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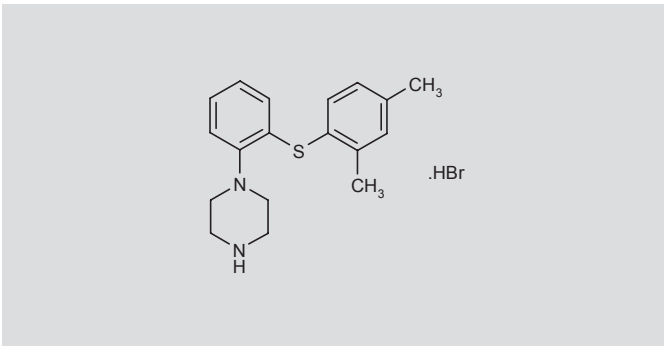
MONOGRAPH

LU-AA-21004

5-HT$_{3/7}$ Receptor Antagonist
5-HT$_{1A}$ Receptor Agonist
5-HT$_{1B}$ Receptor Partial Agonist
5-HT Transporter Inhibitor
Treatment of Depression
Treatment of Anxiety

1-[2-(2,4-Dimethylphenylsulfanyl)phenyl]piperazine hydrobromide

InChI: 1S/C18H22N2S.BrH/c1-14-7-8-17(15(2)13-14)21-18-6-4-3-5-16(18)20-11-9-19-10-12-20;/h3-8,13,19H,9-12H2,1-2H3;1H



$C_{18}H_{23}BrN_2S$

Mol wt: 379.358

CAS: 960203-27-4

CAS: 508233-74-7 (free base)

EN: 355504

SUMMARY

Major depressive disorder is one of the leading causes of disability worldwide. Current treatments for depression mostly target the serotonin (5-HT) signaling pathways because decreased concentrations of 5-HT, a major regulator of mood, sleep, appetite and emotion, in the brain are strongly associated with affective disorders. The most commonly used antidepressants include the tricyclic antidepressants, selective 5-HT reuptake inhibitors, dual 5-HT and norepinephrine reuptake inhibitors, monoamine oxidase (MAO) inhibitors and, more recently, drugs that target the large family of 5-HT receptors. Lundbeck and Takeda have recently developed a new type of antidepressant, Lu-AA-21004, with a novel mode of action in that it functions as a multi-targeted drug affecting multiple 5-HT receptors and the 5-HT transporter to increase synaptic 5-HT concentrations. The drug showed a favorable pharmacokinetic/pharmacodynamic profile in both animals and humans and is currently in phase III trials for the treatment of major depressive disorder and generalized anxiety. Preliminary studies show that Lu-AA-21004 has mild side effects and good efficacy in comparison to other drugs used to treat depression. Longer-term studies on safety, tolerability and efficacy in the treatment of affective disorders are currently under way and the drug is due to be registered with U.S. and European agencies within the next year.

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*Synthesis prepared by S. ShankharaRaman, C. Estivill, R. Castañer. Thomson Reuters, Provença 398, 08025 Barcelona, Spain.

SYNTHESIS*

Lu-AA-21004 can be prepared by several related strategies:

