A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder

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The efficacy and tolerability of Lu AA21004 at 5 mg/day, a novel multimodal antidepressant, were assessed in elderly patients with recurrent major depressive disorder. Patients were randomly assigned (1 : 1 : 1) to Lu AA21004 5 mg/day, duloxetine 60 mg/day (reference) or to placebo in an 8-week double-blind study. The primary efficacy measure was the 24-item Hamilton Depression Scale (HAM-D_{24}) total score (analysis of covariance, last observation carried forward). Patients (mean age 70.6 years) had a mean baseline HAM-D_{24} score of 29.0. Lu AA21004 showed significantly ($P=0.0011$) greater improvement on the primary efficacy endpoint compared with placebo at week 8 (3.3 points). Duloxetine also showed superiority to placebo at week 8, thereby validating the study. HAM-D_{24} response (53.2 vs. 35.2%) and HAM-D_{17} remission (29.2 vs. 19.3%) rates at endpoint were higher for Lu AA21004 than for placebo. Lu AA21004 showed superiority to placebo in cognition tests of speed of processing, verbal learning and memory. The withdrawal rate due to adverse events was 5.8% (Lu AA21004), 9.9% (duloxetine) and 2.8% (placebo). Whereas nausea was the only adverse event with a significantly higher incidence on treatment with Lu AA21004 (21.8%) compared with placebo (8.3%), the incidence of nausea, constipation, dry mouth, hyperhidrosis and somnolence was higher for duloxetine. In conclusion, Lu AA21004 was efficacious and well tolerated in the treatment of elderly patients with recurrent major depressive disorder. *Int Clin Psychopharmacol* **00:000–000** © **2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Clinically significant depression affects up to 14% of the elderly population (aged ≥ 65 years): between 2 and 4% of the population suffers from major depressive disorder (MDD) (Beekman *et al.*, 1999). Only one-third of elderly people suffering from depression receive a formal diagnosis and are eventually treated (Unützer *et al.*, 2003). There are relatively few controlled studies in elderly patients with nonpsychotic, unipolar MDD and even fewer that show a statistically significant difference from placebo (Nelson *et al.*, 2008).

The bis-arylsulfanyl amine compound Lu AA21004 (1-[2-(2,4-dimethyl-phenylsulanyl)-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 an inhibitor of the 5-HT transporter. The antidepressant efficacy of Lu AA21004 has been demonstrated in a placebo-controlled and active treatment-controlled short-term study in adult (aged 18–65 years) MDD patients (Alvarez *et al.*, 2011) and in relapse prevention in adults with MDD (Boulenger *et al.*, 2012).

The aim of this study was to investigate the efficacy, safety and tolerability of Lu AA21004 at 5 mg/day compared with placebo over 8 weeks in elderly patients with MDD. The study included duloxetine (60 mg/day) as an active reference, as it has shown efficacy, including a verbal learning and recall test, in elderly patients with MDD (Raskin *et al.*, 2007). Predefined exploratory analyses assessed the effect of Lu AA21004 on cognitive function.

Methods

This double-blind, randomized, fixed-dose, placebo-controlled, active reference study included 452 randomized patients from 81 psychiatric, psychogeriatric and geriatric settings in seven countries (Canada, Finland, France, Germany, Sweden, Ukraine and the USA) from February 2009 to February 2010. Advertisements were used to recruit patients in Finland and Sweden. The study was conducted in accordance with the principles of Good Clinical Practice (ICH, 1996) and the Declaration of Helsinki (World Medical Association (WMA), 2008).

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Local research ethics committees approved the trial design, and eligible patients provided written informed consent before participating.

At baseline, eligible patients were randomized (1 : 1 : 1) to Lu AA21004 5 mg/day, duloxetine 60 mg/day or placebo for the 8-week, double-blind treatment period. Patients were seen weekly during the first 2 weeks of treatment and then every 2 weeks. Patients who withdrew from the study were seen for a withdrawal visit as soon as possible and were offered a down-taper regimen, as specified below.

Study medication was given as capsules of identical appearance. Following randomization, patients were instructed to take one capsule per day, orally, preferably in the morning. Those who completed the 8-week, double-blind treatment period entered a 1-week, double-blind, taper-down period: patients treated with duloxetine 60 mg/day received duloxetine 30 mg/day; patients treated with Lu AA21004 5 mg/day were not tapered and received placebo immediately; patients treated with placebo remained on placebo. Patients were contacted for a safety follow-up 4 weeks after completion of the study or after withdrawal from the study.

