Synopsis – Study 13546A

Study Title
A double-blind, randomized, placebo-controlled, multicentre, relapse-prevention study of vortioxetine in paediatric patients aged 7 to 11 years with Major Depressive Disorder (MDD)

Investigators
17 principal investigators at 17 sites in 7 countries
Signatory investigator – [redacted]

Study Sites
17 sites – 3 in Colombia, 3 in Mexico, 3 in United States, 1 in Latvia, 2 in Poland, 4 in Russian Federation, and 1 in Ukraine

Publications
None (as of the date of this report)

Study Period
First patient first visit – 10 August 2021 (the date when the first *Informed Consent Form* was signed)
Study terminated – 3 March 2022
Last patient last visit – 28 April 2022 (the date of the last protocol-specified contact with any patient)

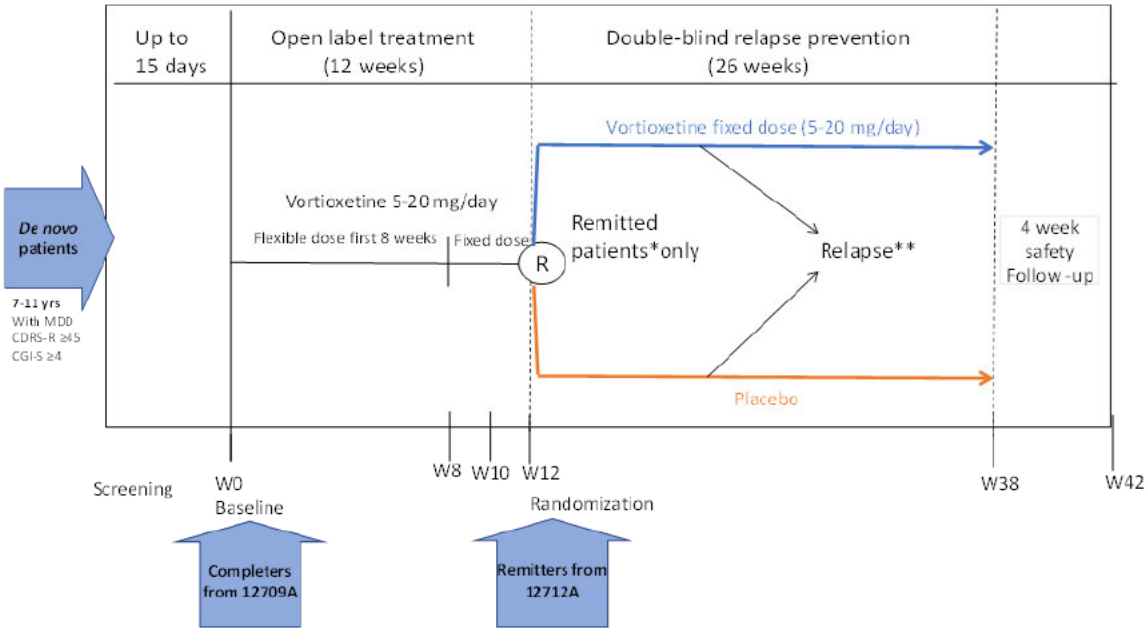
Objectives and Endpoints

Objectives	Endpoints
Primary Objective • to evaluate the efficacy of vortioxetine in the prevention of relapse of major depressive episodes in paediatric patients with MDD	**Depressive Symptoms** • Primary endpoint: – time to relapse in the double-blind period • Secondary endpoint: – relapse rate in the double-blind period
Secondary Objectives • to evaluate the efficacy of vortioxetine during continuation treatment of paediatric patients with MDD • to evaluate the efficacy of vortioxetine on: – clinical global impression – quality of life	**Depressive Symptoms** • Secondary endpoint: – change from baseline to Week 26 in the Children's Depression Rating Scale - Revised Version (CDRS-R) total score – Clinical Global Impression • Secondary endpoints: – change from baseline to Week 26 in the Clinical Global Impression – Severity of Illness (CGI-S) score – Clinical Global Impression – Global Improvement (CGI-I) score at Week 26 **Quality of Life** • Secondary endpoint: – change from baseline to Week 26 in the Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) – Patient rated score
• to assess adherence to investigational medicinal product (IMP) through pharmacokinetic analysis	**Pharmacokinetics** • Secondary endpoints: – plasma exposure to vortioxetine – population pharmacokinetic parameter values

