Synopsis – Study 18498A

Study Title A randomized, double-blind, parallel-group, active-controlled study evaluating the efficacy of vortioxetine *versus* desvenlafaxine in adult patients suffering from major depressive disorder with partial response to SSRI treatment
Investigators 78 principal investigators at 77 sites in 12 countries *Signatory investigator* – [redacted]
Study Sites 77 sites – 14 in Argentina, 1 in Belgium, 6 in Bulgaria, 9 in Czech Republic, 1 in Estonia, 3 in Latvia, 3 in Mexico, 15 in Russian Federation, 6 in Slovakia, 3 in Spain, 5 in Sweden, and 11 in Ukraine
Publications None (as of the date of this report)
Study Period *First patient first visit* – 18 June 2020 (the date when the first *Informed Consent Form* was signed) *Last patient last visit* – 4 February 2022 (the date of the last protocol-specified contact with any patient)

Objectives and Endpoints	
Objectives	**Endpoints**
Primary Objective • to compare the efficacy of vortioxetine (10 to 20 mg/day) *versus* desvenlafaxine (50 mg/day) after 8 weeks of treatment on depressive symptoms in patients with major depressive disorder (MDD) who have responded partially to monotherapy with a selective serotonin reuptake inhibitor (SSRI)	**Depressive Symptoms** • Primary endpoint: – change from Baseline to Week 8 in Montgomery and Åsberg Depression Rating Scale (MADRS) total score • Secondary endpoints: – response (defined as a ≥50% decrease in MADRS total score from Baseline) at Week 8 – remission (defined as a MADRS total score ≤10) at Week 8 – change from Baseline to Week 8 in MADRS anhedonia factor score (based on items 1 (*apparent sadness*), 2 (*reported sadness*), 6 (*concentration difficulties*), 7 (*lassitude*), 8 (*inability to feel*))
Secondary Objectives • to compare the efficacy of vortioxetine (10 to 20 mg/day) *versus* desvenlafaxine (50 mg/day) after 8 weeks of treatment on: – Clinical Global Impression (CGI) – Cognitive functioning – Reward motivation – Functioning – Health-Related Quality of Life	**Clinical Global Impression** • Secondary endpoints: – Clinical Global Impression–Global Improvement (CGI-I) score at Week 8 – change from Baseline to Week 8 in Clinical Global Impression–Severity of Illness (CGI-S) score **Cognition** • Secondary endpoint: – change from Baseline in Digital Symbol Substitution Test (DSST) total score to Week 8 **Reward Motivation** • Secondary endpoints: – patient's choice of Easy or Hard task for each Effort Expenditure for Rewards Task (EEfRT) trial at Week 8 – the proportion of Hard Choice at Week 8 **Functioning** • Secondary endpoints: – change from Baseline to Week 8 in Functioning Assessment Short Test (FAST) total score – change from Baseline to Week 8 in FAST sub-domain scores for *autonomy*, *occupational functioning*, *cognitive functioning*, *financial issues*, *interpersonal relationships*, *leisure time* **Health-Related Quality of Life** • Secondary endpoint: – change from Baseline to Week 8 in the Quality of Life, Enjoyment, and Satisfaction Questionnaire (Q-LES-Q) Long Form subscales for *work*, *household duties*, *school*, *leisure time activities*, *social relations*, *physical health*, *feelings*, *general activities*, *satisfaction with medication*, and *overall satisfaction and contentment*

Objectives and Endpoints (continued) Objectives	Endpoints
Safety Objective • to evaluate the safety and tolerability of vortioxetine (10 to 20 mg/day) and desvenlafaxine (50 mg/day)	**Safety Endpoints** • adverse events • withdrawals due to adverse events • Columbia-Suicide Severity Rating Scale (C-SSRS) score

