Synopsis – Study 12022A

Title of Study Randomised, double-blind, parallel-group, placebo-controlled, and active-referenced study of Lu AA34893 to evaluate the efficacy and safety of three doses Lu AA34893 and quetiapine *versus* placebo in the treatment of depression in patients with Bipolar I or II Disorder
Investigators 48 investigators at 48 centres in 16 countries *Signatory investigator* – Guy Goodwin, MD, PhD, Department of Psychiatry, Warneford Hospital, Oxford, United Kingdom
Study Centres 48 centres – 3 in Australia, 3 in Austria, 3 in Belgium, 3 in Canada, 5 in France, 3 in Germany, 1 in Indonesia, 4 in Lithuania, 4 in Malaysia, 2 in the Philippines, 3 in the Republic of Korea, 4 in Romania, 2 in Slovakia, 5 in Sweden, 1 in Taiwan, and 2 in the United Kingdom
Publications None (as of the date of this report)
Study Period *First patient first visit* – 31 January 2008 *Last patient last visit* – 20 January 2009 *Study terminated* – 9 November 2009
Objectives • *Primary objective*: – to assess the efficacy of Lu AA34893 *versus* placebo in the treatment of depression by means of the change from baseline in MADRS total score at Week 8 in patients with Bipolar I or II Disorder • *Secondary objectives*: – to evaluate the safety and tolerability of three doses of Lu AA34893 *versus* placebo during 12 weeks of treatment – to assess the efficacy of three doses of Lu AA34893 *versus* placebo in the treatment of depression by means of the change from baseline in MADRS and HAM-D total scores and the CGI-BP part I and II scores by visit – to assess the numbers of responders and remitters during treatment with three doses of Lu AA34893 *versus* placebo – to assess the efficacy of three doses of Lu AA34893 on anxiety symptoms by means of the change from baseline in HAM-A total score – to evaluate the occurrence of (hypo)mania, by means of the incidence of diagnosis and change from baseline in YMRS total score, during 12 weeks of treatment with three doses of Lu AA34893 – to assess the potential for inducing extrapyramidal adverse events by means of the change from baseline in SAS, AIMS, and BARS total scores – to assess the efficacy and safety of quetiapine *versus* placebo on the same variables as those for Lu AA34893 – to assess population pharmacokinetic (PK) parameters of Lu AA34893 – to evaluate the effect of treatment with Lu AA34893 on patient-reported outcomes (quality of life, self-reported efficacy, and functioning) and resource utilisation – to explore biological parameters (for example, biomarkers, metabolomics) that may be associated with bipolar illness, the effect of treatment, and the treatment response

Methodology

- This was an interventional, multi-national, multi-centre, randomised, double-blind, parallel-group, placebo-controlled, active-referenced (quetiapine), fixed-dose study.
- The study consisted of the following periods:
  - *Screening Period* – during the 4-week Screening Period, the patients were characterised as extensive or poor metabolisers based on their cytochrome P450 subtype CYP2C19.
  - *12-week Treatment Period* (Weeks 1 to 12) – extensive metabolisers were randomised 7:7:8:7:7 to receive fixed doses of Lu AA34893 4, 12, or 18 mg/day, quetiapine 300 mg/day, or placebo, respectively; 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 one capsule in the morning and one capsule in the evening as follows:
    - Lu AA34893 4 mg/day – 2 mg twice daily (BID) during all 12 weeks
    - Lu AA34893 12 mg/day – uptitrated; the starting dose was 3 mg BID for 3 days, and thereafter 6mg BID from Day 4 up to Week 12)
    - Lu AA34893 18 mg/day – uptitrated; the starting dose was 3 mg BID for 3 days, followed by 6mg BID for another 3 days, and thereafter 9 mg BID from Day 7 up to Week 12
    - quetiapine – uptitrated; the starting dose was 50 mg (in the evening) on Day 1, 100 mg (in the evening) on Day 2, 200 mg (in the evening) on Day 3, and thereafter 300 mg/day (in the evening) from Day 4 up to Week 12
    - placebo – BID
  - *Taper Period* – patients who completed the 12-week Treatment Period entered a 1-week, double-blind Taper Period:
    - Patients randomised to Lu AA34893 4 mg/day received placebo for 7 days.
    - Patients randomised to Lu AA34893 12 mg/day received 3 mg BID for 3 days, followed by placebo for 4 days.
    - Patients randomised to Lu AA34893 18 mg/day received 6 mg BID for 3 days, followed by 3mg BID for another 3 days, and then placebo for 1 day.
    - Patients randomised to quetiapine received 200 mg for 1 day, 100 mg for 1 day, and placebo for 5 days.
    - Patients randomised to placebo remained on placebo.
- Patients who attended the Completion Visit (at the end of the 12-Week Treatment Period) entered a 4-week Safety Follow-up Period, that included the Taper 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 12-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 and who completed treatment, the results of this study should be interpreted with caution.

