Synopsis – Study 12473A

Title of Study A double-blind, randomised, placebo-controlled, multicentre, relapse-prevention study with Lu AA21004 in patients with Generalised Anxiety Disorder
Investigators 80 investigators at 80 centres in 10 countries *Signatory investigator* – David S Baldwin, MD, University of Southampton, Southampton, United Kingdom
Study Centres 80 centres – 11 in Argentina, 8 in Chile, 7 in Colombia, 4 in Costa Rica, 3 in Estonia, 12 in Finland, 12 in France, 6 in Hungary, 5 in Russian Federation, and 12 in South Africa
Publications None (as of the date of this report)
Study Period *First patient first visit* – 20 October 2008 *Last patient last visit* – 14 June 2010
Objectives • *Primary objectives:* – to evaluate the long-term maintenance of efficacy of Lu AA21004 5 and 10mg/day *versus* placebo by a comparison of the time to relapse in patients with Generalised Anxiety Disorder (GAD) who responded to acute treatment with Lu AA21004 • *Secondary objectives*: – to evaluate the maintenance of efficacy of Lu AA21004 *versus* placebo by a comparison of the time to relapse in patients who were in a stable response status for at least 12 weeks prior to randomisation – to evaluate the overall efficacy of Lu AA21004 during continuation treatment in patients with GAD – to evaluate long-term safety and tolerability of Lu AA21004 in patients with GAD – to evaluate potential discontinuation symptoms after abrupt discontinuation of treatment with Lu AA21004 – to evaluate the effect of Lu AA21004 on health-related quality of life, disability, and health-care resource utilisation (the health-care resource utilisation results are to be reported separately)

Methodology

- This was a multi-national, multi-centre, randomised, double-blind, placebo-controlled, relapse-prevention study. The patients were outpatients from psychiatric settings.
- The study consisted of two consecutive periods: a 20-week open-label treatment period (Open-label Period) with Lu AA21004 and a double-blind, placebo-controlled, fixed-dose, treatment period (Double-blind Period) of at least 24 weeks.
- The initial dose of Lu AA21004 was 5 mg/day. If clinically indicated (due to lack of expected efficacy according to the investigator's clinical experience), the investigator could, from Week 2 to Week 8 of the Open-label Period, increase the dose of Lu AA21004 to 10 mg/day at a study visit and could decrease it again (in case of dose-limiting adverse events) to 5 mg/day. From Week 8, the dose was fixed.
- Patients in response (Hamilton Anxiety Rating scale [HAM-A] total score ≤10) at both Weeks 16 and 20 were randomised to the Double-blind Period.
- The patients were randomised equally (1:1) to Lu AA21004 or placebo in the Double-blind Period; patients randomised to Lu AA21004 continued on the dose that was fixed from Week 8 in the Open-label Period; patients randomised to placebo were switched abruptly to placebo.
- Throughout the Double-blind Period, the investigators evaluated the occurrence of relapse. Relapse was defined as a HAM-A total score ≥15 or an insufficient therapeutic response, as judged by the investigator. Patients who relapsed were withdrawn from the study, but were contacted by phone at scheduled time points for health economic evaluation (health-related quality of life, disability, and resource utilisation).
- Efficacy and safety data were collected at Baseline I and Weeks 1, 2, 4, 6, 8, and then at 4-week intervals in the Open-label Period and at Baseline II/Randomisation and Weeks 1, 2, 4, and then at 4-week intervals in the Double-blind Period.
- A safety follow-up contact was scheduled for 4 weeks after completion of the Double-blind Period or after withdrawal from the study.

Number of Patients Planned and Analysed

- 600 patients were planned for enrolment in the Open-label Period, and approximately 300 were planned for randomisation in the Double-blind Period (150 in each treatment group).
- In the Open-label Period, 687 patients (APTS [all-patients-treated set]) were enrolled and treated and 459 (67%) completed and qualified for randomisation; 228 (33%) patients withdrew, 60 (8.7%) due to adverse events, 51 (7.4%) due to lack of efficacy, 47 (6.8%) withdrew consent, 28 (4.1%) did not fulfil the randomisation criterion, and 42 (6.1%) for other reasons.
- Patient disposition in the Double-blind Period is summarised below:

	PBO		AA21004		Total	
	n	(%)	n	(%)	n	(%)
Patients randomised	230		229		459	
Patients treated (all-patients-treated double-blind set [APTS_DB]):	230		229		459	
Patients completed	121	(53)	157	(69)	278	(61)
Patients withdrawn	109	(47)	72	(31)	181	(39)
Primary reason for withdrawal:						
Adverse event(s)	6	(3)	8	(3)	14	(3)
Lack of efficacy	72	(31)	25	(11)	97	(21)
Other	31	(13)	39	(17)	70	(15)
Analysis sets:						
APTS_DB	230		229		459	
Full-analysis set (FAS)	227		224		451	
Full-analysis set X (FAS_X; stable responders)	189		181		370	
Per-protocol set (PPS)	208		206		414	

Diagnosis and Main Inclusion Criteria

Outpatients with a primary diagnosis of GAD according to DSM-IV-TR™ criteria who, at the Screening and Baseline I (entry into the Open-label Period) Visits:

- had a HAM-A total score ≥20
- had a HAM-A score ≥2 on item 1 (*anxious mood*) and item 2 (*tension*)
- had a Montgomery and Åsberg Depression Rating Scale (MADRS) total score ≤16
- were ≥18 and ≤75 years of age

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

Lu AA21004 – 5 or 10 mg/day; encapsulated tablets, orally; batch Nos. PD1698/E05331-028E and 2135750/E05846-002E (5 mg); 2129768/E05331-029E, PD1668/E05331-024E, 2135752/E05846-001E, and 2135752/E05846-001E02 (10 mg)

Duration of Treatment

20 weeks of open-label treatment followed by 24 to 56 weeks of double-blind treatment

Reference Therapy, Dose and Mode of Administration, Batch Numbers

Placebo – capsules, orally; batch Nos. E05331-027E, E04879-0001E, E05846-003E01, and E04879-001E02

Efficacy Assessments

- *Primary variable*:
  - time to relapse in the Double-blind Period based on:
    - a HAM-A total score ≥15 or
    - an unsatisfactory treatment effect (lack of efficacy) as judged by the investigator
- *Secondary variables*:
  - HAM-A total score
  - Clinical Global Impression – Severity of Illness (CGI-S) and Global Improvement (CGI-I) scores
  - Hospital Anxiety and Depression Scale (HAD) – anxiety (HAD-A) and depression (HAD-D) subscale scores (patient-reported outcomes)
  - MADRS total score

Health-related Quality of Life, Disability, and Pharmaco-economic Assessments

- Medical Outcomes Study (MOS) 36-item Short-form Health Survey (SF-36) subscale scores (patient-reported outcome)
- Sheehan Disability Scale (SDS) total score and single-item scores (patient-reported outcome)
- Health Economic Assessment Questionnaire (HEA) score (are to be reported separately)