Study Methodology

- This was an interventional, multi-national, multi-site, randomized, double-blind, parallel-group, active-controlled (desvenlafaxine) study.
- The study consisted of:
  - Screening Period – up to 14 days (±3 days) before the Baseline Visit
  - Treatment Period – 8-week double-blind treatment period with vortioxetine or desvenlafaxine
  - Safety Follow-up Period – approximately 4 weeks after the Primary Outcome/Withdrawal Visit; the first week of which is 1-week taper down of treatment (only for patients randomized to desvenlafaxine)
- At Baseline, the patients were equally randomized (1:1) to 8 weeks of double-blind treatment with either vortioxetine or desvenlafaxine. The patients randomized to vortioxetine received 10 mg/day during the first week of treatment. At Visit 3 (Week 1), the dose was increased to 20 mg/day. The dose may have been adjusted (10 or 20 mg/day) at unscheduled visits or at Visit 4 (only once) based on the patient's response and the investigator's clinical judgement. After Visit 4, no dose changes were permitted. At Week 8, for patients randomized to desvenlafaxine, the dose was gradually decreased, so that the patients received 50mg/day every second day for 1 week after the Primary Outcome/Withdrawal Visit.
- Efficacy and safety data were collected at Baseline and throughout the study.

Number of Patients Planned

600 patients, recruited from psychiatric specialist settings, were planned for randomization: 300 in the vortioxetine group and 300 in the desvenlafaxine group.

Diagnosis and Main Selection Criteria

The patients had to be outpatients with a primary diagnosis of MDD according to DSM-5® criteria, who:

- had a MADRS total score ≥24 at the Screening Visit and Baseline Visit
- were receiving SSRI monotherapy (citalopram, escitalopram, paroxetine, sertraline) for at least 6 weeks prior to the Screening Visit and had responded partially
- were aged ≥18 and ≤65 years

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

- *Vortioxetine* – 10 or 20 mg/day, encapsulated tablets, orally; batch Nos. E211394-0001E and E211394-0002E
- *Desvenlafaxine* – 50 mg/day encapsulated tablets, orally; batch No. E211394-0025E and E211394-0003E

Control Products, Doses and Modes of Administration, Batch Numbers

- *Placebo* (used to maintain the blind during down-tapering) – capsules, orally; batch No. E211394-0004E

Duration of Treatment

8 weeks

Statistical Methodology

- The following analysis sets were defined in the Statistical Analysis Plan:
  - All-patients-randomized set (APRS) – all randomized patients
  - All-patients-treated set (APTS) – all patients in the APRS who took at least one dose of double-blind IMP
  - Full-analysis set (FAS) – all patients in the APTS who had a valid Baseline assessment and at least one valid post-baseline assessment of the primary efficacy variable (MADRS)
  - Per-protocol set (PPS) – all patients in FAS who did not have any major protocol deviations relevant for efficacy
- Unless otherwise specified, all efficacy analyses and data presentations are based on the FAS and all safety analyses and data presentations are based on the APTS.
- Due to the COVID-19 pandemic, some patients had remote visits, therefore additional analyses and safety tabulations were performed with respect to this subpopulation.
- Primary analysis of the primary endpoint:
  - For the primary endpoint (change from Baseline in the MADRS total score to Week 8), estimates were obtained using restricted maximum likelihood-based mixed model for repeated measures (MMRM). The model included the following: country and treatment (vortioxetine and desvenlafaxine) as fixed factors, the Baseline MADRS total score as a continuous covariate, the treatment-by-week interaction, and the Baseline MADRS total score-by-week interaction. An unstructured covariance structure was used to model the within-patient errors. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. The analysis was performed using all available observations (observed case [OC] data) in the Treatment Period.
  - The estimated treatment difference between vortioxetine and desvenlafaxine at Week 8 was based on the least squares means for the treatment-by-week interaction in the MMRM. The estimate presented with its p-value and its associated 95% confidence interval (CI) was used for the non-inferiority comparison of vortioxetine *versus* desvenlafaxine.
- Supplementary analyses of the primary endpoint:
  - The primary analysis, based on the FAS, was repeated based on the PPS.
  - Analyses using both OC and last observation carried forward (LOCF) were performed using an analysis of covariance (ANCOVA) model.
- Secondary efficacy endpoints:
  - For continuous secondary endpoints with repeated post-baseline assessments, the same methodology as that described for the primary endpoint was used. All continuous secondary endpoints were furthermore analysed using an ANCOVA (OC and LOCF), with treatment and country as factors and the Baseline score as a covariate. For binary endpoints, such as response and remission, logistic regression with treatment as a factor and the Baseline score as a covariate was used. The response and remission endpoints were analysed using logistic regression and based on OC, LOCF, and Non-Response/Non-Remission Imputation. The estimated treatment differences between vortioxetine and desvenlafaxine at Week 8 and their associated 95% CIs were used to compare vortioxetine and desvenlafaxine.
  - The EEfRT choices based on the first up to 50 trials out of a maximum of 102 trials were analysed using Generalised Estimating Equations (GEE) for repeated binary outcomes with treatment (vortioxetine or desvenlafaxine) and reward probability as fixed factors, and with hard reward as a continuous covariate. Easy and Hard tasks required different amounts of repeated manual button pressing; for Hard-task choices, the patient was eligible to win higher amounts.
- Safety endpoints were summarized using descriptive statistics.

