Synopsis – Study 12712B

Study Title Long-term, open-label, flexible-dose, continuation extension study with vortioxetine in child and adolescent patients with Major Depressive Disorder (MDD) from 7 to 17 years of age
Investigators 31 principal investigators at 31 sites in 13 countries *Signatory investigator* – [redacted]
Study Sites 31 sites – 2 in Bulgaria, 1 in Estonia, 1 in France, 1 in Germany, 2 in Hungary, 2 in Italy, 1 in Latvia, 6 in Poland, 9 in Russia, 2 in Serbia, 1 in South Africa, 2 in Spain, and 1 in United Kingdom
Publications None (as of the date of this report)
Study Period *First patient first visit* – 1 March 2017 (the date when the first *Informed Consent Form* was signed) *Last patient last visit* – 16 April 2020 (the date of the last protocol-specified contact with any patient)

Objectives and Endpoints	
Objectives	**Endpoints**
Primary Objective • to evaluate the long-term safety and tolerability of vortioxetine in child and adolescent patients with a DSM-5® diagnosis of MDD	**Safety Endpoints** • adverse events (AEs) • tolerability including assessment based on PAERS • Tanner score • absolute values and changes from OLEXB/OLEXA in clinical safety laboratory tests, vital signs, weight, height, and ECG parameters • length of menstrual cycle • potentially clinically significant (PCS) clinical safety laboratory test values, vital signs, weight, and ECG parameter values relative to OLEXB/OLEXA • C-SSRS categorization
Secondary Objectives • to evaluate the long-term effectiveness of flexible doses of vortioxetine in a range of 5 mg/day to 20 mg/day on: – depressive symptoms	**Depressive Symptoms** • Secondary endpoints: – change from OLEXB/OLEXA to Week 78/104 in CDRS-R total score – remission (defined as a CDRS-R total score ≤28) – relapse during the treatment period (defined as a CDRS-R total score ≥40) – loss of remission during the treatment period (defined as a CDRS-R total score >28)
– clinical global impression	**Global Clinical Impression** • Secondary endpoints: – change from OLEXB/OLEXA to Week 78/104 in CGI-S score – remission (defined as a CGI-S score of 1 or 2) – CGI-I score at Week 78 (relative to Enrolment in the lead-in studies)
– cognitive function	**Cognitive Function (Children/Adolescents)Secondary endpoints:** – change from OLEXB/OLEXA to Week 78/104 in BRIEF-P/BRIEF-SR using the *Global Executive Composite* score – change from OLEXB/OLEXA to Week 78/104 in BRIEF-P/BRIEF-SR using the *Metacognition Index*

BRIEF-P = Behavioural Rating Inventory of Executive Function (Parent form); BRIEF-SR = Behavioural Rating Inventory of Executive Function – Self Report (adolescent); CGAS = Children's Global Assessment Scale; CGI-S = Clinical Global Impression – Severity of Illness; CGI-I = Clinical Global Impression – Global Improvement; C-SSRS = Columbia-Suicide Severity Rating Scale; OLEXA = baseline in Study 12712A; OLEXB = baseline in Study 12712B; PAERS = Paediatric Adverse Event Rating Scale; PedQL = Pediatric Quality of Life Inventory; VAS = Visual Analogue Scale

Objectives and Endpoints (continued) **Objectives**	**Endpoints**
– functionality	**Functionality** • Secondary endpoints: – change from OLEXB/OLEXA to Week 78/104 in CGAS score – change from OLEXB/OLEXA to Week 78/104 in PedsQL™ VAS score