Safety Objectives	Safety Endpoints
• to evaluate long-term safety and tolerability of vortioxetine in paediatric patients with MDD	• adverse events • absolute values and changes from baseline in clinical safety laboratory test values (including oestradiol [girls only], luteinizing hormone [LH], and follicle-stimulating hormone [FSH]), vital signs, height, weight, Tanner staging, electrocardiogram (ECG) parameter values, effects on menstrual cycle • potentially clinically significant (PCS) clinical safety laboratory test values, vital signs, weight changes, and ECG parameter values • Columbia-Suicide Severity Rating Scale (C-SSRS) score • General Behaviour Inventory (GBI) score using the 10-item mania subscale (parental version)

Study Methodology

- This was an interventional, multi-national, multi-site, randomized, parallel-group, placebo-controlled, relapse-prevention study in paediatric patients from 7 to 11 years of age with MDD.
- The study consisted of a 12-week, open-label, flexible-dose treatment period with vortioxetine followed by a 26-week, randomized, double-blind, fixed-dose, placebo-controlled, relapse-prevention period.
- The study population included *de novo* patients as well as rollover patients from other paediatric vortioxetine studies (Studies 12709A and 12712A) who, in the investigator's opinion, would benefit from continued treatment with vortioxetine.
- As the placebo-controlled, short-term study (Study 12709A) in children aged 7 to 11 years with MDD was negative (that is, vortioxetine failed to show a significant difference from placebo in acute treatment), the present study was terminated. Only 4 patients were dosed during the double-blind period in the study, with 1 patient completing the study. After study termination, the patients were to be treated at the discretion of the investigator in line with clinical practice.
- The study design is shown below:



* Patients in remission (CDRS total score ≤28) at the 2 last visits in the open-label treatment period / Study 12712A

OR with an adequate clinical response (≥50% reduction in the CDRS-R total score compared to the baseline score and a CDRS-R total score ≤35) at the 2 last visits in the open-label treatment period.

**Relapse: CDRS-R total score of ≥40 with a history of 2 weeks of clinical deterioration, or a clinical deterioration that in the investigator's opinion warrants alteration of treatment to prevent full relapse.

Source: Panel 1 of the study protocol.

***De novo* patients (enrolled to the open-label period)**

– Patients meeting eligibility criteria for *de novo* patients were enrolled in the 12-week, open-label, flexible-dose treatment period.

Rollover patients from Study 12709A (enrolled to the open-label period)

– Patients may have participated in the present study after completing the randomized, 8-week, double-blind, placebo-controlled treatment period of Study 12709A.

– Eligible patients were enrolled in the 12-week, open-label, flexible-dose treatment period.

– The Baseline Visit of the present study took place at the same visit as Visit 12 (Completion Visit) of Study 12709A. Participation in Study 12709A was considered completed when all assessments required at Visit 12 were completed.

Study Methodology (continued)

Open-Label Period

- The patients received 5 mg/day for the first 2 days and 10 mg/day thereafter.
- The target dose was 10 mg/day, however, the investigator had the possibility to increase the dose to a maximum of 20 mg/day in case of unsatisfactory response or decrease the dose to 5 mg/day in case of dose-limiting adverse events. The dose could be up- or down-titrated with 5 mg/day. The patient was to receive the same dose for 2 days before being up- or down-titrated to a new dose. Changes in dosing could have occurred at any visit during the first 8 weeks at the investigator's discretion. In addition, between Week 2 and Week 8, the patient and/or parent(s)/legal representative(s) could have requested an unscheduled visit to discuss the patient's dose.
- From Week 8 onwards, the dose had to remain fixed.
- Patients in remission (defined as CDRS-R total score ≤28) at both Weeks 10 and 12, or with an adequate clinical response (defined as ≥50% reduction in the CDRS-R total score compared to the baseline score in this study [subtracted 17 to avoid flooring effect], and a CDRS-R total score ≤35) at both Weeks 10 and 12 were randomized in the double-blind, placebo-controlled, fixed-dose period.
- Patients who did not fulfil the randomization criteria at Week 10 and/or Week 12 were withdrawn from the study.
- A Safety Follow-up Visit was performed approximately 4 weeks after withdrawal from the open-label period.