Main entry criteria

Patients with a primary diagnosis of MDD according to the *Diagnostic and statistical manual of mental disorders* 4th ed.-Text Revision criteria [American Psychiatric Association (APA), 2000], with a current major depressive episode (MDE) of at least 4-weeks' duration and with at least one previous MDE before the age of 60 years were eligible for inclusion in the study if they were aged at least 65 years, with a Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) total score of at least 26 at screening and baseline visits.

Patients were excluded if they had a Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975) score of less than 24 at screening, any current psychiatric disorder other than MDD as defined in the *Diagnostic and statistical manual of mental disorders* 4th ed.-Text Revision [assessed using the Mini International Neuropsychiatric Interview (Lecrubier *et al.*, 1997)], or a current or past history of a manic or hypomanic episode, schizophrenia or any other psychotic disorder, mental retardation, organic mental disorders or mental disorders due to a general medical condition, any substance abuse disorder within the previous 6 months, the presence or history of a clinically significant neurological disorder, any neurodegenerative disorder, or any Axis II disorder that might compromise their participation in the study. Additional reasons for exclusion, relating to suicidality, treatment resistance, and receipt of formal psychological treatment were as described in Alvarez *et al.* (2011).

Patients were also excluded if they had elevated intraocular pressure or were at risk for acute narrow angle glaucoma, known hypersensitivity to duloxetine, a chronic liver disease, a clinically significant unstable illness, a myocardial infarction within the previous 6 months, a thyroid-stimulating hormone value outside the reference range at screening, history of cancer in remission for less than 5 years, or clinically significant abnormal vital signs as determined by the investigator. Patients taking certain medications or treatments before baseline or during the study period (as described in Alvarez *et al.*, 2011) were also excluded, although antiarrhythmics, antihypertensives (except metoprolol and class 1C antiarrythmics), proton pump inhibitors and aspirin as antiplatelet treatment were permitted. Safety reasons for withdrawal from the study were defined using the criteria described in the study by Alvarez *et al.* (2011). If adverse events (AEs) contributed to withdrawal, they were regarded as the primary reason for withdrawal.

Efficacy rating

Patients were assessed with the 24-item Hamilton Depression Scale ($HAM\text{-}D_{24}$) (Williams, 2001) from baseline to week 8. The $HAM\text{-}D_{24}$ is a modified version of the original 17-item scale suggested by Hamilton (1960). All the raters underwent formal training in the $HAM\text{-}D_{24}$, the MADRS, the Clinical Global Impression (CGI) (Guy, 1976), the Hamilton Rating Scale for Anxiety (HAM-A) (Hamilton, 1959), the MMSE and the Mini International Neuropsychiatric Interview to maximize inter-rater reliability.

To evaluate cognitive effects, patient performance with respect to verbal learning and memory and processing speed [known to be impaired in depressed older patients (Burt *et al.*, 1995; Thomas *et al.*, 2009)] was measured at baseline and at last assessment. The tests were administered in the following order: (a) The Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1964; Lezak, 1983): Each patient was subjected to three trials to learn a list of 15 common nouns, and the acquisition score was the total number of words correctly recalled in the three trials. The delayed recall score was the number of words correctly recalled after the other cognitive tests had been administered. (b) The Digit Symbol Substitution Test (DSST) (Wechsler, 1997): This scale involves the substitution of simple symbols for digits. The number of correct symbols substituted for digits during a 2-min period was measured.

Allocation to treatment

Eligible patients were assigned to double-blind treatment according to a computer-generated randomization list. The details of the randomization series were contained in a set of sealed opaque envelopes. At each site, sequentially enrolled patients were assigned the lowest randomization number available in blocks of six. All investigators, trial personnel and patients were blinded to treatment assignment for the duration of the study. The code envelope was opened for four patients: one was opened during the safety follow-up period; two were damaged after the patients had completed treatment; and one envelope was opened because of a

suspected unexpected serious adverse reaction. The patient was withdrawn due to a serious adverse event (depression).

Analysis sets

Safety analyses were based on the all-patients-treated set (APTS), comprising all randomized patients who took at least one dose of study medication. Efficacy analyses were based on a modified intent-to-treat set – the full-analysis set (FAS), comprising all patients in the APTS who had at least one valid postbaseline assessment of the primary efficacy variable (HAM-D_{24} total score).

Power and sample size calculations

Approximately 450 patients were planned for enrolment in the study. With 150 patients per treatment group and an estimated SD of 8, this cohort size has at least 80% power to detect a true treatment effect of 2.64 HAM-D_{24} points in the change from baseline to week 8, using a 5% level of significance and a standard analysis of covariance (ANCOVA) (*t*-distributed contrast). This study was not powered to detect differences between Lu AA21004 and duloxetine.