Study Methodology

- This was an interventional, prospective, multi-national, multi-site, open-label, flexible-dose, long-term, extension study.
- The population enrolled in Study 12712B were patients aged 7 to 17 years who had completed treatment in Study 12712A.
- The study consisted of:
  - a Treatment Period – 78-week treatment period with vortioxetine 5 to 20 mg/day
  - a Safety Follow-up Period – 4-week period after completion of the study or after withdrawal from the study
- The baseline for OLE Study 12712A (OLEXA) was Visit 12 (Completion/Withdrawal Visit) of lead-in Study 12709A (children) or 12710A (adolescents). The baseline for this study (OLEXB) was Visit 13 (Completion/Withdrawal Visit) of OLE Study 12712A.
- The patients continued on the dose they received in Study 12712A (5, 10, 15, or 20 mg/day). The target dose of vortioxetine was 10 mg/day; the dose could be adjusted based on the investigator's clinical judgement to 5, 10, 15, or 20 mg/day. The patient should receive the same dose for 2 days before being up-titrated to a new dose.
- Safety assessments were performed throughout the study. Efficacy data were collected at OLEXB and thereafter every 13 weeks until the Completion/Withdrawal Visit (Week 104) except for the CDRS-R, which was collected thereafter every 26 weeks, and the BRIEF, which was collected 26 weeks from OLEXB and thereafter every 13 weeks.
- This study was closed with 94 patients enrolled as the regulatory requirements for sample size (at least 20 patients) had been met. All ongoing patients could continue if it was medically relevant, until they completed the study or were withdrawn.
- This study was finalized at the start of the COVID-19 pandemic. This had no consequences for the study procedures or patient safety.

Number of Patients Planned

Up to 170 patients were anticipated to be enrolled.

Diagnosis and Main Selection Criteria

Outpatients with a primary diagnosis of MDD according to DSM-5® at entry in Study 12709A or 12710A, who:

- were ≥7 and <12 years of age (children) or ≥12 and ≤17 years of age (adolescents) at the OLEXB Visit (patients who turned 18 years old during the study were allowed to continue in the study)
- had completed treatment in Study 12712A
- were still indicated for long-term treatment with vortioxetine according to the clinical opinion of the investigator

Investigational Medicinal Products (IMPs), Doses and Mode of Administration, Batch Numbers

Vortioxetine – 5, 10, 15, or 20 mg/day; tablets, orally; batch No(s). 2521683 (5 mg), 2521733 (10 mg), 2521699 (15 mg), and 2521724 (20 mg)

Duration of Treatment

78 weeks

Statistical Methodology

- The following analysis sets were used:
  - *all-patients-treated set* (APTS) – all patients who took at least one dose of vortioxetine in Study 12712B
  - *full-analysis set* (FAS) – all patients in the APTS who had at least one valid post-OLEXB assessment of the CDR-R total score
- Unless otherwise indicated, the efficacy analyses were based on the FAS and the safety analyses were based on the APTS.
- All data collected are tabulated and/or listed, as appropriate. The presentation of results may also include plots. The data from the clinical assessments are summarized by visit using descriptive techniques.
- In this study, 2 baselines were defined:
  - OLEXB refers to Visit 13 (Completion/Withdrawal Visit) in Study 12712A, that is, baseline in Study 12712B, corresponding to nominal Week 26 in Study 12712A or nominal Week 0 in Study 12712B (18 months)
  - OLEXA refers to Visit 1 in Study 12712A or Visit 12 (Completion/Withdrawal Visit) of lead-in Study 12709A or 12710A, that is, baseline in Study 12712A, corresponding to nominal Week 0 (total duration of 24 months)
- For continuous efficacy variables CDRS-R and CGI-S, the changes from OLEXB/OLEXA were analysed using a restricted maximum likelihood-based mixed model repeated measurements approach, using all available observations until completion or withdrawal. The model included country, week, and lead-in study as factors, baseline score as a covariate, and baseline-by-week interaction. An unstructured covariance structure was used to model the within-patient errors.
- In addition, the CDRS-R total score and the CGI-S score were fitted with an analysis of covariance (ANCOVA) model including country and lead-in study as factors and baseline score as a covariate, using observed cases (OC) and last observation carried forward (LOCF). As an exploratory analysis of the CDRS-R total score, the change from OLEXB was analysed using a mixed model, including country as a factor and baseline score and week as continuous covariates. The random effects included slope (week) and intercept. An unstructured random-effects covariance was used.
- The binary outcomes relapse and loss of remission are presented using descriptive statistics.
- Time to withdrawal is presented using Kaplan-Meier plots. The time to withdrawal was calculated from the date of first visit in Study 12712B to the date of completion or withdrawal. Patients who completed the study were regarded as censored.
- The overall incidences of treatment-emergent adverse events (TEAE), serious adverse events, and TEAEs leading to withdrawal were summarized by primary system organ class (SOC) and preferred term.
- Adverse events, clinical safety laboratory test values, vital signs, body measurements (height, weight, body mass index [BMI]), ECG parameters, and C-SSRS scores were summarized using descriptive statistics.