Rollover patients (remitters) from Study 12712A (randomized to the double-blind period)

- Patients who had received vortioxetine for 8 to 12 weeks in the open-label extension study (Study 12712A) were invited to participate in the present study if they were in remission at the last 2 visits in Study 12712A prior to the rollover. In addition, the dose of vortioxetine must have been stable for the last 4 weeks in Study 12712A prior to randomization in the present study.
- Eligible patients were randomized directly to the 26-week, double-blind period.

Double-Blind Period (for all patients)

- A total of 80 patients who fulfilled the randomization criteria were planned to be randomly assigned to receive vortioxetine or placebo in a 1:1 ratio. Randomization was stratified by patient inclusion source (*de novo* patients, rollover patients from Study 12709A, or rollover patients from Study 12712A).
- Patients randomized to vortioxetine were to continue on their final dose from the open-label period or the dose they had on their last visit in Study 12712A, as applicable.
- Patients who relapsed during the double-blind period were to be withdrawn from the study. The criterion for a relapse was a CDRS-R total score ≥40 with a history of 2 weeks of clinical deterioration, or a clinical deterioration that in the investigator's opinion warranted alteration of treatment to prevent full relapse.
- A Safety Follow-up Visit was performed 4 weeks after withdrawal from or completion of the double-blind period.
- An independent Data Monitoring Committee (DMC) monitored safety data at regular intervals as specified in the DMC Charter.
- Throughout both the open-label and double-blind period, the treatment was taken once daily, preferably at the same time each day.

Number of Patients Planned

80 patients were planned for randomization to the 26-week double-blind period (including those who rolled over from Study 12712A): 40 in the vortioxetine group and 40 in the placebo group.

150 patients were planned to be recruited from specialist settings, mainly outpatient clinics, either as *de novo* patients or rollover patients from Study 12709A.

Target Patient Population
Main Inclusion Criteria

***De novo* patients**

- The patient has a primary diagnosis of MDD according to DSM-5™ although co-morbid anxiety disorders are permitted (except Post Traumatic Stress Disorder [PTSD] and Obsessive Compulsive Disorder [OCD]). The diagnosis is confirmed using the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-aged Children, Present and Lifetime version (K-SADS-PL).
- The patient has a CDRS-R total score ≥45 at the Screening and Baseline Visits.
- The patient has a CGI-S score ≥4 at the Screening and Baseline Visits.
- The patient is boy or girl aged ≥7 and <12 years at screening.

Rollover patients from Study 12709A

- The patient has completed Study 12709A (Visit 12, Completion Visit) immediately prior to enrollment into this study.
- In the investigator's opinion, the patient could benefit from participation in a study that includes continued treatment with vortioxetine.
- The patient is a child aged ≥7 and <12 years at Baseline of Study 12709A.

Rollover patients from Study 12712A (randomized to the double-blind period)

- The patient has received 8 to 12 weeks of open-label treatment with vortioxetine in Study 12712A and completed Visit 7 (Week 8), or Visit 8 (Week 10), or Visit 9 (Week 12) immediately prior to enrollment into this study.
- In the investigator's opinion, the patient could benefit from participation in a study that includes continued treatment with vortioxetine.
- The patient is in remission at the last 2 visits in Study 12712A, in which the CDRS-R is assessed every 4 weeks. Hence
  a) If the patient rolls over at Visit 7 or Visit 8 (Week 8 or Week 10): the patient has a CDRS-R total score ≤28 at Visit 5 (Week 4) and Visit 7 (Week 8) in Study 12712A
  b) If the patient rolls over at Visit 9 (Week 12): the patient has a CDRS-R total score ≤28 at Visit 7 (Week 8) and Visit 9 (Week 12) in Study 12712A
- The patient has been on a stable dose of vortioxetine for the 4 weeks prior to rollover to this study.
- The patient is a child aged ≥7 and <12 years at Baseline of Study 12712A.

Target Patient Population (continued)
Main Exclusion Criteria

***De novo* patients and rollover patients from Studies 12709A and 12712A**

- The patient receives ongoing current psychotherapy that is planned to be intensified. Interpersonal psychotherapy or cognitive behavioural therapy are not allowed.
- The patient has any current psychiatric disorder (DSM-5™ criteria) different from MDD, established as the primary diagnosis, as assessed using the K-SADS-PL.
- The patient has any other disorder for which the treatment takes priority over treatment of MDD or is likely to interfere with study treatment or impair treatment compliance.
- The patient had attempted suicide or was at significant risk of suicide (either in the opinion of the investigator or defined as a "yes" to suicidal ideation questions 4 or 5 or answering "yes" to suicidal behaviour on the C-SSRS within the last 12 months).
- The patient had a known intellectual disability (as suggested by an intelligence quotient [IQ] <70), or clinical evidence or known social or school history indicative of intellectual disability).
- The patient has been treated with any antidepressant or anxiolytic medication within 2 weeks prior to Visit 2 (only *de novo* patients).
- The patient had previously been treated with vortioxetine in a clinical study (only *de novo* patients).

