Synopsis – Study 15907A

Study Title

An interventional, randomised, double-blind, parallel-group, active-comparator, flexible-dose study on the efficacy of vortioxetine versus escitalopram on cognitive dysfunction in patients with inadequate response to current antidepressant treatment of major depressive disorder

Investigators

14 principal investigators at 14 sites in 4 countries

Signatory investigator – [redacted]

Study Sites

14 sites – 5 in Finland, 2 in Germany, 5 in Serbia, and 2 in Slovakia

Publications

None (as of the date of this report)

Study Period

First patient first visit – 2 December 2014 (the date when the first *Informed Consent Form* was signed)

Last patient last visit – 1 March 2016 (the date of the last protocol-specified contact with any patient)

Objectives

Primary objective:

- to assess the efficacy of vortioxetine (flexible dose 10 to 20 mg/day) *versus* escitalopram (flexible dose 10 to 20 mg/day) on cognitive performance (focusing on the aspect concerning speed of processing, executive functioning and attention) in patients with major depressive disorder (MDD) who have an inadequate response to current antidepressant treatment

- *Secondary and exploratory objectives*:
  - to assess the efficacy of vortioxetine *versus* escitalopram on cognitive dysfunction (performance and subjective reporting): speed of processing, executive functioning, attention, and learning and memory
  - to assess the efficacy of vortioxetine *versus* escitalopram on:
    - depressive symptoms
    - clinical global impression
    - functionality
  - to assess the safety and tolerability of vortioxetine

Study Methodology

- This was an exploratory, interventional, prospective, multi-national, multi-site, randomised, double-blind, parallel-group, active-comparator, flexible-dose study.
- Patients had to be treated with antidepressant monotherapy for at least 6 weeks at licensed doses and be candidates for a switch due to inadequate response prior to the Screening Visit. Patients had to discontinue all disallowed medications, except the current antidepressant which had to be discontinued at the Baseline Visit. For patients treated with high doses of selective serotonin reuptake inhibitor/serotonin norepinephrine reuptake inhibitor (SSRI/SNRI), the investigator was recommended to gradually decrease the dose of SSRI/SNRI within the week prior to the Baseline Visit.
- The patients were randomised equally (1:1) to double-blind treatment with flexible doses of either vortioxetine 10 to 20 mg/day or escitalopram 10 to 20 mg/day. Patients who completed the 8-week, double-blind treatment period (Core Treatment Period) entered a 1-week, double-blind, taper-down period: patients treated with vortioxetine received placebo; patients treated with 20 mg/day escitalopram received 10 mg of escitalopram; patients treated with 10 mg/day escitalopram received placebo.

Study Methodology (continued)

- During the Core Treatment Period, patients were seen at Week 1, 4 and 8, at which efficacy and safety data were collected.
- Patients who discontinued prematurely were seen for a Withdrawal Visit as soon as possible. Treatment with the 1-week, double-blind, down-taper medication was offered to patients who withdrew prematurely. A safety follow-up visit/contact was done approximately 4 weeks after the Completion/Withdrawal Visit.

Number of Patients Planned

100 patients were planned for randomisation: 50 in the vortioxetine group and 50 in the escitalopram group.

Diagnosis and Main Selection Criterion

In- or outpatients with a primary diagnosis of MDD according to DSM-IV-TR™ criteria, as confirmed using the Mini International Neuropsychiatric Interview (MINI), who:

- had a Montgomery Åsberg Depression Rating Scale (MADRS) total score ≥22 at the Screening Visit
- were ≥18 and ≤65 years of age
- had depressive symptoms currently considered as none or partially responsive (inadequate response) to one adequate course of SSRI/SNRI monotherapy and were candidates for a switch in the investigator's opinion
- wanted to stop taking his/her current SSRI/SNRI treatment due to inadequate response, confirmed by the Antidepressant Treatment Response Questionnaire (defined as <50% response to current treatment)
- had received antidepressant monotherapy (citalopram, paroxetine, sertraline, duloxetine, or venlafaxine) for at least 6 weeks at licensed doses
- had a Patient Health Questionnaire-9 total score ≥14 at the Screening Visit and at the Baseline Visit
- had a Perceived Deficits Questionnaire – Depression total score >25 at the Screening Visit and at the Baseline Visit

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

Vortioxetine – 10 or 20 mg/day; encapsulated tablets, orally; batch No. 2391955 (10 mg) and 2373931 (20 mg)

