Synopsis – Study 12450A

Title of Study A randomised, double-blind, parallel-group, fixed-dose study exploring the efficacy and safety of Lu AE58054 as augmentation therapy to risperidone in patients with schizophrenia
Investigators 25 investigators at 25 centres in 8 countries *Signatory investigator* – Dieter Naber, MD, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
Study Centres 25 centres – 2 in Belgium, 4 in France, 1 in Germany, 1 in Hong Kong, 2 in Italy, 11 in Poland, 3 in Taiwan, and 1 in Thailand
Publications None (as of the date of this report)
Study Period *First patient first visit* – 28 November 2008 *Last patient last visit* – 15 January 2010
Objectives • *Primary objective*: – to explore the efficacy of a fixed dose of Lu AE58054 (120 mg/day) as augmentation therapy to risperidone (4 to 8 mg/day), compared to risperidone with placebo (PBO), after 12 weeks of treatment, by measuring the change in the Positive and Negative Syndrome Scale (PANSS) total score in patients with schizophrenia • *Secondary objectives*: – to explore the effect of a fixed dose of Lu AE58054 (120 mg/day) as augmentation therapy to risperidone (4 to 8 mg/day), compared to risperidone with PBO, after 12 weeks of treatment, on: • neurocognitive performance using the Brief Assessment of Cognition in Schizophrenia (BACS) battery • depressive symptoms using the Calgary Depression Scale for Schizophrenia (CDSS) • quality of life using the Schizophrenia Quality of Life (S-QoL) scale • treatment response using the Clinical Global Impression – Severity of Illness (CGI-S) and the Clinical Global Impression – Global Improvement (CGI-I) scales • body weight, body mass index (BMI), waist circumference, and laboratory variables including fasting serum lipids, blood glucose, and glycosylated haemoglobin A_{1c} (HbA_{1c}) – to determine the population pharmacokinetics (PK) of Lu AE58054 and risperidone in patients with schizophrenia and relate it to relevant pharmacodynamic (PD) parameters (to be reported separately) – to explore the associations between biomarkers (that is, genetic variants) and clinical features such as disease symptoms, drug response, or adverse events (to be reported separately)
Methodology • This was a multi-national, multi-centre, randomised, double-blind, parallel-group, fixed-dose study. • The study consisted of a 2-week, prospective run-in period, after which patients were randomised to double-blind treatment to either augmentation therapy with Lu AE58054 (120 mg/day) or PBO, and entered a 12-week fixed-dose period. • Efficacy assessments (except CGI-I) were made at baseline and at Weeks 1, 2, 4, 6, 10, and 12. Safety assessments were made at screening, during treatment, and at the end of the study. • At predetermined time points, blood samples were drawn for drug plasma concentration analysis of Lu AE58054 and risperidone and its major metabolite, 9-hydroxyrisperidone, and population PK were assessed. PK data are to be reported separately.

Number of Patients Planned and Analysed

- 120 patients were planned for enrolment: 60 in the R+AE58054 group (that is, Lu AE58054 as augmentation therapy to risperidone) and 60 in the R+PBO group (that is, risperidone with placebo)
- Patient disposition is tabulated below:

	R+AE58054		R+PBO		Total	
	n	(%)	n	(%)	n	(%)
Patients randomised	59		65		124	
Patients treated (all-patients-treated set [APTS]):						
Patients completed	44	(75)	50	(78)	94	(76)
Patients withdrawn	15	(25)	14	(22)	29	(24)
Primary reason for withdrawal:						
Adverse event(s)	6	(10)	6	(9)	12	(10)
Lack of efficacy	1	(2)	1	(2)	2	(2)
Other	8	(14)	7	(11)	15	(12)
Analysis sets:						
APTS	59		64		123	
Full-analysis set (FAS)	58		64		122	

Diagnosis and Main Inclusion Criteria

Inpatients or outpatients with a primary diagnosis of schizophrenia according to the DSM-IV-TR™ criteria, for whom a change in antipsychotic treatment was indicated since they were only partially responding to their current risperidone treatment, who:

- had a PANSS total score ≥70 and ≤100 at screening and had an improvement of <20% in the PANSS total score at baseline
- had a CGI-S score ≥4 (*moderately ill*) at screening and baseline
- had a score ≤4 (*moderate*) on the following PANSS items at screening and baseline:
  - P2 (*conceptual disorganisation*)
  - P7 (*hostility*)
  - G8 (*uncooperativeness*)
- had been on an optimised dose of risperidone (4 to 8 mg/day) for the treatment of schizophrenia for ≥4 weeks prior to screening and during the 2-week run-in period prior to baseline
- were ≥18 and ≤65 years of age

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

Lu AE58054 – 120 mg/day; capsules, orally; batch No. C8A0491

Duration of Treatment

12 weeks

Reference Therapies, Doses and Mode of Administration, Batch Numbers

Placebo – capsules, orally; batch No. C8A0492

Risperidone – 4 to 8 mg/day; tablets, orally; batch Nos. 7KL0000 (1 mg); 8AL2L00 (2 mg), 7JL1I00 (4 mg)

Pharmacokinetic/Pharmacodynamic Assessments

Blood samples were collected for determination of population PK/PD of Lu AE58054 and risperidone and its major metabolite 9-hydroxyrisperidone (to be reported separately).

