Synopsis – Study 12712A

Study Title Long-term, open-label, flexible-dose, extension study of vortioxetine in child and adolescent patients with Major Depressive Disorder (MDD) from 7 to 18 years of age	
Investigators 83 principal investigators at 78 sites in 20 countries *Signatory investigator* – [redacted]	
Study Sites 78 sites – 2 in Bulgaria, 1 in Canada, 4 in Colombia, 1 in Estonia, 3 in France, 4 in Germany, 2 in Hungary, 1 in Israel, 6 in Italy, 4 in Latvia, 7 in Mexico, 7 in Poland, 2 in Republic of Korea, 15 in Russian Federation, 5 in Serbia, 1 in South Africa, 3 in Spain, 4 in Ukraine, 2 in United Kingdom, and 4 in United States	
Publications None (as of the date of this report)	
Study Period *First patient first visit* – 17 August 2016 (the date when the first *Informed Consent Form* was signed) *Study terminated* – 3 March 2022 *Last patient last visit* – 19 April 2022 (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 Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5®) diagnosis of MDD	**Primary Endpoints** • adverse events • absolute values and changes from open-label extension baseline (OLEXA) in clinical safety laboratory tests, vital signs, weight, height, and electrocardiogram (ECG) parameters • potentially clinically significant clinical safety laboratory test values, vital signs, weight, and ECG parameter values relative to OLEXA • Tanner score • length of menstrual cycle • Columbia-Suicide Severity Rating Scale (C-SSRS) assessment • Paediatric Adverse Event Rating Scale (PAERS) assessment

Objectives and Endpoints (continued)	
Objectives	**Endpoints**
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 – clinical global impression – cognitive function – functionality • to evaluate the palatability and acceptability of vortioxetine oral drops	**Secondary Endpoints** • Depressive symptoms: – change from OLEXA to Week 26 in Children's Depression Rating Scale Revised Version (CDRS-R) total score • Global Clinical Impression: – change from OLEXA to Week 26 in Clinical Global Impression – Severity of Illness (CGI-S) score – Clinical Global Impression – Global Improvement (CGI-I) score at Week 26. The assessment of the CGI-I score should be in reference to Baseline A in the lead-in studies. The Baseline A lies 12 weeks prior to OLEXA. • Cognitive function: – change from OLEXA to Week 26 in Behaviour Rating Inventory of Executive Function-Preschool/Self Report (BRIEF-P/BRIEF-SR) using the *Global Executive Composite* score – change from OLEXA to Week 26 in BRIEF-P/BRIEF-SR using the *Metacognition Index* • Functionality: – change from OLEXA to Week 26 in Children's Global Assessment Scale (CGAS) score – change from OLEXA to Week 26 in Pediatric Quality of Life Inventory (PedsQL) Present Functioning Visual Analogue Scales (VAS) • Palatability and acceptability: – absolute value of palatability and acceptability item scores for vortioxetine oral drops

Study Methodology

- This was an interventional, prospective, multi-national, multi-site, open-label, flexible-dose, long-term extension study in child and adolescent patients with MDD who completed one of the double-blind, placebo-controlled, active-reference Study 12709A or 12710A.
- The Baseline Visit (OLEXA) of this extension study was Week 12 (Completion Visit) of lead-in Study 12709A or 12710A.
- The study consisted of:
  - a treatment period – 26-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 dosage of vortioxetine was initiated at 5 mg/day for the first 2 days prior to receiving 10 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 was to receive the same dose for 2 days before being up-titrated to a new dose.
- Sparse pharmacokinetic (PK) samples (2) were collected to measure vortioxetine plasma concentration.
- For a subset of patients, palatability and acceptability of vortioxetine oral drops was assessed after intake of a single dose (5 to 20 mg) corresponding to the patient's current vortioxetine dose (replacing the vortioxetine tablet on that day).
- The adolescent cohort was terminated following the Data Monitoring Committee (DMC) recommendation to withdraw all ongoing adolescents from vortioxetine treatment based on the negative outcome of Study 12710A (short-term study in adolescents). The study was terminated following the DMC recommendation to stop all ongoing paediatric studies with vortioxetine based on the negative results on the primary endpoint in Study 12709A (short-term study in children). At that point, the last 10 children were ongoing in the study. In total, 662 patients were enrolled in Study 12712A, 335 from the adolescent study and 327 from the children study.

