24 June 2021
EMA/CHMP/386348/2021
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/P46/007

Note

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

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1. Introduction

On October 12th 2020, the MAH submitted the final clinical study report for study 12712B, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical clinical overview has also been provided.

Study 12712B was an open label, 18-month extension study to the ongoing Study 12712A, which itself is an open label, 6-month extension study to Studies 12709A and 12710A (8 week, double blind, efficacy and safety studies in children and adolescents, respectively).

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study 12712B is part of a clinical development program. A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

The study medication was the approved vortioxetine immediate release 5, 10, 15 and 20 mg tablets.

2.3. Clinical aspects

2.3.1. Description of the study

Title:

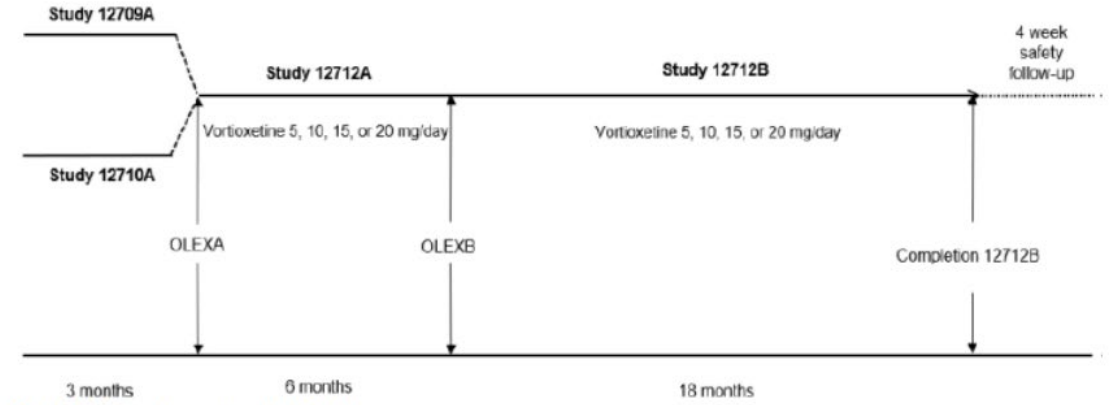
"Long-term, open-label, flexible-dose, continuation extension study with vortioxetine in child and adolescent patients with Major Depressive Disorder (MDD) from 7 to 17 years of age"

Methods

Study design/ Study population /Sample size

• 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 20mg/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.

Panel 4 Studies 12712A and 12712B: Study Designs



OLEXA = baseline in Study 12712A
OLEXB = baseline in Study 12712B

• The patients continued on the dose they received in Study 12712A (5, 10, 15, or 20 mg/day). The target dose of vortioxetine was 10mg/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.

CHMP comment

Indeed, in the PIP decision from the Paediatric Committee of June 2018 EMEA-000455-PIP02-10MO4, it is mentioned for study 12712B that at least 20 patients need to be included (not specifying how many children and how many adolescents). For Study 12712A, at least 100 patients need to be included.

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 5mg/day to 20mg/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*
– 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

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

CDRS-R = Children's Depression Rating Scale – Revised version

Treatment

Vortioxetine immediate release 5, 10, 15 and 20 mg tablets.

Statistical Methods

• 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.

Results

Patients 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	

CHMP comment

The very high rate of withdrawals (47.8 %) in the adolescent population has to be noted and will be commented with the efficacy results.

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%).

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.

CHMP comment

The incidence rate of TEAEs in adolescents (52.2%) was similar to the rate of TEAEs in the double-blind Period study 12710A (59% in the vortioxetine 20mg group, 49% in the fluoxetine group, 47% in the vortioxetine 10mg group, and 41% in the placebo group). The incidence rate of TEAEs in children (48%) was a bit lower that in adolescents. It cannot be compared to the study 12709A since this one is still ongoing.

To compare better the incidence rate of TEAEs in adolescents during the extension study 12712B with the double-blind study 12710A, it would be interesting to know what is the proportion of patients who were treated with the 5 mg; 10 mg dose and 20 mg dosage? ***RSI***

• 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*.

CHMP comment

The incidence rate of TEAEs headache, nausea, nasopharyngitis, abdominal pain upper, respiratory tract infection viral, and vomiting was similar to the rate of TEAEs in the DB Period study 12710A. "Abdominal pain upper" was not mentioned as a TEAE with an incidence of >5% during the DB study study 12710A, but vomiting and diarrhoea were. (See panel 7 of the summary clin safety).

