Synopsis – Study 13926A

Title of Study A randomised, double-blind, parallel-group, active-comparator (venlafaxine extended release), fixed-dosed study of Lu AA21004 in Major Depressive Disorder in Asian countries
Investigators 33 principal investigators at 31 sites in 4 countries *Signatory investigator* – [redacted]
Study Sites 31 sites – 15 in China, 7 in South Korea, 7 in Taiwan, and 2 in Thailand
Publications None (as of the date of this report)
Study Period *First patient first visit* – 23 April 2012 *Last patient last visit* – 30 October 2013
Objectives • *Primary objective*: – to demonstrate non-inferiority of a fixed dose of vortioxetine (10 mg/day) to venlafaxine (150 mg/day) as assessed using the change from baseline in Montgomery and Åsberg Depression Rating Scale (MADRS) total score after 8 weeks of treatment in patients with Major Depressive Disorder (MDD) • *Secondary objectives*: – to evaluate the efficacy of vortioxetine (10 mg/day) *versus* venlafaxine (150 mg/day) during 8 weeks of double-blind treatment – to compare the safety and tolerability of 8 weeks of treatment with a fixed dose of vortioxetine (10 mg/day) *versus* venlafaxine (150 mg/day) in patients with MDD – to compare the proportion of patients who respond to a fixed dose of vortioxetine (10 mg/day) treatment at Week 8 *versus* venlafaxine (150 mg/day) (response is defined as a ≥50% decrease in MADRS total score from baseline) – to compare the proportion of patients who are in remission after 8 weeks of treatment with a fixed dose of vortioxetine (10 mg/day) *versus* venlafaxine (150 mg/day) (remission is defined as a MADRS total score ≤10) – to compare the effect of vortioxetine (10 mg/day) to that of venlafaxine (150 mg/day) at Week 8 on anxiety symptoms as assessed using the Hamilton Anxiety Rating Scale (HAM-A) total score – to compare the effect of a fixed dose of vortioxetine (10 mg/day) on health-related quality of life, disability, and health care resource utilisation *versus* venlafaxine (150 mg/day) – to evaluate the population pharmacokinetics of vortioxetine

Methodology

- This was an interventional, prospective, multi-national, multi-site, randomised, double-blind, parallel-group, active-comparator (venlafaxine), fixed-dose study.
- The patients were randomised equally (1:1) to fixed doses of either vortioxetine (10 mg/day) or venlafaxine (150 mg/day). The patients randomised to vortioxetine received 10 mg/day of vortioxetine for the entire 8-week double-blind treatment period (Core Treatment Period), followed by placebo during the 1-week double-blind down-taper period. The patients randomised to venlafaxine received 75 mg/day of venlafaxine for 4 days and 150 mg/day for the remainder of the 8-week double-blind treatment period, followed by 75 mg/day during the 1-week double-blind down-taper period.
- Patients were seen for efficacy and safety assessments weekly during the first 2 weeks of treatment and then every 2 weeks until the end of the 8-week treatment period.
- A safety follow-up visit was scheduled for 4 weeks after completion of the study or after withdrawal from the study.

Number of Patients Planned and Analysed

- 410 patients were planned for randomisation: 205 in the vortioxetine group and 205 in the venlafaxine group.
- Patient disposition is summarised below:

	VOR		VLF		Total	
	n	(%)	n	(%)	n	(%)
Patients randomised	213		230		443	
Patients treated (all-patients-treated set [APTS]):	211		226		437	
Patients completed	173	82.0	164	72.6	337	77.1
Patients withdrawn	38	18.0	62	27.4	100	22.9
Primary reason for withdrawal:						
Adverse event(s)	14	6.6	32	14.2	46	10.5
Lack of efficacy	8	3.8	3	1.3	11	2.5
Other	16	7.6	27	11.9	43	9.8
Analysis sets:						
APTS	211		226		437	
Full-analysis set (FAS)	209		215		424	
Per-protocol set (PPS)	180		164		345	

- There were more patients in the vortioxetine group (82%) than in the venlafaxine group (73%) who completed the study.
- The overall withdrawal rate during the entire study was 23% (18% in the vortioxetine group and 27% in the venlafaxine group).
- Fewer patients in the vortioxetine group (7%) than in the venlafaxine group (15%) withdrew due to adverse events. Slightly more patients in the vortioxetine group (4%) than in the venlafaxine group (1%) withdrew due to lack of efficacy.

