A Randomized, Double-Blind, Placebo-Controlled 8-Week Trial of the Efficacy and Tolerability of Multiple Doses of Lu AA21004 in Adults With Major Depressive Disorder

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ABSTRACT

Objective: Lu AA21004 is an investigational multimodal antidepressant. This randomized controlled trial evaluated the efficacy and tolerability of multiple doses of Lu AA21004 versus placebo in adults with major depressive disorder (MDD).

Method: Adults diagnosed with MDD (based on *DSM-IV-TR* criteria) with a Montgomery-Asberg Depression Rating Scale (MADRS) score ≥ 26 were randomly assigned (1:1:1:1) to receive Lu AA21004 1 mg, 5 mg, or 10 mg or placebo for 8 weeks (between August 2008 and August 2009). The primary endpoint was reduction in 24-Item Hamilton Depression Rating Scale (HDRS-24) total score after 8 weeks of treatment compared with placebo for Lu AA21004 10 mg. Additional outcomes included response and remission rates, Sheehan Disability Scale (SDS), Clinical Global Impressions-Global Improvement scale (CGI-I), MADRS total score, and HDRS-24 total score in subjects with baseline Hamilton Anxiety Rating Scale (HARS) score ≥ 20. Adverse events were assessed throughout the study.

Results: A total of 560 subjects (mean age = 46.4 years) were randomized. There was a statistically significant reduction from baseline in HDRS-24 total score at week 8 for Lu AA21004 10 mg vs placebo ($P < .001$). There were improvements (nominal P values < .05 with no adjustment for multiplicity) in HDRS-24 total score, response and remission rates, CGI-I score, MADRS total score, and HDRS-24 total score in subjects with baseline HARS score ≥ 20 at week 8 for all Lu AA21004 treatment groups vs placebo. No significant differences were seen in SDS scores between any dose of Lu AA21004 and placebo. The most common adverse events were nausea, headache, and dizziness.

Conclusions: After 8 weeks of treatment with Lu AA21004 10 mg, there was a significant reduction in HDRS-24 total score compared with placebo in adults with MDD. Lu AA21004 was well tolerated in this study.

Trial Registration: ClinicalTrials.gov identifier: NCT00735709

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Major depressive disorder (MDD) is estimated to be the fourth leading cause of disease burden worldwide.[1] However, despite the large number of medications available to treat MDD, considerable unmet needs in pharmacologic treatment remain.[2,3] Overall, about 50% of patients who begin treatment with the most commonly prescribed antidepressants demonstrate significant reductions in depression symptoms, and it can take up to 8 weeks to achieve a clinically significant response (defined as a 50% reduction from baseline).[4,5] Patients with depression and high levels of anxiety are even more difficult to treat. In the Sequenced Treatment Alternatives to Relieve Depression study, for example, patients with high baseline anxiety were significantly less likely to respond to an antidepressant at each step compared with depressed patients with no anxiety.[6] This can be a significant issue for treatment, since approximately half of all depressed patients experience a comorbid anxiety disorder during their lifetime.[7] It has been suggested that new medications that selectively target multiple neurotransmitter systems and receptor subtypes may offer advantages in efficacy and/or tolerability over currently available antidepressants.[8]

Lu AA21004 is an investigational multimodal antidepressant that functions as 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 vitro.[9,10] In vivo nonclinical studies have demonstrated that Lu AA21004 enhances levels of the neurotransmitters serotonin, norepinephrine, dopamine, acetylcholine, and histamine in specific areas of the brain.[9,10] Lu AA21004 is currently in clinical development for the treatment of MDD. A previous study[11] of Lu AA21004 showed that both 5-mg and 10-mg doses significantly decreased Montgomery-Asberg Depression Rating Scale (MADRS)[12] total score in subjects with MDD after 6 weeks of treatment compared with placebo ($P < .0001$ for both doses) and were well tolerated. The goal of the current study was to evaluate the efficacy and tolerability of multiple doses of Lu AA21004 (1 mg, 5 mg, and 10 mg) vs placebo after 8 weeks of treatment in adults with MDD.