Number of Patients Planned

Up to 850 patients

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 ≤18 years of age (adolescents) at OLEXA
- had completed Study 12709A or 12710A (Visit 12, Completion Visit)
- were indicated for long-term treatment with vortioxetine according to the clinical opinion of the investigator

Investigational Medicinal Products, Doses and Mode of Administration, Batch Numbers

Vortioxetine – 5, 10, 15, or 20 mg/day; tablets or oral drops, orally; batch Nos. 2439261, 2596245, 2607467 (5 mg); 2439271, 2596349, 2605952 (10 mg); 2439282, 2594355, 2608404 (15 mg); 2439287, 2592445, 2596379 (20 mg); 2609676 (oral drops; 20 mg/mL)

Duration of Treatment

26 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 12712A
  - *full-analysis set* (FAS) – all patients in the APTS with a valid OLEXA assessment and at least one valid post-OLEXA assessment of the CDRS-R total score
- Unless otherwise indicated, the efficacy analyses were based on the FAS and the safety analyses were based on the APTS.
- Absolute values and changes from OLEXA in the continuous efficacy variables, except CGI-I, are summarized descriptively. Absolute values of CGI-I are summarized. CDRS-R remission and relapse during the treatment period are summarized descriptively by visit.
- For the continuous efficacy variables CDRS-R and CGI-S, changes from OLEXA were analyzed using a restricted maximum likelihood-based mixed model for repeated measurements (MMRM) approach, using all available observations until completion or withdrawal. The model included country and lead-in study interacting with week as factors, and the baseline score interacting with week as a covariate. An unstructured covariance structure was used to model the within-patient errors and the Kenward-Roger approximation was used to estimate denominator degrees of freedom. In addition, analysis of covariance models were fitted for CDRS-R and CGI-S, including country and lead-in study as factors and the baseline score as a covariate; the analysis was conducted by visit, based on observed cases and last observation carried forward.
- Kaplan-Meier plots of time to withdrawal are presented for all patients, by lead-in study and by lead-in treatment. The time was calculated from the date of first dose of investigational medicinal product (IMP) in the current study to the date of completion or withdrawal. Patients who completed the study were regarded as censored.
- The overall incidences of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and TEAEs leading to withdrawal are 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, pubertal stages, menstrual cycle, and C-SSRS scores were summarized using descriptive statistics.

Patient Disposition and Analysis Sets

- Patient disposition is summarized below:

	12709A		VOR 5 mg to 20 mg 12710A		Total	
	n	(%)	n	(%)	n	(%)
All-patients-enrolled Set	327		335		662	
All-patients-treated Set	327	(100)	335	(100)	662	(100)
Patients completed	259	(79.2)	267	(79.7)	526	(79.5)
Patients withdrawn	68	(20.8)	68	(20.3)	136	(20.5)
Primary reason for withdrawal:						
Other	26	(8.0)	13	(3.9)	39	(5.9)
Adverse events	16	(4.9)	18	(5.4)	34	(5.1)
Withdrawal of consent	10	(3.1)	10	(3.0)	20	(3.0)
Non-compliance with IMP	4	(1.2)	11	(3.3)	15	(2.3)
Lost to follow-up	8	(2.4)	5	(1.5)	13	(2.0)
Lack of efficacy	2	(0.6)	8	(2.4)	10	(1.5)
Protocol violation	0		3	(0.9)	3	(0.5)
Rolled over to 13546A	2	(0.6)	0		2	(0.3)

Patient Disposithion and Analysis Sets (continued)

- 136 patients witdrew – the overall withdrawal rate was 21% and the rate was similar in children (21%) and adolescents (20%). The most common primary reasons for withdrawal were *other* (5.9%; 39 patients: 26 children and 13 adolescents) and *adverse events* (5.1%; 34 patients: 16 children and 18 adolescents). Ten patients (1.5%) withdrew due to *lack of efficacy*.
- The palatability and acceptability subset included 153 patients.