Patient Disposition and Analysis Sets

- Patient disposition is summarized below:

	VOR		DES		Total	
	n	(%)	n	(%)	n	(%)
All-patients-randomized Set (APRS)	312		293		605	
All-patients-treated Set (APTS)	310	(100)	293	(100)	603	(100)
Patients completed	295	(95.2)	284	(96.9)	579	(96.0)
Patients withdrawn	15	(4.8)	9	(3.1)	24	(4.0)
Primary reason for withdrawal:						
Adverse event(s)	6	(1.9)	3	(1.0)	9	(1.5)
Lack of efficacy	1	(0.3)	1	(0.3)	2	(0.3)
Withdrawal of consent	5	(1.6)	3	(1.0)	8	(1.3)
Lost to follow-up	1	(0.3)	0		1	(0.2)
Other	2	(0.6)	2	(0.7)	4	(0.7)
Analysis sets:						
FAS	309		293		602	
PPS	294		283		577	

DES = desvenlafaxine; FAS = full-analysis set; PPS = per-protocol set; VOR = vortioxetine

Demographics and Baseline Characteristics of the Study Population

- More than two-thirds of the patients in the total patient population were women. The treatment groups were similar with respect to the proportion of women, ranging from 69% (vortioxetine group) to 72% (desvenlafaxine group).
- The treatment groups were similar with respect to age and race distribution: the median age was 44 years for both treatment groups, and the majority (>92%) of the patients were White.
- The severity of depression was similar in each of the treatment groups, with no clinically relevant differences in mean Baseline scores for the efficacy endpoints. At Baseline, the mean MADRS total score indicated that the patients in both treatment groups had *moderate* to *severe* MDD. The mean CGI-S score indicated that the patients in both treatment groups were *moderately* to *markedly ill*.

Efficacy Results

- The analysis of the primary endpoint, change from Baseline in MADRS total score at Week 8, showed an improvement in both the vortioxetine and desvenlafaxine groups. The estimated treatment difference was -0.47 in favour of vortioxetine, with the upper limit of the associated CI below the pre-defined threshold of 2.5 points, showing that vortioxetine was non-inferior to desvenlafaxine.
- The analyses of the secondary endpoints, MADRS anhedonia factor, CGI-I, CGI-S, DSST, FAST, and Q-LES-Q, showed improvement at Week 8 in both the vortioxetine and desvenflaxine groups. There were no nominally significant differences between treatment groups with the following exceptions: improvements in the FAST subscores *autonomy* and *interpersonal relationships*, and Q-LES-Q subscore *satisfaction with medication* were nominally significantly greater in the vortioxetine group *versus* the desvenlafaxine group. A nominally significant improvement in CGI-S was identified for vortioxetine *versus* desvenlafaxine in the ANCOVA, OC analysis, but not in the MMRM or ANCOVA, LOCF analyses. The proportion of patients who reached remission, as measured by the CGI-S (CGI-S ≤2), was nominally significantly higher in the vortioxetine group *versus* the desvenlafaxine group.
- There were no nominally significant differences between treatment groups in the proportions of responders or remitters based on the MADRS.
- For the patient's choice of Easy or Hard task for each trial (GEE model) at Week 8, the difference between treatment groups was not nominally significant. Patients chose a hard task on average 32% of the time in both treatment groups at Baseline; this increased to 33% at Week 8 for the vortioxetine group and 34% for the desvenlafaxine group.
- For working patients, the change from Baseline at Week 8 in FAST total score was nominally significantly greater for patients in the vortioxetine group than for patients in the desvenlafaxine group. Nominally significant results in favour of vortioxetine were also found in the *autonomy* and the *interpersonal relationships* domains.

