Synopsis – Study 12631A

Title of Study

Randomised, double-blind, placebo-controlled study of Lu AA24493 in patients with Friedreich's Ataxia to evaluate safety and tolerability, and to explore efficacy

Investigators

- 6 investigators at 6 centres in 3 countries
- *Signatory investigator* – Sylvia Boesch, MD, PhD, University Clinic Innsbruck, Innsbruck, Austria

Study Centres

- 6 centres – 1 in Austria, 3 in Germany, 2 in Italy

Publications

- None (as of the date of this report)

Study Period

- First patient first visit – 27 October 2009
- Last patient last visit – 11 March 2011

Objectives

Primary objective:

- to evaluate the safety and tolerability of 2 weeks of treatment with Lu AA24493 in patients with Friedreich's Ataxia (FRDA)

Secondary objectives:

- to explore biomarkers of efficacy (frataxin, 8-hydroxydeguanosine [8-OHdG], peroxides, malondialdehyde [MDA])
- to explore efficacy using neurological assessments (Scale for the Assessment and Rating of Ataxia [SARA] and Friedreich's Ataxia Rating Scale [FARS])
- to explore efficacy using the Clinical Global Impression (CGI) scales (Global Improvement [CGI-I] and Severity of Illness [CGI-S])
- to explore the population (pop) pharmacokinetic (PK) parameters of Lu AA24493
- to evaluate the immunogenicity of Lu AA24493

Methodology

- This was a multi-national, multi-centre, randomised, double-blind, parallel-group, placebo-controlled, fixed-dose study in men and women with FRDA.
- Following screening, the patients were randomised to a 2-week treatment period, followed by a 13-week follow-up period.
- At baseline, each patient was randomised to receive 6 intravenous (IV) administrations of placebo or Lu AA24493 (1:2, placebo to active) over 2 weeks (on Days 1, 3, 5, 8, 10 and 12).
- The patients were under supervision for 24 hours after the first and second administrations of the investigational medicinal product (IMP) and for 2 hours after subsequent administrations of the IMP.
- The first 3 patients were enrolled sequentially with at least 1 week between randomisations.
- After recruitment of the first 6 patients (2 to placebo and 4 to Lu AA24493), all of whom had completed all study visits, recruitment was temporarily stopped as pre-specified in order to allow a data monitoring committee (DMC) to review if recruitment could resume. Thereafter, a further 30 patients were recruited (1:2; placebo to Lu AA24493 randomisation).
- Blood samples for popPK analyses of Lu AA24493 were collected (reported separately).
- Neurological assessments and blood sampling for markers of efficacy were made throughout the treatment period and for 4 weeks post treatment.

Methodology (continued)

- Safety assessments and blood sampling for antibodies were performed throughout the treatment period and for at least 103 days post start of treatment.
- Depending on the presence and clinical significance of antibodies towards Lu AA24493, patients were to be followed up for blood screening of antibodies at monthly visits as long as deemed necessary by the DMC.

Number of Patients Planned and Analysed

- Patient disposition data are presented in Table 4, Table 60 and Listing 1.
  - 36 patients were planned for enrolment: 24 in the Lu AA24493 group; 12 in the placebo group
  - 36 patients were randomised, treated, and completed the study – 23 patients received Lu AA24493 and 13 patients received placebo; no patient was withdrawn from the study
  - 36 patients were analysed – 36 patients were included in the *all-patients-treated set* (APTS) and in the *full-analysis* set (FAS)

Diagnosis and Main Inclusion Criteria

- Men and women (aged ≥18 years) with FRDA, diagnosed according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) and with a genetic test demonstrating >400 GAA nucleotide triplet repeats on the shorter of the 2 frataxin alleles and a SARA (gait) sub-score ≤6, who had provided written informed consent

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

- Lu AA24493 – 325µg 3 times per week; IV bolus injection over 1 to 2 minutes; batch number 2186114 (Renschler 2021821)
- There was 100% IMP compliance in the study; all patients in the study received all IMP doses (Table 52, Table 53; Listing 6).

