Synopsis – Study 12709A

Study Title Interventional, randomized, double-blind, placebo-controlled, active-reference (fluoxetine), fixed-dose study of vortioxetine in paediatric patients aged 7 to 11 years, with Major Depressive Disorder (MDD)
Investigators 86 principal investigators at 86 sites in 18 countries *Signatory investigator* – [redacted]
Study Sites 86 sites – 2 in Bulgaria, 1 in Canada, 4 in Colombia, 1 in Estonia, 3 in France, 2 in Germany, 2 in Hungary, 1 in Israel, 3 in Italy, 2 in Latvia, 8 in Mexico, 5 in Poland, 13 in Russia, 5 in Serbia, 1 in South Africa, 2 in Spain, 4 in Ukraine, and 27 in United States
Publications None (as of the date of this report)
Study Period *First patient first visit* – 18 May 2016 (the date when the first *Informed Consent Form* was signed) *Last patient last visit* – 21 January 2022 (the date of the last protocol-specified contact with any patient)

Objectives and Endpoints	
Objectives	**Endpoints**
Primary Objective	*Primary Endpoint*
• to evaluate the efficacy of vortioxetine 10 mg/day and 20 mg/day *versus* placebo after 8 weeks of treatment on depressive symptoms in children with a DSM-5® diagnosis of MDD	• Δ Children's Depression Rating Scale – Revised version (CDRS-R) total score to Week 8
Secondary Objectives	*Secondary Endpoints*[a]
• to evaluate the efficacy of vortioxetine 10 mg/day and 20 mg/day *versus* placebo during the 8 weeks of treatment on: – clinical global impression (CGI) – functionality – health-related quality of life	• depressive symptoms – Δ CDRS-R total score – Δ CDRS-R Mood (4 items), Somatic (6 items), Subjective (4 items), and Behaviour (3 items) subscores – CDRS-R response[b] – CDRS-R remission (defined as a CDRS-R total score ≤28) – Δ General Behaviour Inventory (GBI) Depression subscale score, using the 10-item depression subscale, assessed by parent (PGBI-10D) and child (CGBI-10D) – Parent Global Assessment – Global Improvement (PGA) score • global clinical impression – Δ Clinical Global Impression – Severity of Illness (CGI-S) score – Clinical Global Impression – Global Improvement (CGI-I) score – CGI-S remission (defined as a CGI-S score of 1 or 2) • functionality – Δ Children's Global Assessment Scale (CGAS) score – Δ Pediatric Quality of Life Inventory (PedsQL) Present Functioning Visual Analogue Scale (PedsQL™ VAS) score in each of the 6 domains – Δ PedsQL™ average score over the 6 domains – Δ PedsQL™ emotional distress summary score • health-related quality of life – Δ Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) total score (items 1 to 14) – Δ PQ-LES-Q overall evaluation score (item 15)
• to assess pharmacokinetics of vortioxetine in paediatric patients aged 7 to 11 years using a population pharmacokinetic approach	• pharmacokinetics – pharmacokinetic (PK) parameters for vortioxetine and fluoxetine
Δ = change from Randomization	
a At each visit assessed during the double blind (DB) Period b Defined as a ≥50% decrease in CDRS-R total score, calculated as: (change from baseline [Randomization]) / (baseline value – 17) x100	

Objectives and Endpoints (continued)	
Objectives	**Endpoints**
Exploratory Objective	*Exploratory Endpoints*
• to explore the efficacy of vortioxetine 10 mg/day and 20 mg/day *versus* placebo on co-morbid symptoms	• co-morbid symptoms – Δ Multidimensional Anxiety Scale for Children short version (MASC-10) total score • depressive symptoms – Δ CDRS-R item scores
Safety Objective	*Safety Endpoints*
• to evaluate the safety and tolerability of vortioxetine 10 mg/day and 20 mg/day *versus* placebo in children with a DSM-5® diagnosis of MDD	• adverse events (AEs) • Paediatric Adverse Event Rating Scale (PAERS) assessment • absolute values and Δ in clinical safety laboratory tests, vital signs, weight, height, and electrocardiogram (ECG) parameters • potentially clinically significant (PCS) clinical safety laboratory test values, vital signs, weight changes, and ECG parameter values • Columbia Suicide Severity Rating Scale (C-SSRS) assessment • Δ GBI Mania subscale score, using the 10-item mania subscale, assessed by parent (PGBI-10M) and child (CGBI-10M)
Δ = change from Randomization	