Safety Assessments

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

Statistical Methodology

- For the analyses, two baselines were defined:
  - Baseline I – beginning of the Open-label Period (that is, Visit 2 at Week 0)
  - Baseline II – beginning of the Double-blind Period (defined as the last visit [that is, Visit 10 at Week 20] in the Open-label Period) when patients were randomised to double-blind treatment
- For data presentation and analyses, the following periods were defined:
  - Entire Study Period – from Baseline I to last visit/contact
  - Screening Period – from screening to Baseline I
  - Open-label Period – from Baseline I to Baseline II/Randomisation; treatment with open-label Lu AA21004
  - Double-blind Period – from Baseline II/Randomisation to the end of double-blind treatment
  - Discontinuation Period I – the first 2 weeks after Baseline II/Randomisation
  - Discontinuation Period II – the first 2 weeks after completion of the Double-blind Period
  - Safety Follow-up Period – 4-week period after the last dose of investigational medicinal product (IMP; open-label or double-blind)
- For the efficacy analyses, only the Open-label and Double-blind Periods were investigated; for the safety analyses, all of the above periods were investigated.
- The following analysis sets were defined:
  - *all-patients-treated set* (APTS) – all patients who took at least one dose of IMP in the Open-label Period
  - *all-patients-randomised set* (APRS) – all patients who completed the Open-label Period and were randomised to double-blind treatment
  - *all-patients-treated double-blind set* (APTS_DB) – all patients in the APRS who took at least one dose of double-blind IMP
  - *full-analysis set* (FAS) – all patients in the APTS_DB who fulfilled the criteria for randomisation
  - *per-protocol set* (PPS) – all patients in the FAS who did not have any major protocol violations
  - *full-analysis set X* (FAS_X) – all patients in the FAS who fulfilled the criteria for stable response for the last 12 weeks prior to randomisation (HAM-A total score ≤13 at Weeks 8 and 12 and HAM-A total score ≤10 at Weeks 16 and 20)
- The APTS was used for the evaluation of safety and efficacy data in the Open-label Period, the APTS_DB was used for the evaluation of safety data in the Double-blind Period, and the FAS was used for the evaluation of efficacy data in the Double-blind Period unless otherwise noted, the FAS_X was used for the key secondary efficacy analysis. The primary efficacy analysis was repeated on the PPS.
- A hierarchical step-down testing strategy was defined *a priori* in the *Statistical Analysis Plan* and comprised the primary efficacy analysis as well as the key secondary efficacy analysis. This was used to ensure multiplicity control in the testing of the primary and key secondary hypotheses, and treatment comparison *versus* placebo was performed at a significance level of 5%. If the primary hypothesis was rejected (that is, there was no statistically significant difference *versus* placebo), the testing procedure was stopped (that is, the key secondary analysis was not performed).
- The primary efficacy variable was the time to relapse in the Double-blind Period. The primary efficacy analysis compared the treatment groups using a Cox model with an exact method to handle ties (based on the FAS).
- The key secondary efficacy variable was the time to relapse in the stable responders in the Double-blind Period (based on the FAS_X). The key secondary efficacy analysis used the same methodology as the primary efficacy analysis.
- To support the results of the primary efficacy analysis, a number of sensitivity analyses were performed using a standard log-rank test and accelerated failure time models, taking the interval-censored nature of the data into account. Various distributions were studied in these models including Weibull and log-normal.

Statistical Methodology (continued)

- A sensitivity analysis, using the same methodology as for the primary efficacy analysis, was performed where patients who relapsed within the first 7 days of the Double-blind Period were excluded (to discount the possible effect of rebound and potential discontinuation symptoms); similar analyses were performed using 14 and 28 days as criteria. The primary analysis was also repeated only counting patients who relapsed up to Week 24 of the Double-blind Period.
- The potential influence of covariates on the primary efficacy analysis was investigated within the Cox model by adding main terms for the covariate as well as interaction terms with treatment. The covariates investigated were: age, sex, centre, country, Baseline I and II efficacy scores, and Baseline I and II weight.
- For all the secondary efficacy, health-related quality of life, and disability variables except for CGI-I, response, and remission, the changes from Baseline I or II by visit in the Double-blind Period were analysed using an ANCOVA (adjusting for Baseline I or II scores and centre) and χ^2analyses to compare treatments, using both observed cases (OC) and last observation carried forward (LOCF) data. For CGI-I, an ANCOVA of the absolute score at each visit was performed, using the Baseline II CGI-S score for adjustment. Response and remission were analysed by visit using χ^2 analyses (OC and LOCF).
- The time to withdrawal for any reason, due to adverse events, or due to lack of efficacy was analysed using Kaplan-Meier plots, Cox models, and log-rank tests.
- On an exploratory basis, the incidences of adverse events (by SOC and preferred term) in the Double-blind Period were compared between the treatment groups using Fisher's exact test.
- The time to first adverse event in the Double-blind Period was analysed when considered relevant (nausea only) using Kaplan-Meier plots, log-rank tests, and the Cox model.

Demography of Study Population

- Approximately two-thirds of the patients in the Open-label Period were women. The mean age of the patients was 43 years, ranging from 18 to 75 years, and the majority (95%) were Caucasian.
- There were no clinically relevant differences in the demographics between the patients in the AA21004 and placebo groups in the Double-blind Period with respect to the proportion of women to men (approximately two-thirds were women), mean age (approximately 44 years), or race (approximately 95% were Caucasian).
- The mean HAM-A total score at Baseline I was 28, indicating that the patients had *moderate* to *severe* anxiety symptoms, and the mean CGI-S score was 4.6, indicating that the patients were *moderately* to *markedly ill*; the mean MADRS total score of 12 indicated that the patients had a low level of depressive symptoms.