METHOD

This was a multicenter, double-blind, randomized, placebo-controlled, parallel-group, phase 3 study of Lu AA21004 1 mg, 5 mg, and 10 mg fixed-dose once-daily treatment in adults with MDD in Europe, Asia, and Africa. Adults aged 18 to 75 years with a diagnosis of MDD (major depressive episode of at least 3 months' duration, based on the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision) and a MADRS total score ≥ 26 were eligible for the study. Subjects who were considered by the investigator to pose a significant risk of suicide, had a score ≥ 5 on item 10 (suicidal thoughts) of the MADRS or had made a suicide attempt in

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Clinical Points

- Depressed patients demonstrated improvements on 24-Item Hamilton Depression Rating Scale and Montgomery-Asberg Depression Rating Scale total scores when treated with Lu AA21004.
- Depressed patients with high levels of anxiety symptoms showed improvements in their depressive symptoms with Lu AA21004.
- Improvements in depression symptoms were seen from week 2 onward for patients treated with Lu AA21004.

the previous 6 months, or had failed 2 previous antidepressant treatments (of at least 6 weeks in duration) were not eligible for the study. Subjects were also excluded from the study if they had a history of a psychiatric (other than MDD, as assessed by the Mini International Neuropsychiatric Interview [MINI][13]), neurologic, or substance abuse disorder; current clinically significant medical illness; or clinically significant abnormalities in vital signs or laboratory values.

Subjects underwent screening 2 to 10 days prior to the start of the study to determine eligibility. Demographic information, medical and medication history, and confirmation of the MDD diagnosis were assessed. Subjects underwent a physical examination, clinical laboratory testing, a 12-lead electrocardiogram (ECG), and psychological assessments including the MINI, 24-Item Hamilton Depression Rating Scale (HDRS-24),[14] MADRS, and Columbia-Suicide Severity Rating Scale (C-SSRS).[15]

Eligible subjects were randomly assigned (1:1:1:1) to receive Lu AA21004 1 mg, 5 mg, or 10 mg or placebo for 8 weeks (between August 2008 and August 2009). Blinding of all participants was maintained throughout the study. All study medication was identical in appearance and dispensed using unique identification numbers. Subjects returned to the study site for assessments at baseline and weeks 1, 2, 4, 6, and 8. The primary efficacy assessment was the change from baseline in HDRS-24 total score after 8 weeks of treatment (Lu AA21004 1, 5, and 10 mg vs placebo). Additional assessments included the Sheehan Disability Scale (SDS),[16] Clinical Global Impressions-Global Improvement scale (CGI-I),[17] HDRS-24 response rate (defined as a ≥ 50% decrease in HDRS-24 total score from baseline), HDRS-17 remission rate (defined as the sum of items 1–17 on the HDRS-24 ≤ 7), HDRS-24 total score in subjects with baseline Hamilton Anxiety Rating Scale (HARS)[18] score ≥ 20, MADRS response rate (defined as ≥ 50% decrease in MADRS total score from baseline), MADRS remission rate (defined as a MADRS total score ≤ 10), and MADRS total score. Safety and tolerability were assessed throughout the 8-week treatment period via collection of adverse events (AEs), vital signs, weight, ECGs, laboratory values, and physical examination findings at each visit. The C-SSRS was administered at each visit in order to assess any potential suicidality during the study. Subjects were contacted 4 weeks after the last dose of study medication for a safety follow-up.

This study was conducted according to the protocol, the World Medical Association Declaration of Helsinki, the ICH Harmonized Tripartite Guideline for Good Clinical Practice, and all applicable local or regional regulatory requirements. An ethics committee for each country or site approved the protocol and written informed consent was obtained from each subject prior to any study procedures. The study is registered with ClinicalTrials.gov (identifier: NCT00735709).

The sample size was based on an assumed standard deviation of 9.5 for the change from baseline in HDRS-24 total score. A total of 560 subjects (140 per treatment group) was calculated as necessary to achieve at least 85% power to detect a difference of 3.5 in HDRS-24 total score between the Lu AA21004 and placebo groups using a 2-sample *t* test with a .05 2-sided significance level.

