Synopsis – Study 12708A

Study Title An open-label study evaluating the pharmacokinetics and tolerability of Lu AA21004 in connection with multiple oral dosing of Lu AA21004 in child and adolescent patients with a DSM-IV-TR™ diagnosis of depressive or anxiety disorder
Investigators 7 principal investigators at 7 sites in 2 countries *Signatory investigator* – [redacted]
Study Sites 7 sites – 6 in the United States and 1 in Germany
Publications None (as of the date of this report)
Study Period *First patient first visit* – 26 April 2012 (the date when the first *Informed Consent Form* was signed) *Last patient last visit* – 8 June 2015 (the date of the last protocol-specified contact with any patient)
Objectives • *Main objectives*: – evaluate the pharmacokinetics and tolerability of vortioxetine, and its metabolites Lu AA34443 and Lu AA39835, in connection with multiple oral dosing in child and adolescent patients with a DSM-IV-TR™ diagnosis of a depressive or anxiety disorder – assess the safety of vortioxetine – provide supportive information for dose regimen in paediatric efficacy and safety studies with vortioxetine • In addition, the specific objective of the 6-month extension period was to: – allow for continued Lu AA21004 treatment up to 6 months in study design with predefined safety and efficacy evaluations
Study Methodology • This was an interventional, prospective, multi-national, multi-site, open-label, multiple-dose study evaluating the pharmacokinetics and tolerability of vortioxetine in child and adolescent patients with a DSM-IV-TR™ diagnosis of depressive or anxiety disorder. • The study consisted of a main study period and an optional 6-month extension period. *Main Study Period* • The main part of the study consisted of 8 cohorts, each including 6 patients. Adolescent patients ≥12 and <18 years of age were allocated to Adolescent Cohorts (ACs) 1 to 4 and children ≥7 and <12 years of age were allocated to Child Cohorts (CCs) 1 to 4.

Study Methodology (continued)

- The main study period consisted of:
  - a Screening/Washout Period – Days -14 to -2
  - a Safety Baseline – Day -1
  - a Treatment Period – a 14- to 20-day treatment period in which the patients received the assigned dose of 5, 10, 15, or 20 mg vortioxetine once daily for 14 days
  - a Safety Follow-up Visit (Visit 11) – 14 days after the last dose of vortioxetine (only for patients not continuing in the extension period)
- Vortioxetine was up-titrated for 2, 4, or 6 days in patients assigned to 10, 15, or 20 mg/day, respectively, as shown below:

Cohort	Initial Dose (2 days/dose)			Assigned Dose (14 days)
AC1/CC1	-	-	-	5mg/day
AC2/CC2	-	-	5mg/day	10mg/day
AC3/CC3	-	5mg/day	10mg/day	15mg/day
AC4/CC4	5mg/day	10mg/day	15mg/day	20mg/day

- The cohorts were initiated in the following order: AC1, AC2, CC1, AC3, CC2, AC4, CC3, and CC4. In this way, the adolescents were exposed to a specific dose of vortioxetine before the children received the same dose. The preliminary safety, tolerability, and pharmacokinetic data from each cohort were evaluated by an external data safety monitoring board (DSMB). The DSMB approved the progression to the next cohort.
- Patients were preferably confined to the investigational site from the Safety Baseline (Day -1) until the last blood sample for pharmacokinetic analysis had been collected on Day 2. The patients were allowed to leave the site if, in the opinion of the investigator, they were considered stable and if acceptable tolerability of vortioxetine was confirmed by the investigator. The patients were also confined to the site during the last 2 days of the main study period, from the morning of the last treatment day until all study-related assessments had been completed on the following morning.
- Separation of the child from the parent(s)/legal representative during the hospitalisation was to be avoided. Their parent(s)/legal representative(s) were to stay at the site or be accommodated close to the site. If the parents were not present, the child was always to be accompanied by a trial-related staff member who could provide reassurance.
- The patients either received a phone call or attended site visits on Days 4 and 6. For patients with a treatment duration exceeding 14 days, that is, for patients receiving 10, 15, or 20 mg/day vortioxetine, an additional site visit was scheduled for Day 13. Patients who withdrew from the study were asked to attend a Withdrawal Visit as soon as possible after withdrawal.
- At predetermined time points on Day 1 and on the last day of dosing in the main study period, blood samples were drawn for determination of the plasma concentrations of vortioxetine and its metabolites Lu AA39835 and Lu AA34443.
- Efficacy (Clinical Global Impression [CGI]) and safety data were collected throughout the main study period.
- In the main part of the study, the total study duration per patient from baseline to the end of follow-up was approximately 4 to 5 weeks.

