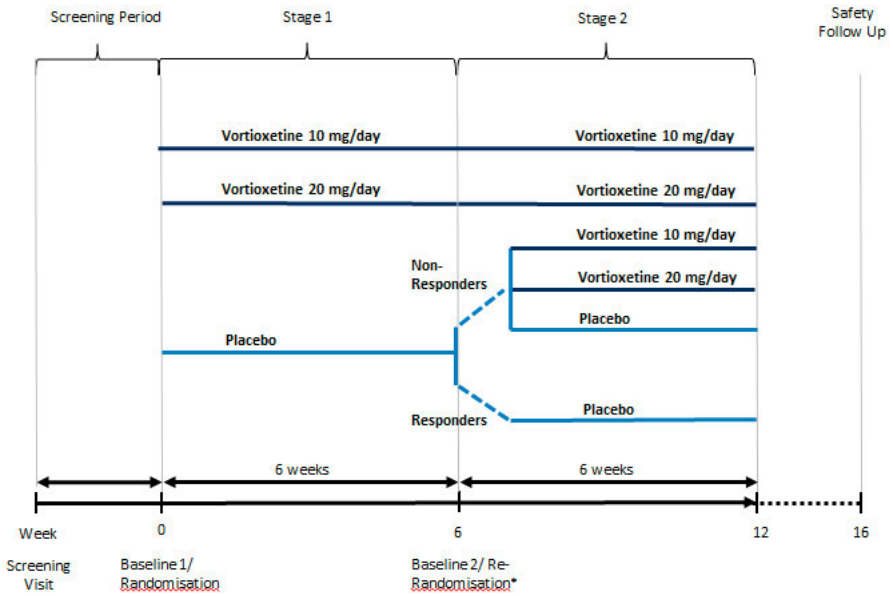
Synopsis – Study 15996A

Study Title Interventional, randomised, double-blind, placebo-controlled, fixed-dose study of vortioxetine in adults with Attention Deficit Hyperactivity Disorder (ADHD)
Investigators 15 principal investigators at 15 sites in the United States *Signatory investigator* – [redacted]
Study Sites 15 sites in the United States
Publications None (as of the date of this report)
Study Period *First patient first visit* – 26 December 2014 (the date when the first *Informed Consent Form* was signed) *Last patient last visit* – 27 September 2016 (the date of the last protocol-specified contact with any patient)
Objectives • *Primary objective*: – to evaluate the efficacy of vortioxetine 10 mg/day and 20 mg/day *versus* placebo on ADHD symptoms in the treatment of adult patients with a DSM-5™ diagnosis of ADHD • *Secondary objectives*: – to evaluate the efficacy of vortioxetine 10 mg/day and 20 mg/day *versus* placebo on: • inattention (patient-reported outcome [PRO]) • overall functioning (PRO) • emotional dysregulation (PRO) • ADHD symptoms (investigator-rated) • ADHD symptoms (PRO) • cognitive function (PRO) • global clinical impression (investigator-rated) • productivity (PRO) • health-related quality of life (PRO) • *Exploratory objectives*: – to evaluate the population pharmacokinetics of vortioxetine in adult patients with ADHD and estimate individual oral clearance (CL/F) values – to evaluate the compliance with vortioxetine treatment for the individual patient based on the plasma concentrations and the estimated CL/F • *Safety objective*: – to evaluate the safety and tolerability of vortioxetine 10 mg/day and 20 mg/day *versus* placebo in adult patients with a diagnosis of ADHD

Study Methodology

- This was an interventional, prospective, multi-site, randomised, double-blind, sequential parallel comparison design (SPCD), placebo-controlled, fixed-dose study.
- In Stage 1, the design is similar to a standard parallel study design, and in Stage 2 all placebo non-responders are re-randomised to drug or placebo allowing measurement of a therapeutic signal against a significantly reduced placebo response.
- A schematic overview of the study design is presented below:



* Re-randomisation will be done blinded using an Interactive Voice/Web Response System (IVRS/IWRS)

