15 September 2022
EMA/827117/2022
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Brintellix

vortioxetine

Procedure no: EMEA/H/C/002717/P46/009

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On July 1st 2022, the MAH submitted a completed paediatric study 12709A for Brintellix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study 12709A, an 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) is part of the Paediatric Investigation Plan for Brintellix (EMEA-000455-PIP02-10-M09; current agreed PIP).

The variation application to reflect the study outcome in the Product Information is expected to be submitted by September 2022. It will consist of the full relevant data package in a consolidated submission including paediatric study updates, once the CSR for the long-term open-label extension study, Study 12712A, is final.

A line listing of all the concerned studies is annexed.

The clinical development programme in children and adolescents was initiated in 2012, with a **PK study** to determine appropriate dosing regimens for the paediatric efficacy and safety studies.

The short-term efficacy and safety study in adolescents, **Study 12710A**, was completed in 2019. In the primary efficacy analysis, vortioxetine (average effect of 10 and 20 mg/day) was not statistically significantly superior to placebo based on the CDRS-R total score. Likewise, neither of the individual doses of vortioxetine showed a nominally significant difference to placebo whereas the reference drug, fluoxetine, separated from placebo on the primary endpoint.

Based on the lack of efficacy of vortioxetine in Study 12710A, the independent DMC for the vortioxetine paediatric studies recommended discontinuation of adolescent patients in open-label extension **Studies 12712A and 12712B**. Therefore, the paediatric study programme continued, but only including children. Study **12709A** was a randomized, two-period, single- and double-blind, parallel-group, placebo-controlled, active-reference (fluoxetine), fixed-dose study in children aged 7 to 11 years with a DSM-5 diagnosis of MDD. The purpose of the study was to evaluate the efficacy and safety of vortioxetine 10 mg/day and 20 mg/day versus placebo in children aged 7 to 11 years.

Due to significant recruitment difficulties, and as agreed with EMA/PDCO in 2018 (EMEA-000455-PIP02-10-M04), an interim analysis was included in the protocol for Study 12709A to potentially terminate the study for futility or efficacy. If the results of the interim analysis met neither the efficacy nor the futility criterion, the study would continue. An interim analysis for efficacy or futility was conducted in July 2019. As neither the futility nor the efficacy boundaries had been crossed at the time of interim analysis, the study continued. Given the lack of superiority of vortioxetine to placebo on the primary scale, CDRS-R, this study does not support the efficacy of vortioxetine, in addition to psychosocial intervention, in the treatment of children aged 7 to 11 years with MDD.

Overall, the safety results were comparable to those previously observed in adults and adolescents, with no new safety findings.

Based on the negative efficacy results of Study 12709A, the DMC recommended that the

ongoing paediatric studies with vortioxetine (Studies **12712A and 13546A**) were terminated.

2.2. Information on the pharmaceutical formulation used in the study 12709A

The study medication was
-Vortioxetine – 10 or 20mg/day; encapsulated tablets, orally
-Placebo – capsules, orally
-Fluoxetine – 20mg/day; encapsulated tablets or capsules, orally

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- study 12709A,

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)

2.3.2. Clinical study

Study 12709A

Description

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).

The purpose of the study was to evaluate the efficacy and safety of vortioxetine 10 mg/day and 20 mg/day versus placebo in children aged 7 to 11 years.

Study Design

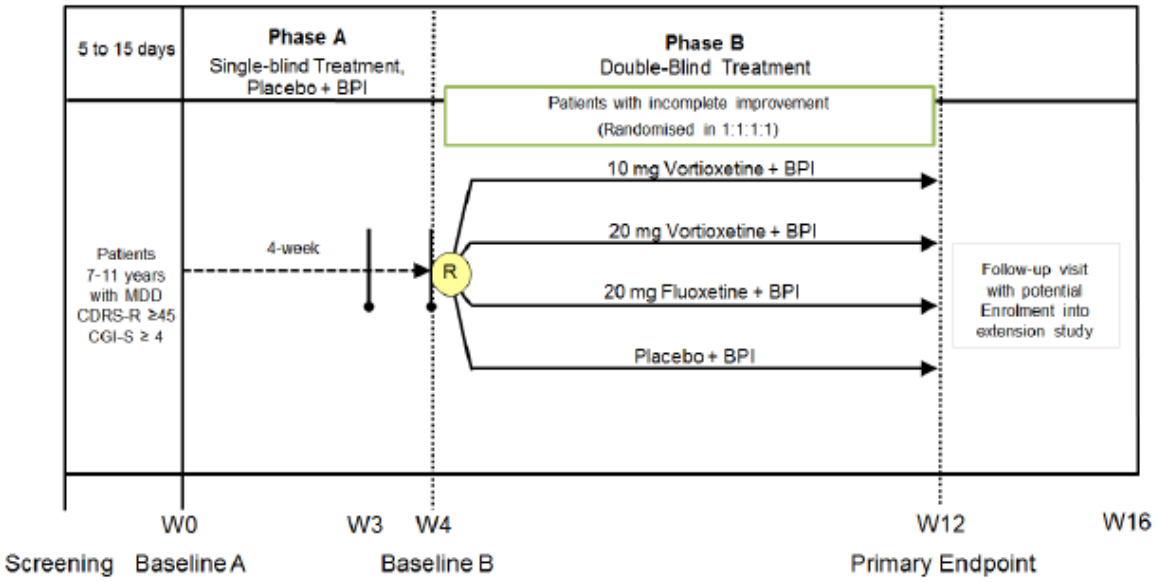
– Screening Period – 5 to 15 days
– Single-blind (SB) Period – 4-week single-blind (patients and parents) period of treatment with standardized brief psychosocial intervention (BPI) and placebo
– Double-blind (DB) Period – 8-week double-blind period of treatment with BPI and placebo, vortioxetine 10mg/day, vortioxetine 20mg/day, or fluoxetine 20mg/day.
– Safety Follow-up (SFU) Period – 4-week period after the last dose of investigational medicinal product (IMP).