Extension Period

- Patients who completed the main study period were, if judged advisable by the investigator, offered to continue in an optional, 6-month, open-label, treatment extension with flexible-dose design.
- The extension period consisted of:
  - a Screening/Baseline procedures – Day 0 (Visit 12)
  - Treatment Period – 24-week treatment period
  - a Safety Follow-up Visit – 14 days after the last dose of vortioxetine

Study Methodology (continued)

- For the patients entering the extension period, Visit 12 (first visit in the extension period) was scheduled on the last day of the treatment period in the main study period. The patients then returned to the site for safety and efficacy assessments every 4 weeks until the end of the 24-week treatment period.
- During the 24-week treatment period, patients initially continued on the assigned dose, but the dose could be adjusted based on the investigator's judgement.
- The dose levels used in the extension period were based on the recommendations from the DSMB.

Number of Patients Planned

48 patients were planned for enrolment: 24 adolescents and 24 children (6 patients in each cohort)

Diagnosis and Main Selection Criterion

Adolescents and children (boys and girls) for whom treatment with antidepressant therapy was warranted, as judged by the investigator, and who:

Main Study Period

- had a diagnosis of depressive or anxiety disorder according to DSM-IV-TR™ criteria
- were between 7 and 17 years of age (extremes included) at Screening
- was able to understand the *Informed Assent Form* and his or her parent(s)/legal representative (s) were able to read and understand the *Informed Consent Form*

Extension Period

- had completed the main study period and were offered to continue treatment for another 6 months, if judged advisable by the investigator

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

Vortioxetine (Lu AA21004) – 5, 10, 15, or 20 mg/day; tablets, orally; batch Nos.: 5 mg: PD 1887, PD 1925, 2345912, 2373927; 10 mg: PD 1888, PD 1926, 2345914, 2391984; 15 mg: PD 1890, PD 1931, 2345916, 2391960; 20 mg: PD 1892, PD 1935, 2345919, 2373931

Duration of Treatment

Main study period: 14 to 20 days, including 2, 4, or 6 days of up-titration for patients assigned to 10, 15, or 20 mg/day vortioxetine, respectively

Extension period: 24 weeks

Pharmacokinetic Assessments

Blood sampling for plasma quantification of vortioxetine and its metabolites Lu AA34443 and Lu AA39835 (main study period only)

Efficacy Assessments

- *Clinical Global Impression – Severity of Illness* (CGI-S)
- *Clinical Global Impression – Global Improvement* (CGI-I)

Safety Assessments

- Adverse events (AEs), clinical safety laboratory tests, vital signs, weight, electrocardiograms (ECGs), and physical examinations
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Paediatric Adverse Events Rating Scale (PAERS)

Endpoints

- *Main endpoints*:
  - pharmacokinetics of vortioxetine and its metabolites Lu AA34443 and Lu AA39835
  - adverse events
  - absolute values and changes from baseline in clinical safety laboratory tests, vital signs, weight, and ECG parameters
  - potentially clinically significant (PCS) clinical safety laboratory test values, vital sign values, weight, and ECG parameter values
  - PAERS
  - C-SSRS
- *Secondary endpoints*:
  - changes from baseline in CGI-S scores
  - CGI-I scores