Duration of Treatment

- 2 weeks

Reference Therapy, Mode of Administration, Batch Number

- *Placebo* – 3 times per week; IV bolus injection over 1 to 2 minutes; batch number 2186115 (Renschler 2017713)

Efficacy Assessments

- Frataxin (blood and buccal), 8-OHdG (urine), peroxides (serum), and MDA (plasma) concentrations; ataxia scale (SARA, FARS) scores; and CGI-I and CGI-S scores

Safety Assessments

- Adverse events, clinical safety laboratory tests, vital signs, electrocardiograms (ECGs), weight/body mass index (BMI), physical and neurological examinations, and antibodies (blood)

Statistical Methodology

- The following data sets were used:
  - *All-patients-randomised set* (APRS) – all randomised patients
  - *All-patients-treated set* (APTS) – all randomised patients who received 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 any efficacy biomarker
- Efficacy analyses were based on the FAS and safety analyses were based on the APTS.
- Clinical examination, demographic, baseline characteristic, exposure to IMP, concomitant medication and withdrawal data were summarised by treatment and by other categorical information of interest using descriptive techniques.
- Adverse events were summarised by system organ class (SOC) and preferred term.
- Absolute values and changes from baseline in clinical safety laboratory tests, vital signs, ECG parameters, and weight/BMI were summarised by treatment and visit using descriptive techniques. Values outside the reference ranges and potentially clinically significant (PCS) values were flagged and tabulated when reference ranges were known.

Statistical Methodology (continued)

- As all efficacy analyses were exploratory; both 90% and 95% confidence intervals were presented for efficacy analyses.
- Descriptive statistics were determined on absolute values and change from baseline for all efficacy variables. For efficacy biomarkers descriptive statistics were also determined for the ratio and relative change from baseline.
- The difference between the two treatment groups for the biomarkers was estimated with a mixed model repeated measurement model (MMRM), an analysis of covariance (ANCOVA) model was used for sensitivity analysis. For distributional reasons, the difference was estimated for the change from baseline log-transformed values.
- For the efficacy rating scales, the difference in the change from baseline between the two treatment groups was estimated with an ANCOVA model.

Patient Demographics and Baseline Characteristics

- No clinically relevant differences were observed between the Lu AA24493 and placebo group at baseline with regard to age, sex, BMI or ethnicity (Table 1; Listing 2):
  - The mean age of patients was 27 years in the Lu AA24493 group and 29 years in the placebo group.
  - The proportion of men was similar (approximately 60%) in both treatment groups.
  - The mean BMI was similar (approximately 22 kg/m^2) in both treatment groups.
  - All patients were Caucasian.
- The treatment groups were also generally similar with regard to time since diagnosis, duration and severity of symptoms and FRDA trinucleotide repeat (that is GAA) sequence (Table 3; Listing 5).
  - The mean/median time since diagnosis was 8.7/9.5 years for patients in the Lu AA24493 group and 7.7/5.9 years for patients in the placebo group. Hence the Lu AA24493 group could potentially have included more severe patients even though the severity of symptoms was comparable.
  - The mean duration of symptoms was similar for both treatment groups (12 years) and most patients in both treatment groups had mild or moderate symptoms (Lu AA24493: 26% mild, 70% moderate; placebo: 39% mild, 62% moderate); severe symptoms were observed in 4% of patients in the Lu AA24493 group.
  - The majority of patients in both treatment groups had between 400 and 800 FRDA trinucleotide triplet repeat sequences (Lu AA24493: 83%; placebo: 92%); the mean number of repeat sequences was 608 in the Lu AA24493 group vs. 561 in the placebo group. A small percentage of patients (Lu AA24493: 17.4%; placebo: 7.7%) had >800 to 1000 repeat sequences; the mean number was 967 in the Lu AA24493 group vs. 999 in the placebo group.
- The treatment groups were also similar with regard to baseline clinical rating scores (SARA, FARS and CGI-S) (Table 3; Table 22 to Table 28; Listing 8 to Listing 10).
  - The mean baseline SARA and FARS total scores were similar in both groups: Lu AA24493 (17.30 and 72.25, respectively); placebo (16.33 and 67.12, respectively).
  - The mean baseline CGI-S scores were also similar: Lu AA24493 (4.1); placebo (3.9).

Efficacy Results

- Efficacy data are summarised in Table 5 to Table 35 (including Table 15a and Table 21a); Figure 1 to Figure 27; and Listing 7 to Listing 10.
  - No statistically significant differences from placebo were observed in the Lu AA24493 group with regard to least squares mean (LSM) changes from baseline in frataxin [blood and buccal], peroxides, 8-OHdG or MDA biomarkers on Day 15 (Table 11 to Table 15).