Randomization Criteria

***De novo* patients and rollover patients from Study 12709A**

- The patient is in remission at both Weeks 10 and 12 or has an adequate clinical response at both Weeks 10 and 12.
- The patient has been on a stable dose of vortioxetine for the 4 weeks prior to randomization.

Investigational Medicinal Product (IMP), Doses and Mode of Administration, Batch Numbers

Open-Label Period

- *Vortioxetine* – 5 to 20 mg/day, film-coated tablets, orally; batch Nos. 2674048 (5 mg), 2669455 (10 mg), 2672909 (15 mg), and 2669011 (20 mg)

Double-Blind Period

- *Vortioxetine* – 5 to 20 mg/day, encapsulated film-coated tablets, orally; batch Nos. E221490-0001E (5 mg), E221490-0002E (10 mg), E221490-0003E (15 mg), and E221490-0004E (20 mg)

Control Product, Dose and Mode of Administration, Batch Number

- *Placebo* – encapsulated film-coated tablets, orally; batch No. E221490-0005E

Duration of Treatment

- The duration of the open-label, flexible-dose treatment period was 12 weeks.
- The duration of the double-blind, fixed-dose treatment period was 26 weeks.

Statistical Methodology

- The following analysis sets were used to analyse and present the data:
  - *all-patients-enrolled* (APES) – all patients enrolled to the 12-week open-label, flexible-dose treatment period who took at least one dose of IMP
  - *all-patients-randomized set* (APRS) – all patients randomized to the 26-week double-blind treatment period
  - *full-analysis set* (FAS) – all patients randomized to the 26-week double-blind treatment period who took at least one dose of double-blind IMP
- Unless otherwise indicated, the efficacy analyses were based on the FAS, and the safety analyses were based on the APES (open-label period) and the FAS (double-blind period).
- Baseline for the primary analysis was defined as the randomization visit (that is, the start of the double-blind period). This baseline is referred to as Randomization (Visit). For the analysis of safety, baseline was defined as the start of the open-label period for the *de novo* and 12709A rollover patients. This baseline is referred to as Baseline (Visit). For the 12712A rollover patients, baseline was defined as the start of the double-blind period (that is, the randomization visit).
- All data collected are tabulated and/or listed, as appropriate.
- The disposition data are summarized for the open-label period (split out by *de novo* patients, rollover patients from Study 12709A, and total), and for the double-blind period (split out by treatment group and total). The numbers of patients in the APES and APRS who completed or withdrew from the study, as well as the number of patients in each analysis set (APES, APRS, and FAS), are presented.
- Summary tables for the demographic and baseline characteristics are presented for both the open-label period (for *de novo* patients, rollover patients [from Study 12709A], and overall) and the double-blind period (by treatment group [vortioxetine and placebo] and total).
- Safety and tolerability were evaluated based on descriptive statistics and listings of adverse events, clinical safety laboratory test values, vital signs, weight, Tanner staging, ECG findings, C-SSRS scores, and GBI scores.
- Due to the termination of the study, the pharmacokinetic data are not reported.
- Due to the limited number of patients who completed the double-blind period, the efficacy analyses were not performed for the following primary and secondary variables: time to relapse, relapse rate, PQ-LES-Q score, CGI-S and CGI-I scores.
- Descriptive statistics and the change from baseline in the CDRS-R total score, by inclusion source, are presented for the open-label period. Descriptive statistics and the total change from randomization are presented for each visit for the double-blind period.

