Synopsis – Study 12279A

Title of Study A randomised, double-blind, parallel-group, placebo-controlled, and active-referenced study evaluating the efficacy and safety of three fixed-dose regimens of Lu AA34893 in the treatment of Major Depressive Disorder
Investigators 14 investigators at 14 centres in 5 countries *Signatory investigator* – Pierre-Michel Llorca, MD, PhD, C.H.U. Gabriel Montpied, Clermont-Ferrand, France
Study Centres 14 centres – 1 in Canada, 2 in Estonia, 3 in Finland, 1 in the Russian Federation, and 7 in South Africa
Publications None (as of the date of this report)
Study Period *First patient first visit* – 17 September 2008 *Last patient last visit* – 15 January 2009 *Study terminated* – 28 April 2009
Objectives • *Primary objective*: – to evaluate the efficacy of three fixed dosages of Lu AA34893 compared to placebo in the treatment of patients with Major Depressive Disorder (MDD) • *Secondary objectives*: – to evaluate the safety and tolerability of Lu AA34893 compared to placebo during the course of treatment – to evaluate the population pharmacokinetic parameters of Lu AA34893 and relevant metabolites • *Other objectives*: – to evaluate the efficacy of Lu AA34893 on anxiety symptoms – to evaluate the effects of Lu AA34893 on sleep and pain – to evaluate the effect of treatment with Lu AA34893 on patient-reported outcomes (quality of life, functioning, and disability) and resource utilisation (health economic assessment) – to explore biological parameters (biomarkers) that may be associated with the depressive illness and the effect of treatment (treatment response)

Methodology

- This was an interventional, multi-national, multi-centre, randomised, double-blind, parallel-group, placebo-controlled, active-referenced (venlafaxine [extended-release formulation]), fixed-dose study. The patients were in- or outpatients from psychiatric hospitals or psychiatric settings.
- The study consisted of the following periods:
  - *Screening Period* – during the 3-week Screening Period, the patients were characterised as extensive or poor metabolisers based on their cytochrome P450 subtype CYP2C19.
  - *8-week Treatment Period* (Weeks 1 to 8) – extensive metabolisers were randomised 1:1:1:1:1 to receive fixed doses of Lu AA34893 2, 12, or 24 mg/day, venlafaxine 225 mg/day, or placebo; poor metabolisers did not receive the highest Lu AA34893 dose, but were randomised 1:1:1:1 to the remaining four treatment groups. The investigational medicinal products (IMPs) were administered as two capsules in the morning and two capsules in the evening as follows:
    - Lu AA34893 2 mg/day – 1 mg twice daily (BID) during all 8 weeks
    - Lu AA34893 12 mg/day – uptitrated; the starting dose was 6 mg/day (3 mg BID) for 3 days and thereafter 12 mg/day (6 mg BID; from Day 4 up to Week 8)
    - Lu AA34893 24 mg/day – uptitrated; the starting dose was 6 mg/day (3 mg BID) for 3 days, followed by 12 mg/day (6 mg BID) for another 3 days, and thereafter 24 mg/day (12 mg BID; from Day 7 up to Week 8)
    - venlafaxine – uptitrated; the starting dose was 75 mg/day once daily for 4 days, followed by 150 mg/day once daily for 4 days, and thereafter 225 mg/day once daily from Day 9 up to Week 8
    - placebo – twice daily
  - *Taper Period* – patients who completed the 8-week Treatment Period entered a 2-week, double-blind Taper Period:
    - Patients randomised to Lu AA34893 2 mg/day received placebo up to Week 10.
    - Patients randomised to Lu AA34893 12 mg/day received 6mg/day (3 mg BID) for 3 days, followed by placebo up to Week 10.
    - Patients randomised to Lu AA34893 24 mg/day received 12 mg/day (6 mg BID) for 3 days, followed by 6 mg/day (3 mg BID) for another 3 days, and then placebo up to Week 10.
    - Patients randomised to venlafaxine received venlafaxine 150 mg/day during the first week of the taper period (Week 9) and 75 mg/day during the second week of the Taper Period (Week 10).
    - Patients randomised to placebo remained on placebo up to Week 10.
  - *Safety Follow-up Period* – patients who completed the Taper Period entered a 4-week Safety Follow-up Period; patients who withdrew were to attend a Withdrawal Visit as soon as possible, and entered a 4-week Safety Follow-up Period after withdrawal.
- Efficacy was assessed at each visit in the 8-week Treatment Period; safety and tolerability were assessed at each visit.
- At predetermined time points, blood samples were drawn for drug concentration analysis of Lu AA34893 and any relevant metabolites.
- The study was put on hold and later terminated due to the detection of a human-specific metabolite with inadequate nonclinical coverage. Due to the small numbers of patients enrolled, the results of this study should be interpreted with caution.