Reference Therapies, Doses and Mode of Administration, Batch Numbers

Placebo – powder-filled capsules, orally; batch No. E103662-0003E

Escitalopram – 10 or 20 mg/day; encapsulated tablets, orally; batch No. 2389938 (10 mg) and 2388070 (20 mg)

Duration of Treatment

8 weeks of double-blind treatment followed by a 1-week double-blind taper-down period

Efficacy Assessments

- *Assessment of cognitive function*
  - Neuropsychological Tests:
    - Digit Symbol Substitution Test (DSST)
    - Rey Auditory Visual Learning Test (RAVLT)
    - Trail Making Test A (TMT-A)
    - Trail Making Test B (TMT-B)
    - Stroop Colour Naming Test (STROOP)
    - Simple Reaction Time (SRT)
    - Choice Reaction Time (CRT)
  - Patient-reported cognitive function outcome:
    - Perceived Deficits Questionnaire – Depression (PDQ-D; 4 subscales: attention/concentration, planning/organisation, prospective memory, and retrospective memory)

Efficacy Assessments (continued)

- *Assessment of depressive symptoms and clinical global impression*
  - Patient Health Questionnaire-9 (PHQ-9)
  - Clinical Global Impression – Severity of Illness (CGI-S)
  - Clinical Global Impression – Global Improvement (CGI-I)
- *Assessment of functionality*
  - University of San Diego Performance-based Skills Assessment – Brief (UPSA-B)
  - Functioning Assessment Short Test (FAST)

Genomic/Metabolomic/Proteomic Assessments

- blood sampling for gene expression profiling (results not included in this *Clinical Study Report*)
- blood sampling for metabolomic/proteomic biomarkers (results not included in this *Clinical Study Report*)
- blood sampling for pharmacogenetics (results not included in this *Clinical Study Report*)

Safety Assessments

- Adverse events (AEs)
- Columbia Suicide Severity Rating Scale (C-SSRS)

Endpoints

- *Primary endpoint*:
  - cognitive performance:
    - change from baseline to Week 8 in DSST (number of correct symbols; domains affected: attention, speed of processing, and executive functioning)
- *Key secondary efficacy endpoint*:
  - functionality, performance-based:
    - change from baseline to Week 8 in UPSA-B total score
- *Secondary endpoints*:
  - cognitive dysfunction, neuropsychological tests:
    - change from baseline to Week 8 in RAVLT score (acquisition: learning; delayed recall: memory)
    - change from baseline to Week 8 in TMT score (TMT-A: speed of processing; TMT-B: executive functioning)
    - change from baseline to Week 8 in reaction time score (SRT: psychomotor speed; CRT: attention)
    - change from baseline to Week 8 in STROOP score (congruent score: speed of processing; incongruent score: executive functioning)
    - Overall cognition composite score (including all neuropsychological tests) - change from baseline to Week 8 in the composite z-score defined as the weighted sum of the z-scores in the DSST, RAVLT, TMT-A, TMT-B, STROOP, SRT and CRT
  - cognitive dysfunction, patient-reported:
    - change from baseline to Week 8 in PDQ-D total score
  - depressive symptoms and clinical global impression:
    - change from baseline to Week 8 in PHQ-9 total score
    - change from baseline to Week 8 in CGI-S score
    - CGI-I score at Week 8
  - functionality, clinician-rated:
    - change from baseline to Week 8 in FAST total score

Endpoints (continued)

- *Exploratory endpoints*:
  - change from baseline to all visits where assessed, in the neuropsychological tests (DSST, RAVLT, TMT-A, TMT-B, STROOP, SRT, and CRT), overall cognition composite score (including all neuropsychological tests), PDQ-D total score and subscale scores, PHQ-9 total score, CGI-S score, and FAST total score
  - CGI-I score, PHQ-9 response, CGI-I response, PHQ-9 remission, and CGI-S remission at all visits where assessed
- *Safety endpoints*:
  - adverse events
  - C-SSRS categorisation based on the Columbia Classification Algorithm for Suicide Assessment (C-CASA) definitions (1, 2, 3, 4, and 7)