Panel 7 Double-blind Period: TEAEs with an Incidence of 5% or More (APTS)

	PBO		VOR 10 mg		VOR 20 mg		FLU 20 mg	
Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Number of Patients	154		147		161		153	
Patient Years of Exposure	22		21		23		22	
Patients with TEAEs with an Incidence of 5% or More	25	(16.2)	44	(29.9)	54	(33.5)	34	(22.2)
Nausea	7	(4.5)	21	(14.3)	31	(19.3)	10	(6.5)
Headache	12	(7.8)	23	(15.6)	20	(12.4)	10	(6.5)
Vomiting	1	(0.6)	7	(4.8)	15	(9.3)	8	(5.2)
Nasopharyngitis	5	(3.2)	6	(4.1)	10	(6.2)	10	(6.5)
Diarrhoea	5	(3.2)	5	(3.4)	9	(5.6)	7	(4.6)
Dizziness	5	(3.2)	11	(7.5)	7	(4.3)	6	(3.9)

Dictionary: /MEDDRA - 21.0

12710A FINAL TLG_AE ST_AE03_5PCT_B 09DEC2019 ADaM:09DEC2019

• 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 170mIU/L (from 238mIU/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.

CHMP comment

The TEAE hyperprolactinaemia (4% in children and 5.8 % in adolescents) was not described in the DB study 12710A and is not mentioned in the SmPC for adult patients. This AE should be further commented by the MAH. Has it been described in unblinded cases in study 12709A? Even if patients are asymptomatic, what could be the consequence of prolonged hyperprolactinaemia in children? On which criteria was the status of these patients defined as "asymptomatic"? ***RSI***

• 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*).

CHMP comment

The MAH is asked to provide more details on these data (a table for example). What is the difference between children and adolescents for these results? The MAH should further discuss these results. ***RSI***

• Based on the C-SSRS, the majority (96%) of the patients had no suicidal ideation or behaviour during the study. Four patients (4%) 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.

CHMP comment

The MAH is asked to provide more details on these data (a table for example). What is the difference between children and adolescents for these results? The MAH should further discuss these results. ***RSI***

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.

Conclusions of the clinical study report

• Flexible doses of vortioxetine 5 to 20mg/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.

MAH's Discussion and Conclusion

Study 12712B was an open label, 18-month extension study to the ongoing Study 12712A, which itself is an open label, 6-month extension study to Studies 12709A and 12710A (8-week, double blind, efficacy and safety studies in children and adolescents, respectively). As Study 12712B constitutes a part of the open-label extension period to investigate the long-term safety of vortioxetine in the paediatric population, Lundbeck is of the opinion that a potential update to the Product Information should await completion of the lead-in study 12712A.
Therefore, Lundbeck deems that no regulatory consequences are warranted at this stage.

2.3.2. Rapporteur's Discussion on clinical aspects

Safety results

Apart from hyperprolactinaemia, the incidence rate of the most common TEAEs in this extension study (headache, nausea, nasopharyngitis, abdominal pain upper, respiratory tract infection viral, and vomiting) was similar to the rate of TEAEs in the DB study 12710A in adolescent patients. Concerning children, it is not possible to make a comparison since the DB study 12709A is still ongoing. For the majority of the patients who had TEAEs, the events were *mild* or *moderate.* No SAEs were reported. No patients withdrew due to adverse events.

Apart from hyperprolactinaemia, no new safety concerns were identified in this open-label extension study. The MAH is asked to discuss further this new TEAE hyperprolactinaemia.

Efficacy results

Results from the randomised, double-blind, placebo-controlled, active-referenced, fixed dose, 8-week study 12710A, conducted in adolescent patients with MDD aged 12 to 17 years, showed that neither vortioxetine 10 mg/day nor 20 mg/day was statistically significantly superior to placebo based on the Children´s Depression Rating Scale-Revised (CDRS-R) total score. The active reference (fluoxetine 20 mg/day) separated statistically from placebo on the CDRS-R total score.