Statistical Methodology

- The following analysis sets were used:
  - *all-patients-treated set* (APTS) – all patients who took at least one dose of investigational medicinal product (IMP)
  - *full-analysis set* (FAS) – all patients in the APTS who had a valid baseline assessment and at least one valid post-baseline assessment of the CGI-S total score
  - *PK-analysis set* (PKS) – all patients in the APTS contributing both with Day 1 pre-dose data and sufficient post-dose pharmacokinetic data for estimation of the pharmacokinetic parameters
  - *extension set* (EXTS) – all patients in the APTS who continued in the optional 6-month extension period
- Unless otherwise indicated, in the main study period, the efficacy analyses were based on the FAS, the pharmacokinetic analyses were based on the PKS, and the safety analyses were based on the APTS. In the extension period, the efficacy and safety analyses were based on the EXTS.
- The pharmacokinetic, efficacy and safety data were summarised using descriptive statistics. The pharmacokinetics of vortioxetine and Lu AA34443 were evaluated by means of non-linear mixed effect analysis (population pharmacokinetics [popPK]). Since more than 50% of the Lu AA39835 plasma concentrations were below the lower limit of quantification, no pharmacokinetic analyses were performed for Lu AA39835.
- In order to reduce the complexity of the popPK model and increase the chance of convergence, each analyte, that is, vortioxetine and Lu AA34443, were modelled separately instead performing of a full integrated model. The initial structural models were a 2-compartment model for vortioxetine and a 1-compartment model for Lu AA34443 with first-order absorption and elimination and lag time. Individual values for CL/F, V_{ss}/F (V2+V3) and the secondary parameters t_{max}, C_{max}, $AUC_{0\text{-}24h}$, $t_{½}$ and metabolic ratio ~~(MR)~~ were estimated.
- The impact of the covariates age (children or adolescents), sex, body size (weight, height, body mass index [BMI], and lean body mass), attention deficit hyperactivity disorder (ADHD) diagnosis, and concomitant medication with a stimulant on the pharmacokinetic parameters was investigated. The stability and predictability of the final models were evaluated using bootstrap analysis, visual predictive check and normalised prediction distribution error plots.
- The proportion of patients who stayed on the same dose and the proportion of patients who changed dose during the extension period are summarised for the extension period. For patients who had their dose adjusted, the duration (number of days) on each dose was summarised.
- For the patients who continued in the extension period, exposure data, all efficacy results, and all safety results, except adverse events and PAERS, are presented for the entire study (that is, from first dose of IMP to the end of the extension period); patient disposition, concomitant medication, adverse events, and PAERS results are presented for the extension period only.

Patient Disposition and Analysis Sets

Main Study Period

- 48 patients were enrolled in the main study period: 24 in the adolescent cohorts and 24 in the child cohorts (6 patients in each of the 8 cohorts):

	AC1	AC2	AC3	AC4	CC1	CC2	CC3	CC4	Total
	n	n	n	n	n	n	n	n	n
All Patients Enrolled Set	6	6	6	6	6	6	6	6	48
All Patients Treated Set	6	6	6	6	6	6	6	6	48
Patients Completed	5	6	6	6	6	6	6	6	47
Patients withdrawn	1	0	0	0	0	0	0	0	1
Efficacy and PK Data Sets									
Full Analysis Set	6	6	6	6	6	6	6	6	48
PK Set	6	6	6	6	6	6	6	6	48

- All 48 patients were analysed and included in the APTS, FAS, and PKS in the main study period.

Extension Period

- 41 patients continued in the extension period: 22 in the adolescent cohorts and 19 in the child cohorts:

	AC1	AC2	AC3	AC4	CC1	CC2	CC3	CC4	Total
	n	n	n	n	n	n	n	n	n
All Patients Treated Extension Set	4	6	6	6	4	5	5	5	41
Patients Completed	1	2	2	4	3	3	2	3	20
Patients withdrawn	3	4	4	2	1	2	3	2	21

- All 41 patients were analysed and included in the EXTS.

Demography and Baseline Characteristics of the Study Population

Main Study Period

- The adolescents were aged between 12 and 17 years and the mean age for each cohort ranged between 14.8 and 15.7 years. An equal number of girls and boys (3:3) were enrolled in AC1 and AC2, while more girls than boys were enrolled in AC3 (5:1) and AC4 (4:2). The mean height, weight, and BMI were similar across the adolescent cohorts, except for a lower mean weight in AC4 (55 kg) than in AC1 to AC3 (72 to 79 kg).
- The children were aged between 7 and 11 years and the mean age for each cohort ranged between 9.7 and 10.5 years. An equal number of girls and boys (3:3) were enrolled in CC1 and CC2, while fewer boys than girls (2:4) were enrolled in CC3 and CC4. The mean height, weight, and BMI were similar across the child cohorts.
- Twelve girls and 5 boys in the adolescent cohorts were postpubertal, that is, they had a Tanner total score of 10. All children were prepubertal.
- The individual CGI-S scores at Baseline ranged between 3 and 5 points, which indicated that the patients were *mildly* to *markedly ill*. There were no clinically relevant differences in the mean baseline CGI-S scores between the cohorts.