Statistical Methodology

- The following analysis sets were used:
  - *all-patients-randomised set* (APRS) – all randomised patients
  - *all-patients-treated set* (APTS) – all patients in the APRS who took at least one dose of investigational medicinal product
  - *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 DSST (number of correct symbols)
- Unless otherwise indicated, the efficacy analyses were based on the FAS and the safety analyses were based on the APTS.
- In the efficacy analyses, all the p-values are nominal and based on two-sided tests; the 95% confidence intervals (CIs) are two-sided.
- *Primary endpoint analyses*:
  - The primary endpoint was analysed using a restricted maximum likelihood-based mixed model for repeated measurements (MMRM) approach, using observed cases (OC), and included site group, week (Weeks 1 and 8), and treatment (vortioxetine flexible dose 10 to 20 mg/day and escitalopram flexible dose 10 to 20 mg/day) as factors, baseline DSST total number of correct symbols as a continuous covariate, treatment-by-week interaction, and baseline 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 based on the missing-at-random assumption and performed using all available observations (OC data) in the Core Treatment Period. The estimated treatment difference at Week 8 was estimated based on the least square means for the treatment-by-week interaction in the model.
  - Sensitivity analyses were performed using an analysis of covariance (ANCOVA) by week using last observation carried forward (LOCF) and OC, with site group and treatment as fixed effects, and baseline score as a continuous covariate. In addition, *post-hoc* ANCOVA analysis was performed using OC for completers.
  - The potential influence of covariates was investigated with an ANCOVA (LOCF and OC) by adding main terms for covariates and interaction terms with treatment to the model. The covariates investigated were site, country, sex, age (continuous), age group (<50 years and ≥50 years), weight, body mass index (BMI), work group (working and not working), most recent previous selective reuptake inhibitors treatment (citalopram, paroxetine, sertraline, duloxetine, venlafaxine), and most recent previous selective reuptake inhibitors treatment group (SSRI and SNRI).

Statistical Methodology (continued)

- *Key secondary efficacy endpoint analyses*:
  - The key secondary endpoint, change from baseline to Week 8 in UPSA-B total score, was analysed with an ANCOVA model, using LOCF, and included site group and treatment as factors and baseline UPSA-B total score as a continuous covariate. The mean differences between treatment groups was estimated based on the least squares means for the treatment factor in the ANCOVA model.
  - Sensitivity analysis of UPSA-B was performed using the same ANCOVA models but excluded patients with a baseline UPSA-B total score of 100, which is the maximum obtainable score. In addition, the UPSA-B was also analysed using ANCOVA, using OC, and included site group and treatment as factors, and baseline UPSA-B total score as a continuous covariate. The analysis was repeated for completers.
  - Similar to the analysis of the primary endpoint, the potential influence of covariates on the key secondary efficacy endpoint was investigated with an ANCOVA (LOCF and OC) by adding main terms for covariates and interaction terms with treatment to the model. The covariates investigated were the same as for the primary endpoint.
- *Testing strategy*
  - A hierarchical testing strategy was defined *a priori* in the *Statistical Analysis Plan* and comprised the primary endpoint, as well as the key secondary efficacy endpoint. The testing continued to the key secondary efficacy endpoint only if statistical significance was reached at the 5% level for the primary endpoint.
- *Secondary endpoints analyses*:
  - Continuous and categorical secondary endpoints were analysed using MMRM and ANCOVA models similar to the models described for the primary endpoint.
- *Exploratory endpoints analyses*:
  - Continuous and categorical exploratory endpoints were analysed using MMRM and ANCOVA models similar to the models described for the primary endpoint.
  - Response and remission were analysed by week using logistic regression, using LOCF and OC, with treatment as factor and baseline score as a covariate and presented as odds ratio. Additional sensitivity analyses were performed where patients having a missing value at the week analysed were classified as a non-responder/non-remitter, using the same logistic regression.
  - Association between functionality (FAST, UPSA-B) and endpoints addressing cognitive dysfunction (DSST, TMT, STROOP, RAVLT, SRT, CRT, and PDQ-D) were performed for Week 8 assessments by means of estimation of a partial correlation coefficient, where the set of controlling variables included treatment group and baseline values of the respective variables. Association for the same outcomes at baseline was performed with the Pearson correlation coefficient.
  - Improvement in depressive symptoms can confound/mediate treatment effects on cognitive dysfunction, especially in subjective measures. To obtain an estimate of the degree to which the effect of treatment on the DSST could be attributed to alleviation of depressive symptoms, the DSST was analysed using an ANCOVA model adjusting for PHQ-9 total score by adding the change from baseline to Week 8 in PHQ-9 total score as a covariate. The baseline PHQ-9 total score was also added as a covariate.
- *Safety Endpoints*:
  - Adverse events and C-SSRS data were summarised using descriptive statistics.

