Synopsis – Study 17797A

Study Title Interventional, open-label, flexible-dose study of vortioxetine on emotional functioning in patients with major depressive disorder with inadequate response to SSRI/SNRI treatment	
Investigators 23 principal investigators at 23 sites in 4 countries *Signatory investigator* – [redacted]	
Study Sites 23 sites – 7 in France, 3 in Italy, 6 in Lithuania, and 7 in Spain	
Publications None (as of the date of this report)	
Study Period *First patient first visit* – 5 February 2019 (the date when the first *Informed Consent Form* was signed) *Last patient last visit* – 21 February 2020 (the date of the last protocol-specified contact with any patient)	
Objectives and Endpoints	
Objectives	**Endpoints**
Primary Objective	*Primary Endpoint*
• to evaluate the effectiveness of 10-20 mg flexible-dose vortioxetine after 8 weeks of treatment on emotional functioning in patients with major depressive disorder (MDD) with inadequate response to selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor (SSRI/SNRI) treatment who are candidates for a switch and have a desire to change medication	• emotional functioning – change from baseline to Week 8 in Oxford Depression Questionnaire (ODQ) total score

Objectives and Endpoints (continued)	
Objectives	**Endpoints**
Secondary Objective	*Secondary Endpoints*
• to evaluate the effectiveness of 10-20 mg flexible-dose vortioxetine after 8 weeks of treatment on: – motivation and energy – family, social, and work functioning – cognitive functioning – depressive symptoms	• motivation and energy – change from baseline to Week 8 in Motivation and Energy Inventory (MEI) total score and subscale scores (mental or cognitive energy, social motivation, and physical energy) • emotional functioning – change from baseline to Week 8 in ODQ domain scores (not caring [NC], emotional detachment [ED], positive reduction [PR], general reduction [GR], and antidepressant as cause [AC], PR-NC, and GR-ED) and ODQ total score calculated only from sections 1 and 2 of the questionnaire (excluding items related to the *Antidepressants as Cause* domain) – answer to the screening question on emotional functioning at Week 8 • overall functioning – change from baseline to Week 8 in Sheehan Disability Scale (SDS) total and individual item scores (family life/home responsibilities, social life, and work/school) – change from baseline to Week 8 in *Days Lost* and *Days Underproductive* as collected in the SDS questionnaire – 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 – response at Week 8 based on the CGI-I (defined as a CGI-I score of 1 or 2) – remission at Week 8 based on the CGI-S (defined as a CGI-S score of 1 or 2) • cognitive functioning – change from baseline to Week 8 in Digit-Symbol Substitution Test (DSST) total score • depressive symptoms – change from baseline to Week 8 in Montgomery and Åsberg Depression Rating Scale (MADRS) total score – change from baseline to Week 8 in MADRS anhedonia factor score – response at Week 8 based on the MADRS (defined as ≥50% reduction in MADRS total score compared to baseline) – remission at Week 8 based on the MADRS (defined as MADRS total score of ≤10)

Objectives and Endpoints (continued)	
Objectives	**Endpoints**
Safety Objectives	*Safety Endpoints*
• to evaluate the safety and tolerability of 10-20 mg/day flexible-dose vortioxetine • to assess potential discontinuation symptoms following abrupt discontinuation of the previous treatment with an SSRI/SNRI and initiation of treatment with vortioxetine	• adverse events • potential discontinuation symptoms assessed at Week 1 after abrupt discontinuation of the current SSRI/SNRI by Discontinuation-Emergent Signs and Symptoms Scale (DESS) total score

Study Methodology

- This was an interventional, prospective, multi-national, multi-site, open-label, flexible-dose study.
- The study consisted of:
  - Treatment Period – 8-week, open-label, flexible-dose treatment period with vortioxetine
  - Safety Follow-up Period – 4-week period after the Primary Outcome Visit or Withdrawal Visit
- At the Baseline Visit, the patients were switched from their previous treatment with an SSRI/SNRI to vortioxetine 10 mg/day. After the first week of treatment, the dose of vortioxetine could be increased to 20 mg/day or remain at 10 mg/day. The dose could be adjusted (to 10 or 20 mg/day) at scheduled or unscheduled visits up to Visit 4 (Primary Outcome Visit).
- Safety data were collected throughout the study.

Number of Patients Planned

150 patients were planned for enrolment.