Efficacy Results (continued)

- Mean changes from baseline in biomarker values from baseline to Day 15 are presented for the FAS below:

Biomarker	Placebo	Lu AA24493
Frataxin (blood) (ng/mg total protein)		
n	9	19
Mean (SD) at baseline	5.49 (1.49)	5.44 (3.62)
Mean (SD) change from baseline	0.57 (1.49)	-0.04 (1.56)
Median change from baseline	1.15	0.23
Relative change from baseline (%)[a]	10.8	5.5
Frataxin (buccal) (ng/mg total protein)		
n	9	18
Mean (SD) at baseline	3.24 (1.65)	2.88 (1.03)
Mean (SD) change from baseline	-0.36 (0.86)	-0.08 (1.03)
Median change from baseline	-0.35	-0.11
Relative change from baseline (%)[a]	-5.4	-3.3
8-hydroxydeguanosine (ng/mL)		
n	13	23
Mean (SD) at baseline	83.6 (41.8)	100.0 (44.7)
Mean (SD) change from baseline	-2.6 (48.9)	2.5 (64.0)
Median change from baseline	0.0	7.0
Relative change from baseline (%)[a]	5.0	-3.7
Peroxides (μmol/L)		
n	11	21
Mean (SD) at baseline	193.47 (136.49)	245.89 (329.67)
Mean (SD) change from baseline	-36.24 (115.10)	-50.60 (201.66)
Median change from baseline	-5.40	-2.10
Relative change from baseline (%)[a]	-28.3	-12.7
Malondialdehyde(μmol/L)		
n	8	14
Mean (SD) at baseline	4.65 (0.85)	4.19 (0.53)
Mean (SD) change from baseline	0.86 (2.02)	1.09 (1.71)
Median change from baseline	0.50	0.00
Relative change from baseline (%)[a]	14.8	20.7

Source: Table 5 to Table 9

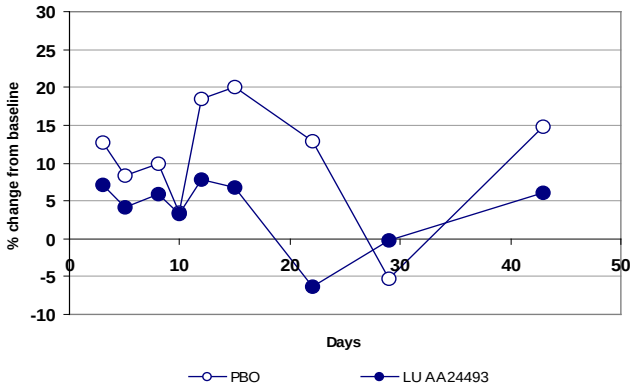
a Relative change from baseline = (exp [log YT - log YB] -1) × 100%, where YT is the value at that particular visit and YB is the value at baseline

Frataxin (blood and buccal)

- No statistically significant differences were observed between the treatment groups with regard to LSM changes from baseline in frataxin blood or buccal concentrations on Day 15 (following 2 weeks of treatment); or Days 22, 29 or 43 (Table 11 and Table 12).
- Small fluctuations in mean blood and buccal frataxin concentrations were observed during the treatment and follow-up period in both treatment groups; however, no meaningful trends were observed over time (Days 3, 5, 8, 10, 12, 15, 22, 29 and 43) in either treatment group (Table 5 to Table 6; Listing 7).
- On Day 15, relative increases (that is improvements) from baseline in mean blood frataxin concentrations were observed in the Lu AA24493 and placebo groups (5.5% vs. 10.8%). Relative increases from baseline were also observed at all other timepoints, except for Day 22 in the Lu AA24493 group and Day 29 in the placebo group when relative mean decreases (of -3.0%) from baseline were observed (Table 5; Listing 7). A plot of the median relative change from baseline in frataxin blood concentration is presented by treatment group and nominal timepoint below, which generally indicates greater relative increases from baseline in the placebo group compared with the Lu AA24493 group at most timepoints.