Study Methodology

- This was an interventional, prospective, multi-national, multi-site, randomized, two-period, single- and double-blind, parallel-group, placebo-controlled, active-reference (fluoxetine), fixed-dose study.
- Originally, 600 patients were planned to be randomized in a 1:1:1:1 ratio to placebo, vortioxetine 10 mg/day, vortioxetine 20 mg/day, or fluoxetine 20 mg/day. To increase power and due to recruitment difficulties, the study design was amended to change the testing strategy for the primary analysis to allow a reduction in sample size. Furthermore, an interim analysis for efficacy or futility was included to potentially terminate the study, if there was sufficient evidence of an effect of vortioxetine, or a clear lack thereof.
- If the results of the interim analysis, including ≥240 randomized patients (either completed or withdrawn), met neither the efficacy nor the futility criterion, the study would continue until the pre-specified sample size had been reached. In addition, the fluoxetine group would be removed from the study.
- The study consisted of:
  - Screening Period – 5 to 15 days
  - Single-blind (SB) Period – 4-week single-blind (patients and parents) period of treatment with standardized brief psychosocial intervention (BPI) and placebo
  - Double-blind (DB) Period – 8-week double-blind period of treatment with BPI and placebo, vortioxetine 10 mg/day, vortioxetine 20 mg/day, or fluoxetine 20 mg/day.
  - Safety Follow-up (SFU) Period – 4-week period after the last dose of investigational medicinal product (IMP)
  - Patients who fulfilled the Randomization criteria for incomplete improvement in depressive symptoms at the end of the SB Period (Week 4) entered the DB Period as follows: Prior to interim analysis, at least 240 patients were randomized in a 1:1:1:1 ratio to vortioxetine 10 mg/day, vortioxetine 20 mg/day, fluoxetine 20 mg/day, or placebo. After interim analysis, patients were randomized in a 1:1:1 ratio to vortioxetine 10 mg/day, vortioxetine 20 mg/day, or placebo.
  - Incomplete improvement was defined as a <40% decrease in CDRS-R total score from Enrolment, CDRS-R total score ≥40, and a PGA score >2.
  - Patients who did not fulfill the Randomization criteria were withdrawn from the study before Week 4. These patients were offered up to 4 outpatient visits to the study site for consultations.

Number of Patients Planned

In the amended protocol, approximately 600 patients were planned for enrolment in the SB Period. At the end of SB Period, a total of 438 patients with incomplete improvement were planned to be randomized to the 8-week DB Period.

The interim analysis was performed based on the primary endpoint data from 271 randomized patients. To maintain the power at 85%, the sample size needed to be increased by a factor of 1.045 to correct for the loss of power due to the sequential approach. As neither the futility nor the efficacy criterion was met, the study continued and the recruitment to fluoxetine 20 mg/day was stopped. The study continued as a 3-arm study until the target sample size of 539 randomized patients (based on sample size reassessment) was reached.

Diagnosis and Main Selection Criteria

Outpatients with a primary diagnosis of MDD according to DSM-5® and confirmed using the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-aged Children, Present and Lifetime version (K-SADS-PL), criteria, who:

- had a CDRS-R total score ≥45 at the Screening Visit and at Enrolment
- had a CGI-S score ≥4 at the Screening Visit and at Enrolment
- were a boy or a girl ≥7 and <12 years of age

To be included in the DB Period, the patients:

- had to have a CDRS-R total score ≥40 at the Week 3 Visit and Week 4 Visit in the SB Period
- had to have a <40% decrease in CDRS-R total score (subtracted by 17 to avoid a flooring effect) compared to Enrolment at the Week 3 Visit and Week 4 Visit in the SB Period
- had to have a PGA score >2 at the Week 3 Visit and Week 4 Visit in the SB Period

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

Vortioxetine – 10 or 20 mg/day; encapsulated tablets, orally; batch Nos. E144509-0006E, E144509-0051E, E144509-0077E, E142869-0076E, P144509-0016E, P144509-0036E, P144509-0058E, P142869-0056E (5 mg); batch Nos. E144509-0002E, E144509-0054E, E144509-0078E, E142869-0077E, P144509-0017E, P144509-0037E, P144509-0059E, P142869-0057E (10 mg); batch Nos. E144509-0003E, E144509-0052E, E144509-0079E, E142869-0078E, P144509-0018E, P144509-0038E, P144509-0060E, P142869-0058E (15 mg); batch Nos. E144509-0004E, E144509-0053E, E144509-0080E, E142869-0079E, P144509-0019E, P144509-0039E, P144509-0061E, P142869-0059E (20 mg)

