A randomized clinical study of Lu AA21004 in the prevention of relapse in patients with major depressive disorder

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Abstract

The efficacy and tolerability of Lu AA21004 in the prevention of relapse of major depressive disorder (MDD) in patients in remission after acute treatment was evaluated. Patients (*n*=639) aged 18–75 years with a primary diagnosis of MDD with a current major depressive episode (MDE) ≥4 weeks' duration, at least one prior MDE and a MADRS total score ≥26 received 12-week, open-label Lu AA21004 at 5 or 10mg/day. Patients in remission (MADRS ≤10) at both weeks 10 and 12 were assigned to double-blind treatment with either placebo or Lu AA21004 (fixed dose from Week 8).Patients (n=396) were treated, after random assignment to placebo (*n*=192) or Lu AA21004 (*n*=204). The primary analysis of time to relapse (full-analysis set, Cox proportional hazard model) showed a statistically significant difference in favour of Lu AA21004 versus placebo with a hazard ratio of 2.01 (95% confidence interval: 1.26–3.21; *p*=0.0035). The proportion of patients who relapsed was 13% in the Lu AA21004 group (*n*=27) and 26% in the placebo group (*n*=50). The withdrawal rates due to adverse events were 8% (open-label), and 3% (placebo) and 8% (Lu AA21004) (double-blind). Thus, Lu AA21004 was effective in preventing relapse of MDD and was well tolerated as maintenance treatment.

Keywords

Lu AA21004, major depressive disorder, placebo-controlled, randomized clinical trial, relapse prevention

Introduction

The bis-arylsulphanyl amine compound Lu AA21004 (1-[2-(2,4-dimethyl-phenylsulphanyl)-phenyl]-piperazine-hydrobromide) is a novel multimodal antidepressant. It is thought to work through a combination of two pharmacological modes of action: reuptake inhibition and receptor activity. In vitro studies indicate that Lu AA21004 is a 5-HT_3 and 5-HT_7 receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist and inhibitor of the 5-HT transporter. In vivo non-clinical studies have demonstrated that acute and sub-chronic treatment with Lu AA21004 enhances levels of the neurotransmitters serotonin, noradrenaline, dopamine, acetylcholine and histamine in both the ventral hippocampus and the median prefrontal cortex (Bang-Andersen et al., 2011; Mørk et al., 2011).

In a phase II clinical study (Alvarez et al., 2011), the predefined primary efficacy endpoint change from baseline in the Montgomery and Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) total score at Week 6 showed a clinically and statistically significant treatment difference from placebo ($p<0.0001$) of approximately six points for Lu AA21004 at both 5 and 10 mg/day doses. Both doses were well tolerated. Tolerability and efficacy have been confirmed in one phase III study (Henigsberg et al., 2011), and tolerability in two others (Baldwin et al., 2011; Jain et al., 2011).

Relapse-prevention studies represent the conventional approach for evaluating long-term efficacy (European Medicines Agency, 2002). The overall aim of this study was to evaluate the efficacy of Lu AA21004 versus placebo in the prevention of relapse of Major Depressive Episodes (MDEs) as well as long-term safety and tolerability of Lu AA21004 versus placebo.

Materials and methods

This double-blind, randomized, placebo-controlled, relapse-prevention study recruited 639 in- and outpatients from 66 psychiatric settings in 17 countries (Australia, Austria, Belgium, Canada, Finland, France, Germany, India, the Republic of Korea, Norway, Poland, South Africa, Sweden, Taiwan, Thailand, Turkey and the United Kingdom). Patients with major depressive disorder (MDD) were recruited from psychiatric settings from December 2007 to September 2009. Advertisements were used to recruit patients in Australia, Austria, Canada, Finland, Germany, the Republic of Korea, South Africa, Sweden and Taiwan. The trial was conducted in accordance with the principles of Good Clinical Practice (ICH, 1996) and the Declaration of Helsinki (World Medical Association, 1964, and its amendments in force at the initiation of the study) Local ethics committees approved the trial design and eligible patients gave their written informed consent before participating.

Study design

The study consisted of two consecutive periods: a 12-week, open-label, flexible-dose treatment period with Lu AA21004 and a

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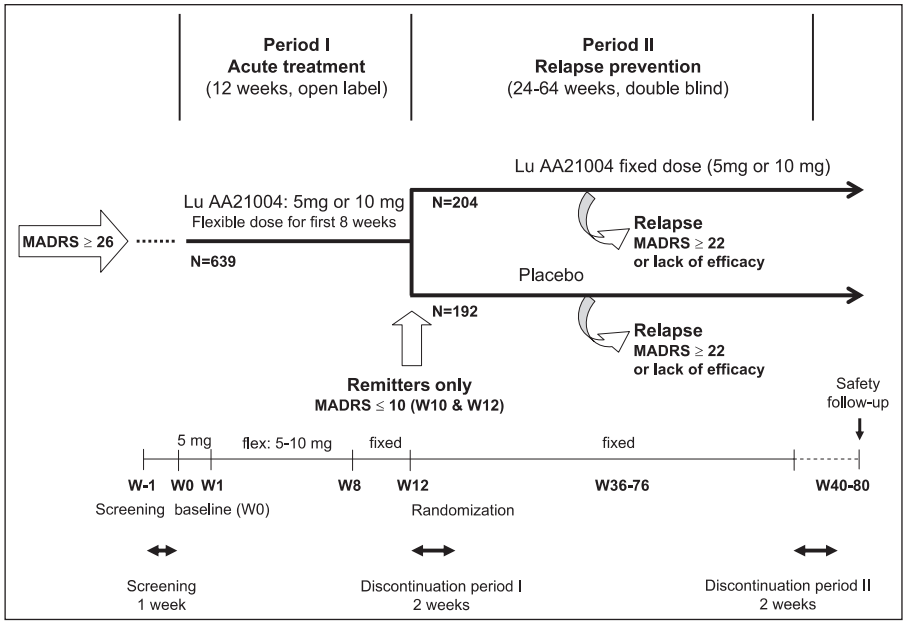