Extension Period

- The demographics and other baseline characteristics of patients who continued in the extension period were similar to those in the main study period.

Pharmacokinetic Results (Main Study Period)

- The pharmacokinetic analyses were performed for vortioxetine and the major, pharmacologically inactive metabolite Lu AA34443. Since more than 50% of the Lu AA39835 plasma concentrations were below the lower limit of quantification, no pharmacokinetic analyses were performed for the minor metabolite Lu AA39835.
- The median pharmacokinetic parameters of vortioxetine on the last day of dosing in the main study period are summarised for the adolescent cohorts below:

PK parameter	AC1 (5 mg/day) n=5	AC2 (10 mg/day) n=6	AC3 (15 mg/day) n=6	AC4 (20 mg/day) n=6	Overall AC1 to AC4 n=23
C_{max} (ng/mL)[a]	4.3 ± 3.7	7.8 ± 2.8	15 ± 6.2	16 ± 8.1	-
t_{max} (h)[a]	5.0 ± 3.7	7.9 ± 2.3	6.5 ± 3.8	4.0 ± 2.4	5.1 ± 3.0
AUC_{0-24h} (ng·h/mL)[b]	82 ± 71	144 ± 60	283 ± 115	304 ± 143	-
CL/F (L/h)[b]	60 ± 55	50 ± 16	50 ± 23	61 ± 20	59 ± 30
V_{ss}/F (L)[b]	3368 ± 286	3866 ± 1381	3421 ± 1077	2719 ± 504	3410 ± 990
$t_{1/2}$ (h)[b]	46 ± 33	56 ± 19	50 ± 16	40 ± 10	47 ± 20

Median values ± standard deviation are presented.

a based on observed values
b based on popPK analysis

- The median pharmacokinetic parameters of vortioxetine on the last day of dosing in the main study period are summarised for the child cohorts below:

PK parameter	CC1 (5 mg/day) n=6	CC2 (10 mg/day) n=6	CC3 (15 mg/day) n=6	CC4 (20 mg/day) n=6	Overall CC1 to CC4 n=24
C_{max} (ng/mL)[a]	5.0 ± 3.3	14 ± 8.2	26 ± 21	31 ± 20	-
t_{max} (h)[a]	5.0 ± 1.5	6.4 ± 2.1	8.0 ± 2.6	6.5 ± 2.7	6.4 ± 2.3
AUC_{0-24h} (ng·h/mL)[b]	89 ± 66	261 ± 137	492 ± 373	562 ± 374	-
CL/F (L/h)[b]	50 ± 16	42 ± 25	29 ± 33	34 ± 17	38 ± 23
V_{ss}/F (L)[b]	2754 ± 348	2597 ± 430	2515 ± 289	2232 ± 712	2648 ± 471
$t_{1/2}$ (h)[b]	45 ± 27	52 ± 18	71 ± 52	62 ± 23	60 ± 33

Median values ± standard deviation are presented.

a based on observed values
b based on popPK analysis

- The exposure of vortioxetine and its metabolite Lu AA34443 (last day of dosing) seemed to increase with dose in an approximately dose-proportional manner in both children and adolescents. The exposures to vortioxetine and its metabolite Lu AA34443, in terms of median C_{max} and AUC, were generally lower in the adolescent cohorts than in the child cohorts.
- The median CL/F of vortioxetine was 38 L/h for the child cohorts and 59 L/h for the adolescent cohorts, while the median $t_{½}$ was 60 hours in children and 47 hours in adolescents.
- In the popPK analysis, statistically significant ($p<0.01$) relationships were found between the volume of distribution (V_{SS}/F) and the patients' weight and between CL/F and the patients' age, whereas sex, height, ADHD diagnosis, and concomitant treatment with a stimulant (ADHD medication) had no statistically significant impact on the pharmacokinetics of vortioxetine.

