Synopsis – Study 12936A

Title of Study Randomised, double-blind, parallel-group, placebo-controlled, fixed-dose study of Lu AE58054 in patients with moderate Alzheimer's Disease treated with donepezil
Investigators 51 investigators in 48 sites in 7 countries *Signatory investigator* – David Wilkinson, MB ChB, MRCGP FRCPsych, MARC-Moorgreen Hospital, Southampton, United Kingdom
Study Sites 48 sites in 7 countries – 5 in Australia, 7 in Canada, 8 in the Czech Republic, 6 in Germany, 7 in Italy, 10 in Poland, and 5 in Spain
Publications None (as of the date of this report)
Study Period *First patient first visit* – 8 December 2009 *Last patient last visit* – 23 December 2011
Objectives • *Primary objective*: – to explore the effect on cognitive performance of a fixed dose of Lu AE58054 (90 mg/day) compared to placebo after 24 weeks of treatment in donepezil-treated patients with moderate Alzheimer's Disease (AD) • *Secondary objectives*: – to explore the effect, safety, and tolerability of a fixed dose of Lu AE58054 (90 mg/day) compared to placebo after 24 weeks of treatment in donepezil-treated patients with moderate AD on: • global impression • Activities of Daily Living (ADL) • behavioural symptoms • caregiver burden – to evaluate the population pharmacokinetics (popPK) of Lu AE58054 and donepezil in patients with moderate AD and relate it to relevant pharmacodynamic (PD) parameters
Methodology • This was an interventional, prospedtive, multi-national, multi-site, randomised, double-blind, parallel-group, placebo-controlled, fixed-dose study of Lu AE58054 as adjunctive treatment to donepezil. • The study comprised a 2-week Screening Period followed by a 24-week Treatment Period during which the patients received Lu AE58054 90 mg/day (given as 30 mg thrice daily) or placebo (patients were randomised in a 1:1 ratio) as adjunctive treatment to donepezil 10 mg/day. • Efficacy and safety data were collected throughout the study. Blood samples for drug concentration analysis were drawn at pre-determined time points. • 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

- 270 patients were planned for enrolment: 135 in the placebo group and 135 in the Lu AE58054 group.
- Patient disposition is summarised below:

	Placebo		Lu AE58054 90mg/day		Total	
	n	(%)	n	(%)	n	(%)
Patients randomised	133		145		278	
Patients treated (all-patients-treated set [APTS]):	133		145		278	
Patients completed	118	(88.7)	114	(78.6)	232	(83.5)
Patients withdrawn	15	(11.3)	31	(21.4)	46	(16.5)
Primary reason for withdrawal:						
Adverse event(s)	7	(5.3)	18	(12.4)	25	(9.0)
Lack of efficacy	1	(0.8)	0	(0.0)	1	(0.4)
Other	7	(5.3)	13	(9.0)	20	(7.2)
Analysis sets:						
APTS	133		145		278	
Full-analysis set (FAS)	132		140		272	
Per-protocol Set (PPS)	127		133		260	

Diagnosis and Main Inclusion Criteria

Outpatients with a primary diagnosis of probable AD consistent with the NINCDS-ADRDA criteria, who:

- had a Mini Mental State Examination (MMSE) score ≥12 and ≤19 at screening and at baseline
- were ≥50 years of age
- had been treated with donepezil for at least 4 months prior to the Screening Visit and had been on a stable dose (donepezil 10 mg/day) for at least 3 months prior to screening

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

Lu AE58054 – 90 mg/day (given as 30 mg thrice daily); capsules, orally; batch Nos. C8A0490, C9H2071, C9H2072, CKGK

Duration of Treatment

24 weeks

Reference Therapy, Doses and Modes of Administration, Batch Numbers

Placebo – thrice daily; capsules, orally; batch Nos. C8A0492, C9A2281, C9H2073

Donepezil (Aricept®; as adunctive therapy) – 10 mg/day, once daily, capsules, orally; batch Nos. 8274503, 8288304, 9176802, CKGH

Efficacy Assessments

- *Primary variable*:
  - Alzheimer's Disease Assessment Scale, Cognitive Subscale (ADAS-cog) total score
- *Secondary variables*:
  - Neuropsychological Test Battery (NTB), (individual tests, as well as composite z-score)
  - Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (ADCS-ADL_{23}) total score
  - Neuropsychiatric Inventory (NPI) total score
  - Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC) score
  - Zarit Burden Interview (ZBI) total score