Number of Patients Planned and Analysed

- 600 patients were planned for enrolment: 120 patients per treatment group.
- Patient disposition, withdrawals by primary reason, and withdrawals by all contributory reasons are summarised in Tables 1, 2, and 3, respectively.
- Patient disposition is tabulated below:

	AA34893_2	AA34893_12	AA34893_24	VEN	PBO	Total
	n	n	n	n	n	n
Patients randomised	9	6	6	7	7	35
Patients treated (all-patients-treated set [APTS])	8	5	6	7	7	33
Patients completed	0	0	0	0	0	0
Patients withdrawn	8	5	6	7	7	33
Primary reason for withdrawal						
Lack of efficacy	0	1	0	0	1	2
Protocol violation	0	0	0	0	1	1
Withdrawal of consent	0	1	0	0	0	1
Administrative or other reason(s)	8	3	6	7	5	29[a]

a 27 of these due to the study being put on hold; Listing 1

Diagnosis and Main Inclusion Criteria

In- and outpatients with a primary diagnosis of Major Depressive Episode (MDE) according to DSM-IV-TR™ criteria, who:

- had an MDE of ≥3 months duration at screening
- had a Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≥26 at screening and at baseline
- were ≥18 and ≤75 years of age

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

Lu AA34893 – 1, 6, or 12 mg BID; encapsulated capsules, orally; batch Nos. PD1730/E05325-024E (1 mg), PD1728/E05325-008E (3 mg), PD1727/E05325-022E (6 mg), and PD1731/E05325-023E (6 mg)

Duration of Treatment

8 weeks of double-blind treatment, 2 weeks of double-blind taper

Reference Therapy, Dose and Mode of Administration, Batch Numbers

Venlafaxine extended release (Efexor XL® [venlafaxine HCl]) – 225 mg/day; encapsulated capsules, orally; batch Nos. C63495/E05831-005E (75 mg), C88887/E05831-007E (75 mg), C76493/E05831-006E (150 mg), and C53287/E05831-008E (150 mg)

Placebo – capsules, orally; batch Nos. E05325-025E and E05325-009E

Pharmacokinetic Assessments

Blood samples were drawn for drug concentration analysis. A total of 51 blood samples drawn from patients who received Lu AA34893 have been analysed, but the results will not be reported since the project has been closed down.

Efficacy Assessments

- MADRS total score
- Hamilton Depression Scale – 17 items (HAM-D_{17}) total score
- Clinical Global Impression – Severity of Illness (CGI-S) score
- Clinical Global Impression – Global Improvement (CGI-I) score
- Hamilton Anxiety Scale (HAM-A) total score
- Leeds Sleep Questionnaire (LSEQ) score
- Pain Intensity Numeric Rating Scale (NRS) total score
- EuroQol scoring system (EQ-5D) score
- Sheehan Disability Scale (SDS) single item scores
- Medical Outcomes Study (MOS) 36-item Short-form Health Survey (SF-36V2) scale score (not reported here)
- Health Economic Assessment Questionnaire (HEA) score (not reported here)

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
- No formal statistical analyses were performed.
- All the efficacy variables, patient-reported outcomes, and pharmaco-economic variables were summarised per visit using the observed cases (OC) approach.
- Exposure to IMP was summarised by duration (days), summary statistics (mean, standard deviation, median, minimum, and maximum), and total exposure (years).
- All adverse events (including pre-treatment, treatment-emergent [adverse events that started after or on the same date as the first dose of IMP and before or on the same date as the last dose of IMP (including taper)], and post-treatment adverse events) were listed and the incidences were tabulated by system organ class (SOC) and preferred term (PT) for each treatment group.
- The absolute values and/or changes from baseline/screening in clinical safety laboratory values, vital signs, and ECGs were summarised per visit using the OC approach.

Demography of Study Population

- Approximately 70% of the patients were women (range: 60% to 83%). The mean age was 46 years, ranging from 30 to 72 years, and the majority (85%) were Caucasian/Hispanic (Table 4).
- The mean height, body weight, BMI, and waist circumference at baseline were 168 cm (range: 150 cm to 186 cm), 79 kg (range: 50 kg to 122 kg), 28 kg/m^2 (range: 18 kg/m^2 to 45 kg/m^2), and 88 cm (range: 70 cm to 115 cm), respectively (Table 5).
- All the patients but one (in the venlafaxine group) were characterised as extensive metabolisers (including one ultra extensive metaboliser [Listing 2]).
- At screening, there were no clinically relevant differences between the treatment groups with respect to medical history, physical examination findings, or the use of concomitant medication (Listings 3, 4, and 5, respectively).
- The mean baseline MADRS total score indicated that the patients had *moderate* to *severe* MDD (Table 7) and the mean baseline CGI-S score indicated that the patients were *moderately* to *markedly ill* (Table 9).