Number of Patients Planned and Analysed

- 600 patients were planned for enrolment: 120 in each treatment group
- Patient disposition, withdrawals by primary reason, and withdrawals by all reasons are summarised in Tables 1, 2, and 3, respectively.
- Withdrawals from the study by primary reason are presented in Listing 1.
- Patient disposition is tabulated below:

	AA34893_4		AA34893_12		AA34893_18		QUE		PBO		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients randomised	27		31		40		38		30		166	
Patients treated (all-patients-treated set [APTS]):	26		30		39		38		30		163	
Patients completed	9	(34.6)	8	(26.7)	10	(25.6)	12	(31.6)	11	(36.7)	50	(30.9)
Patients withdrawn	17	(65.4)	22	(73.3)	29	(74.4)	26	(68.4)	19	(63.3)	113	(69.3)
Primary reason for withdrawal:												
Adverse event(s)	0	(0.0)	5	(16.7)	1	(2.6)	8	(21.1)	1	(3.3)	15	(9.3)
Lack of efficacy	0	(0.0)	2	(6.7)	2	(5.1)	1	(2.6)	4	(13.3)	9	(5.6)
Non-compliance with IMP	1	(3.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)
Protocol violation	1	(3.8)	0	(0.0)	0	(0.0)	1	(2.6)	0	(0.0)	2	(1.2)
Withdrawal of consent	1	(3.8)	4	(13.3)	1	(2.6)	2	(5.3)	0	(0.0)	8	(4.9)
Lost to follow-up	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.3)	1	(0.6)
Administrative or other reason(s)	1	(3.8)	1	(3.3)	1	(2.6)	0	(0.0)	0	(0.0)	3	(1.8)
(Hypo)Manic[a] Symptoms	2	(7.7)	2	(6.7)	2	(5.1)	0	(0.0)	2	(6.7)	8	(4.9)
Study pause	11	(42.3)	8	(26.7)	22	(56.4)	14	(36.8)	11	(36.7)	66	(40.5)
Analysis sets:												
APTS	26		30		39		38		30		163	
Full-analysis set (FAS)	26		29		39		38		30		162	

a Withdrawal due to (hypo)manic symptoms was always set to the primary reason, overruling what was reported as primary reason.

Diagnosis and Main Inclusion Criteria

Inpatients in a psychiatric hospital or outpatients in a psychiatric setting with a primary diagnosis of current Major Depressive Episode (MDE) in Bipolar I Disorder or Bipolar II Disorder according to DSM-IV-TR™ criteria, as confirmed using the Mini International Neuropsychiatric Interview (MINI), who:

- had an MDE of ≥30 days duration at screening
- had a documented history of ≥1 manic and/or hypomanic episode within the past 15 years
- had a Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≥26 at screening and at baseline
- had a Young Mania Rating Scale (YMRS) total score ≤8 at screening and at baseline
- were ≥18 and ≤65 years of age

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

Lu AA34893 – 2, 6, or 9 mg BID; encapsulated capsules, orally; batch Nos. PD1682/E04879-010E (2 mg), PD1729/E05325-004E (2 mg), PD1683/E04879-011E (3 mg), PD1728/E05325-008E (3 mg), PD1685/E04879-013E (6 mg), PD1726/E05325-007E (6 mg), PD1727/E05325-022E (6 mg), PD1686/E04879-014E (9 mg), and PD1725/E05325-006E (9 mg)

Duration of Treatment

12 weeks of double-blind treatment, 1 week of double-blind taper

Reference Therapies, Dose and Mode of Administration, Batch Numbers

Quetiapine (Seroquel®) – 300 mg/day; encapsulated tablets, orally; batch Nos. ER453/E04879-044E (50 mg), KB80A3/E05325-026E (50 mg), ER090/E04879-002E (100 mg), IK368A1/E05325-001E (100 mg), ER090/E04879-008E (200 mg), IK368A1/E05325-002E (200 mg), EJ080/E04879-009E (300 mg), and JK76M1/E05325-003E (300 mg)

Placebo – capsules, orally; batch Nos. E04879-001E and E05325-009E

Pharmacokinetic Assessments

Blood samples were drawn for drug concentration analysis. A total of 460 blood samples drawn from patients who received Lu AA34893 have been analysed, but the results will not be reported here since the project has been closed down.