- The study consisted of:
  - a Screening Period - 3 to 28-day period from screening to randomisation
  - a Treatment period - 12-week double-blind treatment period with placebo or vortioxetine 10 mg or 20 mg.
    - Stage 1 Treatment Period - first 6 weeks of the 12-week Treatment Period (Visit 2 [Baseline 1] to Visit 5 [Week 6])
    - Stage 2 Treatment Period - last 6 weeks of the 12-week Treatment Period (Visit 5 [Baseline 2] to Visit 8 [Week 12])
  - a Safety Follow-up Period - 4-week period after completion of the study or after withdrawal from the study
- Patients were enrolled to the 6-week Stage 1 and randomised in a 1:1:3 ratio to vortioxetine 10 mg, 20 mg, or placebo. At the end of Stage 1, non-responders to placebo were re-randomised to the 6-week Stage 2 in a 1:1:1 ratio to vortioxetine 10 mg, 20 mg, or placebo. Responders to placebo during Stage 1 and patients treated with vortioxetine 10 or 20 mg/day during Stage 1, continued on the same treatment for the following 6 weeks.

Number of Patients Planned

225 patients were planned for enrolment in Stage 1: 45 in the vortioxetine 10 mg and 20 mg group, respectively, and 135 in the placebo group. 69 patients, who were non-responders to placebo in Stage 1, were planned for re-randomisation in Stage 2: 23 in each treatment group (placebo, vortioxetine 10 mg, or vortioxetine 20 mg).

Diagnosis and Main Selection Criterion

Outpatients with a primary diagnosis of ADHD according to DSM-5™ criteria, who:

- had an Adult ADHD Investigator Symptom Rating Scale (AISRS) total score ≥24 at the Screening Visit and at the Baseline Visit
- were ≥18 and ≤55 years of age
- had a Clinical Global Impression – Severity of Illness (CGI-S) score ≥4 (*moderately ill or worse*)

Investigational Medicinal Product, Dose and Mode of Administration, Batch Numbers

Vortioxetine – 10 or 20 mg/day; tablets, orally; batch No. 2391959 (10 mg) and 2373933 (20 mg)

Reference Therapy, Dose and Mode of Administration, Batch Numbers

Placebo – to vortioxetine 10 or 20 mg; tablets, orally; batch No. 2400284 (10 mg) and 2400772 (20 mg)

Duration of Treatment

12 weeks

Efficacy Assessments

- Investigator-rated scales
  - Adult ADHD Investigator Symptom Rating Scale (AISRS)
  - Clinical Global Impression – Severity of Illness (CGI-S)
  - Clinical Global Impression – Global Improvement (CGI-I)
- PRO
  - Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A)
  - Sheehan Disability Scale (SDS)
  - Work Limitation Questionnaire (WLQ)
  - Adult ADHD Self-Report Scale (ASRS)
  - Perceived Deficits Questionnaire – Depression (PDQ-D)
  - Adult ADHD Quality of Life Measure (AAQoL)

Pharmacokinetic Assessments

- blood sampling for plasma quantification of vortioxetine

Safety Assessments

- Adverse events (AEs), clinical safety laboratory tests, vital signs, weight/body mass index (BMI), electrocardiograms (ECGs), and physical examinations
- Columbia Suicide Severity Rating Scale (C-SSRS)

Endpoints

- *Primary endpoint*:
  - change from baseline to 6 weeks after (re-)randomisation in AISRS total score
- *Key secondary endpoints*:
  - Inattention/Metacognition:
    - change from baseline to 6 weeks after (re-)randomisation in BRIEF-A using the Metacognition index
  - Cognitive Function/Global executive function:
    - change from baseline to 6 weeks after (re-)randomisation in BRIEF-A using the Global Executive Composite score
  - Overall functioning:
    - change from baseline to 6 weeks after (re-)randomisation in SDS total score
  - Productivity:
    - change from baseline to 6 weeks after (re-)randomisation in WLQ using the Productivity Loss Score

Endpoints (continued)