Figure 1. Study design.

double-blind, fixed-dose, placebo-controlled treatment period of 24–64 weeks (Figure 1). The initial dose of Lu AA21004 was 5 mg/day. During a window in the open-label period from Week 2 to Week 8, the investigator could, if clinically indicated, increase the dose of Lu AA21004 to 10 mg/day, and could decrease it again (in the case of dose-limiting adverse events) to 5 mg/day in connection with a study visit. From Week 8 and onwards the dose remained fixed.

Patients in remission (MADRS total score ≤10) at both Weeks 10 and 12 were randomized to the double-blind, placebo-controlled, fixed-dose treatment period. Non-remitters at Week 10 and/or Week 12 left the study and were treated at the investigator's discretion. Patients were randomized equally (1:1) to Lu AA21004 or placebo in the double-blind period. Patients randomized to Lu AA21004 continued on the final dose (5 or 10 mg) that was fixed from Week 8 in the open-label period, while patients randomized to placebo were switched abruptly to placebo. Throughout the double-blind period, the investigators evaluated the occurrence of relapse, defined as a MADRS total score ≥22 or an insufficient therapeutic response, as judged by the investigator. Patients who relapsed were withdrawn from the study. All non-withdrawn patients were to complete the study simultaneously in order to optimize the exposure time to treatment and to enable an estimate of the risk of relapse based on a parsimonious number of patients (Allgulander et al., 2006). Therefore, they continued in the double-blind treatment period until the last patient completed 24 weeks of double-blind treatment (i.e. patients were treated between 24 and 64 weeks). Patients who completed the double-blind treatment period entered a two-week double-blind discontinuation period after abrupt discontinuation of study treatment. A safety follow-up contact was scheduled for four weeks after completion of the study or after withdrawal from the study.

Allocation to treatment

Medication was given as encapsulated tablets (Lu AA21004; 5 and 10 mg) or capsules (placebo) for oral administration, supplied as capsules of identical appearance. Patients who fulfilled the randomization criteria after completion of the open-label period were assigned to treatment with either Lu AA21004 or placebo, in accordance with a computer-generated randomization list by H Lundbeck A/S. The details of the randomization series were unknown to any of the investigators and were contained in a set of sealed opaque envelopes. At each study centre, sequentially enrolled patients were assigned the lowest randomization number available in blocks of four. All investigators, trial personnel and participants were blinded to treatment assignment for the duration of the entire study. The randomization code was accidentally broken for three patients, who were withdrawn from the study, and intentionally broken for another two patients after they had relapsed and had been withdrawn from the study.

Main entry criteria

Patients with a primary diagnosis of MDD according to DSM IV-TR criteria (American Psychiatric Association, 2000) presenting with an MDE of at least four weeks' duration and at least one prior MDE were included in the trial if they were an in- or outpatient of either sex, aged from 18 to 75 years, with a MADRS total score ≥26 at both the screening and baseline visits.

Patients were excluded if they had any current psychiatric disorder other than MDD as defined in the DSM-IV-TR (assessed using the Mini International Neuropsychiatric Interview (MINI)) (Lecrubier et al., 1997), or if they had a current or past history of manic or hypomanic episode, schizophrenia or any other psychotic disorder, including major depression with psychotic features, mental retardation, organic mental disorders, or mental disorders due to a general medical condition, any substance abuse disorder (except nicotine and caffeine) within the previous six months, presence or history of a clinically significant neurological disorder (for example, Alzheimer's disease, Parkinson's disease, multiple sclerosis and Huntington disease) or any Axis II disorder that might compromise the study.

Patients at serious risk of suicide, based on the investigator's clinical judgment, or who had a score ≥5 on item 10 of the MADRS scale (suicidal thoughts) were also excluded, as were those receiving formal behaviour therapy or systematic psychotherapy, or were pregnant or breast-feeding, or whose current depressive symptoms were considered by the investigator to have been resistant to two adequate antidepressant treatments of at least six weeks' duration, or had previously been exposed to Lu AA21004.