Therefore, the positive efficacy results described by the MAH for this OLE study (improvements in depressive symptoms, as assessed using the CDRS-R and the CGI, a majority of the patients in remission by the end of the study, and improvements in cognitive function and functionality) have to be interpreted with caution, considering the fact that this is a non-controlled study with few patients analysed (69 adolescent patients). Furthermore, the considerable high rate of withdrawals (47.8 %) in the adolescent population has to be noted.

Finally, the independent Data Monitoring Committee (DMC) recommended to discontinue adolescent patients in the extension Studies 12712A and 12712B, based on the lack of efficacy of vortioxetine in Study 12710A in adolescents. This might explain the high rate of withdrawals (47.8 %) in the adolescent population in study 12712B but the applicant should clarify this very high rate of withdrawals (**RSI**).

The following information was added in the SmPC in September 2020, following to the variation EMEA-H-C-2717-II-0025:

Section 4.2.

Paediatric population
The safety and efficacy of Brintellix in children aged 7 to 11 years have not been established. No data are available (see section 4.4). Brintellix should not be used in adolescents aged 12 to 17 years with major depressive disorder (MDD) because efficacy has not been demonstrated (see section 5.1). The safety of Brintellix in adolescents aged 12 to 17 years is described in section 4.4, 4.8 and 5.1.

Section 4.4.

Use in paediatric population

Brintellix is not recommended for the treatment of depression in children aged 7 to 11 years since the safety and efficacy of vortioxetine have not been established in this age group. Brintellix should not be used in adolescents aged 12 to 17 years with major depressive disorder (MDD) because efficacy has not been demonstrated (see section 5.1). In general , the adverse reaction profile of vortioxetine in adolescents was similar to that seen for adults except for higher incidences reported in adolescents than in adults for abdominal pain-related events and suicidal ideation (see section 4.8 and 5.1). In clinical studies in children and adolescents treated with ~~other~~ antidepressants, suicide-related behaviour (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour, anger) were more frequently observed than in those treated with placebo.

Section 4.8.

Paediatric population
A total of 308 adolescent patients aged 12 to 17 years with major depressive disorder (MDD) were treated with vortioxetine in a double-blind, placebo-controlled study. In general, the adverse reaction profile of vortioxetine in adolescents was similar to that seen for adults except for higher incidences reported in adolescents than in adults for abdominal pain-related events and suicidal ideation.

Section 5.1.

Paediatric population
One randomised, double-blind, placebo-controlled, active-referenced, fixed dose, 8-week study was conducted in adolescent patients with MDD aged 12 to 17 years. The study included a 4-week single-blind placebo lead-in period with standardized psychosocial intervention (N=777); only non-responders from the lead-in period were randomised (N=615). Neither vortioxetine 10 mg/day nor 20 mg/day was statistically significantly superior to placebo based on the Children´s Depression Rating Scale-Revised (CDRS-R) total score. The active reference (fluoxetine 20 mg/day) separated statistically from placebo on the CDRS-R total score. In general, the adverse reaction profile of vortioxetine in adolescents was similar to that seen for adults except for higher incidences reported in adolescent than in adults for abdominal pain-related event and suicidal ideation. Discontinuation due to adverse events (mostly due to suicidal ideation, nausea and vomiting) was highest in patients treated with vortioxetine 20 mg/day (5.6%) as compared to vortioxetine 10 mg/day (2.7%), fluoxetine (3.3%), and placebo (1.3%). The most commonly reported adverse events in the vortioxetine treatment groups were nausea, vomiting and headache. Suicidal ideation and behaviour were reported as adverse events both during the 4-week single-blind lead-in period (placebo 13/777 [1.7%]), and during the 8-week treatment period (vortioxetine 10 mg/day 2/147 [1.4%], vortioxetine 20 mg/day 6/161 [3.7%], fluoxetine 6/153 [3.9%], placebo 0/154 [0%]). Suicidal ideation and behaviour as measured by Columbia-Suicide Severity Rating Scale (C-SSRS) was similar across treatment groups.

Paediatric population

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3. Rapporteur's overall conclusion and recommendation

Overall conclusion

Supplementary information is asked before a conclusion to this report can be drawn.

Recommendation

☒ Not Fulfilled

Based on the data submitted, the MAH should provide additional clarifications as part of this procedure. (see section 4).

4. Request for supplementary information

Question 1.