Exposure

- The mean exposure to open-label Lu AA21004 was 17 weeks. The total amount of exposure to Lu AA21004 accrued in the Open-label Period was 223 patient-years.
- The total amount of exposure accrued in the Double-blind Period was 123 patient-years in the AA21004 group and 107 patient-years in the placebo group.
- Of the 459 patients who were randomised to double-blind treatment with Lu AA21004 or placebo, approximately two-thirds took Lu AA21004 10 mg/day and one-third took Lu AA21004 5 mg/day at the end of the Open-label Period.

Efficacy, Health-related Quality of Life, and Disability Results

- A hierarchical step-down testing strategy was defined *a priori* and comprised the primary efficacy analysis, as well as the key secondary efficacy analysis under multiplicity control. The primary efficacy analysis showed that Lu AA21004 was statistically significantly (Cox model; p <0.001) superior to placebo in the analysis of time to relapse during the Double-blind Period based on the FAS. The key secondary analysis also showed a statistically significant (Cox model; p <0.001) superiority of Lu AA21004 relative to placebo in the analysis of time to relapse during the Double-blind Period in the stable responders based on the FAS_X.
- The risk of relapse was approximately three times higher for placebo-treated patients than for Lu AA21004-treated patients in the overall patient population (FAS) and in the stable responders (FAS_X).
- Lu AA21004 also separated from placebo (nominal p <0.001) in the sensitivity analysis of the time to relapse during the first 24 weeks of the Double-blind Period using the FAS. The robustness of the conclusions of the primary efficacy analysis was also confirmed in the analyses using the PPS, and a 7-, 14-, or 28-day relapse cut-off period after randomisation during which relapses were censored to discount the possible effect of rebound and potential discontinuation symptoms.
- The mean scores (OC) on the secondary efficacy and disability variables at Baselines I and II and the changes from Baseline II at Week 24 of the Double-blind Period are tabulated below:

Efficacy/Disability Variable	Baseline I (APTS)	Baseline II (FAS)	Change from Baseline II at Week 24 of Double-blind Period (FAS)[a,b]	
			PBO	AA21004
HAM-A total score	28.4 ± 4.6	4.4 ± 2.7	1.2	0.3*
CGI-S score	4.6 ± 0.7	1.6 ± 0.7	0.2	-0.1***
CGI-I score	N/A	1.3 ± 0.5	4.1	3.5***
HAD-A subscale score	13.1 ± 3.7	5.1 ± 3.5	0.3	-0.2
HAD-D subscale score	8.2 ± 4.1	3.4 ± 3.6	0.0	-0.2
MADRS total score	11.8 ± 2.7	2.7 ± 2.5	1.4	0.3**
SDS total score	16.6 ± 6.7	4.7 ± 5.7	0.2	-0.2

a For the CGI-I score, the ANCOVA results based on the last assessment are shown.
b p values from ANCOVA (difference to placebo) in the OC analyses (LOCF analyses for CGI-I):
* nominal p<0.05, ** nominal p<0.01, *** nominal p<0.001

- During the Open-label Period, the anxiolytic effect of Lu AA21004 was shown by the substantial decrease in the mean HAM-A total score and the mean HAD-A subscale score of approximately 20 and 6 points, respectively. The anxiolytic effect of long-term Lu AA21004 treatment, as measured using the HAM-A total score and HAD-A subscale score, was maintained and stable over time during the Double-blind Period. The mean HAM-A total scores were consistently lower (superior) in the AA21004 group than in the placebo group and separated from placebo (nominal p <0.05) at Week 24.
- In line with these results, the mean CGI-I and CGI-S scores also decreased (improved) during the Open-label Period. For the CGI-S (the CGI-I was only measured at the Completion/Withdrawal Visit), the scores were maintained and stable over time during the Double-blind Period and separated from placebo (nominal p <0.001) at Week 24. The CGI-I scores in the AA21004 group at the Completion/Withdrawal Visit separated from that in the placebo group (nominal p <0.001) in favour of Lu AA21004.
- The study population included only patients with a low level of depressive symptoms at Baseline I (mean MADRS total score of 12). During the Open-label Period, the depressive symptoms improved with a decrease in the mean MADRS total score and the mean HAD-D subscale score of approximately 3 and 7 points, respectively. This effect was maintained and stable over time during the Double-blind Period. The MADRS total score was consistently lower (superior) in the AA21004 group than in the placebo group and separated from placebo (nominal p <0.01) at Week 24.
- The proportion of responders based on the CGI-I criterion increased substantially throughout the Open-label Period to approximately 80% at Week 20. Generally, in the Double-blind Period there was a higher proportion of CGI-I responders in the AA21004 group than in the placebo group. Similar results were seen in the *post hoc* responder analyses based on the HAM-A criterion.