Statistical analyses were performed using SAS Version 9.1.3 on a UNIX platform (SAS Institute; Cary, North Carolina). Before unblinding the data, centers with fewer than 8 subjects were pooled with geographically similar centers to minimize artifacts in the statistical analyses. Efficacy analyses were based on the full analysis set (FAS), which included all randomized subjects who received at least 1 dose of study drug and had at least 1 valid postbaseline value for assessment of primary efficacy. Safety analyses were based on the safety set, which included all subjects who were randomized and received at least 1 dose of double-blind study medication. Comparisons between all doses of Lu AA21004 and placebo were performed on the FAS using a mixed model for repeated measurements. HDRS-24 response rates, HDRS-17 remission rates, MADRS response rates, and MADRS remission rates were analyzed at all time points by logistic regression, adjusting for baseline score and treatment using the last-observation-carried-forward method to account for missing scores of study noncompleters. Standardized effect sizes were calculated using the difference of mean change between Lu AA21004 at each dose and placebo divided by the pooled standard deviation.

To control for multiplicity, a prespecified sequential testing procedure was applied to compare Lu AA21004 10 mg and 5 mg to placebo. The Lu AA21004 1-mg dose, which was not expected to be effective, was not included in the prespecified testing hierarchy. The efficacy endpoints included in the hierarchy were analyzed in the following sequence at significance level .05: (1) change from baseline in HDRS-24 total score at week 8 (Lu AA21004 10 mg vs placebo), (2) change from baseline in SDS total score at week 8 (Lu AA21004 10 mg vs placebo), (3) CGI-I score at week 8 (Lu AA21004 10 mg vs placebo), (4) HDRS-24 response rate at week 8 (Lu AA21004 10 mg vs placebo), (5) change from baseline in HDRS-24 total score at week 8 in subgroup of subjects with baseline HARS total score ≥ 20 (Lu AA21004 10 mg vs placebo), (6) MADRS remission rate at week 8 (Lu AA21004 10 mg vs placebo), (7) change from baseline in HDRS-24 total score at week 8 (Lu AA21004 5 mg vs placebo), (8) change from baseline in SDS total score at week 8 (Lu AA21004 5 mg vs placebo), (9) CGI-I at week 8 (Lu AA21004 5 mg vs placebo), (10) HDRS-24 response rate at

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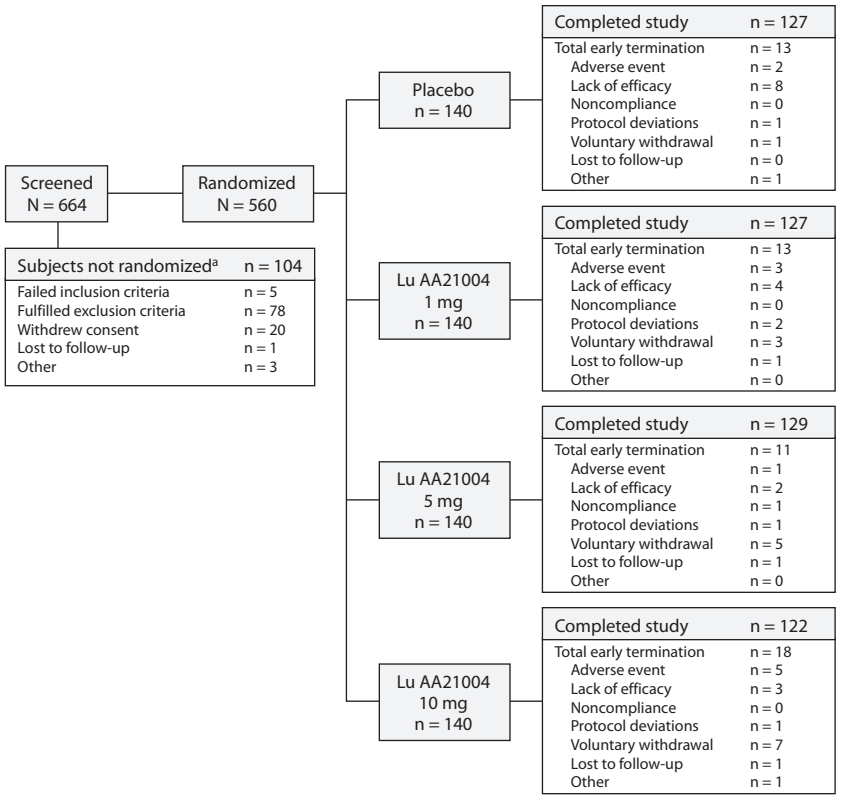
Figure 1. Disposition of Subjects