After 4 weeks of single-blind lead-in treatment with brief psychosocial intervention and placebo, patients who fulfilled the criteria for incomplete improvement (<40% decrease in CDRS-R total score from enrolment, CDRS-R total score ≥40, and a PGA score >2) were randomized to 8 weeks of double-blind treatment with vortioxetine 10 mg/day, vortioxetine 20 mg/day, fluoxetine 20 mg/day (prior to the interim analysis), or placebo. In addition, all patients continued with brief psychosocial intervention (2 sessions) during the DB Period.

To increase power and due to recruitment difficulties, the study design was amended to change 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.

Study part 1:

Applicable prior to interim analysis

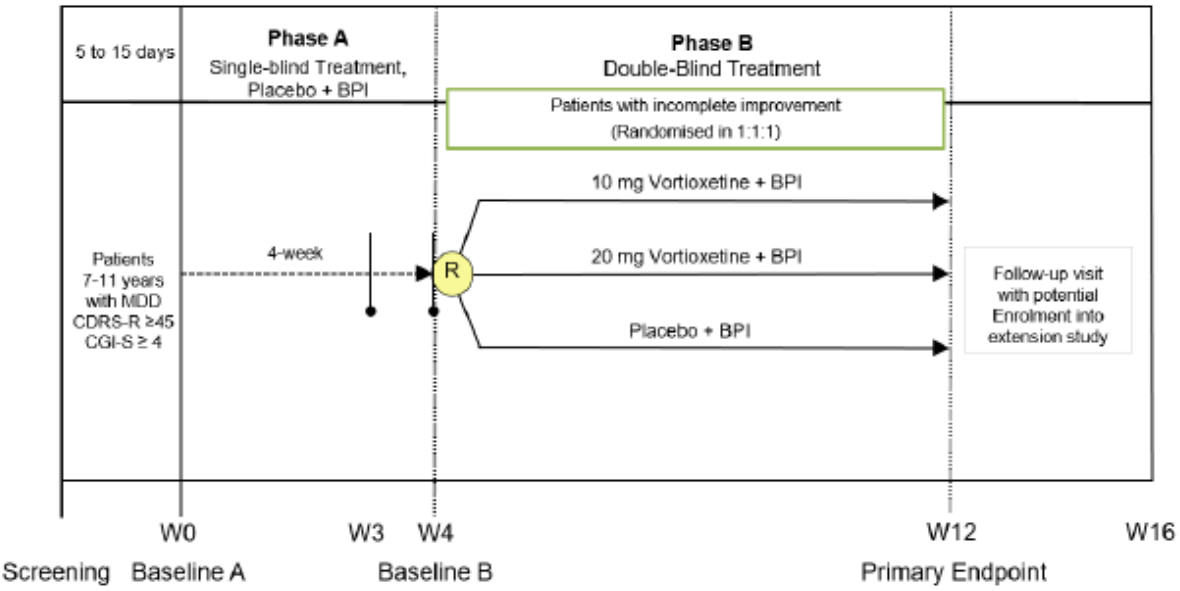


= Patients improving significantly at Week 3 (Phase A) will be excluded before Week 4 (Phase A); patients improving at week 4 (Phase A) will not be randomized to the double-blind Phase B of the study. These patients may receive up to 4 outpatient visits to the study site for consultations over a two-month period.

R = Randomization BPI = Brief Psychosocial Intervention

Study part 2:

Applicable after interim analysis (from June 14th 2019)



= Patients improving significantly at Week 3 (Phase A) will be excluded before Week 4 (Phase A); patients improving at week 4 (Phase A) will not be randomized to the double-blind Phase B of the study. These patients may receive up to 4 outpatient visits to the study site for consultations over a two-month period.