Efficacy, Health-related Quality of Life, and Disability Results (continued)

- The proportion of remitters based on the CGI-S criterion increased substantially throughout the Open-label Period to approximately 66% at Week 20. During the Double-blind Period, the proportion of CGI-S remitters remained close to the Baseline II level and was stable over time in the AA21004 group and decreased slightly in the placebo group. There was a consistently higher proportion of remitters in the AA21004 group than in the placebo group and separation from placebo (nominal $p < 0.05$) in the proportions of CGI-S remitters was seen at Week 24. Similar results were seen the *post hoc* analyses of remission based on the HAM-A criterion.
- During the Open-label Period, the patients improved with respect to their health-related quality of life and disability as assessed using the SF-36 subscale scores and SDS total and single-item scores. During the Double-blind Period, the scores in the health-related quality of life and disability measures remained close to the Baseline II level and were stable over time. The mean SF-36 subscale scores were generally higher (superior) in the AA21004 group than in the placebo group, and there was a separation from placebo (nominal $p < 0.05$) in the mean changes from Baseline II on the SF-36 subscales *general health*, *vitality*, *social functioning*, *role-emotional*, and *mental health* at Week 24. For the SDS total score and single-items *work, social life*, and *family life*, the mean scores were generally lower (superior) in the AA21004 group than in the placebo group.

Safety Results

- The adverse event incidence for the Open-label Period is summarised below:

	OL_AA21004	
	n	(%)
Patients treated	687	
Patients who died	1[a]	
Patients with serious AEs (SAEs)	10	(1.5)
Patients with AEs leading to withdrawal	61	(8.9)
Patients with AEs	528	(76.9)

a The patient committed suicide 2 days after withdrawal from the study (2 days after last dose of open-label IMP).

- The adverse event incidence for the Double-blind Period is summarised below:

	PBO		AA21004	
	n	(%)	n	(%)
Patients treated	230		229	
Patients who died	0		0	
Patients with SAEs	1	(0.4)	3	(1.3)
Patients with AEs leading to withdrawal	3	(1.3)	6	(2.6)
Patients with AEs	124	(53.9)	126	(55.0)

- During the Open-label Period, approximately three-quarters of the patients had adverse events, and 10 patients (1.5%) had SAEs. One patient died (committed suicide) 2 days after withdrawal from the study (2 days after last dose of open-label IMP). None of the SAEs occurred in more than 1 patient. A total of 61 patients (8.9%) had adverse events leading to withdrawal. The incidence of *severe* adverse events was 8.3%.
- During the Double-blind Period, the incidence of adverse events was similar in the AA21004 group and the placebo group (55% and 54%, respectively). The incidence of SAEs was 1.3% (3 patients) in the AA21004 group and 0.4% (1 patient) in the placebo group; none of the SAEs occurred in more than 1 patient. The incidence of adverse events leading to withdrawal was 2.6% (6 patients) in the AA21004 group and 1.3% (3 patients) in the placebo group. The incidence of *severe* adverse events was 5.2% in both treatment groups.
- The adverse events with the highest incidence (≥10%) during the Open-label Period were nausea (27%) and headache (18%).
- The vast majority of nausea events in the Open-label Period were *mild* or *moderate*, approximately half had an onset within the first 2 days after the first dose of IMP, and the median duration was 14 days. The incidence of nausea was lower in the Double-blind Period, with similar incidences in the AA21004 group and placebo group (5.2% and 3.0%, respectively).

