Lu-AA21004, a multitargeted serotonergic agent, for the potential treatment of depression and anxiety

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Lu-AA21004, is an oral, multi-targeted serotonergic agent, currently under development by H Lundbeck and Takeda Pharmaceutical, for the potential treatment of depression and anxiety. Lu-AA21004 belongs to a novel chemical class of antidepressant agents, the bisaryl sulfanyl amines, and possesses a novel pharmacological profile, with activity at serotonergic receptors 5-HT3, 5-HT7, 5-HT1B and 5-HT1A and also at the serotonin transporter. Acute administration of Lu-AA21004 in rats inhibited the firing activity of serotonergic neurons of the dorsal raphe nucleus through 5-HT3 blockade, with rapid recovery of firing activity upon cessation of treatment compared with an antidepressant of the SSRI class. Results from phase II clinical trials have reported improvement in depression and anxiety symptoms after six weeks of treatment. The drug was generally well-tolerated, with side effects related to sexual dysfunction occurring in a lower number of patients receiving Lu-AA21004 compared with venlafaxine. Phase III clinical trials with Lu-AA21004 are underway, and if initial outcomes prove positive, the drug may pave the way for new multi-targeted therapies for the treatment of depression and anxiety.

Introduction

Depression is a severe, chronic mental illness that affects up to 20% of the population worldwide. It is well established that major depressive disorder (MDD) is twice as common in women as in men [550053], [1143824], with the disparity likely rooted in hormonal and psychosocial factors. Depression often coexists with other brain disorders, particularly anxiety [1143828], [1143830], and treating the depression can also provide improvements in comorbid anxiety symptoms [1143831]. The collective symptoms of depression suggest the participation of several different areas of brain, such as the nucleus accumbens (anhedonia), amygdala (fear and anxiety), limbic system (depressed mood), prefrontal cortex (cognitive impairment) and hypothalamus (changes in hormonal secretion, appetite, sexual drive). Serotonin (5-HT), noradrenaline and dopamine are pivotal neurotransmitters in these areas of the brain.

Although the exact link is not fully understood, it is widely believed that the serotonergic system plays a role in depression and anxiety as well as in the response to treatment [1143872]. Drugs that prevent 5-HT and/or noradrenaline from being taken up by their respective nerve endings – thus elevating serotonergic and/or noradrenergic neurotransmission –
constitute > 90% of all current treatments for depression [1143874]. In addition, there is evidence that dual reuptake blockers, such as the tricyclic clomipramine or the selective 5-HT/noradrenaline reuptake inhibitors (such as venlafaxine and duloxetine), are more efficacious than selective 5-HT reuptake inhibitors (SSRIs, such as fluoxetine, fluvoxamine, paroxetine, citalopram, sertraline) [488704], [1143889], [1143890], [1143892]. The theory that 5-HT may also play a role in anxiety is given weight by the fact that SSRIs are also prescribed in the treatment of generalized anxiety disorder [1144729].

Several 5-HT receptors have also been implicated in the treatment of depressive and anxiety symptoms (for a review, see [1143895]). Among them, 5-HT1A receptors have been extensively studied. Two different types of autoreceptors can be found on serotonergic neurons: 5-HT1A receptors, located in the soma compartment in the raphe nuclei of the brainstem, and 5-HT1B/1D receptors in nerve terminals. Stimulation of 5-HT1A receptors by endogenous 5-HT or selective agonists reduces serotonergic cell firing and impulse-dependent 5-HT release, whereas 5-HT1B/1D receptors control 5-HT release without affecting firing rate. Acute effects of SSRIs are self-limited by negative feedback involving the activation of these autoreceptors [195704], [1143898], which likely constrains their clinical effects [1143899]. After long-term treatment with SSRIs, both 5-HT1A and 5-HT1B receptors desensitize [195704], [1143900], which permits 5-HT neurons to resume cell firing, thus leading to a net increase of 5-HT release, which is higher than that observed after acute treatment [263133]. Another method to dampen these negative feedback mechanisms has been the blockade of 5-HT1A and/or 5-HT1B autoreceptors with selective antagonists. Therefore, the working hypothesis was that pharmacological blockade of 5-HT1A autoreceptors would mimic the effect of autoreceptor desensitization and speed the antidepressant action of SSRIs. Some studies have provided evidence that co-administration of the 5-HT1A/β-adrenoceptor antagonist pindolol accelerates patient responses to SSRIs in depression [290977], [382843], [382844], [382846]; however, other studies failed to show this effect [243760], [290981]. A meta-analysis of early and late outcomes from randomized, controlled clinical trials revealed that the efficacy of pindolol in conjunction with SSRIs in treating depression was restricted to the first two weeks of treatment [1143911]. Interestingly, 5-HT1A receptor agonists also possess anxiolytic and antidepressant properties, although this action appears to be dependent on the stimulation of a postsynaptic receptor population [Blier et al., 1997]. In addition, the activation of postsynaptic 5-HT1A receptors is a feature of several types of antidepressant drugs [Haddjeri et al., 1998; Blier and Ward, 2003]. Prolonged treatment with 5-HT1A receptor agonists such as buspirone produce only modest antidepressant and anxiolytic effects in both animals and humans, possibly through a combination of their desensitizing effects on 5-HT1A autoreceptors and their activation of postsynaptic receptors [Kreiss and Lucki, 1997; Sussman, 1998; Blier and Ward, 2003]. In summary, the importance of the 5-HT1A receptor agonists for the treatment of depression is limited by the fact that such agents stimulate both somatodendritic autoreceptors and post-synaptic 5-HT1A receptors, effects that would exert opposing influences on postsynaptic 5-HT1A receptor transmission.