Primary efficacy analysis

The primary efficacy analysis was an ANCOVA of the change from baseline in the HAM-D_{24} total score at week 8 [FAS, last observation carried forward (LOCF)] and, if applicable, at weeks 6, 4, 2 and 1, with treatment and centre as factors and the baseline HAM-D_{24} total score as a covariate. A statistical testing strategy was defined *a priori* and comprised the hierarchically ordered null hypotheses: no difference was detected between Lu AA21004 and placebo at week 8/week 6/week 4/week 2/week 1.

The other predefined efficacy outcome measures (response, remission, cognition, etc.) are of scientific interest and are presented without correction for multiplicity of analysis. The phrase 'separation from placebo' is used to describe findings with nominal *P*-values less than 0.05.

The model included all three treatments, but comparisons with duloxetine were not considered, as the study was not designed to examine any difference between Lu AA21004 5 mg and duloxetine 60 mg, and this was not part of the statistical analytical plan. The primary efficacy analysis was repeated using a mixed model for repeated measurements (MMRM) using available data.

Secondary efficacy analysis

CGI-S and CGI-I were also analysed using a Cochran–Mantel–Haenszel test stratifying for centre (FAS, LOCF). Response ($\geq$ 50% decrease from baseline) and remission (HAM-$D_{17} \leq 7$, CGI-S ≤ 2) were analysed per visit using logistic regression, adjusting for baseline score and treatment (FAS, LOCF). Unless otherwise stated, the terms 'significant' and 'significantly' refer to statistical significance at the 5% level, two-sided. Efficacy analyses that were not multiplicity-controlled were considered secondary. The principal statistical software used was SAS, version 9.2 (SAS Institute Inc., Cary, North Carolina, USA).

Predefined exploratory analyses: cognition

The DSST (number of correct symbols) and RAVLT (acquisition and delayed recall) were analysed with an ANCOVA (FAS) model using available data. In the ANCOVA model, treatment and centre were included as factors, whereas the baseline score of the endpoint was included as a covariate. The standardized effect sizes (Cohen's *d*) for the cognition outcomes were calculated as the difference from placebo in least squares means divided by the square root of the mean SD (Cohen, 1988). Positive standardized effect sizes favour Lu AA21004 compared with placebo treatment.

The post-hoc path analysis (Ditlevsen *et al.*, 2005) consisted of two ANCOVA models: Model 1 for the change from baseline for the HAM-D_{24} and Model 2 for change from baseline in the cognition outcomes. Both models include centre and treatment as categorical covariates, with baseline measurements for the HAM-D_{24} and the cognition outcome as continuous covariates. The ANCOVA model for the cognition outcomes additionally includes change from baseline HAM-D_{24} at last assessment as a continuous covariate. For each active treatment group, the direct effect is the ratio of the treatment effect (difference to placebo) on cognition (from Model 2) to the sum of the same treatment effect (difference to placebo) on cognition plus the product of the regression coefficient of change from baseline HAM-D_{24} on cognition (from Model 2) and the treatment effect (difference to placebo) on the HAM-D_{24} (from Model 1).

Safety and tolerability assessments

At each visit, starting at baseline, patients were asked a nonleading question (such as 'how do you feel?'). All AEs either observed by the investigator or reported spontaneously by the patient were recorded, together with vital signs. AEs were coded using the lowest-level term according to the Medical Dictionary for Regulatory Activities, version 12.1. The incidence of individual AEs was compared between treatment groups using Fisher's exact test. Clinical safety laboratory tests, weight, BMI, ECGs and physical examination findings were also evaluated.