Pharmacokinetic/Pharmacodynamic Assessments

Plasma concentration analyses of Lu AE58054 and donepezil

Safety Assessments

Adverse events (AEs), clinical safety laboratory tests, vital signs, weight, electrocardiograms (ECGs), urinalysis, and physical and neurological 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 product (IMP)
  - *full-analysis set* (FAS) – all patients in the APTS who had at least one valid post-baseline assessment of the ADAS-cog
  - *per-protocol set* (PPS) – all patients in the FAS who did not violate any protocol criteria that would interfere with a reasonable opportunity for the treatment to produce its expected response and significantly modify the interpretation of the study results
- All efficacy analyses were conducted on the FAS. All safety analyses were conducted on the APTS; pre-treatment adverse events were summarised for the APTS; and the PPS was used for robustness analyses to supplement selected efficacy analyses.
- *Primary efficacy analyses*:
  - The primary analysis assessed the treatment difference in efficacy based on the change from baseline in the ADAS-cog at Week 24. The change from baseline at Weeks 4, 12, and 24 was analysed using MMRM, and the treatment difference was estimated at Weeks 4, 12, and 24.
  - Sensitivity analyses included analysis of covariance (ANCOVA) (observed cases [OC] and last observation carried forward [LOCF]) and analysis based on the PPS.
- *Secondary efficacy analyses*:
  - All secondary analyses were performed using OC.
  - For NTB, the z-scores for each individual test, as well as the composite z-score, were analysed using MMRM, similar to the primary analysis, as well as an ANCOVA with baseline z-score as covariate and treatment and pooled site as factors
  - The ADCS-ADL_{23}, NPI, ZBI total scores, Personal Strain Score (sum of ZBI items 1, 4, 5, 8, 9, 14, 16, 17, 18, 19, 20, and 21) and Role Strain Score (sum of ZBI items 2, 3, 6, 11, 12, and 13) were analysed using MMRM, similar to the primary analysis, as well as an ANCOVA with baseline score as covariate and treatment and pooled site as factors
- *Safety analyses*:
  - The overall incidences of adverse events, pre-treatment adverse events, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and TEAEs leading to withdrawal were summarised for each treatment group by primary system organ class (SOC) and preferred term.
  - Absolute values and changes from baseline to the last assessment in clinical safety laboratory tests, vital signs, weight/BMI, and ECG parameters were summarised using descriptive techniques. Values outside the reference ranges, as well as potentially clinically significant (PCS) values, were flagged and tabulated. Urinalysis tests (positive/negative) and physical and neurological examinations (normal/abnormal) were summarised for each treatment group by visit.
  - To investigate the liver function test abnormalities, additional evaluations were performed:
    - an exploratory statistical screening for predictors of aspartate aminotransferase (ASAT) or alanine aminotransferase (ALAT) values >2 times upper limit of normal (ULN)
    - exposure levels of Lu AE58054 and donepezil
    - categorisation of liver injury type

Demography of Study Population

- The patients' baseline characteristics are summarised below (APTS):

		Placebo (n = 133)		Lu AE58054 (n = 145)		Total (n = 278)	
Age, years (SD)		75.0	(7.2)	74.0	(7.5)	74.4	(7.3)
Sex, n (%)	women	89	(66.9)	107	(73.8)	196	(70.5)
BMI, kg/m^2 (SD)		25.9	(4.1)	25.0	(3.9)	25.4	(4.0)

- The treatment groups were comparable with respect to age, BMI, and race. The ratio of women to men was approximately 3:1 in the Lu AE58054 group and approximately 2:1 in the placebo group. Nearly all patients (99%) were White.

Baseline Efficacy Variables

- The patients' baseline efficacy variable scores and severity ratings are summarised below (FAS):

Efficacy variable	Placebo (n = 132)		Lu AE58054 (n = 140)	
	Mean	(25%; 75% percentile)	Mean	(25%; 75% percentile)
MMSE	16.9	(16; 19)	16.7	(15;18)
ADAS-cog	27.6	(20; 36)	28.4	(21; 34)
NTB composite z-score	0.0	(-0.2; 0.2)	0.0	(-0.27; 0.20)
ADCS-ADL_{23}	50.8	(41; 63)	52.6	(44; 62)
NPI	9.3	(1; 12)	8.4	(1; 14)
ADCS-CGIC	4.0	(4; 5)	3.9	(4; 4)
ZBI	22.1	(11; 30)	23.7	(13; 31)

- The treatment groups were comparable at baseline with respect to the efficacy assessments performed. Mean values of the key selection criterion MMSE at baseline were 16.9 and 16.7 in the Lu AE58054 and placebo groups, respectively.

Efficacy Results

- There was better cognitive performance with Lu AE58054 than with placebo throughout the study, with a statistically significant treatment difference in ADAS-cog total score at Week 24 of -2.16 points (95% CI: -3.62; -0.69, p=0.004).
- Though most of the total and composite scores for the secondary endpoints indicated improved performance in the Lu AE58054 group compared with the placebo group, the treatment differences in the OC MMRM analyses were not statistically significant at Week 24. In the OC ANCOVA analyses, there was a tendency towards an improvement in the Lu AE58054 group relative to the placebo group in the ADCS-ADL_{23} and ADCS-CGIC total scores at Week 24 (p=0.046 and p=0.062, respectively).