The importance of the 5-HT1A autoreceptor in depression has been further demonstrated recently in a mouse model [1143912]. Animals expressing a 30% reduction in numbers of this receptor in the dorsal raphe nucleus exhibited a clear
antidepressant-like action in behavioral tests. In contrast, mice with an augmented number of 5-HT<sub>1A</sub> receptors in this nucleus displayed resistance to antidepressant-like effects after SSRI administration. This research may eventually lead to the design of personalized therapeutic interventions depending on the status of serotonergic transmission of the patients.

Two other serotonergic receptors that have been implicated in the treatment of depression are the 5-HT<sub>3</sub> and 5-HT<sub>7</sub> receptors. Antidepressant-like effects of 5-HT<sub>3</sub> receptor antagonists have been demonstrated in various animal behavioral models (for a review, see [1143913]); however, clinical investigations assessing the therapeutic action of these agents on depression and anxiety, existing comorbidly with other diseases, have yielded controversial results. Some studies suggested that treatment with 5-HT<sub>3</sub> receptor antagonists provided some degree of improvement in depression and anxiety scores [1143915], [1143916], [1143918], whereas others did not [196794], [1143921], [1143923]. Although the precise mechanism responsible for the antidepressant-like effects of 5-HT<sub>3</sub> receptor antagonists remains to be fully understood, indirect facilitation of dopamine neurotransmission appears to play a role [1143924], [1143926].

The affinity of clinically effective antidepressant drugs for the 5-HT<sub>7</sub> receptor [210247] and the finding that prolonged administration of antidepressants down-regulates 5-HT<sub>7</sub>-mediated responses and receptor binding in limbic areas [1143930], [1143931], suggest a possible involvement of this receptor in depressive states and antidepressant response. Preclinical studies have demonstrated antidepressant-like effects of 5-HT<sub>7</sub> receptor antagonists in established behavioral tests [665839], [1143933]. Moreover, selective blockade of 5-HT<sub>7</sub> receptors increased the 5-HT concentration and decreased the immobility time in a tail suspension test of rats treated with the SSRI [801101], which is suggestive of potentiation of antidepressant-like effects.

More of 90% existing antidepressant drugs block the reuptake of 5-HT and/or noradrenaline and exhibit limited efficacy and a slow onset of action. A reduced emergence (albeit not a complete disappearance) of unwanted side effects has been achieved with the advent of SSRIs, but their clinical efficacy does not seem to be better than classical tricyclic drugs (see above). The main goal of new pharmacological treatments, therefore, seems to be reducing side effects rather than increasing efficacy. In addition, a major problem in depression therapy is that 20-30% of patients fail to respond to conventional medications (Fava, 2003). In general, electroconvulsive therapy has been recommended for severe refractory depression. Although this intervention generally leads to a positive response, beneficial effects are short-lasting. In the last five years, deep brain stimulation of the subgenual cingulate region (Brodmann area 25) has emerged as a new strategy for treatment-resistant depression (Mayberg et al., 2005). Although invasive, the procedure is well tolerated and thus it shows promise for refractory depression.

H Lundbeck and Takeda Pharmaceutical are codeveloping Lu-AA21004, an oral agent for the potential treatment of depression and anxiety. Lu-AA21004 has a novel pharmacological profile, acting as a 5-HT<sub>3</sub>, 5-HT<sub>7</sub> and 5-HT<sub>1A</sub> antagonist.
and a 5-HT₁₅A agonist, and also exhibits 5-HT transporter inhibitor features. Lu-AA21004 is currently undergoing phase III clinical trials in MDD [862143], [1053829] and anxiety disorder [1043686].

**Synthesis and SAR**

Lu-AA21004 belongs to a novel chemical class of bisaryl sulfanyl amine antidepressant drugs. Several syntheses for Lu-AA21004 (1-[2-(2,3-dimethylphenylsulfanyl)phenyl]piperazine) have been disclosed [WO-03029232A1], [WO-2007144005A1]. For example, in one synthesis, a mixture containing 1 to 1.5 equivalents each of 2,4-dimethylthiol, 1-bromo-2-iodobenzene and piperazine dispersed in toluene was reacted with a mixture containing 2 to 5 equivalents of sodium tert-butoxide and 1 to 2 mole% of bis(dibenzylideneacetone)palladium and racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, also in toluene. The resulting solution was heated at reflux for 3 to 5 h, to afford Lu-AA21004 [WO-2007144005A1].

An initial focused screen for structures with serotonergic activity resulted in a low-molecular-weight phenyl piperazine derivative, with Kᵢ values of 190 and 4000 nM for 5-HT₃A and 5-HT₁₅A, respectively, and a 5-HT transporter IC₅₀ value of 7.9 nM, giving a 5-HT transporter:5-HT₃A:5-HT₁₅A ratio of 1:24:506. However, this agent also demonstrated activity at 5-HT₂C (Kᵢ = 13 nM) and the α₁-adrenergic receptor (IC₅₀ = 23 nM), exhibited poor rat pharmacokinetics, with a clearance rate of 7 l/h/kg and oral bioavailability of 21%, and was a potent inhibitor of CYP2D6 (IC₅₀ = 0.1 μM). Further optimization to create more desirable properties resulted in Lu-AA21004, which demonstrated an IC₅₀ value of 5.4 nM for the 5-HT transporter, and Kᵢ values of 23 and 40 nM, for 5-HT₃A and a 5-HT₁₅A, respectively, giving a 5-HT transporter:5-HT₃A:5-HT₁₅A ratio of 1:4:7 [996223], [1001367].