- *Secondary endpoints*:
  - ADHD symptoms:
    - change from baseline to 6 weeks after (re-)randomisation in AISRS inattention subscale score
    - change from baseline to 6 weeks after (re-)randomisation in AISRS hyperactivity/impulsivity subscale score
    - change from baseline to 6 weeks after (re-)randomisation in AISRS individual item scores
    - response at 6 weeks after (re-)randomisation (defined as ≥30% reduction from baseline in AISRS total score)
    - change from baseline to 6 weeks after (re-)randomisation in ASRS total score
  - Global Clinical Status:
    - change from baseline to 6 weeks after (re-)randomisation in CGI-S score
    - CGI-I score at 6 weeks after randomisation
    - response at 6 weeks after randomisation (defined as a CGI-I score of 1 or 2)
  - Cognitive function:
    - change from baseline to 6 weeks after (re-)randomisation in BRIEF-A using the Behavioural Regulation Index
    - change from baseline to 6 weeks after (re-)randomisation in BRIEF-A scales (Inhibit, Initiate, Organization of Materials, Plan/Organize, Shift, Self Monitor, Task Monitor, Working Memory, Emotional Control)
    - change from baseline to 6 weeks after (re-)randomisation in PDQ-D total score
    - change from baseline to 6 weeks after (re-)randomisation in PDQ-D subscale scores (Attention and concentration, Retrospective memory, Prospective memory, Planning and organisation)
  - Overall functioning:
    - change from baseline to 6 weeks after (re-)randomisation in SDS item scores (family, work, social life, the number of days lost, and the number of underproductive days)
  - Productivity and quality of life:
    - change from baseline to 6 weeks after (re-)randomisation in WLQ using the Global Productivity Index
    - change from baseline to 6 weeks after (re-)randomisation in WLQ Domain scores (Limitations Handling Time, Mental-Interpersonal Work Demands, Physical Demands, Output Demands)
    - change from baseline to 6 weeks after (re-)randomisation in AAQoL total score
    - change from baseline to 6 weeks after (re-)randomisation in AAQoL subscale scores (Life productivity, Psychological Health, Life Outlook, Relationships)
- *Safety endpoints*:
  - adverse events
  - potentially clinically significant (PCS) clinical safety laboratory test values, vital signs, weight changes, and ECG parameter values
  - C-SSRS categorisation based on Columbia Classification Algorithm of Suicide Assessment (C-CASA) definitions