Patient Disposition and Analysis Sets

• Patient disposition is summarised below:

	VOR 10-20mg		ESC 10-20mg		Total	
	n	(%)	n	(%)	n	(%)
Patients randomised	51		50		101	
Patients treated (all-patients-treated set [APTS])	50		49		99	
Patients completed	47	(94.0)	45	(91.8)	92	(92.9)
Patients withdrawn	3	(6.0)	4	(8.2)	7	(7.1)
Primary reason for withdrawal:						
Adverse event(s)	3	(6.0)	1	(2.0)	4	(4.0)
Protocol violation	0	(0.0)	1	(2.0)	1	(1.0)
Withdrawal of consent	0	(0.0)	1	(2.0)	1	(1.0)
Administrative or other reason(s)	0	(0.0)	1	(2.0)	1	(1.0)
Analysis sets:						
APTS	50		49		99	
Full-analysis set	50		49		99	

Demography and Baseline Characteristics of the Study Population

- The treatment groups were comparable with respect to sex and race. The mean age was slightly higher in the escitalopram group than in the vortioxetine group (50 *versus* 47 years). Three-quarters of the patients were women and all patients were White.
- In accordance with the selection criteria, all patients had had at least one previous MDE; the mean number of previous episodes was 2.3. The mean duration of the current episode was approximately 22 weeks in both treatment groups.
- The mean MADRS score of 29 points at baseline indicated that patients had *moderate* to *severe* MDD and the mean CGI-S score of 4.7 points indicated that patients were *moderately* to *markedly ill*.
- The baseline efficacy scores were comparable between the two treatment groups, except the DSST score and PDQ-D total score, both of which were higher in the vortioxetine group than in the escitalopram group (DSST: 42 *versus* 39 points; PDQ-D total score: 48 *versus* 42 points). Patients in the vortioxetine group performed numerically better based on objective measure (DSST) but considered themselves more impaired (PDQ-D).
- There were no relevant differences between the treatment groups in social history (level of education, marital or employment status, and living arrangement, drinking and smoking habits), family psychiatric history, or traumatic life events.

Efficacy Results

Testing Strategy Results

- The results of the testing strategy are summarised below:

Cognitive Function Endpoints	Change from Baseline		Difference to Escitalopram at Week 8 (FAS)			
	N	Mean (SE)	Difference (SE)	95% CI	p-value	Effect Size[a]
Primary endpoint						
DSST score						
Escitalopram	45	6.46 (1.21)				
Vortioxetine	48	8.46 (1.20)	2.00 (1.65)[b]	-1.28; 5.28	0.2280	0.25
Key secondary endpoint						
UPSA-B total score						
Escitalopram	48	9.45 (1.08)				
Vortioxetine	49	10.79 (1.02)	1.34 (1.41)[c]	-1.47; 4.15	0.3457	0.19

a Standardised effect size was calculated as the difference from escitalopram. A positive value indicated that the cognitive performance improved in favour of vortioxetine

b MMRM

c ANCOVA, LOCF

- The pre-defined testing strategy was stopped as the p-value for the primary endpoint was >0.05. For analyses outside the testing strategy, nominal p-values with no adjustment for multiplicity are reported.
- In both the vortioxetine and escitalopram groups, the DSST number of correct symbols increased (improved) at Week 8 by 8.46 and 6.46 points, respectively. The mean difference to escitalopram was 2.00 points (standardised effect size of 0.25) in favour of vortioxetine; the difference was not statistically significant.
- The UPSA-B total score increased (improved) by 10.79 and 9.45 points respectively, in the vortioxetine and escitalopram groups. The mean difference to escitalopram was 1.34 points (standardised effect size of 0.19) in favour of vortioxetine; the difference was not statistically significant.

Cognitive Function

- At Week 8, the patients in both the vortioxetine and escitalopram groups improved in the cognitive performance variables, RAVLT (learning and memory), TMT (A and B), SRT, CRT, STROOP (congruent and incongruent), and overall cognition composite score. The mean differences to escitalopram were numerically in favour of vortioxetine, except for the variables TMT-A and SRT. The results of the ANCOVA, LOCF and OC analyses were similar to the MMRM analyses.
- The results of the exploratory analyses (change from baseline to Week 1) using MMRM or ANCOVA (LOCF and OC) were similar to the results at Week 8, except for RAVLT (learning and memory), where the mean differences to escitalopram at Week 1 were statistically significantly in favour of vortioxetine.
- The patients in both the vortioxetine and escitalopram groups reported improvement in self-perceived cognitive function (measured using PDQ-D total and subscale scores). The mean differences to escitalopram were numerically in favour of vortioxetine.
- For the DSST, after correcting for subjective alleviation of depressive symptoms (assessed using PHQ-9), the result was similar to the primary efficacy analysis.