To compare better the incidence rate of TEAEs in adolescents during the extension study 12712B with the double-blind study 12710A, it would be interesting to know what is the proportion of patients who were treated with the 5 mg; 10 mg dose and 20 mg dosage?

Question 2.

The TEAE hyperprolactinaemia (4% in children and 5.8 % in adolescents) was not described in the DB study 12710A and is not mentioned in the SmPC for adult patients. This AE should be further discussed by the MAH. Was it described in clinical studies in adult populations and has it been described in the post marketing use of vortioxetine? Has it been described in unblinded cases in study 12709A? Even if patients are asymptomatic, what could be the consequence of prolonged hyperprolactinaemia in children? On which criteria was the status of these patients defined as "asymptomatic"?

Question 3.

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).

The MAH is asked to provide more details on these data (a table for example). What is the difference between children and adolescents for these results? The MAH should further discuss these results, in particular because they are contrasting with the improvements in depressive symptoms, described in the efficacy results.

Question 4.

Concerning the results of C-SSRS, the majority (96%) of the patients had no suicidal ideation or behaviour during the study. Four patients (4%) had suicidal ideation without intent to act. None of the patients had suicidal behaviour. The MAH is asked to provide more details on these data (a table for example). What is the difference between children and adolescents for these results? The MAH should further discuss these results.

Question 5.

The applicant should clarify and discuss the very high rate of withdrawals in adolescents patients (47.8 %). Does this corresponds to the adolescent patients discontinued from study 12712B due to the decision of the independent Data Monitoring Committee (DMC) who recommended to discontinue all adolescents patients in the extension Studies 12712A and 12712B, based on the lack of efficacy of vortioxetine in Study 12710A in adolescents?

5. Evaluation of responses

Question 1.

To compare better the incidence rate of TEAEs in adolescents during the extension study 12712B with the double-blind study 12710A, it would be interesting to know what is the proportion of patients who were treated with the 5 mg; 10 mg dose and 20 mg dosage?

Applicant's Response

In Study 12712B (flexible-dose study), patients continued on the vortioxetine dose they received at the completion of the first extension Study 12712A (5, 10, 15, or 20 mg/day) and the dose could be adjusted (up- or down-titrated) during the study based on investigator's judgment. Therefore, the number of patients at the respective vortioxetine dose varied over time, see table below (Table 11 in the 12712B CSR). Overall, it appears that during the 18-month treatment in Study 12712B, approximately one-third (range: 26-36%) of the adolescents from lead-in Study 12710A received vortioxetine 10 mg, approximately one-third (range: 29-35%) received vortioxetine 20 mg, approximately one-fourth (range: 23-32%) received vortioxetine 15 mg, and the remaining approximately 9% (range: 5-12%) received vortioxetine 5 mg.

CHMP comment

The distribution of patients is homogenous between the different doses (1/3 for the 10 mg, 1/3 for the 20mg) which is similar to the distribution in the lead-in study 12710A. This is coherent with the fact that the general incidence rate of TEAEs in adolescents (52.2%) in Study 12712B is similar to the rate of TEAEs in the double-blind Period study 12710A.

Issue resolved.

Question 2.

The TEAE hyperprolactinaemia (4% in children and 5.8 % in adolescents) was not described in the DB study 12710A and is not mentioned in the SmPC for adult patients. This AE should be further discussed by the MAH. Was it described in clinical studies in adult populations and has it been described in the postmarketing use of vortioxetine? Has it been described in unblinded cases in study 12709A? Even if patients are asymptomatic, what could be the consequence of prolonged hyperprolactinaemia in children? On which criteria was the status of these patients defined as "asymptomatic"?

Applicant's Response

Prolactin is part of the clinical safety laboratory tests measured in Studies 12712A and 12712B, but prolactin was not included in the clinical safety laboratory tests measured in Study 12709A and 12710A, nor in the adult MDD studies.
As hyperprolactinaemia was reported in Study 12712B, Lundbeck performed a signal assessment of hyperprolactinaemia for vortioxetine in general, including both the paediatric and adult population, thereby also assessing adult data from the post-marketing setting. Based on cases from both the clinical trial and the post-marketing setting, Lundbeck concluded that there was a possible causal relationship between vortioxetine and hyperprolactinaemia. Therefore, Lundbeck proposed in the PSUR10 EMA procedure no. PSUSA/00010052/202009 (data lock point: 29 September 2020) to update the SmPC to include hyperprolactinaemia in section 4.8. Lundbeck is currently awaiting the assessment report from the PRAC.