[a]Total for subjects not randomized includes subjects with more than 1 reason for screen failure.

Table 1. Subject Demographics (all randomized subjects)

Characteristic	Placebo (n = 140)	Lu AA21004 1 mg (n = 140)	Lu AA21004 5 mg (n = 140)	Lu AA21004 10 mg (n = 140)
Sex, n (%)				
Male	54 (38.6)	47 (33.6)	53 (37.9)	55 (39.3)
Female	86 (61.4)	93 (66.4)	87 (62.1)	85 (60.7
Age, mean (SD), y	46.4 (12.3)	45.4 (11.9)	47.3 (12.0)	46.4 (12.3)
Race, n (%)				
White	120 (85.7)	129 (92.1)	120 (85.7)	114 (81.4)
Black	5 (3.6)	1 (0.7)	2 (1.4)	2 (1.4)
Asian	14 (10.0)	8 (5.7)	17 (12.1)	23 (16.4)
Other	1 (0.7)	2 (1.4)	1 (0.7)	1 (0.7)
BMI, mean (SD), kg/m^2	26.4 (4.6)	26.5 (5.4)	26.4 (5.1)	26.2 (4.6)
Baseline HDRS-24 total score, mean (SD)	32.7 (4.40)	32.5 (5.13)	32.1 (5.04)	33.1 (4.77)
Baseline MADRS total score, mean (SD)	30.6 (2.89)	30.4 (3.01)	30.6 (2.83)	31.6 (3.83)

Abbreviations: BMI = body mass index, HDRS-24 = 24-Item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale.

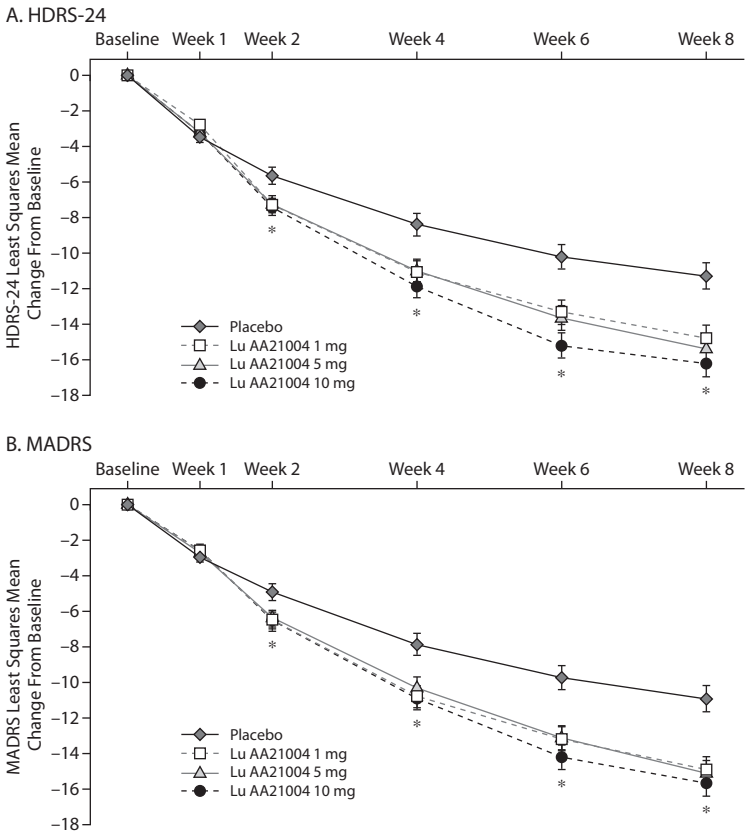
week 8 (Lu AA21004 5 mg vs placebo), (11) change from baseline in HDRS-24 total score at week 8 in subjects with baseline HARS ≥ 20 (Lu AA21004 5 mg vs placebo), and (12) MADRS remission rate at week 8 (Lu AA21004 5 mg vs placebo). Once an endpoint was considered not significant, the formal testing procedure was stopped for all subsequent endpoints. For endpoints that occurred after the prespecified statistical testing procedure was stopped or were outside the testing procedure, nominal *P* values with no adjustment for multiplicity were reported. The phrase *separation from placebo* was used to describe findings with nominal *P* values less than .05.