Diagnosis and Main Selection Criteria

Outpatients with a primary diagnosis of single or recurrent MDD according to DSM-5® criteria, who:

- had been treated with SSRI/SNRI monotherapy for at least 6 weeks at an adequate dose for the current major depressive episode (MDE) and with an inadequate response
- during previous treatment with SSRI/SNRI monotherapy, had experienced emotional blunting, as assessed using the screening question on emotional effect
- had an ODQ total score ≥50 at the Baseline Visit, while on SSRI/SNRI monotherapy
- had a MADRS total score ≥22 and ≤28 at the Baseline Visit
- 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 Nos. 2541565, 2619119 (10 mg); 2572009, 2618143 (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 ODQ total score
- Unless otherwise indicated, the effectiveness analyses were based on the FAS and the observed case (OC) data. All continuous endpoints were presented with descriptive statistics for both absolute values and changes from baseline based on OC data and on last observation carried forward (LOCF) data. The safety analyses were based on the APTS.
- The primary effectiveness analysis was the change from baseline in ODQ total score analysed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM), and the model included the following fixed effects: site and week as factors, baseline ODQ score as a continuous covariate, and baseline score-by-week interaction. An unstructured covariance structure was used to model the within-patient errors. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. The analysis was based on all available observations (OC data).
- The potential influence of additional covariates on the primary endpoint was investigated using an analysis of covariance (ANCOVA) model (OC) at Week 8 (including site as a factor and baseline value as a covariate) by adding main terms separately as additional covariates or fixed factors to the model. The covariates or fixed factors investigated were age, sex, and type of SSRI/SNRI previously taken, number of previous MDEs, and duration of current MDE.
- The same methodology described above for the ODQ total score analysis was used for all secondary endpoints, except for answers to the screening question, response, and remission. All analyses included the baseline score for the specific endpoint as the baseline covariate, except for the CGI-I, where the baseline score for the CGI-S was used. All analyses were based on change from baseline, except for the CGI-I (where the absolute value was used) and analyses of response, remission, and answers to the screening question on emotional effects.
- Answers to the screening question on emotional effects at Week 8 and response and remission at each visit are presented using descriptive statistics and with two-sided 95% confidence intervals (CIs) using the Wald method. For response and remission, descriptive statistics and CIs are presented for OC, LOCF, and non-response imputation (NRI) data.
- The associations between the change from baseline to Week 8 in ODQ total score and the changes from baseline to Week 8 in SDS, SDS subdomains, MEI, CGI-S, MADRS, MADRS anhedonia factor, and DSST scores were described using standard Pearson correlation coefficients and the partial correlation coefficients conditional on the baseline ODQ total score and the baseline score for the other clinical outcome assessments.
- The sample size of 150 patients enrolled was calculated assuming a withdrawal rate of 15% and a standard deviation of 11.5, half the width of the 95% CI on the change from baseline in ODQ total score would be approximately 2 points. Assuming an improvement in the ODQ total score of 3 points for patients treated with vortioxetine would result in an approximately 83% chance of the 95% CI not containing 0.

Patient Disposition and Analysis Sets

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

	Vortioxetine 10-20mg n	(%)
Patients enrolled	151	
Patients treated (APTS)	150	(100)
Patients completed	131	(87.3)
Patients withdrawn	19	(12.7)
Primary reason for withdrawal:		
Adverse event(s)	6	(4.0)
Lack of efficacy	2	(1.3)
Protocol violation	3	(2.0)
Withdrawal of consent	1	(0.7)
Lost to follow-up	6	(4.0)
Other	1	(0.7)
Analysis sets:		
APTS	150	
FAS	143	

Demographics and Baseline Characteristics of the Study Population

- Approximately two-thirds of the patients were women. The mean age of the patients was 47 years, ranging from 19 to 65 years. Escitalopram was the most common (42%) medication taken as previous SSRI/SNRI monotherapy treatment .
- The proportion of patients who had not had an MDE before the current one was 38%. The mean duration of the current episode was 22 weeks (ranging from 3 to 56 weeks).
- At Baseline, the patients in the FAS had the following mean effectiveness scores:
  - ODQ total score of 89 points
  - MADRS total score of 25 points (corresponding to *moderate* to *severe* MDD)
  - CGI-S score of 4.5 points (corresponding to *moderately* to *markedly ill*)
  - DSST total score of 45 points
  - MEI total score of 44 points
  - SDS total score of 20 points