Safety Results

- The adverse event incidence in the Treatment Period is summarized for the APTS below:

	VOR		DES	
	n	(%)	n	(%)
Number of Patients	310		293	
Patient Years of Exposure	46		44	
Patients with treatment-emergent adverse events (TEAEs)	143	(46.1)	116	(39.6)
Patients with treatment-emergent serious adverse events (SAEs)	0		1	(0.3)
Patients with TEAEs leading to withdrawal	6	(1.9)	3	(1.0)
Deaths	0		0	
Total number of TEAEs	268		190	
Total number of SAEs	0		1	
Total number of TEAEs leading to withdrawal	14		5	

DES = desvenlafaxine; VOR = vortioxetine

- The TEAEs with an incidence ≥5% in the Treatment Period are summarized for the APTS below:

Preferred Term (MedDRA, Version 24.0)	VOR		DES	
	n	(%)	n	(%)
Number of Patients	310		293	
Patients with TEAEs with incidence of 5% or more	85	(27.4)	61	(20.8)
Nausea	62	(20.0)	27	(9.2)
Headache	30	(9.7)	25	(8.5)
Dizziness	16	(5.2)	16	(5.5)

DES = desvenlafaxine; VOR = vortioxetine

- In the Treatment Period, 143 (46%) and 116 (40%) patients in the vortioxetine and desvenlafaxine groups, respectively, reported adverse events, the majority of which were *mild* or *moderate*. Five *severe* TEAEs (*vomiting*, *irritability*, *nausea*, *hyperkalaemia*, and *hypoglycaemia*) occurred in 4 patients in the vortioxetine group and 2 *severe* TEAEs (*dizziness* and *headache*) occurred in 1 patient in the desvenlafaxine group. The most commonly reported adverse events, with an incidence ≥5% in both groups, were *nausea*, *headache*, and *dizziness*. A total of 9 patients withdrew due to adverse events, 6 and 3 in the vortioxetine and desvenlafaxine groups, respectively. No SAEs were reported in the vortioxetine group, and 1 SAE (*vomiting*) was reported in the desvenlafaxine group.
- The incidence of potentially clinically significant vital signs and weight changes was low, the mean vital signs values were within the reference ranges in the 8-week Treatment Period, and the mean changes from Baseline at Week 8 were small with no differences observed between treatment groups.
- Based on the C-SSRS, the majority (≥97%) of the patients in both treatment groups had no suicidal ideation or behaviour during the Treatment Period. Two patients, 1 in each treatment group, had *active suicidal ideation with some intent to act, without specific plan* in each instance an adverse event of *suicidal ideation* was reported. *Active suicidal ideation with any methods (not plan) without intent to act* and *non-suicidal self-injurious behaviour* were each reported in 1 patient in the vortioxetine group. In each treatment group, 6 patients reported a *wish to be dead*. None of the patients had suicidal behaviour during the Treatment Period.

Conclusions

- The primary efficacy analysis showed that vortioxetine 10 or 20 mg was statistically non-inferior to desvenlafaxine 50 mg in the mean change from Baseline in MADRS total score at Week 8 in patients suffering from MDD with a partial response to SSRI treatment.
- The analyses of the secondary endpoints based on the MADRS anhedonia factor, CGI-I, CGI-S, DSST, FAST, and Q-LES-Q, showed numerical advantages for vortioxetine except for the FAST subscore *leisure time*, and the Q-LES-Q subscores *school and leisure time activities*. The analysis of the EEfRT secondary endpoint showed numerical advantages for desvenlafaxine. Improvements in the FAST subscores *autonomy* and *interpersonal relationships*, and Q-LES-Q subscore *satisfaction with medication* were nominally significantly greater in the vortioxetine group than in the desvenlafaxine group.
- Once daily doses of 10 to 20 mg vortioxetine or 50 mg desvenlafaxine were safe and generally well tolerated by patients with MDD in this study.

Report Date

30 August 2022

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