RESULTS

A total of 560 subjects from 14 countries (Australia, Croatia, France, Germany, Latvia, Lithuania, Malaysia, Netherlands, Poland, Republic of Korea, Russia, South Africa, Taiwan, and Ukraine) were randomly assigned to receive treatment (n = 140 per treatment group). The percentages of subjects completing treatment in the 4 groups were 90.7%, 92.1%, and 87.1% in the Lu AA21004 1, 5, and 10 mg groups, respectively, compared with 90.7% in the placebo group. The flow of subjects through the trial is shown in Figure 1, and demographic data for all randomized subjects are shown in Table 1.

There was a statistically significant reduction in the primary endpoint of HDRS-24 total score at week 8 for the Lu AA21004 10 mg group compared with placebo ($P < .001$) (Figure 2, Table 2). There was no significant difference in SDS total score between Lu AA21004 10 mg and placebo at week 8, which stopped the formal testing procedure (Table 2). There were reductions in HDRS-24 and MADRS total scores by week 2 for all doses of Lu AA21004 compared with placebo (assessments at weeks 2, 4, and 6 were not considered statistically significant on the basis of the prespecified testing hierarchy but separated from placebo with nominal

Figure 2. Least Squares Mean Change From Baseline in HDRS-24 Total Score (A) and MADRS Total Score (B) During the 8-Week Treatment Period (full analysis set, MMRM)



*$P < .05$ for all doses of Lu AA21004; comparisons at weeks 2, 4, and 6 were not adjusted for multiplicity.
Abbreviations: HDRS-24 = 24-Item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MMRM = mixed model for repeated measurements.

P values < .05) (Figure 2, Table 2). Reductions in CGI-I scores and HDRS-24 total scores in subjects with baseline HARS score ≥ 20 and greater HDRS-24 response rates, HDRS-17 remission rates, MADRS response rates, and MADRS remission rates were demonstrated by week 8 for all Lu AA21004 doses compared with placebo (Figure 3, Table 2). Nominal *P* values were < .05 for all endpoints with the exception of MADRS remission rate for subjects taking Lu AA21004 1 mg.

Of the 559 subjects in the safety analysis set, 252 (45.1%) reported a total of 511 AEs during the study (55 [39.3%] in the Lu AA21004 1 mg group, 79 [56.4%] in the 5 mg group, 58 [41.7%] in the 10 mg group, and 60 [42.9%] in the placebo group). The majority of AEs were considered by the investigators to be mild to moderate in intensity. By the end of the treatment period, 11/560 subjects (2%) had discontinued treatment due to AEs (n = 3, 1, 5, and 2 in the Lu AA21004 1 mg, 5 mg, and 10 mg and placebo groups, respectively). The most frequently reported treatment-emergent AEs for the Lu AA21004–treated groups were nausea, headache, and dizziness. The incidence of sexual dysfunction AEs was low overall (< 1%), with no reports of sexual dysfunction in the Lu AA21004 1 mg or 5 mg or placebo groups and 1 report of decreased libido in the Lu AA21004 10 mg group. Clinical chemistry, hematology, urinalysis, vital signs, ECG, and physical examination results were generally within the normal range, and no clinically meaningful differences between the Lu AA21004 treatment groups and placebo were observed. Weight gain of ≥ 7% of body weight was similar across treatment groups (1.4%, 0.7%, 2.2%, and 2.9% of subjects in the Lu AA21004 1 mg, 5 mg, and 10 mg and placebo groups, respectively). There were no clinically meaningful differences between any dose of Lu AA21004 and placebo in suicidal ideation or behavior using the C-SSRS. All AEs occurring in ≥ 5% of subjects are shown in Table 3.