Effectiveness Results

- In the primary effectiveness analysis, change from baseline to Week 8 in ODQ total score, there was a significant improvement in emotional symptoms. The mean change from baseline to Week 8 in ODQ total score was -29.8 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 improvement in motivation and energy (MEI); family, social, and work/school functioning (ODQ, SDS, CGI); cognitive functioning (DSST); and depressive symptoms (MADRS). Additionally, there was a significant improvement in mean CGI-S score at Week 8 (-1.83 points [$p < 0.0001$, MMRM]).
- At the Baseline Visit, all patients answered "Yes" to the screening question asking if they had experienced emotional effects (such as feeling emotionally "numbed" or "blunted"; lacking positive or negative emotions; "just not caring" about things) during the last 6 weeks. The patients were asked the same question at Week 8 and approximately half (49%) of the patients reported absence of emotional effects, indicating an improvement in their emotional symptoms.
- Response at Week 8 (OC) was observed in 73% of the patients based on the CGI-I and in 62% of the patients based on the MADRS.
- Remission at Week 8 (OC) was observed in 48% of the patients based on the CGI-S and 47% based on the MADRS.
- The change in ODQ total score and other scores, measured using Pearson correlation and partial correlation, showed a strong association (-0.74 and -0.78) with change in MEI total score and a moderate strength association (0.46 to 0.66) with the SDS, CGI-S, and MADRS scores, which suggests that an improvement in emotional functioning was associated with better outcomes in motivation and energy, patient disability, clinical impression, as well as depressive symptoms.

Safety Results

- The adverse event incidence is summarized below for the entire study from baseline up to and including the Safety Follow-up Period:

	Vortioxetine 10-20mg n	(%)
Patients treated	150	(100)
Patients who died	0	
Patients with treatment-emergent serious adverse events (SAEs)	1	(0.7)
Patients with treatment-emergent adverse events (TEAEs)	71	(47.3)
Patients with TEAEs leading to withdrawal	6	(4.0)
Total number of treatment-emergent SAEs	1	
Total number of TEAEs	178	
Total number of TEAEs leading to withdrawal	14	

- In the Entire Period after Baseline, 47% of the patients had one or more TEAEs. All TEAEs occurred during the treatment period and no TEAE occurred during the 4-week Safety Follow-up Period.
- The system organ classes (SOCs) with the highest incidences (≥5%) were *gastrointestinal disorders* (29%), *nervous system disorders* (17%), *psychiatric disorders* (13%), and *skin and subcutaneous tissue disorders* (9%).
- The TEAEs with an incidence ≥5% in the Entire Period after Baseline were *nausea* (21%), *headache* (8%), *dizziness* (7%), *vomiting* (7%), and *diarrhoea* (6%).
- The TEAEs were *mild* or *moderate* for the majority of the patients with TEAEs. A total of 4 patients had severe TEAEs, and the only *severe* TEAE that occurred in >1 patient was *vomiting* (2 patients).
- None of the patients died during the study. One patient had an SAE (*abortion missed*). The patient reported the pregnancy on Day 36 and had *abortion missed* on Day 42. The investigator assessed the event to be *not related* to IMP. The patient completed the study.
- Six patients (4.0%) had TEAEs leading to withdrawal. TEAEs within the SOC *gastrointestinal disorders* were the most frequent TEAEs leading to withdrawal: *vomiting* (2.7%), *nausea* (2.0%), and *diarrhoea* (1.3%).
- The mean DESS total score at Week 1 increased from the baseline mean value of 1.9 points to 2.2 points. DESS items that were reported to be a *new symptom* or *old symptom but worse* in ≥6% of the patients at Week 1 were *nervousness or anxiety*; *irritability*; *trouble sleeping*, *insomnia*; *increased dreaming or nightmare*; and *nausea*. In addition to potential discontinuation symptoms, the symptoms at Week 1 may be a manifestation of the underlying disease or adverse events related to the initiation of vortioxetine.

Conclusions

- The primary effectiveness analysis showed a significant improvement in emotional functioning after treatment with vortioxetine 10 to 20 mg/day for 8 weeks, based on the mean change from baseline in ODQ total score at Week 8 in patients with MDD with inadequate response to SSRI/SNRI treatment.
- Overall, the results of the secondary effectiveness endpoints were in line with those of the primary effectiveness analysis and indicated significant improvement in motivation and energy; family, social, and work/school functioning; cognitive functioning; and depressive symptoms. Moreover, almost 50% of the patients reported absence of emotional effects after 8 weeks of treatment with vortioxetine.
- 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. The evaluation of discontinuation symptoms did not indicate any safety concerns related to an abrupt discontinuation of an SSRI/SNRI to initiate vortioxetine treatment.

Report Date

20 January 2021

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