Hyperprolactinaemia has not been reported in unblinded cases in Study 12709A.
Prolonged hyperprolactinemia may affect progression of puberty (sexual maturation and growth). This was monitored in Study 12712B with Tanner stage and height, weight and BMI measurements. For the specific patients that had hyperprolactinaemia, and for all the patients in general, there were no clinically significant shift in height-for-age percentile or BMI-for-age percentile, and a normal growth spurt among boys and girls was observed. Shifts observed in Tanner stages reflected normal pubertal growth in the paediatric population (Tables 144 and 145 in the 12712B CSR). Menstrual cycle and duration were normal during treatment with vortioxetine (Tables 146 and 147, respectively, in the 12712B CSR).
All events of hyperprolactinaemia were reported based on laboratory results. The investigators were contacted and asked whether the patients had any clinical signs or symptoms of hyperprolactinaemia. Based on the investigators' input, it was confirmed that all patients with hyperprolactinaemia were asymptomatic.

CHMP comment

A signal of Hyperprolactinaemia was opened in the PSUR10 (PSUSA/00010052/202009) (data lock point: 29 September 2020), triggered by 9 cases of hyperprolactinaemia in the paediatric extension study 12712B. Supportive case have been reported in both clinical trial and post-marketing settings. Up to 01-May-2020, 11 (asymptomatic) cases of hyperprolactinemia/ blood prolactin increased were reported in clinical trials, for which causality was assessed as related for all cases except one. The MAH included 34 post-marketing cases in its analysis of this signal, most of them with a compatible temporal relationship where reported, including 7 cases with positive de-challenge. Additionally, although the mechanism by which antidepressants may cause hyperprolactinaemia is not fully understood, nearly all antidepressants are reported to be associated with hyperprolactinaemia. The MAH concluded that causality with vortioxetine treatment is possible and the CCDS was updated to include hyperprolactinaemia in section 4.8 with a frequency as unknown.

Following to the evaluation of this signal in the PSUR AR, the PRAC has recommended to add the ADR "hyperprolactinaemia" in the section 4.8. of the SmPC with a frequency not known. The Package leaflet will be updated accordingly. (Recommendation adopted by the PRAC on 6 May 2021 and decision CHMP on May 20th).

Issue resolved.

Question 3.

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). The MAH is asked to provide more details on these data (a table for example). What is the difference between children and adolescents for these results? The MAH should further discuss these results, in particular because they are contrasting with the improvements in depressive symptoms, described in the efficacy results.

Applicant's Response

As requested, a more detailed overview of the PAERS findings is presented graphically below for selected PAERS items: Irritability (Panel 1), Sad or depressed mood (Panel 2), Fatigue (Panel 3), Insomnia (Panel 4), and Trouble paying attention/concentrating (Panel 5). The proportion of patients in each severity category by visit is shown separately for children and adolescents. A complete set of graphs for all PAERS items is included in Appendix I.

In general, the proportion of children and adolescents who reported no irritability, no fatigue, or no trouble paying attention increased over time (Panel 1, Panel 3, and Panel 5). Although some patients experienced worsening in these signs/symptoms at some point during the study compared to baseline (data summarized in Table 158 in the 12712B CSR), overall, there was a tendency toward improvement in severity for these items. Trouble paying attention was more common problem in children; nevertheless, improvements over time were observed in both age groups.

For item Sad or depressed mood (Panel 2), the proportion of children and adolescents who reported Sad or depressed mood decreased only slightly, in children mostly towards the end of the study; however, decreased symptom severity over time was observed throughout the study in both age groups.

For Insomnia (Panel 4), only a few patients ($\leq$3 children and $\leq$7 adolescents) reported trouble falling asleep at any time point during the 18-month extension period. There appears to be a tendency towards improvement in insomnia in adolescents but no pronounced changes over time in the few children who reported insomnia during the study.

Overall, despite some fluctuations indicating worsening at some point during the study for some patients, decreased symptom severity were observed for most of the symptoms related to MDD compared to baseline. These observations are consistent with improvements in depressive symptoms described in the efficacy results.

CHMP comment

As requested, a more detailed overview of the PAERS related to depressive symptoms was provided by the applicant. The discussion of the applicant is endorsed.