Efficacy Assessments

- PANSS total score
- PANSS Positive Symptoms, Negative Symptoms, and General Psychopathology scores, and PANSS responders (≥20%, ≥30%, ≥40%, or ≥50% decrease in PANSS total score from baseline)
- CGI-S and CGI-I scores and CGI-I responders (CGI-I score ≤2)
- BACS composite and individual test scores
- PANSS cognitive subscale scores (definitions 1 and 2)
- CDSS scores
- S-QoL scores

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 double-blind investigational medicinal products (IMP) (that is, Lu AE58054 or placebo)
  - *full-analysis set* (FAS) – all patients in the APTS who had at least one valid post-baseline assessment of the PANSS total score
- On an exploratory basis, the change from baseline in PANSS total score at Week 12 (last observation carried forward [LOCF]) was analysed using a linear model that included treatment and pooled centre as factors and the PANSS total score at baseline as a covariate. This analysis was repeated on the observed cases (OC) dataset.
- The changes from baseline in PANSS Positive Symptoms, Negative Symptoms, General Psychopathology, and cognitive subscale scores, and in CDSS total, CGI-S, and S-QoL scores were analysed for both the LOCF and OC datasets using analysis of covariance (ANCOVA), with treatment and pooled centre as factors, and the baseline score as a covariate.
- For the CGI-I, the treatment group difference for the absolute values was analysed for both the LOCF and OC datasets using ANCOVA, with treatment and pooled centre as factors and the baseline CGI-S value as a covariate.
- The PANSS responder rates (that is, the percentage of patients with a ≥20%, ≥30%, ≥40%, or ≥50% decrease in PANSS total score from baseline to each visit) was analysed using logistic regression with baseline PANSS total score, treatment, and pooled centre as factors. The CGI-I responder rate (that is, the percentage of patients with a CGI-I score of 1 or 2) at each visit was analysed using logistic regression with the baseline CGI score, treatment, and pooled centre as factors. The responder rates were also analysed using a χ^2 test and Fisher's exact test. The responder rates were analysed using the LOCF, OC, and OC-I (that is, the OC dataset with missing data imputed as non-responders) datasets.
- For each of the six BACS subtests, the change from baseline in actual score and Z-score was analysed for both the LOCF and OC datasets using an ANCOVA model with treatment and pooled centre as factors and the baseline BACS score as a covariate. The Z-score of the BACS composite score was also analysed using the same model.
- The incidences of all TEAEs were summarised by primary system organ class (SOC) and preferred term for each treatment group.

Demography of Study Population

- The ratio of men to women was approximately 2:1 in each treatment group. The mean age was similar in both treatment groups (39 years overall), and the majority of the patients were Caucasian (74% overall). Overall, the mean baseline PANSS total score was approximately 81 (indicating that the patients had *moderate* to *marked* levels of symptoms of schizophrenia) and the mean baseline CGI-S score was approximately 4.3 (indicating that the patients had *moderate* to *marked* levels of psychopathology).
- There were no clinically relevant differences in height, weight, BMI, or waist circumference between the two treatment groups, or for men or women.