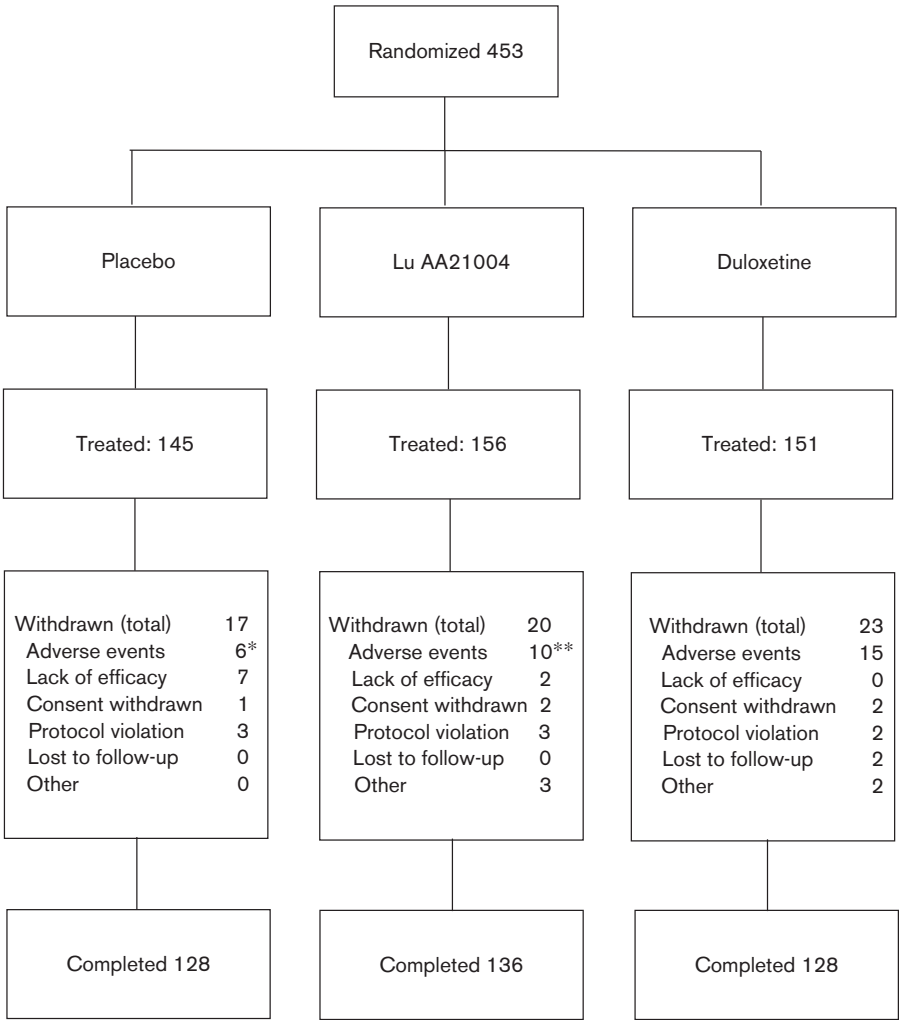
The Columbia-Suicide Severity Rating Scale was implemented to more accurately and systematically assess the relationship between the investigational medicinal products and suicidality. As a post-hoc analysis, the safety database was searched for possible suicide-related AEs (Laughren, 2006).

Results

Patient baseline characteristics

The APTS comprised 453 patients (Fig. 1) after the exclusion of one patient randomized to Lu AA21004 who

Fig. 1



Flow chart of patient disposition. *Two patients withdrawals in the safety follow-up period. **One patient withdrawal in the safety follow-up period.

did not take any study medication. There were no clinically relevant or statistically significant differences between treatment groups with respect to demographic or clinical characteristics at baseline (Table 1). Patients had a mean age of about 71 years; approximately two-thirds were women; 95% were Caucasian and 4% were Black.

The mean baseline MADRS total score was ~30, indicating moderate-to-severe depression, as also reflected in the mean CGI-S score of about 4.7. All the patients had experienced a previous MDE, and the current episode had typically started about 7–8 months before enrolment (Table 1). There was a substantial level of anxiety symptoms, indicated by a mean baseline HAM-A total score of 19. At baseline, ~91% of the patients in each treatment group had concurrent medical, psychiatric or neurological disorders, but these were not clinically relevantly different between groups. Disorders that were present at baseline in at least 5% of the patients in any treatment included osteoarthritis, type 2 diabetes, hypertension, drug hypersensitivity, back pain, benign prostatic hyperplasia and hypercholesterolaemia. Between 69 and 74% of the patients took concomitant medication that they continued with at baseline and 27 to 37% commenced concomitant medication during the study. The most common medications ($\geq$ 5% of the patients) in any treatment group that continued at baseline were simvastatin, aspirin, multivitamins and hydrochlorothiazide.

Withdrawals from the study

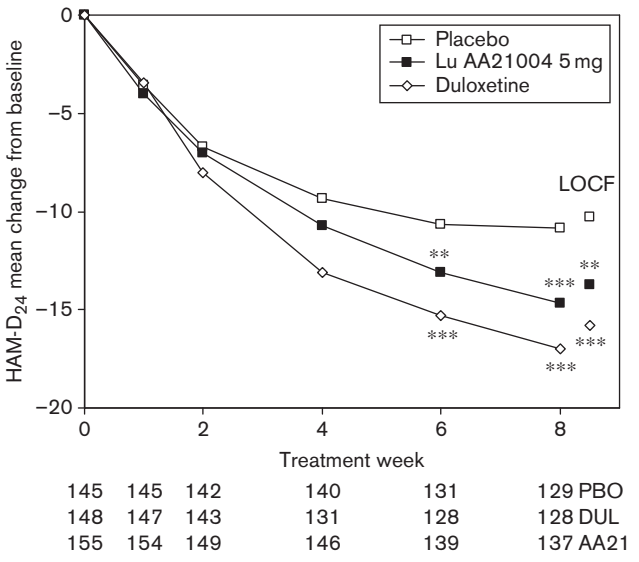
The withdrawal rate due to any reasons during the entire study was 13% (12% for placebo, 13% for Lu AA21004 and 15% for duloxetine) (Fig. 1). The most frequent primary