Diagnosis and Main Inclusion Criteria

In- or outpatients with a primary diagnosis of recurrent MDD according to DSM-IV-TR™ criteria (classification code 296.3x), who:

- had a MADRS total score ≥26
- had a CGI-S score ≥4
- had a reported duration of the current MDE of ≥3 months
- were men or women, aged ≥18 and ≤65 years (for South Korea only: men or women, aged >18 and ≤65 years)
- did not have any current anxiety disorder (DSM-IV-TR™ criteria), as assessed using the Mini International Neuropsychiatric Interview (MINI)
- did not have a current diagnosis or history of manic or hypomanic episode, schizophrenia, or any other psychotic disorder, including major depression with psychotic features, personality disorders, mental retardation, organic mental disorders, and mental disorders due to a general medical condition (DSM-IV-TR™ criteria)

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

Vortioxetine – 10 mg/day; encapsulated tablets, orally; batch Nos. PD1911 / E08635-001E and PD1926 / E08765-005E

Duration of Treatment

8 weeks of double-blind treatment followed by 1 week of double-blind down-taper (for patients who received venlafaxine)

Reference Therapy, Dose and Mode of Administration, Batch Numbers

Venlafaxine extended release (*Effexor*® XL) – 150 mg/day; encapsulated tablets, orally; batch Nos. E46887 / E07863-006E (150 mg), F45629 / E08765-004E (150 mg), E46886 / E07863-005E (75 mg), and F45630 / E08765-003E (75 mg)

Placebo (for blinding) – encapsulated tablets, orally; batch Nos. E06379-001E and E08765-001E

Efficacy, Health-related Quality of Life, Disability, and Pharmacoeconomic Assessments

- Montgomery and Åsberg Depression Rating Scale (MADRS)
- Hamilton Anxiety Rating Scale (HAM-A)
- Clinical Global Impression – Severity of Illness (CGI-S)
- Clinical Global Impression – Global Improvement (CGI-I)
- Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q (SF))
- Sheehan Disability Scale (SDS)
- Health Economics Assessment (HEA)

Safety Assessments

Adverse events (AEs), clinical safety laboratory tests, vital signs, weight, electrocardiograms (ECGs), and physical examinations

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 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 MADRS total score
  - *per-protocol set* (PPS) – all patients in the FAS who:
    - had no major protocol violations that could interfere with the efficacy outcomes
    - had >14 days IMP exposure
    - had >70% IMP compliance in the Core Treatment Period
    - did not have a drug holiday during treatment for >6 consecutive days
- *Primary efficacy analysis*:
  - The primary analysis tested for non-inferiority of vortioxetine to venlafaxine using the change from baseline in MADRS total score at Week 8 based on the FAS using LOCF. Comparison between vortioxetine and venlafaxine was performed using an analysis of covariance (ANCOVA) with treatment and grouped site as fixed factors and the baseline MADRS total score as a covariate. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. Vortioxetine was declared to be non-inferior to venlafaxine if the upper limit of the calculated two-sided 95% confidence interval for the treatment difference at Week 8 between vortioxetine and venlafaxine was less than +2.5 MADRS units *versus* venlafaxine.

Statistical Methodology (continued)

- *Sensitivity analyses*:
  - The primary analysis was repeated using an ANCOVA based on the FAS using observed cases (OC), and using an ANCOVA based on the PPS using LOCF and OC. In addition, the sensitivity analyses of the primary endpoint included an analysis of the change from baseline in MADRS total score from Week 1 to Week 8, which was performed using a mixed model for repeated measurements (MMRM) on the FAS and PPS, with treatment group, grouped site, visit, and interaction between treatment group and visit as factors and interaction between baseline MADRS total score and visit as a covariate.
- *Secondary efficacy analyses*:
  - The following secondary endpoints were defined:
    - change from baseline in MADRS total score at other weeks assessed
    - change from baseline in CGI-S score at each week assessed
    - CGI-I score at each week assessed
    - change from baseline in HAM-A total score at each week assessed
    - MADRS response at each week assessed (response defined as a ≥50% decrease in the MADRS total score)
    - MADRS remission at each week assessed (remission defined as a MADRS total score ≤10)
    - changes from baseline in MADRS single item scores at each week assessed
    - CGI-S remission at each week assessed (remission defined as a CGI-S score ≤2)
    - CGI-I response at each week assessed (response defined as a CGI-I score ≤2)
  - The CGI-I score and the changes from baseline in MADRS total score, CGI-S score, HAM-A total score, and MADRS single item scores were analysed using an ANCOVA, with treatment and grouped site as fixed factors and the baseline score as a covariate. The analyses were based on the FAS, using both LOCF and OC.
  - The CGI-I score and the changes from baseline in CGI-S score, HAM-A total score, and MADRS single item scores from Week 1 to Week 8 were also analysed using an MMRM based on the FAS in a similar manner as the sensitivity analyses for the primary endpoint.
  - For all analysis involving CGI-I, the CGI-S score served as the baseline value.
  - The binary secondary efficacy endpoints were analysed using a logistic regression analysis (LREG) with treatment as a factor and the baseline score as a covariate, based on the FAS using LOCF. This was supplemented with analyses using OC and non-response imputation (NRI).
- *Safety analyses*:
  - The incidences of treatment-emergent adverse events (TEAEs) were summarised by preferred term for each treatment group. TEAEs reported more than once in the same patient were counted only once.
  - Descriptive statistics of absolute values and changes from screening based on the APTS were presented by visit and last assessment for clinical safety laboratory tests, vital signs, weight/BMI, and ECG parameters.