Statistical Methodology

- The following analysis sets were used:
  - *all-patients-randomised set 1* (APRS 1) – all randomised patients in Stage 1
  - *all-patients-treated set 1* (APTS 1) – all patients in the APRS 1 who took at least one dose of investigational medicinal product (IMP) in Stage 1
  - *full-analysis set* (FAS 1) – all patients in the APTS 1 who had a valid Baseline 1 assessment and at least one valid post-Baseline 1 assessment of the AISRS total score in Stage 1
  - *all-patients-randomised set 2* (APRS 2) – all re-randomised patients in Stage 2
  - *all-patients-treated set 2* (APTS 2) – all patients in the APRS 2 who took at least one dose of IMP in Stage 2
  - *full-analysis set* (FAS 2) – all patients in the APTS 2 who had a valid Baseline 2 assessment and at least one valid post-Baseline 2 assessment of the AISRS total score in Stage 2
- Unless otherwise indicated, the efficacy analyses were based on the FAS 1 or 2, and the safety analyses were based on the APTS 1 or 2, depending on the stage.
- All the p-values are based on two-sided tests; the confidence intervals (CIs) are two-sided. Nominal p-values (unadjusted) are presented together with nominal 95% CIs.
- *Primary Efficacy Analyses*
  - In line with the SPCD study design, the study consisted of two double-blind stages of treatment, Stage 1 and Stage 2. The results of the analysis of FAS 1 using data from Stage 1 was combined with the results from FAS 2, Stage 2, which only includes the re-randomised placebo non-responders from Stage 1. The primary analysis was the combined equally weighted analysis at 6 weeks after (re-)randomisation for each dose separately.
  - Stage 1 and Stage 2 analyses: based on the FAS 1 or FAS 2, the change from Baseline to Week 6 after (re-)randomisation in AISRS total score was analysed using a restricted maximum likelihood based mixed model for repeated measures (MMRM) approach. The model included site (Stage 1 only), visit, and treatment in the relevant Stage (placebo, vortioxetine 10 mg/day, vortioxetine 20 mg/day) as factors, Baseline 1 or Baseline 2 AISRS total score as a continuous covariate, treatment-by-visit interaction, and Baseline 1 or Baseline 2 AISRS total score-by-visit interaction.
  - Combined analysis: the mean differences between the treatment groups was estimated based on the least squares means for the treatment-by-visit interaction in the respective stagewise MMRM. The estimates are presented with p-values and 95% CIs. The comparisons at all timepoints for the two doses of vortioxetine 10 or 20 mg/day, respectively, *versus* placebo were used as input for the combined analyses.
- *Key Secondary Efficacy Analyses*
  - The following key secondary endpoints were analysed using the same methodology as that described for the primary analysis:
    - change from baseline to 6 weeks after (re-)randomisation in BRIEF-A using the Metacognition index
    - change from baseline to 6 weeks after (re-)randomisation in BRIEF-A using the Global Executive Composite Score
    - change from baseline to 6 weeks after (re-)randomisation in SDS total score
  - The key secondary endpoint, change from baseline to 6 weeks after (re-)randomisation in WLQ Productivity Loss Score, was analysed using an ANCOVA model by week using last observation carried forward (LOCF) within each stage, as WLQ was only assessed once post-baseline, including site (Stage 1 only) and treatment (placebo, vortioxetine 10 mg/day, vortioxetine 20 mg/day) as factors, and either Baseline 1 or 2, depending on the stage, and WLQ Productivity Loss score as a continuous covariate. The mean difference between vortioxetine 10 mg/day or 20 mg/day *versus* placebo was estimated from the model based on the least squares means for treatment.
    - The estimated stagewise treatment differences to placebo by dose and by week were combined as in the primary analysis.

Statistical Methodology (continued)

- *Testing Strategy*
  - For each of the two doses, the following sequence of hierarchically ordered primary and key secondary endpoints was used:
    - change from baseline to 6 weeks after (re-)randomisation in AISRS total score (Primary)
    - change from baseline to 6 weeks after (re-)randomisation in BRIEF-A using the Metacognition index
    - change from baseline to 6 weeks after (re-)randomisation in BRIEF-A using the Global Executive Composite score
    - change from baseline to 6 weeks after (re-)randomisation in SDS total score
    - change from baseline to 6 weeks after (re-)randomisation in WLQ Productivity Loss score
  - To adjust for multiplicity and keep the overall significance level below 5%, each sequence (that is, per dose) used a Bonferroni-corrected significance level of 2.5% and testing was continued as long as there was significance within each sequence.
  - All analyses within this testing strategy were based on combined analysis results from both stages.
- *Secondary Efficacy Analyses*
  - Continuous outcomes with repeated post-baseline measurements within each stage, with the exception of CGI-I which was analysed for FAS 1, Stage 1 only, were analysed with a stagewise MMRM similar to the model specified for the primary endpoint and a combination of treatment estimates.
  - The analyses were supplemented with stagewise ANCOVA analyses, observed cases (OC) and LOCF. The treatment estimates for the two stages were combined as previously described.
  - Continuous outcomes with one post-baseline measurement in each stage were analysed with a stagewise ANCOVA, LOCF. The treatment estimates for the two stages were combined as previously described.
  - Response based on the AISRS total score and the CGI-I score, using LOCF, were analysed with stagewise logistic regression models by week, including treatment as a factor and baseline AISRS total score or baseline CGI-S score, as relevant, as a covariate. For AISRS, the stagewise response rate difference to placebo for each vortioxetine group seperately was combined as an equally weighted linear combination. Analysis based on CGI-I was performed for Stage 1 only.
- *Pharmacokinetic/Pharmacodynamic Analyses*
  - Compliance was assessed through the plasma concentration data. Compliance to vortioxetine treatment on a study level (that is, at the population level) was assessed by comparing the distribution of individual oral clearance (CL/F) values with the distribution seen in healthy subjects treated under well-controlled conditions.
  - The relationship, if any, between AISRS total score, time and plasma exposure of vortioxetine was investigated using an integrated mixed-effect dynamic model taking placebo, time and drug effects into considerations. It was assumed that the plasma exposure of vortioxetine had reached steady-state after two weeks of treatment.
- *Exploratory Analyses*
  - For the entire study period (12 weeks), all efficacy data for the patients included in FAS 1, but not in APRS 2, are summarised descriptively by treatment group and visit.
  - Exploratory analyses of the primary and key secondary endpoints were performed, where vortioxetine-treated patients that were considered to be non-compliant to IMP were omitted.
  - Exploratory analysis of the primary endpoint was performed where patients with a positive confirmatory drug test were omitted.
- *Safety Analyses*
  - Adverse events, clinical safety laboratory tests, vital signs, weight, ECG parameters, and C-SSRS data were summarised using descriptive statistics