Table 1 Baseline patient characteristics

APTS	Placebo (n=145)	Lu AA21004 (n=156)	Duloxetine (n=151)
Women [n (%)]	90 (62.1%)	107 (68.6%)	100 (66.2%)
Mean age±SD	70.3±4.4	70.5±4.8	70.9±5.5
Range (years)	65–85	65–88	65–87
Caucasian	95.9%	92.9%	95.4%
Length of current MDE±SD (weeks)	33±38	33±52	34±46
Rating scale scores (FAS)	Placebo (n=145)	Lu AA21004 (n=155)	Duloxetine (n=148)
MADRS total score±SD	30.3±3.2	30.7±3.6	30.4±3.1
HAM-D_{24}±SD	29.4±5.1	29.2±5.0	28.5±4.9
HAM-D_{17}±SD	22.7±3.9	22.7±3.9	22.3±3.9
HAM-A total score±SD	19.5±5.7	19.9±5.8	19.2±6.5
CGI-S±SD	4.7±0.7	4.8±0.7	4.7±0.8
DSST correct symbols±SD	44.6±17.9	45.2±17.9	46.3±18.3
RAVLT acquisition±SD	21.8±6.0	22.3±6.4	22.0±6.7
RAVLT delayed recall±SD	6.2±3.0	6.6±3.2	6.5±3.1

APTS, all-patients-treated set; CGI-S, Clinical Global Impression – Severity; DSST, Digit Symbol Substitution Test; FAS, full-analysis set; HAM-A, Hamilton Rating Scale for Anxiety; HAM-D_{17}, Hamilton Rating Scale for Depression (17 items); HAM-D_{24}, Hamilton Rating Scale for Depression (24 items); MADRS, Montgomery–Åsberg Depression Rating Scale; MDE, major depressive episode; RAVLT, Rey Auditory Verbal Learning Test.

Fig. 2



Estimated Hamilton Rating Scale for Depression (24 items) (HAM-D_{24}) total scores from baseline to week 8 (FAS, MMRM by visit) and LOCF (FAS, ANCOVA, week 8). *P<0.05; **P<0.01; ***P<0.001 versus placebo. ANCOVA, analysis of covariance; DUL, duloxetine; FAS, full-analysis set; LOCF, last observation carried forward; MMRM, mixed model for repeated measures; PBO, placebo. Patient numbers at each visit are shown below the x-axis for each treatment group.

reason for withdrawal was AEs (6%). Analysis of time to withdrawal for any reason showed an even distribution of withdrawals over time and no statistically significant differences between the treatment groups. There were no statistically significant differences between men and women in any treatment group. Approximately 87% of the patients in each treatment group received study medication for at least 50 days in the 8-week treatment period.

Efficacy

Primary efficacy endpoint

Lu AA21004 5 mg was statistically significantly superior to placebo (P = 0.0011) on the predefined primary endpoint, an ANCOVA of the mean change from baseline in HAM-D_{24} total score at week 8 (FAS, LOCF), with a treatment difference of −3.3 points. In addition, Lu AA21004 5 mg was statistically significantly superior to placebo (P = 0.0240) at week 6, with a treatment difference of −2.1 points, but not at week 4. Because of the *a priori* hierarchically ordered hypotheses, testing at week 2 or week 1 could no longer be considered to be adjusted for multiplicity (Fig. 2). The results of the MMRM analyses were consistent with that of the ANCOVA LOCF analysis (Table 2).

Analyses of the remaining endpoints within the testing strategy and analyses outside the testing strategy were considered secondary and were tested at the 5% nominal level of significance.

Secondary efficacy analyses

Table 3 summarizes the treatment differences from placebo in the mean change from baseline to week 8 in HAM-D_{24}, MADRS, HAM-A and CGI-S scores and the treatment difference from placebo in mean CGI-I score at week 8. The results of the MMRM analyses were consistent with that of the ANCOVA, LOCF analysis, with separation from placebo for all listed outcomes.