Reference Therapy, Doses and Mode of Administration, Batch Numbers

Placebo – capsules, orally; batch Nos. E144509-0005E, E144509-0076E, E142869-0075E, P144509-0010E, P144509-0033E, P144509-0057E, P142869-0055E

Fluoxetine – 20 mg/day; encapsulated tablets or capsules, orally; batch Nos. E144509-0007E, E144509-0055E, E144509-0081E, P144509-0011E, P144509-0034E, P144509-0062E (10 mg); batch Nos. E144509-0008E, E144509-0056E, E144509-0082E, P144509-0012E, P144509-0035E, P144509-0063E (20 mg)

Duration of Treatment

12 weeks – SB Period: 4 weeks; DB Period: 8 weeks

Statistical Methodology

- The following analysis sets were used:
  - *all-patients-enrolled set* (APES) – all patients enrolled
  - *all-patients-treated set* (APTS_A) – all patients in the APES who took at least one dose of single-blind IMP
  - *all-patients-randomized set* (APRS) – all patients randomized
  - *all-patients-treated set* (APTS) – all patients randomized who took at least one dose of double-blind IMP
  - *full-analysis set* (FAS) – all patients in the APTS who had a valid assessment at randomization and at least one valid post-randomization assessment of the CDRS-R total score.
- Unless otherwise indicated, the efficacy analyses were based on the FAS, the safety analyses for the SB Period were based on the APTS_A, and the safety analyses for the DB Period were based on the APTS.

Statistical Methodology (continued)

- The change from Randomization in CDRS-R total score at Week 8 was analysed using a restricted maximum likelihood (REML) based mixed model for repeated measures (MMRM). The model included the fixed effects of treatment, country, and week and the continuous covariates of CDRS-R total score at Randomization, treatment-by-week interaction, and CDRS-R at Randomization-by-week interaction. The Kenward-Roger approximation was used to estimate denominator degrees of freedom.
- The primary comparison was the average effect of the 2 vortioxetine (Avg. VOR) doses *versus* placebo at Week 8 in the DB Period based on the *SAS lsmestimate statement*. The testing strategy also included comparisons of the individual vortioxetine doses *versus* placebo. First, the comparison of the average effect of the two vortioxetine doses *versus* placebo was tested at a one-sided significance level obtained when taking the alpha-spending for the interim analysis into account (0.02266 one-sided). If the result was statistically significant, each vortioxetine dose was tested separately *versus* placebo at the same alpha-level as for the primary analysis. Statistical significance could be claimed on the individual doses only if significance was claimed for the average vortioxetine dose.
- Sensitivity analyses were performed using:
  - a pattern mixture model
  - an analysis of covariance (ANCOVA) model by visit using both the last observation carried forward (LOCF) and observed cases (OC), including country and treatment
- Continuous secondary endpoints were analysed using an MMRM model similar to the one specified for the primary endpoint, with comparisons from the same model used for all time points. In addition, for the CDRS-R and GBI mania assessed by the parents, an ANCOVA (OC and LOCF) was performed per visit with treatment and country as factors and score at Randomization as a covariate.
- For dichotomous outcomes, the primary methodology for analysis at each week during the DB Period (FAS, LOCF) was logistic regression with treatment as a factor and the score at Randomization as a covariate. This was supplemented by a similar analysis based on OC. In additional sensitivity analyses, patients with a missing value at the week analysed were classified as non-responders/non-remitters. The same logistic regression was applied for both classifications.
- The exploratory endpoints were analysed using an MMRM model similar to the one specified for the primary endpoint. In addition, ANCOVA (OC and LOCF) were performed with treatment and country as factors and the score at Randomization as a covariate.
- The population PK (popPK) of vortioxetine was determined using non-linear mixed effect modelling using NONMEM®. The first-order conditional error with interaction minimization method was used. The structural popPK model used was the one developed in a previous pooled popPK analysis in healthy adult patients, which is a two-compartment model with lag-time and with first-order absorption and elimination.
- Compliance was based on patient reporting and was defined as the percentage of IMP taken as planned.
- Compliance was also assessed using plasma concentration data for fluoxetine and vortioxetine. Plasma drug concentrations below the detection limit lower limit of quantification (<LLOQ) and unrealistically low plasma drug concentrations (estimated oral clearance >120 L/h) estimated from the popPK analysis (vortioxetine) compared to those observed historically in healthy adult patients treated under well-controlled conditions were used in this assessment.
- The overall incidences of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and TEAEs leading to withdrawal for the SB Period and DB Period 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, C-SSRS, PAERS, and mania subscale scores were summarized using descriptive statistics.
- An interim analysis was based on a sequential approach, with binding stopping rules for efficacy and futility and an error-spending approach based on Kim & DeMets method with rho = 2 were applied on the outcome from the MMRM model. The efficacy/futility endpoints were not met as part of the interim analysis and a decision was made to continue the DB Period without the fluoxetine arm. The alpha was adjusted to 0.02266 one-sided based on the alpha-spending in the interim analysis and the final analysis was based on adjusted alpha.