Patient Disposition and Analysis Sets

- Patient Disposition is summarised for the following periods:
  - APTS 1, Stage 1: all patients treated in Stage 1 (6 weeks)
  - APTS 2, Stage 2: all patients that did not respond to placebo in Stage 1 (placebo non-responders) and were re-randomised and treated in Stage 2 (6 weeks)
  - APTS 1 excluding APRS 2, VOR 10 mg and 20 mg: the last 6 weeks of the study for all patients treated with vortioxetine 10 mg or vortioxetine 20 mg in Stage 1 who continued in Stage 2 without being re-randomised (6 weeks). This period will hereafter be referred to as the continued vortioxetine groups, Stage 2.
  - APTS 1 excluding APRS 2, Stage 2, PBO: all patients who responded to placebo in Stage 1 and who continued on placebo in Stage 2 (6 weeks). This period will hereafter be referred to as the placebo responder group, Stage 2.
- Patient disposition is summarised below:

	Placebo		VOR 10mg		VOR 20mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients randomised (APRS 1, Stage 1)	133		49		45		227	
Patients treated (APTS 1, Stage 1)	128		47		44		219	
Patients completed	107	(83.6)	41	(87.2)	33	(75.0)	181	(82.6)
Patients withdrawn	21	(16.4)	6	(12.8)	11	(25.0)	28	(17.4)
Full Analysis Set (Stage 1)	124		46		40		210	
Primary reason for withdrawal (APTS 1, Stage 1)								
Adverse event(s)	2	(1.6)	2	(4.3)	4	(9.1)	8	(3.7)
Lack of efficacy	4	(3.1)	1	(2.1)	0		5	(2.3)
Other	15	(11.7)	3	(6.3)	7	(15.9)	25	(11.4)
Patients randomised (APRS 2, Stage 2)	22		21		16		59	
Patients treated (APTS 2, Stage 2)	21		21		16		58	
Patients completed	19	(90.5)	20	(95.2)	12	(75.0)	51	(87.9)
Patients withdrawn	2	(9.5)	1	(4.8)	4	(25.0)	7	(12.1)
Full Analysis Set (Stage 2)	21		20		16		57	
Primary reason for withdrawal (APTS 2, Stage 2)								
Adverse event(s)	0		0		1	(6.3)	1	(1.7)
Lack of efficacy	0		0		1	(6.3)	1	(1.7)
Other	2	(9.5)	1	(4.8)	2	(6.3)	5	(8.6)

- In the last 6 weeks of the study, additionally 5 and 4 patients in the continued vortioxetine 10 mg and vortioxetine 20 mg group withdrew from the study. Thirteen patients in the placebo responder group withdrew in Stage 2. Primary reasons for withdrawals (adverse event; lack of efficacy; other):
  - continued vortioxetine 10 mg, Stage 2 (2 patients; 1 patient; 2 patients)
  - continued vortioxetine 20 mg, Stage 2 (0; 0; 4 patients)
  - placebo responder group, Stage 2 (1 patient; 0; 12 patients)