R = Randomization BPI = Brief Psychosocial Intervention

Methods

Study participants

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

Treatments

- Vortioxetine – 10 or 20mg/day; encapsulated tablets, orally
- Placebo – capsules, orally
- Fluoxetine – 20mg/day; encapsulated tablets or capsules, orally

Objective(s)

Primary Objective
• to evaluate the efficacy of vortioxetine 10mg/day and 20mg/day versus placebo after 8 weeks of treatment on depressive symptoms in children with a DSM-5® diagnosis of MDD.

Secondary Objectives

• to evaluate the efficacy of vortioxetine 10mg/day and 20mg/day versus placebo during the 8 weeks of treatment on:
– clinical global impression (CGI: CGI-I, CGI-S)
– functionality (CGAS and PedsQL)
– health-related quality of life (PQ-LES-Q)
• to assess pharmacokinetics of vortioxetine in paediatric patients aged 7 to 11 years using a population pharmacokinetic approach.

Exploratory Objective
• to explore the efficacy of vortioxetine 10mg/day and 20mg/day versus placebo on co-morbid symptoms

Safety Objective
• to evaluate the safety and tolerability of vortioxetine 10mg/day and 20mg/day versus placebo in children with a DSM-5® diagnosis of MDD

Outcomes/endpoints

Primary Endpoint
• Δ Children's Depression Rating Scale – Revised version (CDRS-R) total score to Week 8

Secondary Endpoints[a]
• 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 Scales (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)

• 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

Exploratory Endpoints
- co-morbid symptoms
- Δ Multidimensional Anxiety Scale for Children short version (MASC-10) total score
- depressive symptoms
- Δ CDRS-R item scores

Safety Endpoints
- 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)

Sample size

Number of Patients Planned
Approximately 600 patients were planned for enrolment in the DB 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.

Randomisation and blinding (masking)

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 10mg/day, vortioxetine 20mg/day, fluoxetine 20mg/day, or placebo. Patients who did not fulfill the Randomization criteria were withdrawn from the study before Week 4.
After interim analysis, patients were randomized in a 1:1:1 ratio to vortioxetine 10mg/day, vortioxetine 20mg/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.

Statistical Methods

- 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.

• 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 two-sided 5% significance level. If the result was statistically significant, each vortioxetine dose was tested separately versus placebo at a one-sided 2.5% significance level. 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, 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 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 >120L/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 were based on adjusted alpha.

Results

Participant flow/ Recruitment/ Number analysed

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

Baseline data

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.
• In the interim analysis, the mean changes from Randomization to Week 8 in the CDRS-R total scores were -22.78 and -20.53 for the Avg. VOR and placebo groups, respectively. The difference from placebo in the Avg. VOR group was -2.26 at Week 8 and the efficacy/futility criteria were not met. The study therefore continued until the prespecified sample size had been reached and the fluoxetine group was removed as specified in the protocol.
• 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 at 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

• 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 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, and height, and ECG parameters were small and comparable between treatment groups and not clinically relevant. Overall, the proportions of patients with post-Randomization potentially clinically significant (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.
• 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 the proportions of patients with worsening of severity compared to Randomization was >10 percentage points in any treatment group 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. Active suicidal ideation with any methods (not plan) without intent to act was reported in 1 patient in the vortioxetine 10mg group. Non-specific active suicidal thoughts were

reported in a total of 5 patients: 1, 1, and 3 patients in the placebo, vortioxetine 10mg, and fluoxetine groups, respectively. A wish to be dead was reported in a total of 5 patients: 2, 1, 2 patients in the placebo, vortioxetine 10mg, and vortioxetine 20mg groups, respectively.
• Overall, the mean changes from Randomization to Week 8 in General Behaviour Inventory (GBI) Mania subscale score, as assessed by the parent or child, were small as were the differences to placebo (<0.8 points as judged by the parents and <0.5 points as judged by the children) and not clinically relevant. 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.

2.3.3. Discussion on clinical aspects

MAH's Discussion

Efficacy results
In the primary efficacy analysis, the mean change from Randomization to Week 8 in CDRS-R total score was -17.5 points for placebo and -19.6 for the average effect of the two vortioxetine doses, and the difference (-2.09) was not statistically significant (p = 0.0937). The primary endpoint was not met, and subsequent p-values were considered nominal. Likewise, neither of the individual doses of vortioxetine (10 or 20 mg/day) showed a nominally significant difference from placebo. 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 (p = 0.0531). The results from the subgroup analyses of age, race, country, region, and sex were generally in line with those of the primary analysis. The results of the secondary endpoints (CDRS-R, CGI-S, CGI-I, PGA, GBI-D10, CGAS, PedsQL and PQ-LES-Q) were generally in line with the results for the primary endpoint, demonstrating no evidence of effect of vortioxetine. Improvements in depressive symptoms, global clinical impression, functionality, and health-related quality of life were observed in all treatment groups over the 8-week DB Period, however, the differences relative to placebo at Week 8 were generally not nominally statistically significant, with a few exceptions.