Issue resolved.

Question 4.

Concerning the results of C-SSRS, the majority (96%) of the patients had no suicidal ideation or behaviour during the study. Four patients (4%) had suicidal ideation without intent to act. None of the patients had suicidal behaviour. The MAH is asked to provide more details on these data (a table for example). What is the difference between children and adolescents for these results? The MAH should further discuss these results.

Applicant's Response

The number of children and adolescents with suicidal ideation and behaviour in each C-SSRS category is summarized in Table 156 (copied below) in the 12712B CSR. Four patients had suicidal ideation without intent to act: 3 patients (1 child and 2 adolescents) *wish to be dead* and 1 patient (adolescent) had *non-specific active suicidal thoughts.* Further details on the suicidal ideation for these 4 patients, as per the C-SSRS, are described below:

• One subject was an 11-year-old. The patient described the *suicidal ideation without intent to act (wish to be dead)* as 'Is so bad that it is not worth living'. The patient completed the study.

• One subject was a 14-year-old who described the *suicidal ideation without intent to act (wish to be dead)* as 'I'd like to run away'. The patient was withdrawn from the study due to non-compliance with IMP.

• One subject was a 16-year-old who had *suicidal ideation without intent to act (wish to be dead).* There was no further information available in relation to the suicidal ideation. The patient was withdrawn from the study due to non-compliance with IMP.

• One subject was a 17-year-old who described the *suicidal ideation without intent to act (non-specific active suicidal thoughts)* as 'I would like to kill myself'. For this patient, concomitant medication zopiclone is reported, which could be a confounding factor. The patient was withdrawn from the study due to lack of efficacy.

The C-SSRS scores may reflect the patients' underlying depression.

The incidences of suicidal ideation in Study 12712B (4%) are lower than the 17.2% prevalence of suicidal ideations among U.S. adolescents, according to the 2017 Youth Behaviour Risk Surveillance survey1 or the recently reported paediatric 6-month extension study of vilazodone,2 where 12% of all patients experienced suicidal ideation.

Table 156 Suicidal Ideation or Behaviour and Non-suicidal Self-Injury Behaviour by Lead-in Study (APTS) - Study 12712B

	Lead-in Study			
	12709A		12710A	
Worst C-SSRS Score	n	(%)	n	(%)
Patients	25		69	
No Suicidal ideation or behaviour	24	(96.0)	66	(95.7)
Non-suicidal self-injurious behaviour	0		1	(1.4)
Suicidal Ideation				
Wish to be dead	1	(4.0)	2	(2.9)
Non-specific active suicidal thoughts	0		1	(1.4)
Active suicidal ideation with any methods (not plan) without intent to act			0	
Idea, No Intent, No Plan	0			
Active suicidal ideation with some intent to act, without specific plan	0		0	
Active suicidal ideation with specific plan and intent	0		0	
Suicidal Behaviour				
Preparatory acts or behaviour			0	
Aborted attempt			0	
Aborted/Self-Interrupted Attempt	0			
Interrupted attempt	0		0	
Non-fatal suicide attempt	0		0	
Completed suicide	0		0	

C-SSRS child version is used for patients from 12709A

12712B FINAL TLG_Safety_Other ST_CSSRS02 22SEP2020 ADaM:22SEP2020

CHMP comment

As requested, the applicant has further discussed the results of C-SSRS. The incidences of suicidal ideation in Study 12712B (4%) are rather low and concern mainly adolescent patients (3 adolescents and 1 children).

Issue resolved.

Question 5.

The applicant should clarify and discuss the very high rate of withdrawals in adolescents patients (47.8 %). Does this corresponds to the adolescent patients discontinued from study 12712B due to the decision of the independent Data Monitoring Committee (DMC) who recommended to discontinue all adolescents patients in the extension Studies 12712A and 12712B, based on the lack of efficacy of vortioxetine in Study 12710A in adolescents?