Efficacy endpoints (total and composite scores)	Difference to Placebo at Week 24		
	Mean	(95% CI)	p-value
ADAS-cog	-2.16	(-3.62; -0.69)	0.004
NTB composite z-score	0.07	(-0.05; 0.18)	0.237
ADCS-ADL_{23}	1.72	(-0.48; 3.92)	0.124
NPI	-1.45	(-3.78; 0.88)	0.222
ADCS-CGIC	-0.22	-0.49; 0.05)	0.116
ZBI	-0.29	(-2.85; 2.27)	0.822

- For the NTB individual test z-scores, a statistically significant treatment effect, indicating improved performance with Lu AE58054, was seen for Go/No-Go at Week 24.
- Co-administration with Lu AE58054 decreased donepezil clearance with approximately 10%.

Safety Results

- The adverse event incidence is summarised below:

	Placebo		Lu AE58054	
	n	(%)	n	(%)
Patients treated	133		145	
Patients who died[a]	1	(0.8)	1	(0.7)
Patients with serious AEs (SAEs)	13	(9.8)	14	(9.7)
Patients with AEs	81	(60.9)	97	(66.9)
Patients with AEs leading to withdrawal	10	(7.5)	22	(15.2)
Total number of AEs	239		291	
Total number of SAEs	21		17	

a Occurred post-treatment

- During the treatment and follow-up periods, the incidence of TEAEs was slightly higher in the Lu AE58054 group (66%) than in the placebo group (59%). The TEAEs with an incidence ≥4% in the Lu AE58054 group and higher than that in the placebo group comprised: *γ-glutamyltransferase increased* (9.7%), *alanine aminotransferase increased* (6.2%), *benign prostatic hyperplasia* (5.3% [2 patients])), *dizziness* (4.8%), and *aggression*, *aspartate aminotransferase increased*, *headache*, *hypertension*, and *vomiting* (all 4.1%).
- Two patients died, 1 in each treatment group: a [redacted] man incurred a craniocerebral injury 9 days after last dose of Lu AE58054 and died 22 days later from bronchopneumonia and an [redacted] man died from bronchopneumonia approximately 2 months after last dose of placebo; both events were considered *not related* to treatment.
- A total of 14 (9.7%) patients in the Lu AE58054 group and 13 (9.8%) patients in the placebo group had one or more SAEs. There was no apparent pattern in the SAEs with respect to the distribution across SOCs or preferred terms. No SAE was reported in >1 patient in either treatment group, except for *syncope* (2 patients in the Lu AE58054 group), *femoral neck fracture* (2 patients in the placebo group), and *gastroenteritis* (2 patients in the placebo group). One patient (in the Lu AE58054 group) had *epilepsy* and 1 patient (in the placebo group) had *convulsion*.
- The proportion of patients who withdrew due to TEAEs in the Lu AE58054 group was 16% and 7.5% in the placebo group. The difference was almost entirely due to elevations in liver enzyme values.
- The TEAEs leading to withdrawal in ≥3 patients in the Lu AE58054 group were *alanine aminotransferase increased* (6 patients), *γ-glutamyltransferase increased* (4 patients), *dizziness* (3 patients), *hepatic enzyme increased* (3 patients), and *nausea* (3 patients). In the placebo group, none of the events led to withdrawal in ≥3 patients. There was no apparent pattern in the time to withdrawal for TEAEs other than those related to elevated liver enzyme values.
- In the Lu AE58054 group, the changes from baseline in ASAT, ALAT, alkaline phosphatase (AP), and gamma-glutamyltransferase (γ-GT) values were notable and greater than those in the placebo group. The elevated liver enzyme values were seen as early as Week 4, but most were seen at Week 6 or Week 8. A total of 13 patients had ASAT or ALAT >2 times ULN. For all these patients, the liver enzyme values subsequently decreased towards the reference range; for 6 patients during continued treatment and for the remaining 7 patients upon discontinuation of IMP, as per protocol amendments SA02 and SA03.
- The evaluation of the liver enzyme elevations did not identify any patients who met the criteria for potential drug-induced severe liver injury according to Hy's law. Furthermore, no baseline predictors for and no correlation of Lu AE58054 or donepezil exposure levels with ASAT or ALAT values >2 times ULN were identified. Finally, there was no clear indication of a certain type of liver injury underlying the observed liver enzyme abnormalities.
- For the remaining clinical safety laboratory tests and for the vital signs, weight, ECG parameters, and urinalysis, no clinically relevant mean changes over time or differences between the treatment groups were seen; the incidence of potentially clinically significant (PCS) values was low and similar in the two treatment groups.

Conclusions • Lu AE58054 (90 mg/day) was shown to be effective in improving cognitive function in donepezil-treated patients with moderate AD. This was supported by a trend toward improvement in functional and global clinical measures. • Treatment with Lu AE58054 as adjunctive to donepezil was safe and, with the exception of elevated transaminase values, well tolerated.
Date of the Report 17 December 2012
This study was conducted in compliance with the principles of *Good Clinical Practice*.