**Preclinical development**

**In vitro**

In the electrophysiological setting, Lu-AA21004 demonstrated antagonist activity in *Xenopus* oocytes expressing cloned 5-HT₃ receptors, with IC₅₀ values of 12 nM for human receptors, and 0.18 nM for rat receptors. At higher concentrations, however, Lu-AA21004 demonstrated some agonistic activity at 5-HT₃ (EC₅₀ = 2100 nM, efficacy 64%) [996223], [1001367]. Lu-AA21004 demonstrated agonism (EC₅₀ = 200 nM) at the 5-HT₁₅A receptor in a [³⁵S]-GTPγS assay. When tested against a panel of 63 other GPCRs, transporters, enzymes and ion channels, Lu-AA21004 (1 μM) displayed no pharmacologically relevant activity [996223], [1001367], [1036709]. The bromide salt of Lu-AA21004 was highly soluble at pH 5.5 (1.7 mg/ml), but had much lower solubility at pH 7.4 (approximately 100 μg/ml) [996223], [1001367].

In binding studies using CHO cells expressing human 5-HT₃ and 5-HT₁₅A receptors, Lu-AA21004 demonstrated Kᵢ values of 4.5 and 15 nM, respectively [1036709]. In human brain tissue, Lu-AA21004 demonstrated high-affinity binding for 5-HT₁₅A, with a Kᵢ value of 40 nM. In CHO cells stably expressing human 5-HT transporter, norepinephrine transporter (NET) or
dopamine transporter (DAT), Lu-AA21004 had an IC\textsubscript{50} value of 5.4 nM for human 5-HT transporter, with only weak inhibition of human NET and DAT (IC\textsubscript{50} > 100 nM) [1036709].

**In vivo**

The first in vivo preclinical data reported for Lu-AA21004 demonstrated efficacy in behavioral assays predictive of antidepressant activity, such as the forced swim and tail suspension tests in mice (minimum effective dose [MED] = 16 and 17 mg/kg, for the two tests, respectively) [1036708], [1036712], [1048142], [1061337], [1144741]. Lu-AA21004 also demonstrated anxiolytic-like properties in the mouse marble burying (MED = 3.9 mg/kg), rat social interaction (10 mg/kg) and rat conditioned fear (1.0 mg/kg) paradigms [1036708], [1036712], which is in stark contrast to the effects of other known antidepressants, such as duloxetine and paroxetine [1036712].

Further characterization of Lu-AA21004 (2.5 to 10 mg/kg, sc) in rat microdialysis studies demonstrated dose-dependent increases in efflux of 5-HT, noradrenaline, dopamine and acetylcholine in the prefrontal cortex and ventral hippocampus [1036708], [1036713], [1061337], [1144741], regions of the brain that play a key role in the regulation of mood. This profile is substantially different from that of SSRIs, in which enhanced serotonergic transmission usually occurs in conjunction with reduced noradrenergic and dopaminergic activities [1143940]. The elevated activity of these transmitters may result in improved cognition and mood. The increase in dopaminergic transmission is likely caused by agonistic activity of Lu-AA21004 at 5-HT\textsubscript{1A} receptors [1143945], [1143946].

In a rat 3-day microdialysis study of the hippocampus, administration of Lu-AA21004 (5 mg/kg/day, sc) resulted in ~40% 5-HT transporter occupancy [996223], [1001367], [1036708], [1036713], [1048142], [1061337]. Although the inhibition of 5-HT reuptake conferred a potential antidepressant activity, the low occupancy of the 5-HT transporter suggests this mechanism is not the principal cause of therapeutic action. Furthermore, Lu-AA21004 dose-dependently inhibited the Bezold-Jarisch-like reflex (ED\textsubscript{50} = 1.0 mg/kg), demonstrating 5-HT\textsubscript{3} receptor antagonistic action in vivo [1036713], [1048142], [1061337].

More recently, studies have demonstrated that acute administration of Lu-AA21004 (250 to 1000 \(\mu\)g/kg, iv) to Sprague-Dawley rats dose-dependently inhibited the firing activity of serotonergic neurons of the dorsal raphe nucleus (ED\textsubscript{50} = 548 \(\mu\)g/kg, iv) [1061511], [1144679]. This effect was blocked by the prior administration of 5-HT\textsubscript{3} agonist SR-57227 [1144679] or 5-HT\textsubscript{1A} antagonist WAY-10063 (50 \(\mu\)g/kg, iv) [1061511], which is an indication that Lu-AA21004 acts as both a 5-HT\textsubscript{3} receptor antagonist and 5-HT\textsubscript{1A} receptor agonist. In comparison, fluoxetine also inhibited firing of serotonergic neurons (ED\textsubscript{50} = 1.6 \(\mu\)g/kg), but this was not affected by SR-57227. Following repeated administration of Lu-AA21004, recovery of the firing activity of serotonergic neurons was achieved after 1 day, whereas 14 days were usually required for recovery after fluoxetine treatment. This study suggests that Lu-AA21004 possesses faster-acting antidepressant-like features in the preclinical setting than fluoxetine [1061511].
Toxicity

No toxicity data were available at the time of publication.