Efficacy Results (continued)

Depressive Symptoms and Clinical Global Impression

- The patients in both the vortioxetine and escitalopram groups improved in the depressive symptom and clinical global impression variables (PHQ-9 total score, CGI-S score, and CGI-I score). The mean differences to escitalopram at Week 8 were numerically in favour of vortioxetine. The results of the ANCOVA, LOCF and OC analyses were similar to the MMRM analyses.
- The proportion of responders (defined as a ≥50% reduction from baseline in PHQ-9 total score, or a CGI-I score ≤2) and remitters (defined as a PHQ-9 total score ≤4, or a CGI-S score ≤2) at Week 8 was numerically in favour of vortioxetine and statistically significant in PHQ-9 remitters (logistic regression). The results of the FAS, OC, logistic regression and non-response imputation analyses were similar to the FAS, LOCF, logistic regression analyses.
- At Week 1, the magnitude of improvement in depressive symptoms and clinical global impression variables was comparable between the vortioxetine and escitalopram groups. However, the results at Week 4 were similar to the results at Week 8, that is, numerically in favour of vortioxetine, except the CGI-I score at Week 4, which improved statistically significantly in the vortioxetine group when analysed using MMRM. In addition, the proportion of CGI-I responders (CGI-I score ≤2) at Week 4 was statistically significantly higher in the vortioxetine group than in the escitalopram group when imputed using LOCF and NRI.
- In general, patients in both the vortioxetine and escitalopram groups reported improvement in PHQ-9 single items; the mean differences to escitalopram were numerically in favour of vortioxetine.

Functionality

- In addition to the effect on UPSA-B, the patients in both the vortioxetine and escitalopram groups improved in the functionality performance variable, FAST. The mean difference to escitalopram in FAST total score was numerically in favour of vortioxetine. The results of the ANCOVA, LOCF and OC analyses were similar to the MMRM analyses.

Safety Results

- The adverse event incidence in the Entire Study Period is summarised below (APTS):

	VOR 10-20mg		ESC 10-20mg	
	n	(%)	n	(%)
Patients treated	50		49	
Patients who died	0		0	
Patients with treatment-emergent serious AEs (SAEs)	0		0	
Patients with treatment-emergent adverse events (TEAEs)	21	(42.0)	19	(38.8)
Patients with AEs leading to withdrawal	3	(6.0)	1	(2.0)
Total number of TEAEs	54		42	
Total number of AEs leading to withdrawal	8		2	

- No deaths or serious adverse events occurred during the study.
- In the Entire Study Period, the overall incidence of adverse events was 42% in the vortioxetine group and 39% in the escitalopram group.
- In the Core Treatment Period, the TEAEs with an incidence ≥5% and with a higher incidence in the vortioxetine group than in the escitalopram group were nausea and dizziness.
- The majority of the patients with TEAEs had *mild* or *moderate* events. A total of 3 patients had *severe* TEAEs, 1 patient in the vortioxetine group and 2 patients in the escitalopram group.
- A total of 4 patients had adverse events leading to withdrawal, 3 patients in the vortioxetine group and 1 patient in the escitalopram group. Adverse events leading to withdrawal were single events reported in individual patients.
- The incidence of TEAEs related to insomnia was 6% each (3 patients) in the vortioxetine and escitalopram groups. One patient in the vortioxetine group withdrew from the study due to the event. No patients reported TEAEs related to sexual dysfunction in either treatment group.

Safety Results (continued)

- In the majority of the patients with nausea, the event had an onset within the first week of treatment. One patient in the vortioxetine group withdrew due to the event.
- Based on the C-SSRS, a total of 3 patients (2 patients in the vortioxetine group and 1 patient in the escitalopram group) had *suicidal ideation* during the study. One patient each in the vortioxetine and escitalopram groups were classified in the mildest category (*wish to be dead*) and the remaining patient (vortioxetine group) was classified in the moderate category (*active suicidal ideation without intent to act*).

Conclusions

- Vortioxetine did not separate from escitalopram on the primary endpoint, DSST number of correct symbols. In general, compared to the escitalopram group, patients in the vortioxetine group had a greater numerical improvement in executive function, attention, and memory, as assessed using a range of objective neuropsychological tests as well as subjective patient-reported cognitive function outcome.
- Patients in the vortioxetine group had a greater numerical improvement on depressive symptoms, clinical global impression, and functionality, compared to patients in the escitalopram group.
- Vortioxetine 10-20 mg/day was safe and well tolerated.

Report Date

12 December 2016

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