Demography of Study Population

- In the APTS, 60% of the patients were women. The mean age of the patients was approximately 40 years and all of the patients were Asian. The treatment groups were comparable with respect to age and sex.
- At baseline, the treatment groups were comparable with respect to height, weight, and body mass index.
- There were no clinically relevant differences in mean baseline efficacy scores between the treatment groups.
- At baseline, the mean MADRS total score (32 points) indicated that the patients had *moderate* to *severe* MDD. The mean CGI-S score (4.9 points) indicated that the patients were *moderately* to *severely ill* and the mean HAM-A total score (21 points) indicated that the patients had a substantial level of anxiety symptoms.

Efficacy Results

- The mean change from baseline in MADRS total score at Week 8 based on the ANCOVA using LOCF (FAS) was -19.4 and -18.2 points in the vortioxetine group and the venlafaxine group, respectively, giving a mean difference of -1.20 points in favour of vortioxetine (95% CI: -3.03 to 0.63; p = 0.199).
- Non-inferiority was established, as the upper bound of the 95% CI for the vortioxetine and venlafaxine comparison was 0.63 MADRS points, and therefore clearly below the non-inferiority margin of +2.5 MADRS points *versus* venlafaxine.
- The results were confirmed by the sensitivity analyses (ANCOVA based on the FAS using OC, and the PPS using LOCF and OC, and MMRM based on the FAS and PPS).

- The results of the other secondary efficacy analyses are summarised below:

	Difference to VLF at Week 8	
Efficacy Variable	**ANCOVA, LOCF**	**MMRM**
Δ MADRS total score	-1.2[a]	0.3
Δ HAM-A total score	-0.8	0.0
Δ CGI-S score	-0.2	0.0
CGI-I score	-0.1	0.0

Δ = change from baseline
Negative values are in favour of vortioxetine.
Mean values are presented.

a Primary efficacy analysis

- Comparable reductions (improvements) from baseline in mean HAM-A total score and in mean CGI-S score were observed in the vortioxetine and venlafaxine groups at Week 8. The mean CGI-I score was comparable between the vortioxetine and venlafaxine groups at Week 8.

- The proportions of responders and remitters are summarised below (FAS, LOCF, LREG):

	Week 8			
	VOR		VLF	
Variable	**n**	**%**	**n**	**%**
Response				
MADRS	139	67%	132	61%
CGI-I	155	74%	145	67%
Remission				
MADRS	90	43%	89	41%
CGI-S	104	50%	101	47%

- The proportions of MADRS responders, CGI-I responders, MADRS remitters, and CGI-S remitters were comparable between the vortioxetine and venlafaxine groups at Week 8.

Efficacy Results (continued)

- The health-related quality of life and overall functioning results are summarised below:

	Difference to VLF at Week 8	
Variable	**ANCOVA,LOCF**	**MMRM**
Δ SDS total score	-1.0	-0.7
Δ SDS work	-0.3	-0.2
Δ SDS social life	-0.2	-0.2
Δ SDS family life	-0.3	-0.2
Δ SDS days lost	-0.2	-0.2
Δ SDS days unproductive or lost	-0.3	-0.2
Δ Q-LES-Q (SF) total score	-0.1	-0.5
Δ Q-LES-Q Item 15	-0.2	-0.2
Δ Q-LES-Q Item 16	0.1	0.1

Δ = change from baseline
Negative values are in favour of vortioxetine.
Mean values are presented.