Metabolism and pharmacokinetics

Lu-AA21004 has demonstrated a low drug-drug interaction potential and is extensively metabolized in the liver, with at least five cytochrome P450 (CYP) isoenzymes involved [1115747], [1115756], [1135495]. The CYP profile in human liver microsomes (CYP2D6 IC\textsubscript{50} = 34 µM, CYP1A2 IC\textsubscript{50} > 40 µM, CYP2C9 IC\textsubscript{50} = 15 µM, CYP3A4 IC\textsubscript{50} > 40 µM, CYP2C19 IC\textsubscript{50} > 40 µM) demonstrated reduced activity at the 3A4 and 2C19 isoforms than in the rat (CYP2D6 IC\textsubscript{50} = 9.8 µM, CYP1A2 IC\textsubscript{50} > 40 µM, CYP2C9 IC\textsubscript{50} = 39 µM, CYP3A4 IC\textsubscript{50} = 10 µM, CYP2C19 IC\textsubscript{50} > 0.1 µM) [996223], [1001367]. In a phase I clinical trial to assess the interaction potential of Lu-AA21004 with CYP2C19, healthy volunteers (n = 18) were administered omeprazole (a CYP2C19 substrate; 40 mg) on day 1, then Lu-AA21004 (10 mg/day) on days 2 to 15, and, finally, a combined dose of omeprazole (40 mg) and Lu-AA21004 (10 mg) on day 16 [1115747]. Lu-AA21004 had no significant effect on the pharmacokinetics of omeprazole, and vice versa.

Absorption of a single dose of Lu-AA21004 (50 mg, po) was assessed in healthy male volunteers (n = 6) [1115737]. Maximum plasma concentrations were reached 6 h after dosing. In metabolic analyses, it was found that 56% of the drug was excreted into the urine and 26% into feces, with 18% unaccounted for [1115737]. In the rat, the rate of clearance was 7.1 l/h/kg, the t\textsubscript{1/2} value was 1.8 h and oral bioavailability was 14%, and in the dog the rate of clearance was 1.8 l/h/kg, the t\textsubscript{1/2} value was 6.0 h and oral bioavailability was 47% [996223], [1001367]. These data led to predicted human values of 0.25 l/h/kg for clearance, which was in close agreement with the observed value of 0.43 l/h/kg (around 31% of liver blood flow). Human bioavailability was high (65%) [996223], [1001367], with an apparent volume of distribution of 3789 l and a t\textsubscript{1/2} value of ~ 60 h [1115737].

To assess the effect of food on the absorption of Lu-AA21004, healthy volunteers (n = 24) were administered Lu-AA21004 (10 mg, po), either after a 10-h fast, or 30 min after a high-fat breakfast. Results demonstrated that absorption of the drug is independent of food intake [1115740]. In addition, multiple doses of Lu-AA21004 (10 mg/day on days 1 to 20) demonstrated no effect on platelet aggregation, or on the pharmacokinetics of aspirin (150 mg/day on days 15 to 20) or its salicylic acid metabolite, when administered to healthy volunteers (n = 28) [1135485], nor did Lu-AA21004 have any influence on the pharmacokinetics or pharmacodynamics of combined contraceptive (ethinyl estradiol [30 µg] and levonogestrel [150 µg]) when administered to healthy women (n = 28) [1115757].

Clinical development

Phase I

Data from phase I clinical trials in healthy volunteers are described in the metabolism and pharmacokinetics section.
Phase II

In a phase II multicenter, randomized, parallel-assignment, double-blind, placebo-controlled, active comparator clinical trial (ClinicalTrials.gov identifier: NCT00839423; 11984A), patients (n = 426) with MDD and a Montgomery-Åsberg depression rating scale (MADRS) score of ≥ 30 at baseline, received Lu-AA21004 (5 or 10 mg/day) for 6 weeks, venlafaxine XR (75 mg/day for the first 4 days, 150 mg/day for the following 3 days and 225 mg/day thereafter up to the end of the 6-week trial period) or placebo [1061513], [1143903]. All active treatment groups exhibited significantly improved depressive and anxiety symptoms versus placebo. The mean difference in MADRS score versus placebo after 6 weeks was -6.4 ± 1.4, -5.9 ± 1.4 and -5.7 ± 1.4, for venlafaxine, 5 mg Lu-AA21004 and 10 mg Lu-AA21004, respectively. With an alternative definition of remission, patients were assessed according to the Hamilton Rating Scale for Depression (HAM-D). The mean difference in 24-item HAM-D (HAM-D24) score versus placebo after 6 weeks was -5.1 ± 1.2, -5.3 ± 1.2 and -5.3 ± 1.3, for venlafaxine, 5 mg Lu-AA21004 and 10 mg Lu-AA21004, respectively. All of these results were significant versus placebo (p < 0.001). Clinical Global Impression (CGI) scores were evaluated in terms of global improvement (CGI-I) and severity of illness (CGI-S) versus baseline. CGI-S scores versus placebo after 6 weeks were -1.0 ± 0.2, -1.0 ± 0.2 and -0.9 ± 0.2 for venlafaxine, 5 mg Lu-AA21004 and 10 mg Lu-AA21004, respectively, and CGI-I scores versus placebo after 6 weeks were -0.7 ± 0.2, -0.6 ± 0.2 and -0.6 ± 0.2 for venlafaxine, 5 mg Lu-AA21004 and 10 mg Lu-AA21004, respectively, all of which were significant (p < 0.001). A clinically significant response, defined as ≥ 50% reduction in MADRS scores after 6 weeks, was documented in 67% (p < 0.01) of patients assigned to the 5-mg dose of Lu-AA21004, 68% (p < 0.01) receiving Lu-AA21004 at 10 mg, 72% (p < 0.001) of the venlafaxine group, and 45% of placebo-treated control patients. Remission (defined as achieving a MADRS score of ≤ 10) at 6 weeks was achieved in 49% (p < 0.01) of patients receiving either dose of Lu-AA21004, 55% (p < 0.001) of patients receiving venlafaxine, and 27% of patients receiving placebo. Significant differences were observed between placebo and both doses of Lu-AA21004 and venlafaxine beginning in weeks 2 to 3. In terms of HAM-D score, from a mean baseline of ≥ 30, 47% (p < 0.01) of patients in the 5-mg Lu-AA21004 group, 45% (p < 0.05) in the 10-mg dose group, 46% (p < 0.01) in the venlafaxine group and 28% in the placebo group reported a reduction in HAM-D7 score to ≤ 7 at 6 weeks. Using the Hamilton Rating Scale for Anxiety (HAM-A), patients also demonstrated significant (p < 0.01) improvement in anxiety symptoms in all active treatment groups. Mean scores on the HAM-A scale reduced from a mean baseline score of ~ 22, to ~ 10 at 6 weeks in all three active treatment arms (p < 0.01) [1061513], [1143903].