Efficacy Assessments

- MADRS total score
- Response (≥50% decrease from baseline in MADRS total score and YMRS total score ≤10)
- Remission (MADRS total score ≤10 and YMRS total score ≤10)
- Clinical Global Impression – Bipolar Version – Severity of Illness (CGI-BP-S [mania, depression, and overall bipolar illness]) score
- Clinical Global Impression – Bipolar Version – Improvement from Baseline (CGI-BP-I [mania, depression, and overall bipolar illness]) score
- Hamilton Depression Scale – 17 items ($HAM\text{-}D_{17}$) score (not reported)
- Hamilton Anxiety Scale (HAM-A) total score (not reported)
- Beck Depression Inventory (BDI-II) score (not reported)
- Medical Outcomes Study (MOS) 36-item Short Form Health Survey (SF-36) scale score (not reported)
- Life Functioning Questionnaire (LFQ) score (not reported)
- Health Economic Assessment Questionnaire (HEA) score (not reported)

Safety Assessments

- Adverse events (AEs), clinical safety laboratory tests, vital signs, weight, electrocardiograms (ECGs), and physical examinations.
- Extrapyramidal adverse events and other motor symptoms were assessed using the Simpson Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and Barnes Akathisia Rating Scale (BARS).
- The occurrence of (hypo)mania symptoms was assessed using the YMRS.

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 at least one valid post-baseline assessment of the MADRS total score
- No formal statistical testing was performed.
- An exploratory mixed-effects model repeated measures (MMRM) analysis was performed to estimate the mean change from baseline in MADRS total score (FAS) at each visit.
- Selected efficacy variables were summarised per visit using the observed cases (OC) approach.
- Exposure to IMP was summarised by duration (days), summary statistics (mean, median, standard deviation, minimum, and maximum), and total exposure (years).
- All adverse events were listed and the incidences of treatment-emergent (from date of first dose of IMP to last visit/contact) adverse events (TEAEs) were tabulated by system organ class (SOC) and preferred term (PT) for the 12-Week Treatment Period, and by PT for the Taper Period and Post-dose Period, for each treatment group. The definition of a TEAE was changed from the statistical analysis plan to include the Post-dose Period.
- 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.
- The changes from baseline in SAS, BARS, and AIMS total scores were summarised per visit using the OC approach.
- Patients with (hypo)mania (YMRS score >15), as assessed using the YMRS, were listed.

Demography of Study Population

- Approximately two-thirds of the patients were women (range: 61% to 73%); the mean age was 43 years, ranging from 18 to 64 years, and the majority (80%) were Caucasian (Table 4).
- All the patients but 4 (2 in the AA34893_12 group; 1 each in the quetiapine and placebo groups) were characterised as extensive metabolisers (Table 4).
- The mean height, body weight, BMI, and waist circumference at baseline were 167 cm (range: 146 cm to 194 cm), 75 kg (range: 40 kg to 132 kg), 27 kg/m^2 (range: 17 kg/m^2 to 47 kg/m^2), and 91 cm (range: 60 cm to 137 cm), respectively (Table 5).
- 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 2, 3, and 4, respectively).
- The proportions of patients with Bipolar I Disorder or Bipolar II Disorder were roughly equal in each treatment group, with the exception of the AA34893_12 group, where 80% of the patients had Bipolar I Disorder (Table 6).
- The mean baseline MADRS total score indicated that the patients had a current *moderate* to *severe* MDE (Table 8), and the mean baseline CGI-BP-S Depression and CGI-BP-S Overall Bipolar Illness scores indicated that the patients were *moderately* to *markedly ill* (Tables 18 and 19).