Demography and Baseline Characteristics of the Study Population

- In APTS 1, the treatment groups were comparable with respect to age and sex: the mean age of the patients was 37 years, approximately half were men, and the majority (approximately 75%) was White.
- In APTS 1, the treatment groups were comparable with respect to mean height, weight, and BMI for all patients, for men, and for women.
- In APTS 2, Stage 2, there were more women than men in the placebo group (62% [13 patients] and 38% [8 patients], respectively), and more men than women in the vortioxetine 10mg group (62% [13 patients] and 38% [8 patients], respectively). Apart from this, the demographics in APTS 2 was similar to those in APTS 1
- Except for the BMI, the results in APTS 2 were similar to APTS 1. Differences between the treatment groups in BMI were observed in APTS 2, with mean values ranging from 30kg/m^2 to 32kg/m^2.
- In APTS 1, the patients were *markedly* to *severely ill* with a mean overall AISRS total score of 41.2 points, consistent with a CGI-S score of 4.8 points (*markedly ill)* and were functionally impaired with a SDS total score of 21.0 points. The AISRS hyperactive/impulsive and inattentive subscale scores was approximately 18 and 23 points, respectively.
- The mean Baseline 2 efficacy scores were similar, but slightly improved, compared to Baseline 1.

Efficacy Results

- The results of the primary and key secondary analyses are summarised below:

Treatment Group	Stage 1		Stage 2		Combined	Difference to placebo for combined estimate[a] (FAS1, FAS2, MMRM)		
	N	Mean	N	Mean	Mean (SE)	LS Mean	95% CI	p-value
Primary endpoint								
ΔAISRS total score								
Placebo	109	-12.4	20	-4.1	-8.3 (1.1)			
Vor 10mg	41	-12.8	20	-3.9	-8.3 (1.4)	-0.1	-3.6;3.5	0.9723
Vor 20mg	34	-11.6	12	-2.9	-7.3 (1.6)	1.0	-2.8;4.8	0.6010
Key secondary endpoints								
ΔBRIEF-A metacognition index								
Placebo	107	-10.0	20	-3.1	-6.5 (1.3)			
Vor 10mg	41	-11.2	20	-2.6	-6.9 (1.5)	-0.3	-4.2;3.6	0.8646
Vor 20mg	34	-10.2	12	0.9	-4.6 (1.8)	1.9	-2.4;6.2	0.3833
ΔBRIEF-A global executive composite score								
Placebo	107	-9.9	20	-3.0	-6.5 (1.3)			
Vor 10mg	41	-12.5	20	-3.5	-8.0 (1.5)	-1.6	-5.4;2.3	0.4223
Vor 20mg	34	-11.4	12	2.1	-4.6 (1.8)	1.8	-2.4;6.0	0.3929
ΔSDS total score								
Placebo	92	-5.3	18	0.6	-2.4 (0.6)			
Vor 10mg	34	-7.9	17	-0.9	-4.4 (0.8)	-2.0	-3.9;-0.1	0.0345
Vor 20mg	28	-7.4	11	-1.4	-4.4 (0.9)	-2.0	-4.1;-0.0	0.0475
ΔWLQ productivity loss score[b]								
Placebo	91	-2.4	15	-0.8	-1.6 (0.6)			
Vor 10mg	36	-2.5	17	-0.9	-1.7 (0.6)	-0.1	-1.8; 1.6	0.9128
Vor 20mg	27	-2.4	11	-0.7	-1.5 (0.8)	0.1	-1.8; 2.0	0.9144

Δ = Change from baseline; CI = confidence interval; LS = least squares; SE = standard error

a 6 weeks after (re-)randomisation
b FAS1, FAS2, LOCF, ANCOVA

Efficacy Results (continued)