Patients were also excluded if they were taking any of the following drugs within two weeks prior to baseline or during the study: any investigational drug, narcotic analgesics, anorexics, anticonvulsants, antidepressants (including MAOIs and RIMAs), psychoactive herbal remedies, antidiarrhoeal agents, antihistamines, antimigraine agents, antiemetics, antiobesity agents, antipsychotics, anxiolytics (including benzodiazepines), cough or cold agents, diuretics, systemic steroids, mood stabilizers, sedatives or hypnotics and episodic use of insulin, hypoglycaemic agents and hormones. Episodic use of zolpidem, zopiclone, or zaleplon for insomnia (for a maximum of two days per week, but not the night before a study visit), of antidiarrhoeal agents loperamide, bismuth and kaolin preparations, of antihistamines loratadine, desloratadine and cetirizine, cough or cold agents (except preparations with pseudoephedrine or narcotics), anticoagulants (including aspirin), NSAIDs and diuretics was allowed.

Patients had to be withdrawn if they became pregnant during the study, if the investigator considered it to be in the best interest of the patient for safety/efficacy reasons, if laboratory values were outside normal ranges and were considered by the investigator to be a potential safety risk, if they were considered to be at significant risk of suicide, if they scored ≥5 points on item 10 (suicidal thoughts) of the MADRS, if the randomization code for a patient was broken, if consent to participate was withdrawn, if they did not take study medication for more than six consecutive days, or if the patient was lost to follow-up. The patient could be withdrawn from the study if a serious adverse event (SAE) (death, life-threatening condition, hospitalization) occurred. If adverse events (AEs) were contributory to withdrawal, they were always regarded as the primary reason for withdrawal. Patients completing the open-label period had to be withdrawn if they did not fulfil the remission criterion at Week 10 or Week 12.

Assessments

Efficacy and safety data were collected at two-week intervals in the open-label period and at one, two, and four weeks after randomization, and then at four-week intervals in the double-blind period. Potential discontinuation symptoms were assessed at two visits at weekly intervals during a two-week period, both at the completion of the open-label treatment in patients randomized to placebo and at the end of the double-blind period in patients who completed treatment with Lu AA21004. Patient ratings were assessed by the same investigator at each visit, whenever possible. Patients' depressive symptoms were evaluated using the MADRS. With a few exceptions, the raters were experienced psychiatrists. Rater training of MADRS and scoring conventions was undertaken to increase inter-rater reliability and was chaired by an experienced investigator. Only those investigators who had actively participated in rater training sessions prior to inclusion of patients into the study and had received rater certification were allowed to rate patients. The raters were also trained in the 17-item Hamilton Depression Rating scale (HAM-D17) (Hamilton, 1960), the Hamilton Anxiety scale (HAM-A) (Hamilton, 1959) and Clinical Global Impression (CGI) (Guy, 1976). A MINI training session was organized prior to the start of the study. The MADRS, HAM-D, HAM-A, MINI and patient-reported outcomes were used in local language versions and only the linguistically validated translations provided by H Lundbeck A/S were used.

Analysis sets

All safety analyses were based on the all-patients-treated set (APTS), comprising all randomized patients who took at least one dose of study medication. The APTS was used for the evaluation of all data in the open-label period. Efficacy analyses of all data in the double-blind period were based on the full-analysis set (FAS), comprising all randomized patients who took at least one dose of investigational medicinal product in the double-blind period.

Power and sample size calculations

The sample size and power calculations were based on the analysis of time to relapse in the double-blind period at a 5% level of significance, using a log-rank test. A sample size of 420 patients (210 patients per treatment group) would provide 91% power to find a statistically significant difference between placebo and Lu AA21004, assuming cumulative relapse rates of 0.20 and 0.10, respectively. Approximately 65% of the patients enrolled in the open-label period were eligible for the double-blind period. This meant that at least 650 patients needed to be enrolled in the open-label period.

Primary efficacy analysis

The primary efficacy variable was the time to relapse of MDD within the first 24 weeks of the double-blind period. The primary efficacy analysis used a Cox model using an exact method to handle ties. Withdrawals due to reasons other than lack of efficacy (relapse) were considered as non-relapsed and received the date of withdrawal as censoring time. The principal statistical software used was SAS®, Version 9.1.3. The potential influence of covariates on the primary efficacy analyses 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, race, centre, country, efficacy scores at baseline and at randomization, and weight at baseline and at randomization. A sensitivity analysis, using the same methodology as for the primary efficacy analysis, was performed where patients with relapses that occurred within the first seven, 14, or 28 days of the double-blind period were excluded to discount the possible effect of rebound and discontinuation symptoms. No statistical testing was performed regarding patient characteristics after randomization to placebo or Lu AA21004.

Secondary efficacy analysis

For all secondary efficacy variables, the changes from baseline or randomization by visit were analysed to compare treatments using ANCOVA (adjusting for scores at baseline or randomization, and centre) and chi-square tests, using both last observation carried

forward (LOCF) and observed cases (OC) approaches. Due to lack of convergence, the mixed models repeated measurement (MMRM) analyses of the efficacy variables were not performed. Response and remission were analysed per visit using chi-square analyses (OC and LOCF).