Efficacy Results (continued)

Plot of median relative change of the biomarker frataxin in blood by treatment group and nominal timepoint



Source: Figure 12

- On Day 15, relative decreases (that is worsening) from baseline in mean buccal frataxin concentrations were observed in the Lu AA24493 and placebo groups (-3.3% vs -5.4%). Relative decreases from baseline were also observed at all other timepoints except for Days 5, 8, 10 and 29 (range: 0.9 to 6.0%) in the Lu AA24493 group and Days 5, 43 and the last assessment day (range: 0.5% to 12.0%) in the placebo group when relative increases from baseline were observed (Table 6; Listing 7).

Other biomarkers (8-OHdG, peroxides, MDA, frataxin mRNA)

- No statistically significant differences from placebo were observed in the Lu AA24493 group with regard to LSM changes from baseline in peroxides or MDA at Days 15, 22, 29 or 43, or in 8-OHdG at Days 15 or 43 (Table 13 to Table 15; Listing 7).
- No meaningful trends were observed over time (Days 3, 5, 8, 10, 12, 15, 22, 29 and 43) in either treatment group with regard to 8-OHdG, peroxides or MDA concentrations.
- On Day 15, a relative decrease (that is improvement) from baseline in mean 8-OHdG concentrations was observed in the Lu AA24493 group whereas a relative increase was seen in the placebo group (-3.7% vs. 5.0%). However, relative increases from baseline were observed at all other timepoints except for Day 43 and the last assessment day (-8.7% for both) in the Lu AA24493 group; and Days 10 and 29 (range: -2.6% to -15.0%) in the placebo group when relative decreases from baseline were observed; and Day 3 in the Lu AA24493 group when no change from baseline was observed (Table 8; Listing 7).
- On Day 15, relative decreases (that is improvement) from baseline in mean peroxide concentrations were observed in the Lu AA24493 and the placebo groups (-12.7% vs. -28.3%). Relative decreases from baseline were observed at all other timepoints in both treatment groups (Table 7; Listing 7).
- On Day 15, relative increases (that is worsening) from baseline in MDA concentrations were observed in the Lu AA24493 and placebo groups (20.7% vs. 14.8%). Relative increases from baseline were also observed at all other timepoints, except for Day 8 (-1.3%) in the Lu AA24493 group; and Days 3, 8, 12 and 29 (range: -1.1% to -9.0%) in the placebo group when relative decreases from baseline were observed (Table 9; Listing 7).
- On Day 12, no statistically significant differences from placebo were observed in the Lu AA24493 group with regard to LSM changes from baseline in frataxin mRNA concentrations (Table 16).
- On Day 12, actual increases from baseline (that is improvements) in mean frataxin mRNA concentrations were observed in the Lu AA24493 and placebo groups (1.29 vs 7.36); no other timepoints were presented (Table 10; Listing 7).

Efficacy Results (continued)

Clinical rating scales (SARA, FARS and CGI)

- No statistically significant differences from placebo were observed in the Lu AA24493 group with regard to LSM changes from baseline in clinical rating scores to Days 12 and 43 (SARA, FARS and CGI-S) (Table 29 to Table 35; Listing 8 to Listing 10).
- No meaningful trends were observed over time (Days 8, 12, 22, 43 and last assessment) in either treatment group with regard to the clinical rating scores (Table 22 to Table 28).
- On Day 12, actual decreases (that is improvements) from baseline in mean total SARA scores were observed in the Lu AA24493 and placebo groups (-0.57 vs -0.83). Decreases from baseline were observed at all other timepoints except Day 8 in the placebo group when no change from baseline occurred and Day 22 in the placebo group when an increase from baseline of 0.50 was observed (Table 22; Listing 8).
- On Day 12, actual decreases (that is improvements) from baseline in total FARS scores were observed in the Lu AA24493 and placebo groups (-1.64 vs. -1.73). Decreases from baseline were observed at all other timepoints. These changes were mainly due to changes in the daily activity and neurological examination subscores; the functional staging subscores remained relatively unchanged (Table 23 to Table 26, Listing 9).
- On Day 12, no change from baseline in mean CGI-S scores was observed. No change in CGI-S score occurred at any timepoint. The mean CGI-I score was similar in the Lu AA24493 and placebo groups on Day 12 (3.9 vs. 3.7); similar scores were observed at all other timepoints (Table 27 and Table 28; Listing 10).
- Overall, the efficacy data indicated no notable differences between the Lu AA24493 and placebo groups.