Patient Disposition and Analysis Sets

- 840 patients were screened
- Patient disposition for the SB Period is summarized below:

	PBO	
	n	(%)
Patients enrolled (APES)	683	
Patients treated (APTS_A)	677	
Patients completed	540	79.8
Patients withdrawn	137	20.2
Primary reason for withdrawal		
Adverse events	2	0.3
Lack of efficacy	8	1.2
Non-compliance with IMP	3	0.4
Protocol violation	3	0.4
Withdrawal of consent	15	2.2
Lost to follow-up	1	0.1
Failure to meet randomization criteria	85	12.6
Other	20	3.0

PBO = placebo

- Patient disposition for the DB Period is summarized below:

	PBO		VOR 10mg		VOR 20mg		FLU[a]	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients randomized (APRS)	153		151		153		83	
Patients treated (APTS)	153	100	151	100	153	100	83	100
Patients completed	138	90.2	135	89.4	133	86.9	78	94.0
Patients withdrawn	15	9.8	16	10.6	20	13.1	5	6.0
Primary reason for withdrawal								
Adverse events	1	0.7	2	1.3	3	2.0	0	
Lack of efficacy	2	1.3	0		0		1	1.2
Non-compliance with IMP	1	0.7	3	2.0	6	3.9	1	1.2
Protocol violation	1	0.7	0		0		0	
Withdrawal of consent	4	2.6	4	2.6	4	2.6	1	1.2
Lost to follow-up	1	0.7	0		2	1.3	0	
Other	5	3.3	7	4.6	5	3.3	2	2.4
Analysis sets								
Full-analysis set (FAS)	153		148		148		81	

FLU = fluoxetine; PBO = placebo; VOR = vortioxetine

Demographics and Baseline Characteristics of the Study Population

Randomized Patients

- Demographics were comparable across treatment groups: the mean age of the patients was 9 years and approximately half (49%) were White. Slightly more than half of the patients were boys (55%). The mean height, weight, and BMI at Randomization were similar across treatment groups.
- Overall, the demographics, height, weight, and BMI at Randomization for the patients in the APTS were similar to what was seen at Enrolment for the patients in the APTS_A.
- At Enrolment, the majority of the children were pre-pubertal (Tanner stage I: 56% of the girls and 65% of the boys) and 43% of the girls and 35% of the boys were pubertal (Tanner stage II to IV).
- At Enrolment, the mean CDRS-R total score for patients in the FAS was 63.4 points (ranging from 45 to 95 points) and the mean CGI-S score for patients in the FAS was 4.8 points (ranging from 4 to 6 points) (corresponding to *moderate to marked illness*).
- At Randomization, the mean CDRS-R total score for patients in the FAS ranged from 60.1 to 61.1 points and the mean CGI-S score for patients in the FAS was 4.6 to 4.7 points (corresponding to *moderate to marked illness*).