Table 2 Change from baseline in Hamilton Rating Scale for Depression (24 items) total score at week 8 (full-analysis set)

Analysis	Treatment Group	n	Mean	Difference to placebo	P-value
LOCF, ANCOVA	Placebo	145	−10.3±0.8	–	–
	Lu AA21004	154	−13.7±0.7	−3.3±1.0	0.0011
	Duloxetine	147	−15.8±0.8	−5.5±1.0	<0.0001
MMRM	Placebo	129	−10.8±0.7	–	–
	Lu AA21004	137	−14.7±0.7	−3.8±1.0	0.0001
	Duloxetine	128	−17.0±0.7	−6.1±1.0	<0.0001

Changes from baseline are mean±SE scores.
ANCOVA, analysis of covariance; LOCF, last observation carried forward; MMRM, mixed model for repeated measures.

Response and remission

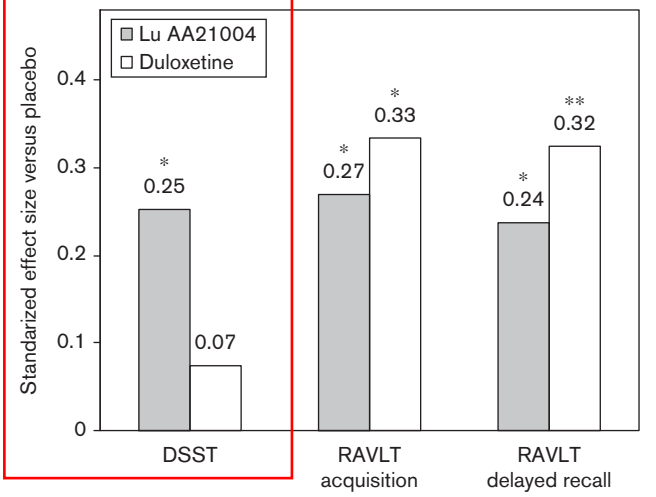
Response and remission were defined on the basis of the MADRS total score, HAM-D_{24} total score (response only), HAM-D_{17} total score (remission only), CGI-I score (response only) or CGI-S score (remission only). Both Lu AA21004 and duloxetine separated from placebo on all measures of response and remission (FAS, LOCF and logistic regression) (Table 4).

Table 3 Mean change from baseline in secondary efficacy variables at week 8, difference from placebo (full-analysis set)

	LOCF, ANCOVA		MMRM	
Efficacy variables	Lu AA21004	DUL	Lu AA21004	DUL
HAM-D_{24}[a]	−3.32**	−5.48***	−3.82***	−6.12***
MADRS	−4.29***	−6.83***	−4.74***	−7.59***
HAM-A	−2.35**	−3.54***	−2.69***	−3.89***
CGI-S	−0.60***	−1.02***	−0.65***	−1.11***
CGI-I[b]	−0.56***	−0.84***	−0.62***	−0.92***
DSST (# correct)	2.79*	0.77	–	–
RAVLT acquisition	1.14*	1.41**	–	–
RAVLT delayed recall	0.47*	0.64**	–	–

ANCOVA, analysis of covariance; CGI-I, Clinical Global Impression – Improvement; CGI-S, Clinical Global Impression – Severity; DSST, Digit Symbol Substitution Test; DUL, duloxetine; HAM-A, Hamilton Rating Scale for Anxiety; HAM-D_{24}, Hamilton Rating Scale for Depression (24 items); LOCF, last observation carried forward; MADRS, Montgomery–Åsberg Depression Rating Scale; MMRM, mixed model for repeated measures; RAVLT, Rey Auditory Verbal Learning Test.
[a]Primary efficacy variable: HAM-D_{24}, FAS, LOCF, ANCOVA; other efficacy assessments are outside the statistical testing hierarchy and nominal *P*-values are shown.
[b]Treatment difference from placebo in mean CGI-I score at week 8.
* $P<0.05$; ** $P<0.01$; *** $P<0.001$ vs. placebo.

Fig. 3



Standardized effect sizes of Lu AA21004 5 mg/day and duloxetine 60 mg/day compared with placebo on the Digit Symbol Substitution Test (DSST) and the Rey Auditory Verbal Learning Test (RAVLT). *$P<0.05$; **$P<0.01$ versus placebo.