Efficacy Results

- The limited number of patients enrolled and who completed treatment resulted in insufficient data for the pre-specified analyses of efficacy. Selected efficacy variables are presented per visit (FAS, OC) in Tables 8 to 21.
- The exploratory MMRM analysis of the mean change from baseline in MADRS total score revealed that all active treatment groups, except the AA34893_4 group, separated significantly from placebo at Week 6. In addition, the AA34893_18 group separated from placebo at Week 12; the quetiapine group separated from placebo at Weeks 4 and 12 (Table 22).

Safety Results

- The adverse event incidences are summarised below (Table 23):

	AA34893_4		AA34893_12		AA34893_18		QUE		PBO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients treated	26		30		39		38		30	
Patients with treatment-emergent AEs (TEAEs)	19	(73.1)	23	(76.7)	32	(82.1)	26	(68.4)	21	(70.0)
Patients with serious AEs (SAEs)	1	(3.8)	3	(10.0)	3	(7.7)	4	(10.5)	3	(10.0)
Patients with AEs leading to Withdrawal	4	(15.4)	5	(16.7)	4	(10.3)	8	(21.1)	5	(16.7)
Total number of TEAEs	48		81		103		96		68	
Total number of SAEs	1		4		3		4		3	

- A total of 95 patients were exposed to Lu AA34893. The mean duration of exposure to Lu AA34893 was 48 days (range: 1 to 92 days), and the total exposure to Lu AA34893 was 12.7 years (Table 7).
- All adverse events in the study are summarised in Table 23; patients with adverse events are presented in Listing 5.
- TEAEs are presented by SOC and preferred term in Table 24 and by preferred term in Table 25. In the Lu AA34893 groups, the incidence of TEAEs ranged from 73% in the AA34893_4 group to 82% in the AA34893_18 group. In the quetiapine and placebo groups, the incidence of TEAEs was 68% and 70%, respectively.
- The majority of the patients had TEAEs that were considered by the investigator to be *mild* or *moderate* (Listing 5). A total of 27 patients had *severe* TEAEs (1 in the AA34893_4 group; 6 in the AA34893_12 group; 9 in the AA34893_18 group; 8 in the quetiapine group; 3 in the placebo group). With the exception of *dizziness* and *nausea* (4 and 2 patients, respectively, in the quetiapine group) no *severe* adverse events occurred in >1 patient in any treatment group.
- The following TEAEs occurred in ≥3 patients in any treatment group (Table 25):

Preferred Term	AA34893_4 (n = 26)		AA34893_12 (n = 30)		AA34893_18 (n = 39)		QUE (n = 38)		PBO (n = 30)	
(MedDRA Version 12.0)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Nausea	5	(19.2)	8	(26.7)	9	(23.1)	3	(7.9)	3	(10.0)
Headache	6	(23.1)	6	(20.0)	8	(20.5)	1	(2.6)	4	(13.3)
Dizziness	4	(15.4)	2	(6.7)	6	(15.4)	11	(28.9)	1	(3.3)
Dry mouth			3	(10.0)	4	(10.3)	8	(21.1)	3	(10.0)
Fatigue	1	(3.8)	3	(10.0)	4	(10.3)	6	(15.8)	2	(6.7)
Hyperhidrosis	2	(7.7)	1	(3.3)	4	(10.3)	1	(2.6)	2	(6.7)
Influenza					3	(7.7)				
Insomnia	1	(3.8)	2	(6.7)	3	(7.7)	2	(5.3)	3	(10.0)
Tremor			2	(6.7)	3	(7.7)			1	(3.3)
Constipation			1	(3.3)	2	(5.1)	4	(10.5)	2	(6.7)
Diarrhoea	2	(7.7)	2	(6.7)	2	(5.1)	1	(2.6)	3	(10.0)
Weight increased	3	(11.5)	2	(6.7)	2	(5.1)	1	(2.6)	1	(3.3)
Somnolence	1	(3.8)	4	(13.3)	1	(2.6)	5	(13.2)		
Abdominal pain									3	(10.0)