Patient Disposition and Analysis Sets

- Patient disposition for the open-label period (APES) and the double-blind period (APRS) is presented in Table 1 and Table 2, respectively. A summary of the analysis populations is presented in Table 3. Patient withdrawal from the open-label period and the double-blind period is summarized in Table 4 and Table 5 and presented by patient in Listing 1 and Listing 2, respectively.
- Overall, 35 patients were treated in this study: 33 patients in the open-label period (24 *de novo* patients and 9 rollover patients from Study 12709A [Table 1]) and 4 patients in the double-blind period (2 of whom rolled-over from Study 12712A).
- A total of 28 patients withdrew during the open-label period (Table 4 and Listing 1):
  - 24 (73%) patients (19 [79%] *de novo* and 5 [56%] rollover patients from Study 12709A) due to Lundbeck's decision to terminate the study
  - 2 (8%) *de novo* patients due to withdrawal of consent
  - 1 (11%) rollover patient due to lack of efficacy
  - 1 (11%) rollover patient due to an adverse event
- Of the 5 patients (3 *de novo* and 2 rollover patients) who completed the open-label period, 3 patients were not randomized to the double-blind period due to not meeting the randomization criteria (Listing 3).
- A total of 4 patients were randomized in the double-blind period and dosed (vortioxetine or placebo): 2 *de novo* patients who completed the open-label period and 2 rollover patients from Study 12712A (Table 2).
- 3 (75%) patients withdrew during the double-blind period due to Lundbeck's decision to terminate the study (Table 5 and Listing 2).
- A single patient in the vortioxetine group completed the double-blind period (Table 2).
- All 33 patients enrolled in the open-label period were included in the APES; all 4 patients randomized in the double-blind period were included in the APRS and FAS (Table 3).

Demographics and Baseline Characteristics of the Study Population

- The patient demographics for the open-label period and the double-blind period are summarized in Table 6 and Table 7, respectively. Concomitant and disallowed medications for the open-label period are presented in Listing 4 and Listing 5, respectively. Concomitant medications for the double-blind period are presented in Listing 6. Previous and ongoing medical history conditions (open-label period) are presented in Table 8; no data are available for the double-blind period. The medical history (including MDD history) prior to the open-label period and double-blind period is listed in Listing 7 and Listing 8, respectively. Baseline disease characteristics for the open-label period and the double-blind period are presented in Table 9 and Table 10, respectively.
- In the open-label period, 15 (46%) patients were boys and 18 (55%) patients were girls. The mean (range) age was 10 (7 to 12) years and the mean (range) body mass index (BMI) was 19 (13.9 to 42.8) kg/m^2 (Table 6).
- In the double-blind period, 2 (50.0%) patients were boys. The mean (range) age was 10 (8 to 11) years and the mean (range) BMI was 18 (14.8 to 19.2) kg/m^2 (Table 7).

Exposure

- Total exposure to IMP for the open-label period (APES) and double-blind period (APRS) is summarized in Table 13 and Table 14, respectively.
- The mean (SD) exposure to IMP among all patients in the open-label period (APES) was 54 (27.9) days, with a mean (SD) daily dose of 9.9 (5.8 to 10.0) mg. The total amount of exposure accrued was 4.8 patient years (Table 13).
- The mean (SD) exposure to IMP among all patients in the double-blind period (APRS) was 109 (73.1) days, with a mean (SD) daily dose of 7.5 (3.5) mg. The total amount of exposure accrued was 1.2 patient years (Table 14).

Efficacy Results

- No relapses were observed in the patients during the double-blind period (FAS) (Table 15).
- Descriptive statistics and the change from baseline in the CDRS-R total score, by inclusion source, are presented in Table 16 for the open-label period (APES). Descriptive statistics and the change from randomization in the CDRS-R total score are presented in Table 17 for each visit, by treatment group and overall for the patients enrolled in the double-blind period (FAS).
- Due to the small sample size and incomplete dataset, it was not possible to perform any robust and meaningful statistical analysis of the data.