Efficacy Results

- The primary efficacy results are summarized below (FAS, MMRM):

Endpoint	N	Mean	Treatment Difference to PBO (95% CI)	p-value
Δ CDRS-R total score at Week 8				
PBO	136	-17.48		
Avg. VOR		-19.57	-2.09 (-4.54; 0.36)	0.0937
VOR 10mg	132	-19.20	-1.72 (-4.56; 1.11)	0.2336
VOR 20mg	134	-19.94	-2.46 (-5.29; 0.37)	0.0879
FLU 20mg[a]	78	-20.78	-3.30 (-6.65; -0.04)	0.0531

CI = confidence interval; FLU = fluoxetine; PBO = placebo; VOR = vortioxetine

- In the primary efficacy analysis, the mean change from Randomization to Week 8 in CDRS-R total score was -17.48 for placebo and -19.57 for Avg. VOR, and the difference (-2.09) was not statistically significant (p = 0.0937). The primary endpoint was therefore not met, and subsequent p-values were considered nominal.
- [redacted]
- The analyses of the mean change from Randomization to Week 8 in CDRS-R total score for the individual vortioxetine doses (10 and 20mg/day) did not show a nominally significant difference from placebo; the nominal p-value was >0.05 for both doses.
- In the fluoxetine group, the mean change from Randomization to Week 8 in CDRS-R total score was -20.8 points and the difference to placebo was -3.3 points with a nominal p-value of 0.0531.
- In general, the results of the secondary and exploratory efficacy analyses were consistent with those of the primary efficacy analysis.

Pharmacokinetic Results

- Vortioxetine steady-state exposures in children were comparable to those previously reported in adolescent and adult populations both for vortioxetine 10 and 20mg/day. A total of 77 (28%) of the 273 patients treated with vortioxetine were considered non-compliant based on the PK data.

Safety Results

- The adverse event incidence is summarized below for the DB Period (APTS):

	PBO		VOR 10mg		VOR 20mg		FLU 20mg	
	n	(%)	n	(%)	n	(%)	n	(%)
Number of Patients	153		151		153		83	
Patients Years of Exposure	22		21		22		12	
Patients with TEAEs	66	43.1	74	49.0	72	47.1	40	48.2
Patients with SAEs	3	2.0	1	0.7	2	1.3	1	1.2
Patients with TEAEs leading to withdrawal	1	0.7	2	1.3	3	2.0	0	
Deaths	0		0		0		0	
Total number of TEAEs	119		177		156		88	
Total number of SAEs	3		1		2		1	
Total number of TEAEs leading to withdrawal	1		2		3		0	

FLU = fluoxetine; PBO = placebo; VOR = vortioxetine

Safety Results (continued)

- TEAEs with an incidence ≥2% in any treatment group for the APTS are summarized by preferred term below:

	PBO		VOR 10mg		VOR 20mg		FLU 20mg	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)
Number of Patients	153		151		153		83	
Patients Years of Exposure	22		21		22		12	
Patients with TEAEs with an Incidence of 2% or more	45	29.4	55	36.4	42	27.5	28	33.7
Nausea	7	4.6	19	12.6	17	11.1	5	6.0
Headache	17	11.1	14	9.3	14	9.2	4	4.8
Vomiting	3	2.0	14	9.3	10	6.5	3	3.6
Abdominal Pain	2	1.3	9	6.0	6	3.9	2	2.4
Dizziness	5	3.3	7	4.6	5	3.3	3	3.6
Illness	0		0		5	3.3	0	
Nasopharyngitis	5	3.3	6	4.0	4	2.6	3	3.6
Abdominal Pain Upper	4	2.6	4	2.6	3	2.0	3	3.6
Weight Increase	4	2.6	1	0.7	3	2.0	2	2.4
Decreased Appetite	2	1.3	1	0.7	2	1.3	3	3.6
Diarrhoea	4	2.6	5	3.3	1	0.7	3	3.6
Dry Mouth	4	2.6	4	2.6	1	0.7	0	
Weight Decrease	0		0		1	0.7	2	2.4
Epistaxis	0		1	0.7	0		2	2.4
Forearm Fracture	0		0		0		2	2.4