In a long-term phase II, multicenter, randomized, single-group-assignment, open-label, uncontrolled clinical trial (NCT00761306; 11492C) patients with MDD (n = 74), who had completed a prior 6-week clinical trial with Lu-AA21004 (presumably NCT00839423), received Lu-AA21004 (5 to 10 mg qd, po) for 52 weeks. The primary endpoint of this trial was safety and tolerability, as assessed by adverse events, clinical safety laboratory tests, vital signs, weight, ECG and physical examination at 52 weeks. The secondary endpoints included maintenance of the therapeutic effect of Lu-AA21004
over the 52-week trial period, pharmacokinetics and effect on quality of life. This trial was completed in October 2008, although no results had been reported at the time of publication.

**Phase III**

*(sub) Major depressive disorder*

In a phase III, multicenter, randomized, parallel-assignment, double-blind, placebo-controlled clinical trial (NCT00672620; LuAA21004_304; U1111-1114-3497), patients (n = 611) with MDD were treated with Lu-AA21004 (2.5 or 5 qd, po), duloxetine (60 mg qd, po) or placebo for up to 8 weeks. In a further phase III, multicenter, randomized, parallel-assignment, double-blind, placebo-controlled clinical trial (NCT00735709; LuAA21004_305; U1111-1114-0326), patients (n = 560) with MDD received Lu-AA21004 (1, 5 or 10 mg qd, po) or placebo for up to 8 weeks. The primary endpoint of both of these trials was the least squares mean change in HAM-D24 score from baseline at week 8. Secondary endpoints included the least squares mean change in HAM-D24, MADRS, CGI-I, CGI-S and HAMA-A scores from baseline at weeks 1, 2, 4, 6 and 8, change from baseline in disability score (assessed using the Sheehan Disability Scale [SDS]), number of patients with sustained response from week 1 (defined as a decrease of ≥ 20% in HAM-D24 score versus baseline after 1 week and sustained to week 5, with a total decrease of ≥ 50% in HAM-D24 score versus baseline at week 8), remission (MADRS ≤ 10) at week 8 or final visit and healthcare resource use as assessed by health economic assessment questionnaire (HEAQ). These trials were completed in December 2008 and August 2009, respectively.

In a third phase III, multicenter, randomized, parallel-assignment, double-blind, placebo-controlled clinical trial (NCT00672958; LuAA21004_303; U1111-1114-2328), patients with MDD (n = 597) were treated with Lu-AA21004 (5 mg qd, po) or placebo for 6 weeks. The primary endpoint of this trial was the least squares mean change in HAM-D24 score from baseline at weeks 1 to 6. Secondary endpoints included the proportion of patients responding to treatment (with response defined as a ≥ 50% decrease in HAM-D24 score versus baseline at weeks 1 to 6), the proportion of patients in remission at week 6 (MADRS ≤ 10), the proportion of patients with a sustained response from week 1 (as defined previously), change in HAMA-A score at weeks 1, 2, 4 and 6, change in CGI-I score, change in Medical Outcomes Study 36-item Short-Form (SF-36) at weeks 2, 4 and 6, change in SDS score at weeks 1, 2, 4 and 6 and healthcare resource use (HEAQ). This trial was completed in November 2008.

In a fourth phase III, multicenter, randomized, parallel-assignment, double-blind, placebo-controlled clinical trial (NCT00635219; 11984A), patients with MDD (n = 776) were treated with Lu-AA21004 (2.5, 5 or 10 mg qd, po), duloxetine (60 mg qd, po) or placebo for 8 weeks. The primary endpoint of this trial was efficacy of the three doses of Lu-AA21004 versus placebo after 8 weeks of treatment. Secondary endpoints included the proportion of patients responding to treatment (response as defined previously), the proportion of patients in remission at week 6 (MADRS ≤ 10), the proportion of patients with sustained response from week 1 (as defined previously), pharmacokinetics, the effect of Lu-
AA21004 on fatigue, sexual function, disability, quality of life and healthcare resource use, and also efficacy and safety of duloxetine. This trial was completed in April 2009.