Table 4 Responder and remission rates (full-analysis set, logistic regression, last observation carried forward)

	n (%)		
Response/remission criterion	PBO	Lu AA21004	DUL
Response			
HAM-D_{24}[a]	51 (35.2%)	82 (53.2%)**	93 (63.3%)***
MADRS[a]	52 (35.9%)	92 (59.7%)***	104 (70.7%)***
CGI-I ≤ 2	55 (38.0%)	95 (61.7%)***	106 (72.1%)***
Remission			
HAM-D_{17} ≤ 7	28 (19.3%)	45 (29.2%)*	51 (34.7%)**
MADRS ≤ 10	30 (20.7%)	52 (33.8%)*	69 (46.9%)***
CGI-S ≤ 2	28 (19.3%)	51 (33.1%)**	60 (40.8%)***

CGI-I, Clinical Global Impression – Improvement; CGI-S, Clinical Global Impression – Severity; DUL, duloxetine; HAM-D_{17}, Hamilton Rating Scale for Depression (17 items); LOCF, last observation carried forward; MADRS, Montgomery–Åsberg Depression Rating Scale; PBO, placebo.
[a] ≥ 50% decrease from baseline in total score.
*Nominal $P<0.05$; **nominal $P<0.01$; ***nominal $P<0.001$ vs. placebo.

Table 5 Adverse events with an incidence of ≥ 5% in the 8-week treatment period (all-patients-treated set)

	n (%)		
Preferred terms	Placebo (*n*=145)	Lu AA21004 (*n*=156)	Duloxetine (*n*=151)
Patients with AEs	89 (61.4)	97 (62.2)	118 (78.1)
Nausea	12 (8.3)	34 (21.8)**	50 (33.1)***
Headache	25 (17.2)	18 (11.5)	18 (11.9)
Dizziness	10 (6.9)	14 (9.0)	14 (9.3)
Fatigue	5 (3.4)	11 (7.1)	16 (10.6)*
Constipation	6 (4.1)	10 (6.4)	21 (13.9)**
Dry mouth	7 (4.8)	10 (6.4)	33 (21.9)***
Diarrhoea	10 (6.9)	8 (5.1)	14 (9.3)
Decreased appetite	2 (1.4)	7 (4.5)	8 (5.3)
Hyperhidrosis	4 (2.8)	6 (3.8)	16 (10.6)*
Somnolence	3 (2.1)	4 (2.6)	16 (10.6)**
Ejaculation delayed§	–	–	3 (5.9)
Erectile dysfunction§	–	–	3 (5.9)

AEs, adverse events.
*$P<0.05$; ** $P<0.01$; *** $P<0.001$ vs. placebo.
§ men.

Cognition

On the DSST, Lu AA21004, but not duloxetine, showed an improvement compared with placebo (nominal $P < 0.05$) on the number of correct symbols (Table 3). On the RAVLT, both Lu AA21004 (nominal $P < 0.05$) and duloxetine (nominal $P < 0.01$) showed an improvement compared with placebo on acquisition time and longer delayed recall (Table 3). The standardized effect sizes relative to placebo are shown in Fig. 3. Path analysis showed that Lu AA21004 had an 83% direct effect on the DSST (duloxetine 26%). On RAVLT acquisition, Lu AA21004 had a 71% direct effect (duloxetine 65%). On RAVLT delayed recall, Lu AA21004 had a 72% direct effect (duloxetine 66%).

Tolerability and safety

During the 8-week treatment period, approximately two-thirds of patients in the placebo (61%) and Lu AA21004 (62%) groups and approximately four-fifths of patients in the duloxetine (78%) group had one or more AEs. None of the patients in the placebo or Lu AA21004 groups had AEs related to sexual dysfunction, whereas six patients (all men) in the duloxetine group did (Table 5): one had abnormal orgasm and erectile dysfunction, one had decreased libido and erectile dysfunction, one had erectile dysfunction and three had delayed ejaculation.

No AEs relevant for suicide were reported. Five patients took an overdose (one to four capsules) of investigational medicine by mistake, with no suicidal intent. An improvement in the scores for MADRS item 10 (suicidal thoughts) and HAM-D item 3 (suicide) from baseline was seen in all treatment groups at all visits, with significant and borderline difference compared with placebo at week 8 for the duloxetine and Lu AA21004 groups, respectively. The Columbia-Suicide Severity Rating Scale data showed no clinically relevant differences between active treatment groups and placebo.

In the 8-week treatment period, 28 patients withdrew because of AEs: four (3%) in the placebo group, compared with nine (6%) in the Lu AA21004 group ($P = 0.2605$, Fisher's exact test), and 15 (10%) in the duloxetine group ($P = 0.0160$, Fisher's exact test) (Fig. 1). AEs leading to withdrawal of at least two patients in any of the treatment groups comprised dizziness in the placebo group, nausea in the Lu AA21004 group and nausea and dizziness in the duloxetine group.

SAEs were reported by six patients: four in the placebo group and one patient each in the Lu AA21004 and duloxetine groups. No SAE was reported by more than one patient. No deaths occurred during this study.