Safety Results

- Adverse events for the open-label period (APES) and double-blind period (APRS) are summarized in Table 18 and Table 19, and listed in Listing 9 and Listing 10, respectively. Adverse events leading to withdrawal from treatment for the open-label period are listed in Listing 11. There were no adverse events leading to withdrawal from treatment during the double-blind period.
- Treatment-emergent adverse events (TEAEs) for the open-label period (APES) and the double-blind period (APRS) by system organ class (SOC) and preferred term (PT) are presented in Table 20 and Table 21, respectively, and by PT in Table 22 and Table 23, respectively. TEAEs by SOC, PT, and intensity for the open-label period (APES) and the double-blind period (APRS) are presented in Table 24 and Table 25, respectively, and by SOC, PT, and causality in Table 26 and Table 27, respectively. TEAEs by PT occurring in >2 patients in the open-label period (APES) are presented in Table 28. There were no equivalent data available for the double-blind period.
- Clinical safety laboratory test values and changes from baseline for the open-label period (APES) are summarized in Table 29 (haematology), Table 31 (clinical chemistry), and Table 33 (urinalysis). Clinical safety laboratory test values and changes from randomization for the double-blind period (FAS) are summarized in Table 30 (haematology), Table 32 (clinical chemistry), and Table 34 (urinalysis). Patients with post-baseline PCS laboratory values for the open-label period (APES) are listed in Listing 12.
- Descriptive statistics and changes from baseline or randomization (as appropriate) in ECG parameters for the open-label period (APES) and the double-blind period (FAS) are summarized in Table 35 and Table 36 respectively.
- Vital signs and weight for the open-label period (APES) and the double-blind period (FAS) are presented in Table 37 and Table 38.
- The C-SSRS scores by week for the open-label period (APES) and the double-blind period (FAS) are presented in Table 39 and Table 40.
- The GBI mania total scores and changes from baseline and randomization (as appropriate) for the open-label period (APES) and the double-blind period (FAS) are presented in Table 41 and Table 42, respectively.
- Tanner staging and menstrual cycle recordings for the open-label period (APES) and the double-blind period (APRS) are listed in Listing 13 and Listing 14, respectively.
- The adverse event incidence by period and treatment is summarized below:

	Open-Label Period				Double-Blind Period			
	De Novo Patients		12709A Rollover Patients		Vortioxetine		Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients treated	24		9		2		2	
Patients with any treatment-emergent serious adverse events (SAEs)	0		0		0		0	
Patients with treatment-emergent adverse events (TEAEs)	5	(20.8)	3	(33.3)	0		1*	(50.0)
Patients with any TEAEs leading to death	0		0		0		0	
Patients with any TEAEs leading to withdrawal	0		1	(11.1)	0		0	
Total number of treatment-emergent SAEs	0		0		0		0	
Total number of TEAEs	11		4		0		1	

* 12712A rollover patient

Source: Table 18, Table 19 and Listing 11.

Safety Results (continued)

- No SAEs were reported.
- A total of 5 (21%) *de novo* and 3 (33%) rollover patients had 11 adverse events and 4 adverse events, respectively, during the open-label period (Table 18). The most frequent TEAE (occurring in >2 patients) was nausea; 7 events were reported by 6 (18%) patients (Table 28).
- 1 rollover patient had TEAEs leading to withdrawal (nausea and vomiting) during the open-label period (Listing 11). For further details, refer to the individual narrative (Patient S1849).
- All TEAEs were either *mild* or *moderate*; hence, no patients had any *severe* TEAEs (Table 24 and Table 25).
- Post-dose PCS clinical laboratory safety values for the open-label period were noted for the following parameters (Listing 12):
  - glucose (low for 1 rollover patient at Week 10)
  - eosinophils/leukocytes (high for 1 *de novo* patient at Week 4 and Week 10 [this was in the same patient], high for 1 *de novo* patient at Week 1, high for 1 *de novo* patient at Week 4)
  - fasting glucose (1 *de novo* patient at Week 8)
- Abnormal urinalysis values were reported for the following parameters:
  - fasting glucose (1 *de novo* patient at Week 4 during the open-label period)
  - occult blood (1 *de novo* patient at Week 4 during the open-label period)
  - protein (1 *de novo* patient at Week 1, 1 *de novo* and 2 rollover patients at Week 4, 1 *de novo* patient at Week 8 and 1 rollover patient at Week 10 and Week 12 [open-label period; Table 33], 1 placebo patient at Week 10 [double-blind period; Table 34]).
- 1 rollover patient had an adverse event of ECG QT prolongation during the open-label period (Listing 9). There were no post-baseline PCS ECG values for any patient.
- There were no clinically significant findings in Tanner staging or menstrual cycle (Listing 13 and Listing 14).
- There were no clinically significant findings in C-SSRS (Table 39 for the open-label period [APES] and Table 40 for the double-blind period [FAS]) or GBI scores (Table 41 for the open-label period [APES], and Table 42 for the double-blind period [FAS]).

Conclusions

- The main primary and secondary efficacy objectives were not assessed due to termination of the study and the limited number of patients who completed the double-blind period.
- There were no safety or tolerability concerns identified in the study.

Report Date

4 August 2022

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