Efficacy Results

The limited number of patients resulted in insufficient data for any meaningful analyses of efficacy. All the efficacy parameters (including patient-reported outcomes and pharmaco-economic variables) are summarised per visit (APTS, OC) in Tables 7 to 21.

Safety Results

- The adverse event incidences are summarised below:

	AA34893_2		AA34893_12		AA34893_24		VEN		PBO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients treated	8		5		6		7		7	
Patients who died	0		0		0		0		0	
Patients with serious AEs (SAEs)	0		0		0		0		0	
Patients with AEs	6	(75.0)	4	(80.0)	4	(66.7)	4	(57.1)	4	(57.1)
Patients with treatment-emergent AEs (TEAEs)	5	(62.5)	4	(80.0)	4	(66.7)	4	(57.1)	3	(42.9)
Total number of AEs	15		14		31		11		5	
Total number of TEAEs	14		8		19		9		4	

- A total of 19 patients were exposed to Lu AA34893, with a mean duration of 24 days (range: 4 to 42 days), and a total exposure to all doses of Lu AA34893 of 1.2 years (Table 6).
- No SAEs were reported during the study (Table 22).
- All adverse events are summarised by SOC and PT in Table 23.
- The majority the adverse events were *mild* or *moderate* (Listing 6).
- A total of 4 patients (3 patients in the AA34893_24 group and 1 patient in the venlafaxine group) had *severe* adverse events (Listing 6). All but 1 of the *severe* adverse events were either TEAEs or post-treatment adverse events. In 1 patient (in the AA34893_24 group), 4 of the 5 *severe* adverse events (anxiety, dizziness, insomnia, and hyperhidrosis) started 2 days after abrupt discontinuation of Lu AA34893, and were suggestive of discontinuation symptoms.
- The incidence of TEAEs was highest in the AA34893_12 group (Table 24), and the total number of TEAEs was highest in the AA34893_24 group, although these figures should be interpreted with great caution due to the low number of patients in the study.
- The following TEAEs occurred in ≥2 patients in any treatment group (Tables 24 and 25):

Preferred Term (MedDRA Version 11.1)	AA34893_2		AA34893_12		AA34893_24		VEN		PBO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients treated	8		5		6		7		7	
Nausea	2	(25.0)	2	(40.0)	3	(50.0)				
Diarrhoea	2	(25.0)			1	(16.7)			2	(28.6)
Dry mouth			1	(20.0)	3	(50.0)	1	(14.3)		
Headache	1	(12.5)	2	(40.0)					1	(14.3)
Flatulence	2	(25.0)			1	(16.7)				

Safety Results – continued

- Clinical safety laboratory values are presented per visit in Listing 7. Absolute values and changes from baseline/screening per visit for vital signs and ECGs are summarised in Tables 26, 27, 28, and 29, respectively.
- Potentially clinically significant (PCS) definitions for clinical safety laboratory values, vital signs, and ECGs are presented in Listing 8.
- Eight patients had post-baseline PCS laboratory values (Listing 9). No post-baseline PCS laboratory values were reported as adverse events. There was no post-baseline PCS laboratory value that occurred in >1 patient in any treatment group:
  - All but 2 post-baseline PCS laboratory values were related to lipid parameters.
  - One patient (in the AA34893_2 group) had a post-baseline PCS laboratory value related to haematology parameters (PCS high eosinophils at withdrawal).
  - One patient (in the AA34893_2 group) had a post-baseline PCS laboratory value related to liver parameters (PCS high γ glutamyl transferase at withdrawal).
- Two patients had PCS vital signs (Listing 10): 1 patient in the AA34893_12 group had low orthostatic blood pressure at Week 2, and 1 patient in the placebo group had high diastolic blood pressure at withdrawal.
- Two patients (in the AA34893_2 group) had PCS ECGs (Listing 11): 1 patient had high RR interval both at Week 4 and at withdrawal, and 1 patient had low heart rate and high RR interval at Week 4.

Conclusions

The adverse events were consistent with the known safety profile of Lu AA34893. However, due to the limited number of patients and duration of exposure, the results should be interpreted with caution.

Date of the Report

23 April 2010

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