No clinically relevant changes over time or differences between treatment groups were seen in clinical laboratory test results, vital signs, weight or ECG parameters.

Discussion

In the Nelson *et al.* (2008) meta-analysis of 13 comparisons compared with placebo from 10 randomized studies on depression in elderly patients, there was significantly greater efficacy for the four 10–12-week studies (three positive comparisons; odds ratio for response of 1.73) compared with the six 6–8-week studies (three positive comparisons; odds ratio of 1.22). Four of the six positive studies included patients aged between 60 and 64 years, and the two active-referenced studies (Kasper *et al.*, 2005; Schatzberg and Roose, 2006) failed to show a statistically significant difference from placebo for both investigational drug and active reference. Thus, this 8-week randomized, double-blind placebo-controlled study, in which both Lu AA21004 5 mg and the active reference duloxetine 60 mg were efficacious in the treatment of elderly patients with MDD, is one of a few such positive studies.

In addition to their depression, older depressed patients often have impaired cognition (Gotlib and Joormann, 2010), which needs to be distinguished from dementia. For this reason, the inclusion and exclusion criteria were chosen to select patients with moderate-to-severe MDD, and an MMSE score of at least 24 was required to exclude patients with mild dementia. Patients with hyperthyroidism were also excluded, as hyperthyroidism can produce symptoms similar to those seen in depression.

In-vivo nonclinical studies with Lu AA21004 have shown increased levels of the neurotransmitters serotonin, noradrenaline, dopamine, acetylcholine and histamine in specific areas of the brain (Bang-Andersen *et al.*, 2011; Mørk *et al.*, 2011). In addition, Lu AA21004 has shown cognitive enhancing properties in animal models (Mørk *et al.*, 2011). In the present study, the RAVLT and the DSST were selected because they cover aspects of cognition known to be impaired in patients with MDD and were equivalent to tests in another study on depressed elderly patients that showed positive cognitive results (Raskin *et al.*, 2007). In the present study, both Lu AA21004 and duloxetine showed statistically significant differences on the RAVLT, whereas only Lu AA21004 showed a statistically significant difference on the DSST. The data confirm the previously reported finding that the effect of duloxetine on cognition in elderly MDD patients is primarily driven by verbal learning and memory (Raskin *et al.*, 2007) and suggest that Lu AA21004 may improve cognitive dysfunction beyond verbal learning and memory. Performance of the DSST is reliant on several cognitive domains including processing speed, executive functioning and attention. The improved performance of Lu AA21004 in both the DSST and RAVLT on cognition might be explained by its broad effects on neurotransmitter levels involved in cognitive processes, as seen in microdialysis experiments with animals, and reflected in procognitive effects in rats (Mørk *et al.*, 2011). 5-HT_{1A} receptor stimulation and 5-HT_3 receptor antagonism, both properties of Lu AA21004, enhance cortical glutamatergic neuronal firing by disinhibition of γ-aminobutyric acidergic interneurons (Puig *et al.*, 2004; Lladó-Pelfort *et al.*, 2011). Both mechanisms may potentially contribute to the observed improvement in cognitive performance observed in the present study. Moreover, post-hoc path analysis revealed that more than two-thirds of the effect of Lu AA21004 on both DSST and RAVLT was a direct treatment effect rather than an indirect effect through improvement of depressive symptoms. Although the effect of Lu AA21004 was similar to duloxetine on the RAVLT, the effect of duloxetine on the DSST was nonsignificant and primarily driven by an improvement in depressive symptoms.

Lu AA21004 was well tolerated by the elderly patients in this study, with placebo-level withdrawals due to AEs and no treatment-emergent sexual dysfunction. Nausea was the only AE with a significantly higher incidence in the Lu AA21004-treated group compared with placebo, whereas the incidences of dry mouth, hyperhidrosis, constipation, fatigue and somnolence were also significantly higher in the duloxetine-treated group. There was also a significantly higher AE withdrawal rate in duloxetine-treated patients.

As patients with comorbid psychiatric disorders were excluded from the study, the results of this study cannot automatically be generalized to routine healthcare settings. First-episode patients and patients with clinically significant unstable medical illnesses were also excluded. In addition, only one Lu AA21004 dose was used in this study, and the treatment period was only 8 weeks. Finally, cognitive assessments were exploratory, limited to two tests, and were only measured at baseline and at the end of the study.

In summary, Lu AA21004 was efficacious and well tolerated in the treatment of elderly patients with MDD. The incidence of most adverse effects was comparable to that of placebo.

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Conflicts of interest

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