Safety Results – continued

- TEAEs in the 12-week Treatment Period are presented by SOC and preferred term in Table 26 and by preferred term in Table 27. In the Lu AA34893 groups, the incidences of TEAEs ranged from 65% in the AA34893_4 group to 74% in the AA34893_18 group. In the quetiapine and placebo groups, the incidence of TEAEs was 68% and 70%, respectively
- The incidence of TEAEs during the Taper Period was highest in the AA34893_18 group (32%; Table 28). With the exception of *dizziness* (2 patients in the AA34893_18 group), *decreased appetite,* and *insomnia* (2 patients each in the quetiapine group), no TEAEs in the Taper Period occurred in >1 patient in any treatment group.
- The incidence of TEAEs during the Post-dose Period was highest in the AA34893_12 group (17%; Table 29). With the exception of *headache* and *nausea* (2 patients each in the AA34893_18 group), no TEAEs in the Post-dose Period occurred in >1 patient in any treatment group.
- The incidence of SAEs in the AA34893 groups and the quetiapine group was at the placebo level (Table 30).
- A total of 14 patients in the APTS had SAEs (Table 30, Listing 6). With the exception of *depression* (2 patients in the AA34893_12 group), none of the SAEs occurred in >1 patient in any treatment group. A total of 6 SAEs were considered *related* to IMP (*mania* [AA34893_4 and AA34893_18 group]; *bipolar disorder* [AA34893_12 group]; *syncope* [quetiapine group]; *depression suicidal* and *insomnia* [placebo group]). For one of the 14 patients in the APTS with SAEs, the SAE started in the Screening Period (*depression*; quetiapine group). In addition, 1 patient who was randomised to the AA34893_12 group but never received any IMP had an SAE in the Screening Period (*bipolar disorder*). For further details see *Narratives of Serious Adverse Events and Other Significant Adverse Events*
- In addition, 3 non-randomised patients had SAEs in the Screening Period:
  - One patient died (*completed suicide*): A [redacted] man committed suicide, 5 days after giving informed consent.
  - One patient had *suicidal ideation*: A [redacted] woman was hospitalised, 2 days after giving informed consent, due to suicidal ideation and severe depression.
  - One patient made a *suicide attempt*: A [redacted] woman attempted suicide, 6 days after giving informed consent, by taking 60 tablets of quetiapine in a condition of acute depression. The patient was hospitalised, treated for the event, and recovered.
- A total of 3 patients had TEAEs potentially related to suicidal behaviour and self-harm (Listing 5):
  - One patient (AA34893_12 group) had *suicidal ideation* (MADRS item 10 [*suicidal thoughts*] score ≥5 and HAM-D_{17} item 3 [*suicide*] score ≥3 on Day 28; non-serious adverse event).
  - One patient (AA34893_18 group) had an *intentional overdose* (SAE).
  - One patient (placebo group) had *depression suicidal* (HAM-D_{17} item 3 score ≥3 on Day 19; SAE).
    - For further details see *Narratives of Serious Adverse Events and Other Significant Adverse Events*
- In addition, 1 patient (placebo group) had a score ≥5 on MADRS item 10, and a score ≥3 on HAM-D_{17} item 3 at the Completion Visit.

Safety Results – continued

- A total of 26 patients had adverse events leading to withdrawal (Table 23, Listing 7). In addition, 1 patient (in the AA34893_12 group) was withdrawn due to an adverse event (Listing 1), but the investigator did not specify which adverse event was the primary reason for withdrawal, thus the patient is not in Listing 7. The patient had *dizziness* and *nausea* (Listing 5).
- With the exception of *somnolence* (2 patients in the AA34893_12 group), *dizziness*, *dry mouth,* and *nausea* (2, 3, and 2 patients each, respectively, in the quetiapine group), and *hypomania* (2 patients in the placebo group), no adverse event lead to withdrawal in >1 patient in any of the treatment groups (Listing 7).
- Absolute laboratory values and the changes from baseline are summarised in Tables 31 and 32, respectively; post-baseline potentially clinically significant (PCS) laboratory values are summarised in Table 33, and patients with PCS laboratory values are presented in Listing 8.
- With the exception of PCS high cholesterol fasting (all AA34893 groups and quetiapine group), PCS high glucose fasting (AA34893_18 group), and PCS low high-density lipoprotein (HDL) fasting (AA34893_18 group), none of the post-baseline PCS laboratory values occurred in >3 patients in any treatment group.
- One patient (in the quetiapine group) had post-baseline PCS laboratory values reported as an adverse event (Listings 5 and 8): *lipids increased* (PCS high triglycerides and PCS low HDL cholesterol).
- A total of 5 patients had TEAEs related to clinical safety laboratory tests, although the values did not meet the PCS criteria (1 in the AA34893_4 group, 2 in the quetiapine group, and 2 in the placebo group; Listings 5 and 8). No overall pattern with respect to the type and distribution of TEAEs related to clinical safety laboratory tests was detected.
- All TEAEs related to clinical safety laboratory values were non-serious, and none led to withdrawal.
- The urine laboratory tests are summarised in Table 34. The urine laboratory tests did not show any clinically relevant changes during the study.
- Vital signs (including weight) and the changes from baseline are summarised in Tables 35 and 36, respectively; post-baseline PCS vital signs are summarised in Table 37, and patients with PCS vital signs are presented in Listing 9.
- With the exception of PCS high pulse orthostatic (AA34893_4 group, AA34893_18 group, and placebo group), none of the post-baseline PCS vital signs occurred in >3 patients in any treatment group.
- Five patients had post-baseline PCS vital signs reported as an adverse event (Listings 5 and 9):
  - 3 patients in the AA34893_4 group and 1 patient in the AA34893_18 group had *weight increased* (PCS high weight)
  - 1 patient in the quetiapine group had *hypotension* (PCS low systolic blood pressure and PCS low diastolic blood pressure)
- A total of 13 patients had TEAEs related to vital signs, although the values did not meet the PCS criteria (3 in the AA34893_12 group, 4 in the AA34893_18 group, 2 in the quetiapine group, and 4 in the placebo group; Listings 5 and 9).
- All TEAEs related to vital signs were non-serious, and none led to withdrawal.