- Comparable reductions (improvements) from baseline in mean SDS total score, in each of the 3 single-item scores, in the number of lost days per week, and in the number of unproductive or lost days per week were observed in the vortioxetine and venlafaxine groups at Week 8.
- Comparable increases (improvements) from baseline in mean Q-LES-Q (SF) total score, mean Q-LES-Q Item 15 score (*satisfaction with medication*), and mean Q-LES-Q Item 16 score (*overall life satisfaction and contentment*) were observed in the vortioxetine and venlafaxine groups at Week 8 (FAS, LOCF, ANCOVA).
- The proportion of patients who used ≥1 health care resource (as assessed using the HEA) decreased in both treatment groups from 35% (vortioxetine) and 37% (venlafaxine) at baseline to 14% (vortioxetine) and 15% (venlafaxine) at Week 8.

Safety Results

- The adverse event incidence for the Entire Study Period is summarised below:

	VOR		VLF	
	n	**(%)**	**n**	**(%)**
Patients treated	211		226	
Patients who died	0	0	0	0
Patients with treatment-emergent serious AEs (SAEs)	2	0.9	8	3.5
Patients with TEAEs	128	60.7	157	69.5
Total number of TEAEs	337		442	

- The incidence of adverse events in the Entire Study Period was lower in the vortioxetine group than in the venlafaxine group (61% and 69%, respectively).
- The TEAEs with an incidence ≥5% in either treatment group in the Core Treatment Period are summarised below (APTS):

Preferred Term	VOR		VLF	
(MedDRA Version 16.0)	**n**	**(%)**	**n**	**(%)**
Patients treated	211		226	
Nausea	51	24.2	53	23.5
Dizziness	17	8.1	29	12.8
Headache	17	8.1	15	6.6
Dry mouth	12	5.7	24	10.6
Accidental overdose	10	4.7	12	5.3
Decreased appetite	10	4.7	23	10.2
Constipation	9	4.3	18	8.0
Insomnia	5	2.4	16	7.1

Safety Results (continued)

- In both treatment groups, the TEAE with the highest incidence was *nausea* (24% in the vortioxetine group *versus* 23% in the venlafaxine group). Apart from *nausea*, the only other TEAE with an incidence ≥5% in either treatment group for which the incidence was numerically higher in the vortioxetine group than in the venlafaxine group was *headache*. For the following TEAEs with an incidence ≥5% in either treatment group, the incidence was numerically lower in the vortioxetine group than in the venlafaxine group: *dizziness*, *dry mouth*, *decreased appetite*, *constipation*, and *insomnia*. The incidence of *accidental overdose* was similar between the two treatment groups.
- Overall, the majority of the patients with TEAEs had TEAEs that were either *mild* or *moderate*. The proportion of patients with *severe* TEAEs was lower in the vortioxetine group than in the venlafaxine group (1% *versus* 5%, respectively).
- For the majority of the patients with TEAEs *related* to IMP, the events were either *mild* or *moderate*. The only *severe* and *related* events that occurred in ≥2 patients in either treatment group were *nausea* (none in the vortioxetine group *versus* 1% [n = 3] in the venlafaxine group), *vision blurred* (none in the vortioxetine group *versus* 1% [n = 2] in the venlafaxine group) and *dyspnoea* (none in the vortioxetine group *versus* 1% [n = 2] in the venlafaxine group).
- No deaths occurred during the study. The incidence of treatment-emergent SAEs was low in both treatment groups (1% *versus* 4% in the vortioxetine and venlafaxine groups, respectively). In the vortioxetine group, none of the treatment-emergent SAEs occurred in >1 patient, and in the venlafaxine group, the only treatment-emergent SAE that occurred in >1 patient was *suicide attempt* (n = 2).
- The incidence of adverse events leading to withdrawal was lower in the vortioxetine group (7%) than in the venlafaxine group (14%). The only TEAEs leading to withdrawal in >2 patients in either treatment group were *nausea*, *palpitations*, *asthenia*, *dizziness*, and *dry mouth*; for each of these TEAEs leading to withdrawal in >2 patients in either treatment group, the incidence was higher in the venlafaxine group than in the vortioxetine group.
- No clinically relevant mean changes in clinical safety laboratory test values, vital signs, weight, or ECG values were seen, and the incidence of PCS values was low and comparable in the two treatment groups.

Conclusions

- Vortioxetine was established to be non-inferior to venlafaxine in the treatment of patients with MDD, as assessed based on the primary analysis of the change from baseline in MADRS total score at Week 8 (FAS, LOCF, ANCOVA), with the difference being numerically in favour of vortioxetine. The non-inferiority of vortioxetine to venlafaxine was supported by the sensitivity analyses.
- Vortioxetine was at least as efficacious as venlafaxine in improving the majority of the secondary efficacy endpoints.
- Vortioxetine was safe and well tolerated, and appeared to be better tolerated than venlafaxine.

Date of the Report

27 February 2014

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