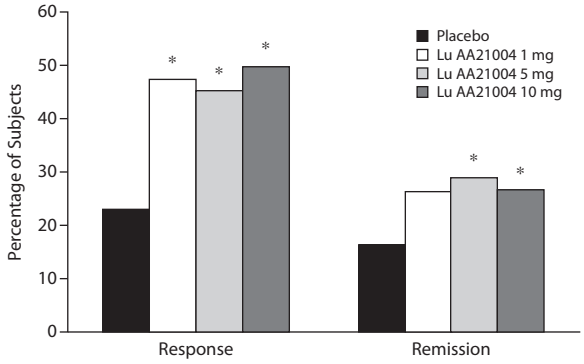
A total of 6 (1.1%) subjects overall experienced a serious AE during the study, and the incidence was similar across treatment groups (pancreatitis and suicide attempt in the Lu AA21004 10 mg group, tachycardia in the Lu AA21004 5 mg group, hypertensive crisis in the Lu AA21004 1 mg group, and severe dizziness and pancreatitis in the placebo group). Only the incidence of pancreatitis in the Lu AA21004 10 mg group was judged by the investigator to be possibly related to the study drug. No deaths occurred during the study.

Table 2. Efficacy Endpoints at Week 8 (full analysis set)

Endpoint	Placebo	Lu AA21004		
		1 mg	5 mg	10 mg
HDRS-24 total score (MMRM)				
Total treatment group n	128	124	129	122
LS mean change from baseline (SE)	−11.30 (0.738)	−14.82 (0.745)	−15.42 (0.743)	−16.23 (0.755)
LS mean difference from placebo (SE)		−3.52 (1.04)	−4.12 (1.04)	−4.93 (1.05)
P value		<.001[a]	<.001[a]	<.001
95% CI		(−5.57 to −1.47)	(−6.17 to −2.08)	(−6.99 to −2.86)
Standardized effect size[b]		0.37	0.41	0.54
MADRS total score (MMRM)				
Total treatment group n	128	124	129	122
LS mean change from baseline (SE)	−10.91 (0.708)	−14.89 (0.715)	−15.09 (0.712)	−15.65 (0.728)
LS mean difference from placebo (SE)		−3.99 (1.00)	−4.18 (1.00)	−4.75 (1.01)
P value		<.001[a]	<.001[a]	<.001[a]
95% CI		(−5.95 to −2.02)	(−6.14 to −2.22)	(−6.74 to −2.76)
Standardized effect size		0.44	0.50	0.58
SDS (MMRM)				
Total treatment group n	94	90	97	83
LS mean change from baseline (SE)	−6.54 (0.716)	−6.58 (0.729)	−7.65 (0.713)	−8.08 (0.756)
LS mean difference from placebo (SE)		−0.05 (1.01)	−1.11 (1.00)	−1.54 (1.03)
P value		.963	.263	.135
95% CI		(−2.03 to 1.94)	(−3.07 to 0.84)	(−3.56 to 0.48)
Standardized effect size[b]		0.01	0.15	0.24
CGI-I (MMRM)				
Total treatment group n	128	124	129	122
LS mean (SE)	2.84 (0.089)	2.37 (0.090)	2.37 (0.089)	2.29 (0.091)
LS mean difference from placebo (SE)		−0.47 (0.13)	−0.47 (0.13)	−0.55 (0.13)
P value		<.001[a]	<.001[a]	<.001[a]
95% CI		(−0.72 to −0.23)	(−0.71 to −0.22)	(−0.80 to −0.30)
Standardized effect size[b]		0.40	0.42	0.46
HDRS-24 total score with HARS ≥ 20 (MMRM)				
Total treatment group n	62	65	57	65
LS mean change from baseline (SE)	−11.02 (1.017)	−15.16 (0.991)	−15.50 (1.063)	−15.61 (0.984)