Safety Results – continued

- The ECG values and the changes from screening are summarised in Tables 38 and 39, respectively; post-baseline PCS ECG values are summarised in Table 40, and patients with PCS ECG values are presented in Listing 10.
- None of the post-baseline PCS ECG values occurred in >2 patients in any treatment group.
- One patient (in the AA34893_4 group) had a post-baseline PCS ECG parameter reported as an adverse event (Listings 5 and 10): *atrioventricular block first degree* (PCS high PR interval)
- Two patients had TEAEs related to ECG parameters, although the values did not meet the PCS criteria (1 in the AA34893_12 group and 1 in the AA34893_18 group; Listings 5 and 10); the patient in the AA34893_12 group withdrew due to the adverse event (*arrhythmia*).
- All TEAEs related to ECG parameters were non-serious; 1 (noted above) led to withdrawal.
- Changes from baseline in SAS, AIMS, and BARS total scores were generally small in all treatment groups, at all visits, indicating that the patients did not develop extrapyramidal symptoms during the study (Tables 41, 42, and 43). Items 11 and 12 of the AIMS (*dental status*; Tables 44 and 45) supported the general conclusion that patients did not develop extrapyramidal symptoms during the study.
- Eight patients had (hypo)mania, as assessed using the YMRS, at any time during the study (1 in the AA34893_4 group, 2 in the AA34893_12 group, 2 in the AA34893_18 group, and 3 in the placebo group; Listing 11).
- Eight patients were withdrawn due to (hypo)manic symtoms: 2 in the AA34893_4 group, 2 in the AA34893_12 group, 2 in the AA34893_18 group, and 2 in the placebo group (Table 2 and Listing 1). Withdrawal due to (hypo)manic symptoms was always set to the primary reason, overruling what was reported as primary reason.
- Of the 8 patients who were withdrawn due to (hypo)manic symtoms, 5 had an adverse event (*hypomania* or *mania*) leading to withdrawal (2 in the AA34893_4 group, 1 in the AA34893_18 group, and 2 in the placebo group; Listing 7), and 3 (2 in the AA34893_12 group and 1 in the AA34893_18 group) were withdrawn due to an YMRS score >15. In addition, 1 patient (in the placebo group) had an YMRS score of 19 at the Completion Visit (Week 12).
- All patients with (hypo)mania are in Table 46.

Conclusions

- There is a clear signal of an effect of Lu AA34893. However, due to the limited number of patients and the change in the pre-specified primary analysis, no conclusion can be drawn regarding the appropriate dose or size of efficacy.
- Lu AA34893 appears to be safe and well tolerated. The adverse events reported were consistent with the known safety profile of Lu AA34893. There were no remarkable effects on clinical safety laboratory values, vital signs, or ECGs. The patients did not develop extrapyramidal symptoms during the study. The proportion of patients on Lu AA34893 switching to (hypo)mania was at the placebo level. However, due to the limited number of patients and duration of exposure, the results should be interpreted with caution.

Date of the Report

2 November 2010

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