Efficacy Results

- The exploratory ANCOVA of the mean change from baseline to Week 12 in PANSS total score (based on the FAS, LOCF) showed comparable improvements in PANSS total score in the R+AE58054 and R+PBO groups (12.9 *versus* 14.0 [FAS, LOCF]).
- Improvements from baseline in PANSS total, Positive Symptoms, Negative Symptoms, and General Psychopathology scores were observed in both treatment groups at all timepoints assessed, for both the LOCF and OC analyses. For the majority of the timepoints assessed, there were greater (but small) estimated mean improvements from baseline in the R+PBO group than in the R+AE58054 group.
- Both treatment groups showed improvements from baseline in CGI-S scores at all timepoints assessed, for both the LOCF and OC analyses. At all timepoints assessed, the differences between the R+AE58054 and R+PBO groups in the estimated mean improvements from baseline in CGI-S scores were small.
- Both treatment groups showed improvements in CGI-I score over time, for both the LOCF and OC analyses. At all timepoints assessed, the differences between the R+AE58054 and R+PBO groups in the estimated mean CGI-I scores were small.
- Both treatment groups showed improvements from baseline in BACS composite Z-score, most BACS subscale scores (and their corresponding Z-scores), and CDSS total score at Weeks 8 and 12, for both the LOCF and OC analyses. At all timepoints assessed, the differences between the R+AE58054 and R+PBO groups in the estimated mean improvements from baseline in each of the scores were small.
- Both treatment groups showed improvements from baseline in PANSS cognitive subscale scores at all timepoints assessed, for both the LOCF and OC analyses. For the majority of the timepoints assessed, there were greater (but small) estimated mean improvements from baseline in the R+PBO group than in the R+AE58054 group.
- Both treatment groups showed improvements from baseline in S-QoL total and subscale scores at Week 12. At Week 12, there was a greater (but small) estimated mean improvement from baseline in S-QoL total score in the R+AE58054 group than in the R+PBO group in the LOCF analysis, and in the R+PBO group than in the R+AE58054 group in the OC analysis. In both the LOCF and OC analyses, there were greater (but small) estimated mean improvements from baseline in *self-esteem*, *resilience*, *physical well-being*, and *autonomy* subscale scores in the R+AE58054 group than in the R+PBO group, and in *psychological well-being*, *family relationships*, *relationships with friends*, and *sentimental life* subscale scores in the R+PBO group than in the R+AE58054 group.
- The proportion of patients with a ≥20%, ≥30%, ≥40%, or ≥50% reduction in PANSS total score from baseline was comparable (that is, the absolute percentage point differences were ≤5%) in the R+AE58054 and R+PBO groups at the majority of the timepoints assessed, based on the FAS and using LOCF, OC, or OC-I. At Week 12, the proportion of patients with a ≥20% reduction in PANSS total score from baseline was 45% and 39% in the R+AE58054 and R+PBO groups, respectively (FAS, LOCF).
- The proportion of patients with a CGI-I score ≤2 was comparable in the R+AE58054 and R+PBO groups (that is, the absolute percentage point difference was ≤5%) at all timepoints assessed, based on the FAS and using LOCF, OC, or OC-I.

Safety Results

- The adverse event incidence is summarised below:

	R/PBO		R+AE58054	
	n	(%)	n	(%)
Patients treated	64		59	
Patients who died	1	(2)	0	(0)
Patients with serious AEs (SAEs)	3	(5)	2	(3)
Patients with TEAEs	27	(42)	26	(44)
Total number of TEAEs	56		46	

- The incidence of TEAEs was similar in the R+AE58054 group (44%) and the R+PBO group (42%). The TEAEs with an incidence ≥5% in the R+AE58054 group comprised: *nausea* (7%), *akathisia* (5%), *anxiety* (5%), and *weight increased* (5%). There were no TEAEs in the R+PBO group with an incidence ≥5%.
- One patient (in the R+PBO group) died: the patient had a *cardiac arrest* on Day 112 and died that same day, which was approximately 4 weeks after completing the study. The investigator assessed the event as *not related* to IMP.
- A total of 5 patients had SAEs during the study (R+AE58054: 2 patients; R+PBO: 3 patients). Except for 2 SAEs (*cardiac arrest* and *intentional overdose*; R+PBO group), all SAEs were psychiatric events. One of the 5 patients also had a pre-treatment SAE (*social stay hospitalisation*; R+AE58054 group).
- The incidence of adverse events leading to withdrawal was 10% in the R+AE58054 group and 9% in the R+PBO group. In the R+AE58054 group, there was no adverse event leading to withdrawal that was reported in more than 1 patient.
- The changes from baseline to Week 12 in SAS, BARS, and AIMS total scores were comparable in the R+AE58054 and R+PBO groups.
- Almost all mean post-baseline laboratory blood test values in both treatment groups were within the reference ranges, and the mean changes were small and similar between both treatment groups and not considered of clinical relevance.
- The mean changes from baseline in vital signs were small (blood pressure: -3/+3 mmHg; pulse: -4/+3 bpm). There were no clinically relevant differences within or between groups were present.
- In both treatment groups, the mean changes in weight and waist circumference were minor (less than 1 kg and 1 cm, respectively) and considered not clinically relevant.
- In both treatment groups, there were no clinically relevant changes in ECG parameters over time. Nor were there clinically relevant differences between the treatment groups in ECG parameters.

Conclusions

- In patients with schizophrenia, augmentation therapy with 120 mg/day Lu AE58054 did not offer any treatment advantage over placebo in improving overall schizophrenia symptoms (as assessed using the PANSS total score). There also did not appear to be any treatment advantage with 120 mg/day Lu AE58054 over placebo in improving patients' overall neurocognitive performance (as assessed using the BACS composite Z-score and the PANSS cognitive subscale scores). A substantial placebo response was observed in this study, which may have a role in the results. In addition, these results may suggest that 120 mg/day Lu AE58054 is suboptimal for augmentation therapy.
- The safety profile of augmentation therapy with Lu AE58054 *versus* augmentation therapy with placebo was comparable and no new safety issues were raised in this study.
- This is an exploratory study and generalisation of the results is restricted by the limited number of patients.

Date of the Report

26 November 2010

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