Safety Results (continued)

- During the Open-label Period, the incidences of nausea and headache were higher in women than men; the incidence of adverse events leading to withdrawal was similar in women and in men. During the Open-label Period, the overall incidence of adverse events was similar in patients aged ≤50 years and patients aged >50 years. During the Double-blind Period, the overall adverse event incidence was similar in women and in men and in patients aged ≤50 years and patients aged >50 years in both treatment groups.
- During the Double-blind Period, the only adverse event with an incidence ≥10% in the AA21004 group was influenza; and only influenza and accidental overdose had an incidence ≥5% and a significantly higher incidence (Fisher's exact test; $p < 0.05$) in the AA21004 group than in the placebo group.
- The incidence of adverse events of special interest (vomiting and adverse events related to pruritus/rash, sexual dysfunction, and sleep) was generally low in the Open-label and Double-blind Periods.
- The incidence of adverse events in Discontinuation Period I (the first 2 weeks after Baseline II/Randomisation) was 17% in the AA21004 group and 27% in the placebo group. In the AA21004 group the incidence of adverse events was similar in the first and second weeks of Discontinuation Period I (10% *versus* 7.9%); in the placebo group, it was higher in the first week than in the second week (21% *versus* 10%). During Discontinuation Period I, headache was the only adverse event with an incidence ≥5% in either treatment group (AA21004 group: 3.1%; placebo group: 6.1%). During the first week, the only adverse event with an incidence ≥2% in either treatment group was headache (placebo group only [4.8%]). During the second week of Discontinuation Period I, no adverse event had an incidence ≥2% in either treatment group.
- During Discontinuation Period II (the first 2 weeks after completion of the Double-blind Period), the incidence of adverse events was 22% in the AA21004 group and 17% in the placebo group. The only adverse event with an incidence ≥5% in either treatment group was insomnia (AA21004 group [5.1%], only). The incidence of adverse events was higher in the first week than in the second week of Discontinuation Period II in both treatment groups (AA21004 group: 15% *versus* 8.9%; placebo group: 14% *versus* 4.1%). During the first week, adverse events with an incidence ≥2% in the AA21004 group comprised insomnia, fatigue, headache, and irritability; no adverse event had an incidence ≥2% in the placebo group during the first week. During the second week of Discontinuation Period II, adverse events with an incidence ≥2% in the AA21004 group comprised tension and anxiety; no adverse event had an incidence ≥2% in the placebo group during the second week.
- Seven patients had suicide-related adverse events: 1 patient committed suicide 2 days after withdrawal from the study (2 days after last dose of open-label IMP); 4 patients had suicidal ideations in the Open-label Period, 1 of these continued in the study and 3 were withdrawn; 2 patients (both in the placebo group) had suicidal ideations in the Double-blind Period, 1 continued in the study and 1 was withdrawn.
- Based on the C-SSRS scores, none of the patients had a score of 1 (*completed suicide*) or 2 (*suicide attempt*) during the study. The numbers of patients with a C-CASA score of 3 or 4 were low during treatment with Lu AA21004 and similar to that in the placebo group during double-blind treatment.
- A total of 6 women became pregnant during the entire study; of them 2 had spontaneous abortions after withdrawal from the study and 4 gave birth to healthy babies.
- During both the Open-label Period and Double-blind Period, there were no clinically relevant mean changes in clinical safety laboratory values, vital signs, weight, or ECG values, and the incidence of PCS values was low.

Conclusions

- Based on the predefined testing hierarchy, the primary efficacy analysis showed that Lu AA21004 at doses of 5 and 10 mg/day was statistically significant superior to placebo in the analysis of time to relapse in patients with GAD. In the key secondary analysis, Lu AA21004 at doses of 5 and 10 mg/day was also statistically significantly superior to placebo in the analysis of time to relapse in the stable responders (who had showed stable response on the HAM-A for at least 12 weeks prior to randomisation).
- The risk of relapse was approximately three times higher for placebo-treated patients than for Lu AA21004-treated patients in the overall patient population and in the stable responders.
- Lu AA21004 had an anxiolytic effect during 20 weeks of open-label treatment and the effect was maintained during continued double-blind treatment (24 to 56 weeks) with consistently better HAM-A total scores in Lu AA21004-treated patients than in placebo-treated patients.
- Lu AA21004 had a beneficial impact on health-related quality of life and disability during 20 weeks of open-label treatment, as measured using the SF-36 and SDS. This effect was maintained during continued double-blind treatment, generally with better scores in Lu AA21004-treated patients than in placebo-treated patients.
- Long-term treatment with Lu AA21004 5 and 10 mg/day in patients with GAD was well tolerated.
- The types and incidences of adverse events during the discontinuation periods, both after short- and long-term treatment, did not indicate that Lu AA21004 at doses of 5 and 10 mg/day caused discontinuation symptoms.

Dates of the Reports

11 July 2012 (Amendment 1), 8 June 2011 (Integrated Clinical Study Report)

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