Efficacy Results

Main Study Period

- There was a general improvement in the CGI-S scores on Day 14 compared to baseline. The mean CGI-S scores were lower on Day 14 than at baseline for all cohorts, with the mean change from baseline ranging from -0.8 to -1.5 points.
- Similarly, the CGI-I indicated an improvement in the patients' illness, with the mean CGI-I scores ranging from 2.2 to 3.0 points on Day 14.
- There were no apparent differences in CGI-S or CGI-I between adolescents and children or between dose groups.

Entire Study

- Based on observed cases, there was a general improvement in the CGI-S scores on Day 182 compared to baseline in patients who continued in the extension period. The mean CGI-S scores were lower on Day 182 than at baseline for all cohorts, with the mean change from baseline ranging from -1.0 to -3.0 points. Similarly, the CGI-I indicated an improvement in the patients' illness, with the mean CGI-I scores ranging from 1.8 (*much improved*) to 3.0 points (*minimally improved*) on Day 182. Based on last observation carried forward, the CGI-S and CGI-I scores showed similar results. There were no differences in the changes from baseline in CGI-S or in CGI-I scores between adolescents and children or between dose groups.

Safety Results

Main Study Period

- The adverse event incidence in the main study period is summarised by cohort below:

	AC1	AC2	AC3	AC4	CC1	CC2	CC3	CC4	Total
	n	n	n	n	n	n	n	n	n
Patients treated	6	6	6	6	6	6	6	6	48
Patients with TEAEs	4	4	5	5	5	5	5	4	37
Patients with SAEs	0	0	0	0	0	0	0	0	0
Total number of TEAEs	23	13	16	14	21	8	19	7	121
Total number of SAEs	0	0	0	0	0	0	0	0	0

TEAE = treatment-emergent adverse event; SAE = serious adverse event

- No SAEs occurred during the main study period and none of the patients had an adverse event leading to withdrawal. Overall, the majority of the patients (77%) had one or more TEAE during the main study period.
- Overall, the vast majority (approximately 80%) of the TEAEs were *mild* and one of the events was *severe*. There were no apparent differences in the intensity of the TEAEs between the age or dose groups. The majority of the TEAEs had an onset during the first days of dosing.
- TEAEs with an overall incidence ≥10% in the main study period are summarised below:

Preferred Term	Adolescents		Children		Total	
(MedDRA Version 16.1)	n	(%)	n	(%)	n	(%)
Patients treated	24		24		48	
Headache	7	(29)	5	(21)	12	(25)
Nausea	8	(33)	3	(13)	11	(23)
Sedation	7	(29)	4	(17)	11	(23)
Abdominal pain upper	1	(4)	7	(29)	8	(17)
Fatigue	5	(21)	1	(4)	6	(13)
Vomiting	2	(8)	4	(17)	6	(13)

- The TEAEs with the highest overall incidence (≥10%) during the main study period were headache, nausea, sedation, abdominal pain upper, fatigue, and vomiting.

Safety Results (continued)

Extension Period

- The adverse event incidence in the extension period is summarised by cohort below:

	AC1	AC2	AC3	AC4	CC1	CC2	CC3	CC4	Total
	n	n	n	n	n	n	n	n	n
Patients treated	4	6	6	6	4	5	5	5	41
Patients with TEAEs	4	4	6	6	3	4	5	3	35
Patients with SAEs	0	0	1	2	0	0	0	0	3
Patients with AEs leading to withdrawal	1	1	1	1	0	0	0	0	4
Deaths	0	0	0	0	0	0	0	0	0
Total number of TEAEs	8	11	16	22	12	4	12	4	89
Total number of SAEs	0	0	1	3	0	0	0	0	4
Total number of AEs leading to withdrawal	1	1	1	1	0	0	0	0	4