In initial reports from two of the completed phase III clinical trials in MDD (trials unspecified), Lu-AA21004, tested at doses of 2.5, 5 and 10 mg (qd, po), did not demonstrate significance versus placebo [1016259]. A third (unspecified) trial provided mixed results, with the 2.5 mg dose not reaching statistical significance versus placebo, and the 5 and 10 mg doses providing improvement over placebo in some, but not all, analyses. These results suggested that a higher dose of Lu-AA21004 may provide better clinical efficacy, and so further trials have been initiated to test this hypothesis.

A phase III, multicenter, randomized, parallel-assignment, double-blind, placebo-controlled clinical trial (NCT00596817; 11985A), has also been conducted to assess the efficacy of Lu-AA21004 in preventing relapse in patients (n = 404) with MDD. Patients, who had previously responded to open-label treatment with Lu-AA21004, were administered Lu-AA21004 (5 or 10 mg qd, po) or placebo. The primary endpoint of this trial was time to relapse following up to 24 weeks of treatment. Secondary endpoints included efficacy of Lu-AA21004 from weeks 24 to 64, safety and tolerability following up to 76 weeks of treatment, discontinuation symptoms after abrupt discontinuation of treatment, effect on quality of life, fatigue and healthcare resource use, and pharmacokinetics and pharmacodynamics. This trial was completed in October 2009, although no results had been reported at the time of publication.

A phase III, multicenter, randomized, parallel-assignment, double-blind, placebo-controlled clinical trial (NCT00811252; 12541A), has also been conducted to assess the efficacy of Lu-AA21004 in patients (n = 453) with MDD, aged 65 years or over. Patients received Lu-AA21004 (5 mg qd po), duloxetine (60 mg qd, po) or placebo for 8 weeks. The primary endpoint of this trial was change in HAM-D score over the 8-week trial period, and secondary endpoints included changes in MADRS score, HAM-A score, CGI-I, CGI-S and geriatric depression score. This trial was completed in March 2010, although no results had been reported at the time of publication.

In a long-term phase III, multicenter, randomized, single-group-assignment, open-label, uncontrolled clinical trial (NCT00694304; 11984B) patients with MDD (n = 536), who had completed a prior 8-week clinical trial with Lu-AA21004, received Lu-AA21004 (2.5 to 10 mg qd, po) for 52 weeks. The primary endpoint of this trial was safety and tolerability, as assessed by adverse events, clinical safety laboratory tests, vital signs, weight, ECG and physical examination at 52 weeks. The secondary endpoints included therapeutic effect of Lu-AA21004 over the 52-week trial period, pharmacokinetics and pharmacodynamics, and effect on quality of life, healthcare resource use and disability. This trial was completed in April 2010, although no results had been reported at the time of publication.

In another long-term phase III, multicenter, randomized, single-group-assignment, open-label, uncontrolled clinical trial (NCT00707980; LuAA21004_301; U1111-1113-9564) patients with MDD (n = 836), who had completed either the
NCT00672620 or the NCT00735709 clinical trial with Lu-AA21004, received Lu-AA21004 (2.5, 5 or 10 mg qd, po) for 52 weeks. The primary endpoint for this trial was safety and tolerability, assessed as in the NCT00694304 trial, and secondary endpoints included mean change from baseline in: HAM-D24 total score; SDS at weeks 24 and final visit; MADRS total score at weeks 4, 24 and final visit; HAM-A total score at weeks 4, 24 and final visit; and CGI-S scale at weeks 4, 24 and final visit; and SF-36 and healthcare resource use, as assessed by HEAQ. This trial was completed in August 2010, although no results had been reported at the time of publication.

Four further phase III, multicenter, randomized, parallel-assignment, double-blind, placebo-controlled clinical trials have been initiated in patients with MDD. In the first of these trials (NCT01140906; 13267A), patients (n = 600) were to receive Lu-AA21004 (15 or 20 mg qd, po), duloxetine (60 mg qd, po) or placebo for 8 weeks. In the second of these trials (NCT01153009; LuAA21004_315; U1111-1114-8191), patients (n = 600) were to receive Lu-AA21004 (15 or 20 mg qd, po), duloxetine (60 mg qd, po) or placebo for 8 weeks. In the third of these trials (NCT01163266; LuAA21004_316; U1111-1115-8770), patients (n = 450) were to receive Lu-AA21004 (10 or 20 mg qd, po) or placebo for 8 weeks. In the fourth of these trials (NCT01179516; LuAA21004_317; U1111-1116-3223), patients (n = 450) were to receive Lu-AA21004 (10 or 15 mg qd, po) or placebo for 8 weeks. The primary endpoint of these trials was efficacy of Lu-AA21004 versus placebo after 8 weeks of treatment, assessed by change in MADRS score versus baseline. Secondary endpoints included the effect of Lu-AA21004 versus placebo on patients responding to treatment (response defined as previously), patients in remission at week 8 (MADRS ≤ 10), depressive symptoms of patients with high anxiety levels (HAM-A ≥ 20) at baseline, and change from baseline in SDS. At the time of publication patients were still being recruited to these trials, with completion planned for the first trial in June 2011, the second and third trials in January 2012 and the fourth trial in February 2012.

A further long-term phase III, non-randomized, single-group-assignment, open-label, uncontrolled clinical trial (NCT01152996; LuAA21004_314; U1111-1115-4927) has recently been initiated. Patients (n = 1000) with MDD, who had completed the NCT01153009 trial, the NCT01163266 trial or the NCT01179516 were to receive Lu-AA21004 (10 mg qd po, for one week, then 15 or 20 mg qd, po for 51 weeks). Primary endpoints were related to rates of adverse events and trial discontinuations resulting from adverse events. Secondary endpoints included change from baseline in: MADRS total score at weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 36, 44 and 52; HAM-A total score at weeks 4, 24 and 52; CGI-S score at weeks 4, 24 and 52; and SDS total score at weeks 12, 24, 36 and 52. At the time of publication patients were still being recruited to this trial, with completion planned for January 2013.