Tolerability assessments

Each patient was asked a non-leading question (such as, 'How do you feel?') at each visit, starting at baseline. All AEs (including any change in concurrent illnesses or new illnesses) either observed by the investigator or reported spontaneously by the patient were recorded. AEs were coded using the lowest level term according to the Medical Dictionary for Regulatory Activities, version 12.1. The time to withdrawal due to AEs was analysed using the Cox model. The incidences of individual adverse events in the double-blind period were compared between the treatment groups using Fisher's exact test.

To identify possibly suicide-related AEs, the database was searched at the verbatim (investigator's term) level for possible suicide-related AEs, as described by the FDA (Laughren, 2006). Potential discontinuation symptoms were assessed by spontaneously reported AEs during a two-week period, both at the end of the 12-week open-label treatment in patients randomized to double-blind period, and in patients who completed the study. In both periods the treatment with Lu AA21004 was abruptly discontinued.

Clinical safety laboratory tests, vital signs, weight, ECGs and physical examination findings were evaluated for the open-label and double-blind periods.

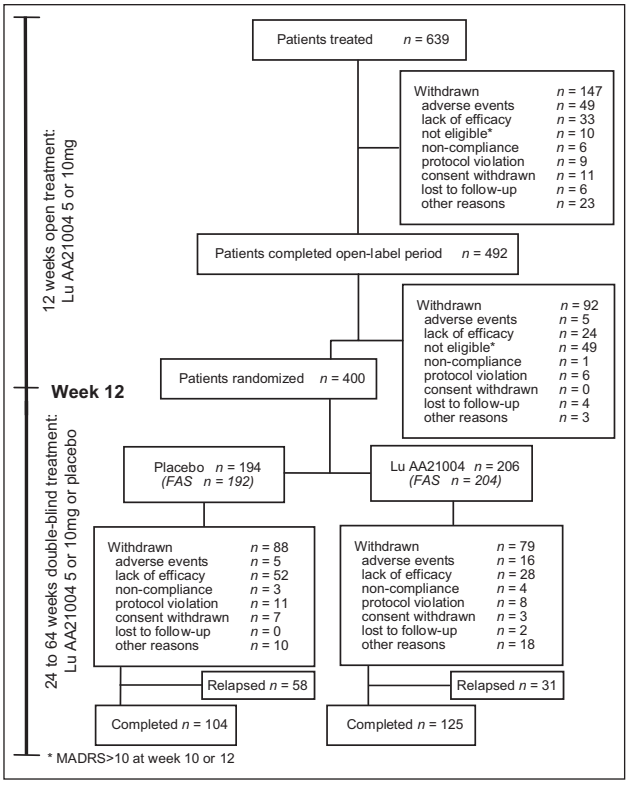

Figure 2. Flow chart of patient disposition.
MADRS: Montgomery-Åsberg Depression Rating Scale

Results

Patient characteristics at inclusion

Of the 639 patients entering the open-label period, 400 patients (63%) were randomized to double-blind treatment: 206 patients to Lu AA21004 and 194 patients to placebo. Two patients in each treatment group received no study medication; the FAS dataset thus comprised 396 patients (Figure 2).

Patient demographics at inclusion are shown in Table 1. Approximately two-thirds of the patients were female, the average age was 45 years, the mean length of the current MDE was about 23 weeks, ranging from four weeks to four years, and the mean number of MDEs was 2.1. There were no significant differences between patients treated with Lu AA21004 or placebo at randomization.

Exposure and dosage

In the open-label period, the total exposure to Lu AA21004 was approximately 127 patient-years, with a median exposure per patient of 84 days (range 1–140 days). A total of 441 patients (69%) changed dose during the open-label period. Approximately two-thirds of the patients (n=414) changed dose only once during the open-label period and then remained on Lu AA21004 10 mg/day. At the last assessment in the open-label period 221 patients (35%) were on Lu AA21004 5 mg/day and 418 patients (65%) on Lu AA21004 10 mg/day. Of the 400 patients who were randomized to double-blind treatment, 154 patients (75%) in the AA21004 group and 128 patients (66%) in the placebo group took Lu AA21004 10 mg/day at the end of the open-label period. In the double-blind period, the total exposure was approximately 116 patient-years for Lu AA21004 and approximately 98 patient-years for placebo. Of patients treated, 66.7% (136/204) in the Lu AA21004 group and 59.9% (115/192) patients in the placebo group were treated for more than 36 weeks (12 weeks in the open-label period plus at least 24 weeks in the double-blind period).

Efficacy

Open-label period (APTS)

The mean MADRS total score decreased from 32.3 ± 4.1 at baseline to 7.0 ± 6.4 (APTS, OC) at Week 12, and the CGI-S from 4.8 ± 0.7 to 1.8 ± 1.0 (APTS, OC). At Week 12, 75.7% (n=476) of patients had responded based on the MADRS total score (≥50% decrease from baseline) and 68.7% (n=432) had achieved remission (MADRS total score ≤10) (APTS, LOCF).