LS mean difference from placebo (SE)		−4.13 (1.40)	−4.47 (1.45)	−4.59 (1.40)
P value		.004[a]	.002[a]	.001[a]
95% CI		(−6.90 to −1.37)	(−7.32 to −1.62)	(−7.34 to −1.84)
Standardized effect size[b]		0.40	0.48	0.49
HDRS-24 response rate (LOCF)				
Total treatment group n	139	139	139	139
n (%)	32 (23.0)	66 (47.5)	63 (45.3)	69 (49.6)
P value		<.001[a]	<.001[a]	<.001[a]
Odds ratio vs placebo		3.02	2.74	3.35
95% CI		(1.799 to 5.063)	(1.631 to 4.598)	(1.995 to 5.618)
HDRS-17 remission rate (LOCF)				
Total treatment group n	139	139	139	139
n (%)	16 (11.5)	29 (20.9)	34 (24.5)	33 (23.7)
P value		.044[a]	.008[a]	.007[a]
Odds ratio vs placebo		1.982	2.425	2.447
95% CI		(1.019 to 3.855)	(1.264 to 4.653)	(1.273 to 4.706)
MADRS remission rate (LOCF)				
Total treatment group n	139	139	139	139
n (%)	23 (16.5)	36 (25.9)	40 (28.8)	37 (26.6)
P value		.062[a]	.015[a]	.026[a]
Odds ratio vs placebo		1.75	2.06	1.95
95% CI		(0.97 to 3.16)	(1.15 to 3.67)	(1.08 to 3.52)
MADRS response rate (LOCF)				
Total treatment group n	139	139	139	139
n (%)	34 (24.5)	65 (46.8)	61 (43.9)	68 (48.9)
P value		<.001[a]	<.001[a]	<.001[a]
Odds ratio vs placebo		2.717	2.414	2.929
95% CI		(1.631 to 4.527)	(1.447 to 4.027)	(1.752 to 4.885)

[a]Nominal *P* values with no adjustments for multiplicity.
[b]Based on observed cases.
Abbreviations: HARS = Hamilton Rating Scale for Anxiety, HDRS-17 = 17-Item Hamilton Depression Rating Scale, HDRS-24 = 24-Item Hamilton Depression Rating Scale, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, MMRM = mixed model for repeated measurements.

Figure 3. Percentage of Subjects Achieving HDRS-24 Response and MADRS Remission at Week 8 (full analysis set, LOCF)



*$P < .05$ vs placebo (comparisons were not adjusted for multiplicity).
Abbreviations: HDRS-24 = 24-Item Hamilton Depression Rating Scale, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale.

Table 3. Adverse Events Occurring in ≥ 5% of Subjects for Any Treatment Group (safety analysis set), No. of Patients (%)

		Lu AA21004		
Adverse Event	Placebo	1 mg	5 mg	10 mg
Total	60 (42.9)	55 (39.3)	79 (56.4)	58 (41.7)
Nausea	6 (4.3)	11 (7.9)	22 (15.7)	18 (12.9)
Headache	11 (7.9)	9 (6.4)	16 (11.4)	7 (5.0)
Nasopharyngitis	8 (5.7)	5 (3.6)	7 (5.0)	3 (2.2)
Dizziness	3 (2.1)	1 (0.7)	5 (3.6)	9 (6.5)