(sub) Generalized anxiety disorder

Three phase III, multicenter, randomized, parallel-assignment, double-blind, placebo-controlled, clinical trials have been conducted in patients with generalized anxiety disorder. In the first of these trials (NCT00730691; LuAA21004_308; U1111-1114-3966), patients (n = 781) were treated with Lu-AA21004 (2.5, 5 or 10 mg qd, po), duloxetine (60 mg qd, po)
or placebo for up to 8 weeks. In the second of these trials (NCT00731120; LuAA21004_309; U1111-1114-2380) patients (n = 457) received Lu-AA21004 (2.5 or 10 mg qd, po) or placebo for up to 8 weeks. In the third of these trials (NCT00734071; LuAA21004_310; U1111-1114-4876) patients (n = 309) received Lu-AA21004 (5 mg qd, po) or placebo for up to 8 weeks. The primary endpoints of these trials were the least squares mean change in HAM-A score from baseline at week 8. Secondary endpoints included the least squares mean change in HAM-A, CGI-I and CGI-S score from baseline at weeks 1, 2, 4, 6 and 8, the proportion of patients responding to treatment (defined as a \( \geq 50\% \) decrease in HAM-A score versus baseline at week 8) and the proportion of patients in remission (HAM-A \( \leq 7 \)) at week 8. These trials were completed in February 2009, but no results had been reported at the time of publication.

A further phase III multicenter, randomized, parallel-assignment, double-blind, placebo-controlled, clinical trial (NCT00744627; LuAA21004_311; U1111-1112-3487) has been conducted in patients (n = 301) with generalized anxiety disorder. Patients received Lu-AA21004 (5 mg qd, po) or placebo for up to 8 weeks. The primary endpoint of this trial was the least squares mean change from baseline in the 14-item HAM-A score (HAM-A_{14}) at week 8. Secondary outcomes included mean change from baseline in: hospital anxiety and depression scale anxiety sub-score at weeks 1, 4 and 8; CGI-I score at weeks 1, 2, 4, 6 and 8; SDS total score at weeks 1, 2, 4 and 8; HAM-A score in patients with baseline HAMA-A score \( \geq 25 \) at weeks 1, 2, 4, 6 and 8; SF-36 social functioning sub-score at week 8; HAM-A total score at weeks 1, 2, 4 and 6; and CGI-S score at weeks 1, 2, 4, 6 and 8; and also response rates at weeks 1, 2, 4, 6 and 8 (response as previously defined) and remission rates at weeks 1, 2, 4, 6 and 8 (HAM-A \( \leq 7 \)). This trial was completed in July 2009, but no results had been reported at the time of publication.

A phase III, multicenter, randomized, parallel-assignment, double-blind, placebo-controlled clinical trial (NCT00788034; 12473A) has also been initiated to assess the efficacy of Lu-AA21004 (5 or 10 mg qd, po) in preventing relapse in patients (n = 459) with generalized anxiety disorder, who had responded to acute Lu-AA21004 treatment. The primary endpoint of this trial was time to relapse after at least 24 weeks of treatment, and the secondary endpoints included relapse rates, changes in HAM-A, CGI and SDS scores, SF-36, rates of adverse events, results from clinical laboratory tests and changes in vital signs and ECG. This trial was completed in July 2010, but no results had been reported at the time of publication.

**Side effects and contraindications**

In the NCT00839423 phase II clinical trial, 30 patients of the 429 enrolled withdrew because of side effects; 4 patients from the placebo group, 3 patients from the 5-mg Lu-AA21004 group, 7 patients from the 10-mg Lu-AA21004 group and 16 patients from the venlafaxine group [1143903]. The most commonly reported side effects were nausea, headache, hyperhidrosis and dry mouth [1061513], [1143903]. In both of the Lu-AA21004 groups, there was a significantly greater incidence of nausea (29.6 and 38.0% of patients in the 5- and 10-mg dose groups, respectively) relative to placebo (61.0%; \( p < 0.001 \)). In the 10-mg Lu-AA21004 group, incidences of hyperhidrosis (10.0%) and vomiting (9.0%) were also significant (\( p < 0.05 \)) versus placebo (1.9% and 1.0%, respectively). It is possible that the high incidence of nausea with
Lu-AA21004 did not result in a greater occurrence of vomiting as a result of the anti-emetic properties of 5-HT\textsubscript{3} receptor antagonism. In the venlafaxine groups, incidences of nausea (33.6%), hyperhidrosis (15.0%), dry mouth (16.8%), constipation (9.7%) and anorgasmia (6.2%) were all significant (p < 0.05) versus placebo. In terms of adverse events related to sexual dysfunction (ie, anorgasmia, delayed ejaculation and erectile dysfunction), incidences in both of the Lu-AA21004-treated groups (1.9 and 1.0% at 5- and 10-mg, respectively) were similar to placebo (1.9%). In the venlafaxine group, 12.4% of patients experienced adverse events related to sexual dysfunction (p < 0.0033 versus placebo). No possibly suicide-related adverse events were reported in any of the groups during the trial, and there were no deaths.