Applicant's Response

The withdrawal rate observed in this study, 38.3%, is not unexpectedly high, given the long study duration (18 months, on top of 9 months in Studies 12709A or 12710A, and 12712A) and in light of previous experience with long-term, 52-week studies in adults where 43% of the patients withdrew prematurely (3).
Overall, 36 patients withdrew in this paediatric long-term study, 33 adolescents (47.8%) and 3 children (12%). Indeed, *Sponsor's decision based on the results of Study 12710A* did contribute to higher withdrawal rate in adolescents compared to children; however, there were also other reasons for premature withdrawal.
As shown in Panel 10 (copied below) and in Listing 1 in the 12712B CSR, most patients in the study withdrew for reasons categorized as *other,* which included the following:

- Adolescents (24 patients)
  - sponsor's decision based on the results of Study 12710A (10 patients)
  - patient/parent decision or refusal to attend study visits (6 patients)

– logistic/relocation reasons (3 patients)
– patient decision to stop medication due to significant improvement (3 patients)
– parental concerns about patient's non-compliance (1 patient)
– taking disallowed medication/non-compliance with study requirements (1 patient)
• Children (3 patients)
– patient/parent decision or refusal to attend study visits (2 patients)
– parent decision to stop therapy due to significant improvement (1 patient)

Note : regarding withdrawals due to *Sponsor's decision based on the results of Study 12710A:* Given that enrolment in extension Study 12712B was stopped in October 2019, most patients were close to completion at the time when the sponsor became aware of the negative adolescent study results (November 2020). The duration in Study 12712B for these patients ranged from 497 to 531 days (14.5 to 15 months).

It is also noted that several of the reasons for withdrawal listed above may be related to long study duration and/or study burden. Patient/parent decision or refusal to attend further study visits was reported for 6 adolescents and 2 children. Four patients (3 adolescents and 1 child) withdrew due to significant improvement/being in remission. These withdrawals are not unexpected given that a typical MDD episode lasts 7-9 months (4) and the paediatric MDD literature recommends 9-12 months of antidepressant treatment. (5)

Panel 10 Withdrawals from Study by Primary Reason (APTS)

	12709A		12710A		Total	
	n	%	n	%	n	%
Number of Patients	25		69		94	
Completed Study	22	(88.0)	36	(52.2)	58	(61.7)
Withdrawn from Study	3	(12.0)	33	(47.8)	36	(38.3)
Reason						
Lack of efficacy	0		2	(2.9)	2	(2.1)
Non-compliance 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)

12712B FINAL TLG_Patients ST_WDPrim01 22SEP2020 ADaM:22SEP2020

CHMP comment

As requested, the applicant clarified and further discussed the rate of withdrawals in adolescents patients.

Issue resolved.

References

1. Kann L, McManus T, Harris WA, Shanklin SL, Flint KH, Queen B, et al. Youth Risk Behavior Surveillance – United States, 2017. MMWR Surveill Summ. 2018; 67(8): 1-114.

2. Findling RL, McCusker E, Strawn JR. A randomized, double-blind, placebo-controlled trial of vilazodone in children and adolescents with major depressive disorder with twenty-six-week open-label follow-up. J Child Adolesc Psychopharmacol. 2020; 30(6): 355-365.

3. Vieta E, Loft H, Florea I. Effectiveness of long-term vortioxetine treatment of patients with major depressive disorder. Eur Neuropsychopharmacol. 2017; 27: 877-884.

4. Kovacs M, Obrosky S, George C. The course of major depressive disorder from childhood to young adulthood: recovery and recurrence in a longitudinal observational study. J Affect Disord. 2016; 203: 374-381.

5. Hathaway EE, Walkup JT, Strawn JR. Antidepressant treatment duration in pediatric depressive and anxiety disorders: how long is long enough? Curr Probl Pediatr Adolesc Health Care. 2018; 8(2): 31-39.

6. Rapporteur's overall conclusion and recommendation

Overall conclusion

The Applicant has answered satisfactorily to all questions and all issues are resolved.

Study 12712B was an open label, 18-month extension study to the ongoing Study 12712A, which itself is an open label, 6-month extension study to Studies 12709A and 12710A (8 week, double blind, efficacy and safety studies in children and adolescents, respectively). As Study 12712B constitutes a part of the open-label extension period to investigate the long-term safety of vortioxetine in the paediatric population, **the Rapporteur agrees with the company's opinion that a potential update to the Product Information should await completion of the lead-in study 12712A.**

Recommendation

☒ **PAM fulfilled - No further action required**

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

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	Expected: 30/06/2022	Not applicable

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	Expected: 30/06/2024	Not applicable
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	Expected: 30/06/2022	Not applicable
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