- This study failed to show a statistically significant difference between vortioxetine (10 or 20 mg) and placebo in the primary efficacy endpoint, AISRS total score. Hence, the testing procedure was stopped at this step.
- Except for SDS total score (nominal p <0.05), the other key secondary efficacy endpoints, BRIEF-A (metacognition index and global composite score) and WLQ productivity loss score, also failed to demonstrate an advantage of vortioxetine (10 and 20 mg) over placebo.
- The results of the secondary and exploratory efficacy analyses were in line with those of the primary and key secondary efficacy analyses.
- Based on pharmacokinetic compliance data, 32% of the vortioxetine-treated patients were regarded as non-compliant (CL/F ≥120 L/h). When these non-compliant patients were excluded from the analyses in Stage 1, the mean differences to placebo in the primary and key secondary endpoints were numerically in favour of both doses of vortioxetine.
- In the popPK/PD model, there was a statistically significant relationship between change from baseline in AISRS total score and the individual average plasma vortioxetine concentration.

Safety Results

- Adverse events are summarised for the following periods:
  - APTS 1, Stage 1
  - APTS 2, Stage 2
  - APTS 1 excluding APRS 2, VOR 10 mg and 20 mg: all patients treated with vortioxetine 10 mg or vortioxetine 20 mg in Stage 1 who continued for another 6 weeks without being re-randomised (12 weeks). This period will hereafter be referred to as the continued vortioxetine groups.
  - APTS 1 excluding APRS 2, Stage 2, PBO
- The adverse event incidence is summarised below:

	Placebo		VOR 10mg		VOR 20mg	
	n	(%)	n	(%)	n	(%)
APTS 1, Stage 1						
Patients treated	128		47		44	
Patients with treatment-emergent serious AEs (SAEs)	1	(0.8)	0		0	
Patients with treatment-emergent adverse events (TEAEs)	73	(57.0)	27	(57.4)	31	(70.5)
Total number of SAEs	1		0		0	
Total number of TEAEs	154		75		80	
APTS 2, Stage 2						
Patients treated	21		21		16	
Patients with treatment-emergent SAEs	0		0		0	
Patients with TEAEs	7	(33.3)	9	(42.9)	6	(37.5)
Total number of SAEs	0		0		0	
Total number of TEAEs	12		14		15	

- No deaths occurred during the study.
- The incidence of SAEs was low; a total of 3 patients had SAEs. One SAE (*suicidal ideation*) was considered *related* to IMP (continued vortioxetine 10 mg group).
- In APTS 1, Stage 1, the overall incidence of TEAEs was similar in the placebo and vortioxetine 10 mg groups and highest in the vortioxetine 20 mg group (57% [73 patients], 57% [27 patients], and 70% [31 patients], respectively). In APTS 2, Stage 2, the number of patients having TEAEs was similar in all treatment groups (33% [7 patients], 43% [9 patients], and 38% [6 patients]). Following 12 weeks of treatment with vortioxetine 10 mg or 20 mg, the number of patients having TEAEs was similar in the vortioxetine 10 and 20 mg groups (66% [31 patients] and 75% [33 patients] patients, respectively).

Safety Results (continued)