**Patent summary**

Lu-AA21004 was first claimed in WO-03029232, as one of a series of phenyl-piperazine and -piperidine derivatives, disclosed as SSRIs for treating affective disorders including depression and anxiety disorders, filed in October 2001 by H Lundbeck. Lu-AA21004 is claimed specifically, along with several other compounds, in claim 11 (1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine). This filing has been granted in Europe as EP-01436271, and in the US as US-07138407, US-07148238, US-07683053 and US-07144884, all with basic expiry dates of October 2022; however, US-07144884 has a US154 extension bringing its expiry to January 2023. A further German national grant DE-60233608 has a basic expiry date of October 2022. WO-03029232 has also been granted in Canada (CA-02462110), China (CN-01319958), and Japan (JP-03896116, JP-03955613, JP-03955614).

Crystalline salts of Lu-AA21004, and processes for their preparation were disclosed in WO-2007144005, filed in June 2006 by Lundbeck. Lu-AA21004 is the only compound specifically claimed (claim 1). Crystalline Lu-AA21004 hydrobromide salt is particularly preferred (claim 5). The compound is stated to be a combined 5-HT\textsubscript{transporter inhibitor, 5-HT\textsubscript{3} antagonist and 5-HT\textsubscript{1}\textsubscript{agonist. Claimed indications include affective disorders, depression, anxiety disorders and cognitive impairment. As of October 2010, the corresponding European regional filings, EP-02044043 and EP-02142193, were still pending, and no corresponding US filings had yet been published. An equivalent PCT was later published as WO-2008113359 (use of 4-[2-(4-methylphenylsulfanyl)phenyl]piperazine or its hydrobromide salt).

In WO-2009062517 (filed in November 2007), Lundbeck and co-developer Takeda claim the use of Lu-AA21004, particularly its hydrobromic acid salt, for the treatment of circadian rhythm disorders, depression, mood disorders, dementia, autism, Alzheimer’s disease, anxiety, abuse, phobias, chronic pain, Down’s syndrome, stress-related disorders, sexual disorders, and a variety of other neurological, psychological and behavioral disorders. As of October 2010, the corresponding European filing, EP-02219647, is pending grant. It has also been filed in Argentina (AR-00069260), Australia (AU-2008323390) and Canada (CA-02705163). A related US application has yet to be published.

Lundbeck further filed WO-2010094285 (filed February 2009), claiming a process for the purification of Lu-AA21004.
specifically, comprising the reaction of its hydrobromide salt in isopropanol solvent. A liquid solution of Lu-AA21004 (claim 21), and Lu-AA21004 hydrobromide isopropanol solvate (claim 22) are also claimed. As of October 2010, no corresponding national or regional filings had been published.

**Current opinion**

Different potential, pharmacological antidepressant treatments have emerged in the last two decades with different modes of action: from monoamine reuptake inhibition, to blockade of transmitter receptors, such as serotonin 5-HT<sub>2A/2C</sub>, corticotrophin-releasing factor (CRF), neurokinin (NK<sub>1</sub>), and more recently, 5-HT<sub>3</sub> receptors. In a drug developmental story that looks like that of antipsychotic drugs. In this regards, all known antipsychotic drugs are antagonists of dopamine D2 receptors, and that the great majority (> 90%) of currently marketed antidepressant drugs possess some degree of monoamine transporter inhibition. With regard to SSRIIs, it is now known that these drugs must achieve a sustained threshold of 80% occupancy of serotonin transporter to exert antidepressant action [1143949]. Lu-AA21004, discovered by Lundbeck and being jointly developed by Lundbeck and Takeda, belongs to a new chemical class having a mode of action that is different from currently marketed antidepressants. Clinical studies carried out so far show encouraging results in terms of potential efficacy and safety/tolerability profile of Lu-AA21004. However, a better dose-response curve is yet to be established. The antidepressant-like activity of Lu-AA21004 was initially attributed to a combination of low occupancy of 5-HT transporter, 5-HT<sub>3</sub> receptor antagonism and 5-HT<sub>1A</sub> partial agonism. The pharmacological profile of Lu-AA21004 is thus notably different from that of other known antidepressants.

The field of antidepressant therapy has envisaged several so-called promising drugs that have eventually stalled. The pipeline of pharmaceutical industries are filled with drugs currently under development for the treatment of depression having single or multiple mechanisms of action. Lu-AA21004 is one of these drugs with more than one mechanism of action. From an efficacy point of view Lu-AA21004 has not demonstrated superior efficacy compared to venlafaxine [1061513], [1143903], although the apparent absence of serious adverse events makes this drug very attractive. The winding path from promise to market will depend on positive results from phase III clinical trials and the approval of post-phase III trials. The results of these trials are expected in 2011. Given this novel mechanism of action, Lu-AA21004 could provide an alternative option for patients with treatment-resistant depression. However, no such trial has commenced yet.

Drug therapies for mental disorders have serious difficulties to get approval from regulatory offices. In the particular field of antidepressant drugs, market penetration will therefore only be gained, at least initially, in treatment refractory patients. Lu-AA21004 is at early clinical stage of testing. If initial positive outcome is confirmed in phase III ongoing clinical trials, the drug will surely pave the way of new multitargeted therapies for depression.

**References**

- of special interest
- of outstanding interest


15


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IDdb author IDDB MEETING REPORT 2009 March 15-18


• Extensive in vitro experiments examining the different affinities of Lu-AA21004 for multiple receptors.


Development programme - Lundbeck


Pharmacological profile of Lu AA21004, a novel multi-target drug for the treatment of mood disorders


- This is the first large multi-center study demonstrating a robust antidepressant and anxiolytic efficacy of Lu-AA21004.