Patient Disposition and Analysis Sets

- Patient disposition is summarized by lead-in study below:

	12709A		12710A		Total	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Patients enrolled	25		69		94	
Patients treated (APTS)	25		69		94	
Patients completed	22	(88.0)	36	(52.2)	58	(61.7)
Patients withdrawn	3	(12.0)	33	(47.8)	36	(38.3)
Primary reason for withdrawal:						
Lack of efficacy	0		2	(2.9)	2	(2.1)
Non-compliant with IMP	0		3	(4.3)	3	(3.2)
Withdrawal of consent	0		4	(5.8)	4	(4.3)
Other	3	(12.0)	24	(34.8)	27	(28.7)
Analysis sets:						
APTS	25		69		94	
FAS	24		65		89	

Demographics of the Study Population

In this study, 22% were children and 78% were adolescents. Slightly more than half of the patients were girls (59%), the mean age of the patients was 14 years, and the majority were White (97%).

Efficacy Results

- During the 18-month open-label treatment with vortioxetine, improvements from baseline (OLEXB [baseline in Study 12712B]/OLEXA [baseline in Study 12712A]) were observed in depressive symptoms (based on the CDRS-R and CGI), cognitive function (based on the BRIEF), and functioning (based on the CGAS and PedsQL).
- The mean CDRS-R total score at OLEXB was 33 points and it decreased to 23 points (OC) and 25 points (LOCF) at the end of treatment; the MMRM estimate of the mean change was -9 points. The mean CGI-S score at OLEXB was 2.6 points and it decreased to 1.3 points (OC) and 1.5 points (LOCF), indicating that patients were *normal* to *borderline ill* at the end of the treatment period; the mean MMRM estimate of the change was -1.3 points. These improvements in CDRS-R total and CGI-S scores were reflected in the proportion of remitters: at Week 78, 84% (OC) and 78% (LOCF) of the patients were in remission (based on the CDRS-R), and 97% (OC) and 89% (LOCF) of the patients were in remission (based on the CGI-S).
- In both children and adolescents: at OLEXB, the mean BRIEF-P and BRIEF-SR *Global Executive Composite* scores were 57 and 55 points and they decreased to 48 and 44 points (both OC and LOCF) at Week 78; the mean BRIEF-P and BRIEF-SR *Metacognition Index* was 57 and 55 points and it decreased to 49 and 45 points (both OC and LOCF) at Week 78, indicating improvements in executive function.
- The mean CGAS score at OLEXB was 73 points and it increased to 87 points (OC) and 84 points (LOCF) at Week 78, indicating *good functioning in all areas* in the past 4 weeks. Concordant with the clinician's assessment of improved functioning, patients also reported improvement in functioning based on the PedsQL: both the PedsQL total and PedsQL Emotional Distress total scores, respectively, improved from 1.85 and 1.74 points (at OLEXB) to 1.12 and 1.06 points (OC) and 1.31 and 1.20 points (LOCF) at Week 78.

Safety Results

- The adverse event incidence is summarized by lead-in study below:

	12709A		12710A		Total	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Patients treated	25		69		94	
Patients who died	0		0		0	
Patients with treatment-emergent serious adverse events (SAEs)	0		0		0	
Patients with treatment-emergent adverse events (TEAEs)	12	(48.0)	36	(52.2)	48	(51.1)
Patients with TEAEs leading to withdrawal	0		0		0	
Total number of TEAEs	35		100		135	

- The TEAEs with an incidence ≥5% are summarized by lead-in study below:

Preferred Term	12709A		12710A		Total	
(MedDRA Version 22.0)	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Patients treated	25		69		94	
Headache	4	(16.0)	9	(13.0)	13	(13.8)
Nausea	2	(8.0)	5	(7.2)	7	(7.4)
Nasopharyngitis	2	(8.0)	4	(5.8)	6	(6.4)
Abdominal pain upper	1	(4.0)	4	(5.8)	5	(5.3)
Hyperprolactinaemia	1	(4.0)	4	(5.8)	5	(5.3)
Respiratory tract infection viral	3	(12.0)	2	(2.9)	5	(5.3)
Vomiting	0		5	(7.2)	5	(5.3)

- None of the patients died or had an SAE and none of the patients had an adverse event leading to withdrawal.
- Approximately half (51%) of the patients had TEAEs. For the majority of the patients who had TEAEs, the events were *mild* or *moderate*; 1 patient had an event (*eosinophil count increased*) that was *severe*. Approximately 18% of the patients had TEAEs considered *related* to IMP by the investigator.
- Overall, the adverse event profile was similar in children and adolescents. The TEAEs with an incidence ≥5% were *headache*, *nausea*, *nasopharyngitis*, *abdominal pain upper*, *hyperprolactinaemia*, *respiratory tract infection viral*, and *vomiting*.
- During the 18-month Treatment Period, 1 patient had a suicide-related TEAE captured using the SMQ *Suicide/Self-injury*: the patient (adolescent) had a non-serious suicide-related TEAE (*self-injurious ideation*). The event was assessed as *mild* and *unrelated* to IMP by the investigator; the patient recovered from the event. Based on the C-SSRS, this patient had no suicidal ideation or behaviour.
- Except for prolactin, the mean changes from OLEXB/OLEXA in all the other safety laboratory tests, vital signs, and ECG parameters were small and not clinically relevant. The proportions of patients with post-OLEXB/OLEXA PCS values for these variables were low. For prolactin, an increase in mean value was observed during treatment with vortioxetine. The greatest increase was 170 mIU/L (from 238 mIU/L at OLEXB) after 52 weeks of treatment in this study (or after 78 weeks of the start of vortioxetine treatment in Study 12712A). The mean value then decreased to near OLEXB value at the end of the treatment period (Week 78). Four patients had post-OLEXB PCS high prolactin (Week 52) and 1 patient had a prolactin level above the reference range (Week 78), in line with the reported TEAE of *hyperprolactinaemia*; all patients were asymptomatic. Prolactin levels returned to normal at Week 78 in 3 patients; for the remaining 2 patients whose prolactin levels were PCS high or out-of-range at Week 78, a re-test was not done.
- The proportions of patients with elevated liver enzymes were low and none of the elevated liver enzymes met the criteria of Hy's law (defined as ALT/AST >3xULN and bilirubin >2xULN and ALP <2xULN).
- The majority of the patients did not have a clinically significant shift in height-for-age percentile or BMI-for-age percentile from OLEXB to Week 78; only 1 patient shifted from normal weight to obese. Shifts in Tanner stages reflect normal pubertal growth in the paediatric population. Menstrual cycle and duration were normal during treatment with vortioxetine.
- On the PAERS, the most common (≥20%) symptoms that showed worsening compared to baseline (OLEXB) were related to MDD (such as items related to *irritability*, *sad*, *fatigue*, *insomnia*, *attention*).
- Based on the C-SSRS, the majority (96%) of the patients had no suicidal ideation or behaviour during the study. Four patients had suicidal ideation without intent to act (3 patients had *wish to be dead* and 1 patient had *non-specific active suicidal thoughts*). None of the patients had suicidal behaviour.

Conclusions

- Flexible doses of vortioxetine 5 to 20 mg/day were safe and well tolerated in the paediatric patients with MDD who continued treatment for an additional 18 months. The safety and tolerability profile of vortioxetine in the paediatric patients after long-term use was comparable to what has been observed in paediatric patients after short-term use. No new important risks were identified in the paediatric population beyond those established for the adult population.
- Improvements in depressive symptoms (as assessed using the CDRS-R and the CGI) were observed and the majority of the patients were in remission towards the end of the study. Similar to the results in depressive symptoms, improvements in cognitive function (as assessed using the BRIEF) and functionality (as assessed using the CGAS and PedsQL VAS) were also observed.

Report Date

24 September 2020

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