Double-blind period (FAS)

There were no clinically relevant differences in the severity of depression as measured by MADRS or CGI-S between patients randomized to Lu AA21004 or placebo at the start of the double-blind period. Four hundred patients were randomized to double-blind treatment with placebo (n=194) or Lu AA21004 (n=206), with a mean MADRS total score of 4.8. Of the 396 patients in the FAS continuing into the double-blind period of the study, 229 (125 Lu AA21004-treated and 104 placebo-treated patients) completed the study.

Table 1. Baseline patient characteristics

	Open-label (APTS)	Double-blind (FAS)	
	Lu AA21004 (*n*=639)	Placebo (*n*=192)	Lu AA21004(*n*=204)
Females	397 (62.1%)	120 (62.5%)	130 (63.7%)
Age (years)			
Mean ± SD	44.6 ± 12.4	45.1 ± 12.1	44.8 ± 12.4
Range	18–75	18–74	19–74
Caucasian	78.2%	80.2%	80.9%
Asian	18.8%	17.7%	15.7%
Days since start of current MDE ± SD	160 ± 162	164 ± 152	146 ± 126
Number of previous episodes ± SD	2.1 ± 1.7	2.1 ± 1.8	2.1 ± 1.7
Efficacy scores (mean ± SD)			
MADRS total score	32.3 ± 4.1	4.7 ± 3.2	4.9 ± 3.0
HAM-D17	22.8 ± 4.5	4.0 ± 3.2	4.7 ± 3.3
HAM-A total score	22.6 ± 6.6	4.6 ± 3.6	5.1 ± 3.8
CGI-S	4.8 ± 0.7	1.5 ± 0.7	1.6 ± 0.7

APTS: all patients treated set; CGI-S: Clinical Global Impression – Severity; FAS: full-analysis set; HAM-A: Hamilton Rating Scale for Anxiety; HAM-D17: Hamilton Rating Scale for Depression (17 items); MADRS: Montgomery–Åsberg Depression Rating Scale; MDE: major depressive episode; SD: standard deviation.

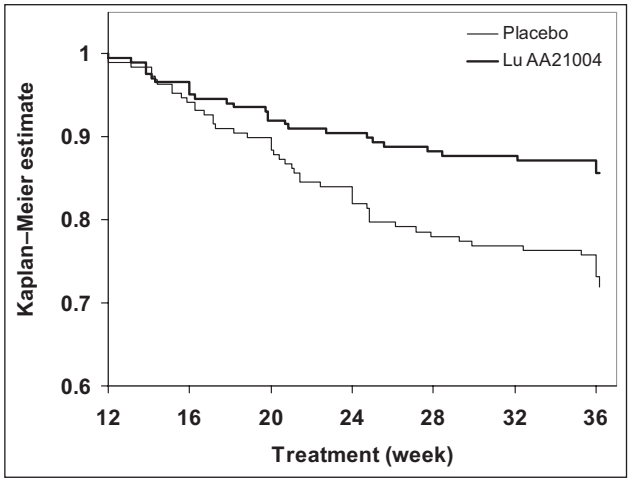

Figure 3. Kaplan–Meier survival analysis of relapse over 24 weeks after 12 weeks' open-label treatment. Time to relapse showed a significant advantage for patients treated with Lu AA21004 compared with patients treated with placebo (FAS, Cox proportional hazard model; p=0.0035).

The results of the primary efficacy analysis (FAS, Cox model, p=0.0035) showed a statistically significant difference in the time to relapse in favour of Lu AA21004 versus placebo within the first 24 weeks of the double-blind period, with a hazard ratio of 2.01 (95% confidence interval, CI: 1.26–3.21; p=0.0035) (Figure 3). The proportion of patients who relapsed was statistically significantly lower in the Lu AA21004 group (13%, n=27) than in the placebo group (26%, n=50; p=0.0013, chi-square test).

The log-rank test and accelerated failure time models also showed a clear beneficial effect of Lu AA21004 relative to placebo on the time to relapse of MDD within the first 24 weeks of the double-blind period (log-rank test, p=0.003; accelerated failure time model, p=0.004). Sensitivity analyses, excluding patients with relapses that occurred within the first seven to 28 days of the double-blind period, gave hazard ratios of 2.01 (seven days, p=0.0040), 2.32 (14 days, p=0.0008) and 2.50 (28 days, p=0.0010). The secondary analysis of the time to relapse of MDD considered all relapses that occurred during the entire double-blind period (up to 64 weeks) confirmed that the proportion of patients who relapsed was lower in the Lu AA21004 group (15%, n=31) than in the placebo group (30%, n=58) with a hazard ratio of 2.09 (95% CI: 1.35–3.23; p=0.0010). During the double-blind period, 18 patients (five in the AA21004 group and 13 in the placebo group) relapsed as judged by the investigator, but did not have a MADRS total score ≥22 points. Excluding these patients from the analysis resulted in a hazard ratio of 1.87 (95% CI: 1.10–3.16, p=0.0205). An additional post-hoc sensitivity analysis, in which all AE withdrawals were treated as relapses (placebo: n=60, Lu AA21004: n=45), gave a hazard ratio of 1.49 (95% CI: 1.01–2.10, p=0.0410). The mean MADRS total score at the time of withdrawal of the patients withdrawn due to AEs was 17.6 for placebo (n=5) and 9.3 for Lu AA21004 (n=16). At randomization, approximately 30% of patients (n=118) were treated with Lu AA21004 5 mg, for whom the hazard ratio was 2.26 (95% CI: 0.89–5.74, p=0.0852), compared with patients treated with 10 mg (n=278), for whom the hazard ratio was 1.94 (95% CI: 1.12–3.35, p=0.0179).

