general activities score of 39
    - satisfaction with medication score of 41
    - overall satisfaction and contentment score of 25

Effectiveness Results

- In the primary analysis of the primary endpoint, change from baseline to Week 8 in MADRS total score, there was a significant decrease in MADRS total score, indicating a reduction in depression symptoms. The mean change from baseline to Week 8 in MADRS total score was -17 points ($p < 0.0001$, MMRM).
- Overall, the results of the analyses of the secondary effectiveness endpoints were in line with those of the primary effectiveness analysis and showed significant improvement ($p < 0.0001$, MMRM) across all clinical outcome assessments at Week 8. The mean changes from baseline to Week 8 indicated significant reduction in anxiety (HAM-A and HADS A-subscale) and depressive symptoms (HADS D-subscale and MADRS response and remission), with a significantly improved overall functioning (FAST) and health-related quality of life (Q-LES-Q LF). Additionally, on the CGI, there was a significant reduction in illness severity (CGI-S) at Week 8 and the CGI-I score decreased significantly over time compared to a CGI-I score of 4 (that is, no change).
- Response at Week 8, defined as at least 50% decrease in MADRS total score was observed in 61% of the patients.
- Remission at Week 8, defined as a MADRS total score of 10 or less was observed in 35% of the patients.
- For all the study endpoints, a difference from baseline was already significant from Week 1 and the effect increased by Week 8.
- Over time, the exploratory analyses showed increasing response (CGI-I, HAM-A, and composite response on both MADRS and HAM-A) and remission rates (CGI-S, HAM-A, and composite remission on both MADRS and HAM-A). The mean change from baseline at Week 8 in HAM-A total score and the mean change from baseline at Week 8 in FAST total score measured using standard Pearson correlation coefficients and partial correlation coefficients showed a significant correlation (0.63 and 0.76, respectively), indicating that lesser anxiety was associated with the greater overall functioning.
- The results of the primary and secondary effectiveness analyses were generally similar in both the patient groups.

Safety Results

The adverse event incidence in the Treatment Period is summarized below:

	First-Treatment Group N=23 (n%)	**Switch Group N=77 (n%)**	**Total N=100 (n%)**
Patients with TEAEs	15 (65.2)	31 (40.3)	46 (46.0)
Patients with SAEs	0	0	0
Patients with TEAEs leading to withdrawal	3[a] (8.7)	0	2 (2.0)
Total number of TEAEs	23	38	61

a One patient had a TEAE leading to withdrawal in the Safety Follow-Up Period.

- In the Treatment Period, 46.0% of the patients had one or more TEAEs. The incidence of TEAEs in the Treatment Period was higher in the First-Treatment Group (15 of 23 patients [65%]) than in the Switch Group (31 of 77 patients [40%]).
- One TEAE occurred during the 4-week Safety Follow-up Period.
- No patients had any SAEs.
- The system organ classes (SOCs) with the highest incidences (>2%) of TEAEs were *gastrointestinal disorders* (30%), *nervous system disorders* (7%), *psychiatric disorders* (7%), and *musculoskeletal and connective tissue disorders* (3%).
- The TEAEs with an incidence >2% in the Treatment Period were *nausea* (21%), *abdominal pain* (6%), *anxiety* (3%), *back pain* (3%), and *dizziness* (3%).
- All TEAEs were either *mild* or *moderate*; hence, no patients had any *severe* TEAEs.
- Three patients (3%) had TEAEs leading to withdrawal. The TEAEs of *blood pressure increased*, *dysgeusia*, and *hypersensitivity* led to the withdrawal in individual patients.

Conclusions

- The primary effectiveness analysis showed a significant reduction in depression symptoms after treatment with vortioxetine 10 to 20 mg/day for 8 weeks, based on the mean change from baseline in MADRS total score at Week 8 in patients with MDD with comorbid GAD. Significant improvement was observed from Week 1 and increased to Week 8 of treatment.
- Overall, the results of the analyses of the secondary effectiveness endpoints were in line with those of the primary effectiveness analysis. There was a significant reduction in anxiety symptoms as measured by the HAM-A and HADS A-subscale, illness symptoms as measured by the CGI-S, and depression symptoms as measured by response and remission based on the MADRS and by the HADS D-subscale, and significant improvement in overall functioning as measured by the FAST and health-related quality of life as measured by the Q-LES-Q LF. The patients' condition as measured by the CGI-I significantly improved over time compared to a CGI-I score of 4 (that is, no change).
- Vortioxetine was generally safe and well tolerated. The safety and tolerability profile was comparable to what has been observed in previous clinical studies of vortioxetine in adults with MDD.

Report Date

09 September 2021

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