FLU = fluoxetine; PBO = placebo; VOR = vortioxetine

- In the DB Period, the incidence of TEAEs was similar in the vortioxetine (10mg: 49% and 20mg: 47%), and fluoxetine (48%; no patients enrolled post interim analysis) groups and was low in the placebo (43%) group.
- The incidence of SAEs was 2.0% in the placebo group, 0.7% and 1.3% in the vortioxetine 10mg and 20mg groups, respectively, and it was 1.2% in the fluoxetine group.
- TEAEs leading to withdrawal was low in the placebo (0.7%) and vortioxetine (10mg: 1.3% and 20mg: 2%) groups. No TEAEs leading to withdrawal were reported in the fluoxetine group.
- The most commonly reported TEAEs (incidence >5% in any treatment group) were *nausea, headache, vomiting*, and *abdominal pain*. The incidence of these TEAEs was higher in the vortioxetine groups than in the placebo or fluoxetine group, except for headache, where the incidence was highest in the placebo group.
- The majority of TEAEs were *mild* or *moderate*; no *severe* TEAEs occurred in >1 patient in any treatment group.
- No deaths were reported. A total of 7 patients had SAEs in the DB Period, with no apparent difference in incidence between treatment groups. None of the SAEs occurred in >1 patient in any treatment group. Major depression and mania, reported in the vortioxetine 20mg group, were considered *related* to IMP; the remainder of SAEs were considered *not related* to IMP.
- In the SB Period, 3 patients had suicide-related TEAEs captured using the standardized MedDRA Queries (SMQ) *Suicide / Self-injury. Intentional overdose* and *suicide attempt* were reported in the same patient and *intentional self-injury* and *suicidal ideation* were each reported in 1 patient; all of these events were reported as SAEs. In the DB Period, 2 patients had suicide-related TEAEs captured using the SMQ *Suicide / Self-injury*; *suicide attempt* was reported by 1 patient in the placebo group and *suicide ideation* was reported by 1 patient in the vortioxetine 10mg group.
- In the DB Period, 6 patients had TEAEs leading to withdrawal; none of the events occurred in >1 patient.
- The mean changes from Randomization in all the clinical safety laboratory tests, vital signs, weight, BMI, height, and ECG parameters were small and comparable between treatment groups and not clinically relevant. Overall, the proportions of patients with post-Randomization PCS values for these variables were low and similar across treatment groups.
- In the DB Period, the proportions of patients with elevated liver enzymes were low and none met the criteria of Hy's law.

Safety Results (continued)

- Overall, the proportion of patients with worsening of severity compared to Randomization on the PAERS was similar across treatment groups. The PAERS items for which there was a >10% difference between treatment groups in the proportions of patients with worsening of severity compared to Randomization were irritability, angry, and nausea. The proportion of patients who reported none of these items increased over time and across treatment groups. Although some patients experienced worsening at some point, overall there was a tendency toward improvement in severity in these symptoms.
- During the study, based on the C-SSRS, the proportions of patients with no suicidal ideation or behaviour were similar to what was seen at Randomization. A non-fatal suicide attempt was reported in 1 patient in the placebo group. Non-suicidal self-injurious behavior was reported in 1 patient in the vortioxetine 20 mg group. Active suicidal ideation with any methods (not plan) without intent to act was reported in 1 patient in the vortioxetine 10 mg group. Non-specific active suicidal thoughts were reported in a total of 5 patients: 1, 1, and 3 patients in the placebo, vortioxetine 10 mg, and fluoxetine groups, respectively. A wish to be dead was reported in a total of 5 patients: 2, 1, and 2 patients in the placebo, vortioxetine 10 mg, and vortioxetine 20 mg groups, respectively.
- Overall, the mean changes from Randomization to Week 8 in GBI Mania subscale score, as assessed by the parent or child, were small and not statistically significantly different to placebo. A GBI Mania subscale score ≥18 points, indicating a potential risk of mania, was reported only sporadically, with no clinically relevant difference across treatment groups. None of the scores ≥18 points were considered clinically significant by the investigator and none were reported as adverse events.

Conclusions

- In the primary efficacy analysis, the average of the two vortioxetine doses (10 and 20 mg) was not statistically significantly different to placebo based on the change from Randomization to Week 8 in CDRS-R total score in paediatric patients with MDD.
- The mean change from Randomization to Week 8 in CDRS-R total score for the individual vortioxetine doses (10 and 20 mg/day) did not show a nominally significant difference from placebo; the nominal p-value was >0.05 for both doses.
- In general, the results of the secondary and exploratory efficacy analyses were in line with those of the primary efficacy analyses.
- Vortioxetine exposures based on PK data in paediatric patients were similar to those previously reported in adolescents and adults.
- Vortioxetine was generally safe and well tolerated in children with MDD. The safety and tolerability profile of vortioxetine in children was comparable to what has been observed in clinical studies of vortioxetine in adolescents and adults with MDD.

Report Date

16 September 2022 (Amendment 1), 22 June 2022 (Clinical Study Report)

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