There were no statistically significant main effects on the primary efficacy analysis of the time to relapse (within the first 24 weeks of the double-blind period) of the following covariates: baseline MADRS score, sex, centre, country, weight. No statistically significant interaction was found between treatment and any of the investigated covariates at the 5% level of significance, except for race, where there was a statistically significant (p=0.016) interaction between treatment and the covariate Asians. There was a greater effect of treatment and a lower risk of relapse for Caucasian patients than for Asian patients (Cox model hazard ratio: 2.47 versus 0.42, respectively). However, the number of Asian patients was relatively low (Table 1).

The effect of long-term treatment as measured by the MADRS total score was stable after randomization for the Lu AA21004 group and showed a consistent slight deterioration in the placebo

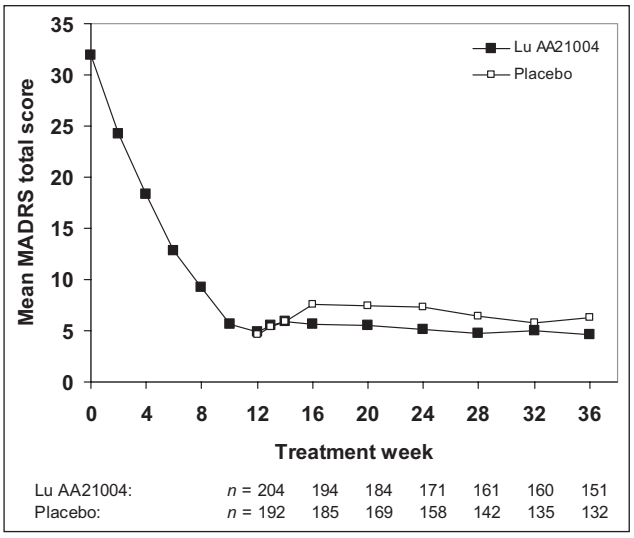

Figure 4. MADRS total mean scores during the open-label and double-blind (first 24 weeks) periods. The numbers of patients at each visit are shown below the x-axis. Values are for the full-analysis set (FAS) using observed cases (OC) by visit.

group during the double-blind period (Figure 4). A similar pattern was seen for most secondary measures. These differences in favour of Lu AA21004 were statistically significant for most secondary measures (FAS, OC) (Table 2).

Tolerability

Open-label period (APTS)

Of the 147 (23%) patients withdrawn during open-label treatment, 49 (7.7%) withdrew due to AEs. An additional 92 patients who completed the open-label period were not randomized, five because of AEs (Figure 2). Fourteen patients had serious AEs (2.2%), none of which occurred in more than one patient, except depression (two patients). Of the AEs that occurred during the open-label period (Table 3), only nausea and headache had an incidence ≥10%. In most cases (87%) AEs were considered mild to moderate by the investigator. AEs relating to sexual dysfunction were reported by 16 patients (2.5%), comprising libido decreased (*n*=9), erectile dysfunction (*n*=4), ejaculation delayed (*n*=3), loss of libido (*n*=2) and female orgasmic disorder (*n*=1). Three patients withdrew due to AEs related to sexual dysfunction. The most common AEs leading to withdrawal were nausea (*n*=17), vomiting (*n*=8), headache (*n*=5) and fatigue (*n*=4). One patient was withdrawn due to a score ≥5 on MADRS item 10 (suicidal thoughts), one patient attempted suicide and was withdrawn and one patient had suicidal ideation, but continued in the study.

Double-blind period (FAS)

The overall withdrawal rate, excluding relapses, was 15.5% for patients treated with placebo (*n*=30) and 23.3% for patients treated with Lu AA21004 (*n*=48) (*p*=0.0480, chi-square test; Figure 2). Of these, 2.6% of the patients in the placebo group and 7.8% of the patients in the Lu AA21004 group withdrew due to AEs. In both groups, the majority of the AEs reported during the double-blind period were mild to moderate (approximately 90%) and the incidence of AEs was similar (63.5% in the placebo group and 62.3% in the Lu AA21004 group) (Table 3). The AEs with the highest incidence (≥10%) in the Lu AA21004 group were headache (12% versus 13% in the placebo group) and nasopharyngitis (11% versus 14% in the placebo group). The only AE with an incidence ≥5% in the Lu AA21004 group and for which the incidence was statistically significantly higher than that in the placebo group was nausea (8.8% versus 3.1%). AEs relating to sexual dysfunction were reported by two patients in the placebo group and three patients in the Lu AA21004 group. These comprised erectile dysfunction and female orgasmic disorder (one patient each in the placebo group), and in the Lu AA21004 group erectile dysfunction (*n*=1), libido decreased (*n*=2) and anorgasmia (*n*=1). One patient (in the placebo group) had an intentional overdose and alcohol poisoning in the post-dose period. Four females, all in the Lu AA21004 group, became pregnant during the study: three had an elective abortion and were withdrawn, and the fourth was found to be pregnant at the completion visit and subsequently gave birth to a healthy male baby.