Demographics and Baseline Characteristics of the Study Population

- In this study, approximately 45% of the patients were children and 55% were adolescents. Slightly more than half of the patients were girls (55%), the mean age of the patients was 12 years, and the majority were White (68%).
- For each of the baseline efficacy scores, the mean scores, overall, and for children and adolescents who participated in lead-in Study 12709A or 12710A, were similar.
- For patients who received placebo in the lead-in studies, the baseline CDRS-S, CGI-S, CGI-I, and PedsQL mean scores were generally higher than for patients who received vortioxetine or fluoxetine in the lead-in studies. The mean CGAS score in patients who received placebo or vortioxetine in the lead-in studies was similar, and slightly lower than that in patients who had received fluoxetine.

Efficacy Results

- During the 26-week extension study, improvements from OLEXA were observed in depressive symptoms (based on the CDRS-R) CGI, cognitive function (based on the BRIEF), and functionality (based on the CGAS and PedsQL).
- The mean CDRS-R total score at OLEXA was 44 points and it decreased to 29 points at Week 26, a mean change of -17 points; the MMRM mean estimate of the change from OLEXA was -16 points. The magnitude of the decrease (improvement) was larger in children (from lead-in Study 12709A; -18 points) than in adolescents (lead-in Study 12710A; -15 points) and was larger in patients who had received placebo in the lead-in study (-19 points), compared to patients who had received vortioxetine 10mg or 20mg or fluoxetine (-16, -15, and -15 points, respectively).
- The mean CGI-S score at OLEXA was 3.5 points and it decreased to 2.1 points, indicating that patients were *mildly to moderately ill* at OLEXA and were *borderline ill* at the end of the treatment period; the MMRM mean estimate of the change was -1.5 points. These improvements in CDRS-R total and CGI-S scores were reflected in the proportion of remitters: at Week 26, 59% of the patients were in remission based on the CDRS-R (defined as a CDRS-R total score $\leq$28), and 69% of the patients were in remission based on the CGI-S (defined as a score of 1 or 2). The mean CGI-I score was 2.7 points at OLEXA and was 1.7 points at Week 26; 86% of patients were classified as responders (defined as a CGI-I score $\leq$2) at Week 26.
- In both children and adolescents: at OLEXA, the mean BRIEF-P and mean BRIEF-SR *Global Executive Composite* score was 58 points and decreased to 51 and 50 points, respectively, at Week 26; the mean BRIEF-P and mean BRIEF-SR *Metacognition Index* was 58 points and it decreased to 52 and 51 points, respectively, at Week 26, indicating improvements in cognitive function.
- The mean CGAS score at OLEXA was 66 points and it increased to 80 points at Week 26, indicating *no more than slight impairments in functioning*. 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 2.9 and 2.8 points (at OLEXA) to 1.5 and 1.4 points at Week 26.

Acceptability and Palatability Results

- The formulation met the protocol-specified criteria to declare acceptability; the mean hedonic scores were $\leq$3 (neutral or positive face) for all four aspects of palatability and <60% patients responded *no* to each of the 3 questions.

Safety Results

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

	5 to 20 mg Vortioxetine					
	12709A		12710A		Total	
	n	%	n	%	n	(%)
Patients treated	327		335		662	
Patients who died	0		0		0	
Patients with serious adverse events (SAEs)	3	(0.9)	11	(3.3)	14	(2.1)
Patients with TEAEs leading to Withdrawal	18	(5.5)	22	(6.6)	40	(6.0)
Patients with treatment-emergent adverse events (TEAEs)	193	(59.0)	211	(63.0)	404	(61.0)
Total number of SAEs	5		14		19	
Total number of TEAEs leading to Withdrawal	24		27		51	
Total number of TEAEs	597		793		1390	

• Adverse events with a total incidence ≥5% in the treatment period are summarized below:

	5 to 20 mg Vortioxetine					
Preferred Term	12709A		12710A		Total	
(MedDRA Version 22.0)	n	(%)	n	(%)	n	(%)
Patients treated	327		335		662	
Nausea	60	(18.3)	78	(23.3)	138	(20.8)
Headache	49	(15.0)	67	(20.0)	116	(17.5)
Vomiting	41	(12.5)	28	(8.4)	69	(10.4)
Abdominal Pain	28	(8.6)	18	(5.4)	46	(6.9)
Nasopharyngitis	24	(7.3)	22	(6.6)	46	(6.9)
Dizziness	10	(3.1)	28	(8.4)	38	(5.7)

Safety Results (continued)

- More than half (61%) of the patients had TEAEs. The most commonly reported TEAEs, with an incidence ≥5%, were *nausea*, *headache*, *vomiting*, *abdominal pain*, *nasopharyngitis*, and *dizziness*. For the majority of patients with TEAEs, the TEAEs were *mild* or *moderate*; 26 patients (3.9%) had *severe* TEAEs. Approximately 37% of the patients had TEAEs considered *related* to IMP by the investigator.
- During the 26-week treatment period, 14 (2.1%; 3 children and 11 adolescents) patients reported SAEs; 9 (1.4%) patients had SAEs in the *psychiatric disorders* SOC, the most common being *suicide attempt* and *suicidal ideation*. *Suicide attempt* was recorded as an SAE for 4 patients (3 adolescents and 1 child), 2 of whom (1 adolescent and 1 child) also had an SAE of *suicide ideation*; 1 child had SAEs of *suicidal ideation* and *suicidal behaviour* and 1 adolescent had an SAE of *suicidal ideation*. *Intentional overdose* was reported in 3 (0.5%) patients, all adolescents, no other SAE was reported in >1 patient.
- TEAEs leading to withdrawal were reported in 40 (6.0%) patients, the SOC with the highest incidence was *psychiatric disorders* (15 [2.3%] patients); *suicidal ideation* and *suicide attempt* were each reported in 4 patients, and *irritability*, *major depression*, and *mania* were each reported in 2 patients (1 child and 1 adolescent for each).
- The mean changes from OLEXA in all clinical safety laboratory tests were not clinically relevant. The urine laboratory tests did not show any clinically relevant findings during the study. The proportions of patients with elevated liver enzymes were low and none of the elevated liver enzymes met the criteria of Hy's law.
- There were in general no clinically relevant mean changes from OLEXA in vital sign values, including weight, height, and BMI. There were no notable findings in reproductive hormones, Tanner scores, or menstrual cycle duration. The mean changes from OLEXA for all ECG parameter values were small and not clinically relevant.
- According to C-SSRS results, the majority (94%) of the patients had no suicidal ideation or behaviour during the study. Five (0.8%) of the patients had suicidal behaviour (*non-fatal suicide attempt*). The number of patients who had suicidal ideation without intent to act were as follows: 11 patients had *non-suicidal self-injurious behaviour*, 27 patients *wish to be dead*, 5 patients had *non-specific active suicidal thoughts*, 5 patients had *active suicidal ideation with any methods (not plan) without intent to act*, and 2 patients had *self-injurious behaviour*, *intent unknown*.
- On the PAERS, despite some fluctuations indicating worsening at some point during the study for some patients, decreased symptom severity was observed for approximately 42% (18/43) of the symptoms related to MDD compared to OLEXA. These observations are consistent with improvements in depressive symptoms described in the efficacy results.

Conclusions

- Over the 26-week extension period, flexible doses of vortioxetine 5 to 20 mg/day were safe and well tolerated in children and adolescents with MDD. 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) were observed and the majority of the patients (59%) were in remission at Week 26. Similar to the results in depressive symptoms, improvements in CGI, cognitive function (as assessed using the BRIEF) and functionality (as assessed using the CGAS and PedsQL VAS) were also observed.
- The oral drops formulation met the palatability and acceptability criteria.

Report Date

12 September 2022

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