- In APTS 1, Stage 1, TEAEs with an incidence ≥5% and with a higher incidence in both vortioxetine groups than in the placebo group were (placebo; vortioxetine 10mg; vortioxetine 20mg): *nausea* (3.9%; 21%; 30%), *fatigue* (7.0%; 15%; 16%), *diarrhoea* (3.1%; 6.4%; 9.1%), and *insomnia* (6.3%; 8.5%; 6.8%). In APTS 2, Stage 2, the only TEAE with an incidence ≥5% and with a higher incidence in both vortioxetine groups than in the placebo group was *nausea* (0% [placebo]; 9.5% [vortioxetine 10mg]; 25% [vortioxetine 20mg]).
- For the majority of the patients with TEAEs, the events were *mild* or *moderate*. *Severe* TEAEs were single events reported in individual patients.
- A total of 12 patients had adverse events leading to withdrawal; 8 patients in Stage 1 (2 patients each in the placebo and vortioxetine 10mg group, and 4 patients in the vortioxetine 20mg group), 1 patient in Stage 2 (vortioxetine 20mg), 2 patients in the continued vortioxetine 10mg group, and 1 patient in the placebo responder group in Stage 2.
- During any of the treatment periods, TEAEs leading to withdrawal were reported in ≤4 patients. Apart from *nausea* and *fatigue*, the TEAEs leading to withdrawal were single events reported in individual patients.
- In APTS1, Stage 1 and APTS 2, Stage 2, both incidence and prevalence of nausea was lower in the placebo group than in the vortioxetine 10 and 20mg groups during Days 1-14. Whereas both incidence and prevalence of nausea in the placebo group were stable over time, the incidence in the vortioxetine 10 and 20mg groups decreased to zero after the first 14 days and 28 days respectively. The prevalence of nausea in the vortioxetine 20mg group was approximately 25% during the first 6 weeks, which was higher than in the placebo and vortioxetine 10mg groups. From Day 43 and onwards, both incidence and prevalence in the continued vortioxetine groups were stable. There were no incidences of nausea in the placebo responder group in Stage 2.
- The majority of nausea TEAEs were *mild* or *moderate*. A total of 4 patients withdrew due to nausea; 3 patients during the first 14 days in APTS 1, Stage 1 (2 patients in the vortioxetine 10mg group and 1 patient in the vortioxetine 20mg group) and 1 patient in the APTS 2, Stage 2 during Day 15 to 28 (vortioxetine 20mg group).
- In APTS 1, Stage 1 and APTS 2, Stage 2, the incidence of TEAEs related to *insomnia* in the vortioxetine 10 or 20mg groups was comparable to the placebo group. The majority of TEAEs related to *insomnia* were *mild* or *moderate.* Two patients withdrew due to *insomnia* (1 patient in APTS 1, Stage 1 [vortioxetine 20mg group] and 1 patient in the placebo responder group, Stage 2).
- A total of 5 patients had TEAEs related to *sexual dysfunction*; 3 patients in the placebo group (2 patients in Stage 1 and 1 patient in the placebo responder group in Stage 2), and 2 patients in the vortioxetine 20mg group in Stage 1. All sexual dysfunction TEAEs were either *mild* or *moderate.* No patients withdrew due to sexual dysfunction.
- A total of 11 patients had a PCS weight increase, 5 patients in the placebo group (3 patients in Stage 1 and 2 patients in the placebo responder group), 4 patients in the vortioxetine 10mg group (1 patient in Stage 1, and 3 patients in the continued vortioxetine 10mg group), and 2 patients in the vortioxetine 20mg group (1 patient in Stage 1 and 1 patient in the continued vortioxetine 20mg group). None of the patients with PCS weight increase were withdrawn due to weight changes.

Safety Results (continued)

- The only post-baseline PCS laboratory value that occured in >3 patients in any treatment group in any of the analyses sets was PCS high cholesterol (fasting), and the majority of these findings occured in patients treated with placebo.
- Suicidality was assessed using C-SSRS and C-CASA. During the study, one patient in the continued vortioxetine 10mg group reported suicide with some intent to act, without specific plan on the C-SSRS, which was reported as an SAE (*suidical ideation*).

Conclusions

- The study failed to show efficacy of vortioxetine 10 or 20 mg/day *versus* placebo on ADHD symptoms based on AISRS total score. Except for the SDS total score, the other key secondary efficacy endpoints also failed to demonstrate an advantage of vortioxetine over placebo.
- The results of the secondary and exploratory efficacy analyses were in line with those of the primary and key secondary efficacy analyses.
- In the vortioxetine treatment groups, patient compliance, based on plasma concentration data, was low; 32% of the patients in the vortioxetine treatment groups were regarded as non-compliant.
- Vortioxetine 10 mg and 20 mg was safe and well-tolerated in the ADHD adult population.

Report Date
22 August 2017

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