Safety Results

- Adverse events are presented in Table 36 to Table 38 and Listing 11 to Listing 13.
- Clinically safety laboratory tests are presented in Table 39 to Table 51.
- Vital signs are presented in Table 54 and Table 55 and Listing 28, Listing 29 and Listing 30.
- ECGs are presented in Table 56 and Table 57 and Listing 31.
- Echocardiogram data are presented in Listing 27.
- Physical and neurological examination data are presented in Table 58 and Table 59.
- The adverse event incidence in the APTS is summarised below:

	Placebo N=13 n (%)	Lu AA24493 N=23 n (%)
Patients treated	13 (100.0)	23 (100.0)
Patients with AEs	13 (100.0)	22 (95.7)
Total number of AEs	54	78
Patients who died	0 (0.0)	0 (0.0)
Patients with SAEs	0 (0.0)	0 (0.0)

AE: adverse event; SAE: serious adverse event
Source: Table 36; Listing 11, Listing 12

- In the placebo group, all 13 patients had a total of 54 adverse events; in the Lu AA24493 group, 22 patients had 78 adverse events.
- There were no serious adverse events and no patients withdrew due to an adverse event (Listing 12 and Listing 13).
- The SOCs with the highest incidences of adverse events were as follows: *infections and infestations* (Lu AA24493: 10 patients; placebo: 5 patients); *nervous system disorders* (Lu AA24493: 7 patients; placebo: 5 patients); *gastrointestinal disorders* (Lu AA24493: 6 patients; placebo: 4 patients); and *injury, poisoning and procedural complications* (Lu AA24493: 3 patients; placebo: 7 patients) (Table 36).
- The overall pattern of adverse events was similar in the two treatment groups.
- No clinically relevant differences were observed between the treatment groups with regard to clinical safety laboratory tests; vital signs; ECGs; or physical and neurological examinations.
- No anti-Lu AA24493 antibodies were elicited by any of the 23 patients who received Lu AA24493 (Listing 32a to Listing 32c).

Safety Results (continued)

- The adverse events that occurred in >2 patients in either treatment group are summarised for the APTS by preferred term below.

Preferred Term (MedDRA Version 13.1)	Placebo N=13 n (%)	Lu AA24493 N=23 n (%)
Any AE	11 (84.6)	18 (78.3)
Headache	3 (23.1)	6 (26.1)
Nasopharyngitis	3 (23.1)	4 (17.4)
Influenza	1 (7.7)	3 (13.0)
Oropharyngeal pain	2 (15.4)	3 (13.0)
Diarrhoea	0 (0.0)	3 (13.0)
Dysmenorrhoea	0 (0.0)	3 (13.0)
Cough	1 (7.7)	2 (8.7)
Fall	3 (23.1)	2 (8.7)
Pruritus	2 (15.4)	2 (8.7)
Pyrexia	2 (15.4)	2 (8.7)
Accidental overdose	3 (23.1)	1 (4.3)
Gastroenteritis	3 (23.1)	0 (0.0)
Nausea	3 (23.1)	0 (0.0)

AE: adverse event
Source: Table 38, Listing 11

Conclusions

- Overall, patients treated with Lu AA24493 had a similar safety profile to those treated with placebo.
- Six single doses of IV dose at a fixed dose of 325µg of Lu AA24493 were found to be safe and well tolerated by all patients over the 2-week treatment period.
- No safety concerns were raised based on the adverse events, clinical safety laboratory tests or other safety assessments.
- Overall, no changes in the exploratory efficacy variables were observed for patients treated with Lu AA24493 compared with those in the placebo group.
- The frataxin biomarker, as analysed via blood, buccal and frataxin mRNA assessments, did not reveal any statistically or clinically significant differences from placebo in the Lu AA24493 group during the treatment or follow-up period; no consistent changes occurred over time in either group.
- The other oxidative stress biomarkers, such as 8-OHdG, MDA and peroxides, also did not reveal any statistically or clinically significant differences from placebo in favour of the Lu AA24493 group over the treatment or follow-up period; no consistent changes occurred over time in either group.
- Consistently with this, the neurological rating scales SARA and FARS (including FARS subscores) did not show any statistically or clinically significant differences from placebo in the Lu AA24493 group. In addition, patient outcome as assessed by CGI-S and CGI-I remained stable over the study period.
- Lu AA24493 did not elicit antibodies in any of the 23 patients who received Lu AA24493.

Date of the Report

11 November 2011

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