Serious AEs were reported by four patients in the placebo group and seven patients in the Lu AA21004 group, none of which occurred in more than one patient, except road traffic accident (two patients). One patient died due to pancreatic cancer approximately eight months after the last dose of open-label treatment. In addition, two patients died during the screening period, both by suicide. After abrupt discontinuation of short- and long-term treatment with Lu AA21004, the incidence and type of AEs reported during the discontinuation periods were at placebo level. AEs with

Table 2. Secondary efficacy measures – change from randomization to Week 24 of the double-blind period (FAS, ANCOVA, OC).

Efficacy parameter	Start of double-blind period Mean ± SD		Mean change from randomization after 24 weeks double-blind treatment[a]		
	Placebo (*n*=192)	Lu AA21004 (*n*=204)	Placebo (*n*=192)	Lu AA21004 (*n*=204)	Treatment difference mean (95% CI)
MADRS total score	4.7 ± 3.2	4.9 ± 3.0	1.4	−0.6	−2.1 (−3.4 to -0.8)*
HAM-D17 total score	4.0 ± 3.1	4.5 ± 3.3	1.6	0.3	−1.3 (−2.4 to -0.2)**
HAM-A total score	4.6 ± 3.6	5.1 ± 3.8	0.9	−0.2	−1.1 (−2.3 to 0.1)
CGI-S	1.5 ± 0.7	1.6 ± 0.7	0.2	−0.1	−0.4 (−0.6 to -0.2)***

CI: confidence interval; CGI-S: Clinical Global Impression – Severity; FAS: full analysis set; HAM-A: Hamilton Rating Scale for Anxiety; HAM-D17: Hamilton Rating Scale for Depression (17 items); MADRS: Montgomery–Åsberg Depression Rating Scale; OC: observed cases; SD: standard deviation

[a]Adjusted mean change relative to score at the start of double-blind period,

*p<0.01, **p<0.05, ***p<0.001 versus placebo

Table 3. Adverse events (AEs) with an incidence ≥5% in any treatment group.

Preferred term	Open-label period (APTS)	Double-blind period (24 weeks) (FAS)	
	Lu AA21004 (*n*=639)	Placebo (*n*=192)	Lu AA21004 (*n*=204)
Patients with AEs	451 (70.6%)	122 (63.5%)	127 (62.3%)
Nausea	164 (25.7%)	6 (3.1%)	18 (8.8%)*
Headache	117 (18.3%)	25 (13.0%)	25 (12.3%)
Nasopharyngitis	52 (8.1%)	27 (14.1%)	22 (10.8%)
Dizziness	44 (6.9%)	3 (1.6%)	5 (2.5%)
Dry mouth	41 (6.4%)	0	4 (2.0%)
Accidental overdose[a]	37 (5.8%)	15 (7.8%)	16 (7.8%)
Insomnia	36 (5.6%)	1 (0.5%)	3 (1.5%)
Fatigue	32 (5.0%)	3 (1.6%)	3 (1.5%)
Influenza	7 (1.1%)	10 (5.2%)	14 (6.9%)
Gastroenteritis	12 (1.9%)	6 (3.1%)	11 (5.4%)

[a]An overdose was pre-defined as an amount, for example number of tablets, greater than what had been prescribed for that patient.
APTS: all patients treated set; FAS: full-analysis set
*$p<0.05$ versus placebo

an incidence ≥2% in the two weeks after randomization to placebo (group of interest) or Lu AA21004 were headache (4.2% and 6.4%), nausea (1.6% and 3.9%), nasopharyngitis (2.6% and 1.0%), dizziness (1.6% and 2.0%) and gastroenteritis (1.0% and 2.0%), respectively. In the two weeks following the end of the double-blind period, the AEs with an incidence ≥2% in patients treated with Lu AA21004 (group of interest) and placebo were headache (4.0% and 1.9%), nausea (3.2% and 1.9%), insomnia (1.6% and 2.9%), anxiety (3.2% and 1.0%), abdominal pain upper (2.4% and 0%) and depression (0% and 3.8%), respectively.

During both the open-label period and the double-blind period, there were no clinically relevant mean changes in clinical safety laboratory values, vital signs, weight or ECG values, and the incidences of patients with potentially clinically significant values were low.

Discussion

Lu AA21004 is a novel multimodal antidepressant that works through a combination of two pharmacological modes of action: reuptake inhibition and receptor activity (Adell, 2010). A previous phase II double-blind, placebo-controlled, venlafaxine-referenced six-week study conducted in 426 patients with MDD, showed that 5 mg and 10 mg Lu AA21004 were efficacious and well tolerated (Alvarez et al., 2011). Due to the character of the disorder, long-term studies are necessary to demonstrate that the short-term effects are maintained over time, since relapses may occur if the treatment is stopped as soon as symptomatic relief is obtained (Geddes et al., 2003). In accordance with recommendations issued by the CHMP, relapse-prevention studies using a standard randomized withdrawal design are required to show that short-term effects persist during the full length of the episode (European Medicines Agency, 2002).