Pk 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. However, the results of a sensitivity analysis in which noncompliant patients in the vortioxetine and fluoxetine groups had been removed (based on PK data) were in line with those of the primary analysis.

Safety Results
Vortioxetine was well tolerated, and no new safety concerns were identified. This study supported the acceptable safety profile of vortioxetine, with nausea as the most common adverse event, previously seen in adolescents and in the adult MDD population. Other common adverse events reported in the DB Period included headache, vomiting, dizziness, and abdominal pain. Nausea, vomiting and abdominal pain occurred more frequently in patients receiving vortioxetine than in the placebo group. For the majority of patients with TEAEs, the TEAEs were mild or moderate; severe TEAEs occurred in a total of 8 patients.
The incidences of serious adverse events were 2.0% in the placebo group, 0.7% and 1.3% in the vortioxetine 10 mg and 20 mg groups, respectively, and 1.2% in the fluoxetine group.
The incidence or worsening of suicidal ideation and behaviour was low and did not differ between placebo and treatment groups. The one instance of suicide attempt in the DB Period occurred in a patient in the placebo group. In addition, suicide ideation was reported by 1 patient in the vortioxetine 10 mg group.

MAH's Conclusion

• In the primary efficacy analysis, the average of the two vortioxetine doses (10 and 20mg) 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 20mg/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.

Given the lack of superiority of vortioxetine to placebo on the primary scale, CDRS-R, this study does not support the efficacy of vortioxetine, in addition to psychosocial intervention, in the treatment of children aged 7 to 11 years with MDD.

• 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.

Rapporteur's comment:

The current MAH's conclusions can be accepted for the time being. Given that the data are still incomplete without the long term data from study 12712A, an in-depth evaluation will be performed when the complete data are submitted in the context of a type II variation.

Since the MAH has agreed with EMA to submit a variation to reflect the study outcome in the Product information in a consolidated submission including paediatric study updates, once the CSR for long-term open-label extension study 12712A, is final, no action is required at present. Further data are expected in the context of the type II variation.

3. Rapporteur's CHMP overall conclusion and recommendation

☒ Fulfilled:

No further action required, however further data are expected in the context of a variation

☐ Not fulfilled:

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies

Product Name: Brintellix Active substance: vortioxetine

Study title	Study number	Date of completion	Date of submission of final study report
Toxicokinetic study in juvenile CD rats following single oral administration	Study 2 LBK0251	31/08/2011	Study report was submitted as part of the EU MAA on 06-08-2012
Range finding toxicity study in the juvenile CD rat by twice daily (oral gavage) administration	Study 3 LBK0256	31/08/2011	Study report was submitted as part of the EU MAA on 06-08-2012
Toxicity study in the juvenile CD rat by twice daily oral gavage administration	Study 4 NTK0006	31/08/2011	Study report was submitted as part of the EU MAA on 06-08-2012

Clinical studies

Product Name: Brintellix Active substance: vortioxetine

Study title	Study number	Date of completion	Date of submission of final study report
Open-label study to assess the pharmacokinetics and tolerability of multiple oral dosing of vortioxetine in children and adolescent patients with a DSM-IV diagnosis of depressive or anxiety disorder.	Study 5 12708A	Main: 10/12/2014 Extension: 08/06/2015	02/09/2015
Two-phase, single- and double-blind, randomised, placebo-controlled, multicentre, short-term study of vortioxetine and fluoxetine in paediatric patients with major depressive disorder (MDD) from 7 to less than 12 years of age.	Study 6 12709A	21/01/2022	05/07/2022

Study title	Study number	Date of completion	Date of submission of final study report
Two-phase, single- and double-blind, randomised, placebo-controlled and active comparator, 4 arm, multicentre, short-term study of vortioxetine and fluoxetine in paediatric patients with major depressive disorder (MDD) from 12 to less than 18 years of age.	Study 7 12710A	30/07/2019	30/01/2020
Double-blind, randomised, placebo-controlled, multicentre, relapse-prevention study of vortioxetine in paediatric patients with major depressive disorder (MDD) from 7 to less than 18 years of age.	Study 8 13546A	28/04/2022	Expected:28/09/2022
Long-term, open-label, flexible-dose, extension study of vortioxetine in paediatric patients with major depressive disorder (MDD) from 7 to less than 18 years of age.	Study 9 12712A	19/04/2022	Expected:28/09/2022
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.	Study 10 12712B	16/04/2020	12/10/2020