DISCUSSION

There was a statistically significant reduction in HDRS-24 total score at week 8 in the Lu AA21004 10 mg group, with separation from placebo by week 2. Since change from baseline in SDS total score for Lu AA21004 10 mg was not significantly different from placebo at week 8, all subsequent assessments were not considered statistically significant, despite their nominal *P* values, using the prespecified testing procedure. Several assessments did show separation from placebo with nominal *P* values < .05 in the Lu AA21004 10 mg, 5 mg, and 1 mg groups. Reductions in HDRS-24 total scores for the Lu AA21004 10-mg (only dose considered statistically significant), 5-mg, and 1-mg doses compared with placebo were evident by week 2, and by week 8 had moderate standardized effect sizes (0.54, 0.41, and 0.37, respectively), with the Lu AA21004 10 mg group demonstrating a trend toward greater efficacy, indicating a potential dose effect. Reductions in MADRS total scores showed similar improvements for all doses that were evident by week 2. These results build upon the data from a previous study[11] in the European Union of Lu AA21004 5 mg and 10 mg that demonstrated significant improvements in MADRS and HDRS-24 total scores at 6 weeks in adults with MDD.

Response rates for all doses of Lu AA21004 at week 8 were just under 50% compared with 23% for placebo, and remission rates ranged from 25.9% to 28.8% compared with 16.5% for placebo. The lower placebo response may have contributed to the ability to detect a response in the Lu AA21004 groups. Other studies of Lu AA21004 have demonstrated inconsistent efficacy results in MDD,[11,19] with some studies indicating positive improvement with both the 5-mg and 10-mg Lu AA21004 doses on multiple endpoints and others showing improvement on only some measures. One potential reason for the inconsistent trial results may be the placebo response rates. Increased responses to placebo may be masking potential effects of treatment and have been suggested as playing a role in the increasingly common failure of antidepressant trials.[20,21] However, the current results are supported by a previous European study[11] of Lu AA21004 5 mg and 10 mg in MDD, which demonstrated significant improvements in both response and remission rates compared with placebo, despite a higher placebo response in that study. Further studies may be needed to fully understand the efficacy profile of Lu AA21004.

Similar to a previous clinical trial[11] of Lu AA21004, HDRS-24 total score in the subgroup of subjects with high baseline anxiety demonstrated improvement with all doses of Lu AA21004. Improving depression symptoms in this subset of patients may be clinically meaningful because of the common occurrence of anxiety symptoms in depression; these patients may be slower to respond to treatment and have lower rates of response to antidepressants with corresponding higher rates of AEs and suicide attempts.[6,22,23]

This study provides additional data to support the tolerability profile of Lu AA21004. Similar to previous studies, the most commonly occurring AEs for Lu AA21004 with instances greater than placebo were gastrointestinal.[11,19] Notably, sexual side effects and weight gain, which are often cited as reasons for discontinuation of antidepressant treatment,[24,25] were similar to those seen with placebo in this study, and the incidences were less than 3% of subjects in each group. The rate of withdrawals due to AEs in the current study was low for all of the Lu AA21004 doses and was similar to that of the placebo group, suggesting good tolerability for Lu AA21004 at doses up to 10 mg.

Additional studies may be needed to determine the optimal dose of Lu AA21004 and efficacy for depression symptoms in different populations of patients. The suggestion of a dose effect observed in this study indicates that higher doses may potentially demonstrate greater improvements. The generalizability of the results from the current study, as in most clinical trials, is limited by the exclusion of subjects with significant psychiatric, substance abuse, or medical disorders, which are common comorbid conditions in depressed patients.[26–28] In addition, this study was conducted outside the United States, and studies have demonstrated differences in patient populations and study conduct between European and Asian countries and the United States that may affect the outcome of clinical trials in each geographical region.[29,30]

In conclusion, after 8 weeks of treatment with Lu AA21004 10 mg, there was a significant reduction in the primary endpoint (HDRS-24 total score compared with placebo at week 8) in adults diagnosed with MDD. On the

basis of the prespecified testing procedure, the improvements in secondary endpoints were considered nonsignificant but did show improvement with Lu AA21004 1 mg, 5 mg, and 10 mg. All doses of Lu AA21004 were well tolerated in this study. Further studies are needed to fully define the optimal doses of Lu AA21004 for the treatment of MDD.

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