TEAE = treatment-emergent adverse event; SAE = serious adverse event

- A total of 3 patients had SAEs and 4 patients had an adverse event leading to withdrawal. Overall, 85% (35 patients) of the patients had one or more TEAE during the extension period. In patients who had SAEs, all the SAEs were considered *not related* to IMP by the investigator. One patient had *suicidal ideation*, 1 patient had an *intentional overdose* and *suicide attempt*, and 1 patient had *appendicitis*.
- For most of the patients who had TEAEs, the events were either *mild* or *moderate*; the events were *severe* in 5 patients. Approximately half of the TEAEs were considered *related* to IMP. There was no relationship between the intensity of TEAEs and age or dose.
- TEAEs with an overall incidence ≥10% in the extension period are summarised below:

Preferred Term	Adolescents		Children		Total	
(MedDRA Version 16.1)	n	(%)	n	(%)	n	(%)
Patients treated	22		19		41	
Headache	8	(36)	3	(16)	11	(27)
Nausea	7	(32)	1	(5.3)	8	(20)
Dysmenorrhoea (sex specific)	3	(14)	1	(5.3)	4	(19)
Vomiting	3	(14)	3	(16)	6	(15)

- The TEAEs with the highest overall incidence (≥10%) during the extension period were headache, nausea, dysmenorrhoea, and vomiting.

Safety Results (continued)

Entire Study

- There were no clinically relevant changes in the mean clinical safety laboratory values, vital signs, weight changes, or ECG parameter values and there were no differences in these variables between the age groups or cohorts. No PCS clinical safety laboratory values were reported in the entire study and no PCS weight changes were reported in the main study period. The following post-baseline PCS vital signs, weight changes, and ECG parameter values were reported:
  - In the main study period, a total of 19 patients (11 adolescents and 8 children) had PCS vital signs values; the most frequent PCS vital signs values were PCS low and PCS high pulse rate. The only ECG parameter for which a PCS value was observed was heart rate (PCS low); it was reported in 3 patients.
  - In patients who continued in the extension period, a total of 21 patients (13 adolescents and 8 children) had PCS vital signs values in the entire study (some of which were already reported in the main study period); the most frequent post-baseline PCS vital signs was PCS low and PCS high pulse rate. As for body weight, of the 14 patients (5 adolescents and 9 children) who had PCS weight changes, the weight change was PCS high in 12 patients. The only ECG parameter for which a PCS value was observed was heart rate (PCS low); it was reported in a total of 6 patients (5 adolescents and 1 child) in the entire study (some of which were already reported in the main study period).
- Based on the C-SSRS:
  - In the main study period, no suicidal behaviour or preparatory actions towards suicidal behaviour were reported at baseline or during the main study period. A total of 4 patients (3 adolescents and 1 child) reported suicidal ideation (a wish to be dead and/or non-specific suicidal thoughts) during the main study period; 3 out of these 4 patients reported suicidal ideation also at baseline.
  - In the extension period, 5 patients reported suicidal ideation (a wish to be dead [4 patients] or active suicidal ideation without intent to act [1 patient]), 2 patients had non-suicidal self-injurious behaviour, and 1 patient had suicidal behaviour (non-fatal suicide attempt), all of whom were adolescents. One of these patients reported a wish to be dead and 1 patient had non-suicidal self-injurious behaviour also during the main study period.
- There was generally a decrease over time in the incidence and intensity of the signs and symptoms collected using the PAERS.

Conclusions

- The pharmacokinetic evaluation in the main study period showed that the exposures to vortioxetine and its metabolite Lu AA34443, in terms of C_{max} and AUC, were generally lower in the adolescents than in the children. The population pharmacokinetic analysis showed a statistically significant increase in vortioxetine clearance with age and a statistically significant effect of weight on the volume of distribution.
- Treatment with vortioxetine at doses of 5, 10, 15, or 20 mg/day for 14 days was safe and well tolerated in children and adolescents with depressive or anxiety disorders and data from the 6-month extension period support this conclusion.
- The pharmacokinetic and safety data suggests that the doses tested (5 to 20 mg/day vortioxetine) and the up-titration scheme employed in the main study period are appropriate in paediatric efficacy and safety studies with vortioxetine. The results of the extension period provide additional support for the chosen dosing regimen.

Report Dates

21 April 2015 (Integrated Clinical Study Report)

25 June 2015 (Amendment 1)

8 December 2015 (Addendum 1)

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