In the present relapse-prevention study, the patients recruited were representative of non-comorbid MDD. The Cox proportional hazard model gave a hazard ratio of 2.01 (95% CI: 1.26–3.21; p=0.0035); that is, the risk of relapse for the patients in the placebo group was twice that for patients in the Lu AA21004 group. After 24 weeks, the relapse rate observed in patients receiving Lu AA21004 was 13%, compared with 26% in the placebo group ($p<0.0001$).

When compared with the results of a meta-analysis based on seven clinical trials using a relapse-prevention design with placebo substitution after a one to two month open-label antidepressant treatment of MDD followed by a six-month relapse prevention period (Geddes et al., 2003), our results appear to be similar for the active treatment (13% versus 15% in Geddes) and at the lower end of the relapse rate reported on placebo (26% versus 34% in Geddes et al. (2003)). The lower relapse rate in our placebo group might be explained by the randomization criterion that required patients to be in remission (MADRS total score ≤10) for two consecutive visits prior to randomization and by the fact that relapse was not driven by discontinuation symptoms (based on the incidence and type of AEs) after abrupt cessation of Lu AA21004 at randomization.

In our study, although all patients had a history of at least one previous episode and an average intensity of depressive symptomatology considered as moderate to severe, the relapse rate may also have been limited by the selection of patients without comorbidity.

A strength of the present study is that relapse, for the majority of the patients, was based on the application of the objective criterion of a MADRS total score ≥22, rather than the investigator's judgement. In addition, the hazard ratio was not significantly affected by the sensitivity analyses, in which relapses that occurred within the first seven, 14, or 28 days were excluded. Furthermore, there were no significant differences in the hazard ratios for a number of factors, including the patient's sex, baseline MADRS, age, country, weight and dose (5 or 10 mg/day). The results of the OC analyses of all the secondary efficacy measures consistently are in favour of Lu AA21004. The strong bias within the framework of these analyses would most likely reduce the differences between the two treatments. That this is not the case further illustrates the robustness of the data presented here.

In the present study, Lu AA21004 was well tolerated. During open-label treatment 70.6% of patients reported AEs, mainly

gastrointestinal problems and headaches, with 7.6% of the patients withdrawn because of AEs. During the double-blind phase of the study, a similar rate of AEs was reported in both treatment groups (62.3% *vs.* 63.5%), leading to withdrawal in 7.8% of patients receiving Lu AA21004 and 2.6% of those receiving placebo (p=0.020, chi-square test). During this period, the only statistically significant difference between the two groups was observed for nausea occurring in 8.8% of patients receiving Lu AA21004 and 3.1% of patients receiving placebo. It is noteworthy that, in contrast to the usual long-term AE profile of SSRIs (Baldwin, 2004), sexual adverse events were reported by three patients receiving Lu AA21004 and two receiving placebo during the 24–64 weeks of placebo-controlled double-blind treatment, although it should be remembered that a specific scale was not used to assess sexual dysfunction in this study. The incidence of AEs related to sexual dysfunction with Lu AA21004 was also at placebo level in a short-term, double-blind, placebo-controlled study (Alvarez et al., 2011). Furthermore, 67 out of 136 patients in the Lu AA21004 group were treated for more than 36 weeks and the mean treatment time was more than three weeks longer than that for the placebo group, suggesting that the long-term safety profile was consistent with the good tolerability observed in the short-term study (Alvarez et al., 2011).

Several limitations of our study should be stressed here. The strict criteria used in this study, e.g. excluding patients with comorbid diagnosis, may limit the generalizability of our results to real-world-patients (Seemüller et al., 2010; Zetin and Hoepner, 2007; Zimmerman et al., 2002). Furthermore, comparing rates of relapse across studies is inherently difficult because of the differences in criteria used to define remission during the open-label phase and relapse during the double-blind phase of such studies (Bandelow et al., 2006). In addition, relapse was measured as a pre-defined cut-off on a rating scale, as is usual for this type of study, and not on the basis of DSM-IV-defined MDD. A further limitation is that this study did not evaluate several clinical factors also reported to influence relapse rates in MDD patients, such as family history (Hollon et al., 2006), coping styles (Doesschate et al., 2010), neurovegetative symptoms and melancholic subtype (McGrath et al., 2000). Finally, interpretations of the tolerability results are limited by the fact that a specific scale was not used to assess sexual dysfunction, nor was a checklist used for adverse events or for discontinuation signs and symptoms (e.g. Rosenbaum et al., 1998).

This study demonstrates that Lu AA21004 was effective in preventing relapse of MDD, with short-term benefits maintained in long-term treatment, and was well tolerated as a maintenance treatment, with low incidence of sexual side-effects. The incidence of most adverse events, both during randomized treatment and after discontinuation, was comparable to that of placebo.

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Conflict of interest

J-PB is a consultant for, has received honoraria from and has conducted clinical research supported by H Lundbeck A/S. HL and IF are employed by H Lundbeck A/S.

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