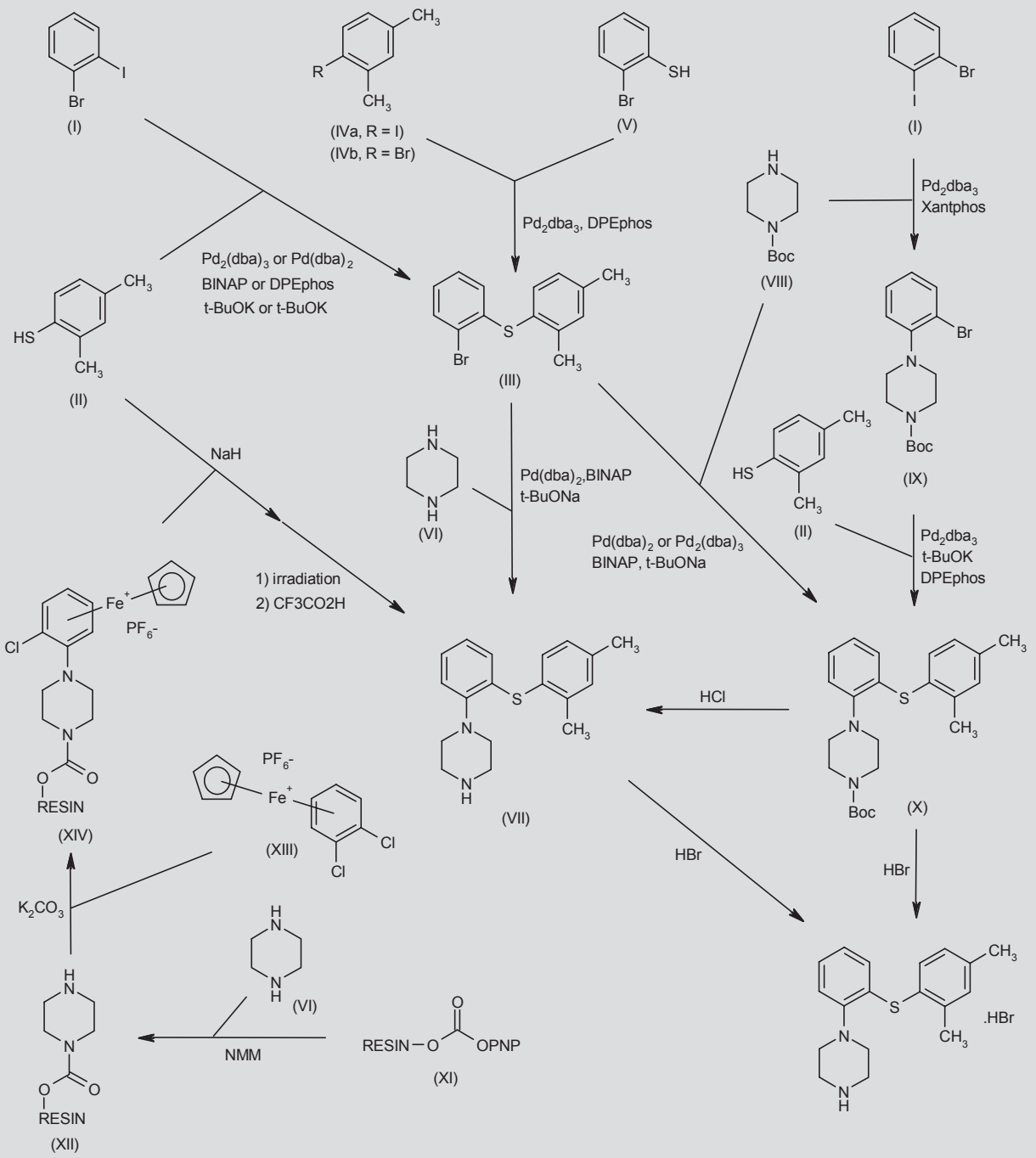
Condensation of 2-bromoiodobenzene (I) with 2,4-dimethylthiophenol (II) by means of either $Pd_2(dba)_3$ or $Pd(dba)_2$, *t*-BuOK and DPEphos or $Pd(dba)_2$, BINAP and *t*-BuONa in toluene yields 1-(2-bromophenylsulfanyl)-2,4-dimethylbenzene (III) (1, 2), which alternatively can be prepared by reaction of either 1-iodo- or 1-bromo-2,4-dimethylbenzene (IVa or IVb) with 2-bromobenzenethiol (V) in the presence of $Pd_2(dba)_3$ and DPEphos (2). Then, aryl bromide (III) is condensed with piperazine (VI) in the presence of $Pd(dba)_2$, BINAP and *t*-BuONa in toluene to give the free base (VII) (1), which is finally treated with HBr in MeOH (1), EtOAc (3) or toluene (4). Scheme 1.

The free base (VII) can be alternatively prepared in a one-pot procedure by reaction of 2-bromoiodobenzene (I) with 2,4-dimethylthiophenol (II) and piperazine (VI) in the presence of $Pd(dba)_2$, BINAP and *t*-BuONa (4). Scheme 1.

Reaction of 2-bromoiodobenzene (I) with *N*-Boc-piperazine (VIII) by means of $Pd_2(dba)_3$ and xantphos affords the arylpiperazine (IX) (2), which is then condensed with 2,4-dimethylthiophenol (II) in the presence of $Pd_2(dba)_3$, *t*-BuOK and DPEphos in toluene at 100 °C to give the thioether (X) (5). Finally, compound (X) is submitted to *N*-deprotection with HBr in refluxing H_2O (1). Scheme 1.

Alternatively, reaction of thioether (III) with *N*-Boc-piperazine (VIII) in the presence of $Pd(dba)_2$ (1) or $Pd_2(dba)_3$, BINAP (1, 2), and optionally, *t*-BuONa in toluene (1), provides the *N*-Boc-protected arylpiperazine (X), which is then *N*-deprotected with HCl in refluxing MeOH to give the free base (VII) (1, 2). Scheme 1.

Scheme 1. Synthesis of Lu-AA-21004



In a solid-phase method, binding of piperazine (VI) to the *p*-nitrophenyl carbonate resin (XI) in the presence of NMM in DMF results in the 4-[(1-piperazinyl)carboxymethyl]phenoxymethyl polystyrene (XII), which is then condensed with [η^6-1,2-dichloro-benzene][η^5-cyclopentadienyl]iron hexafluorophosphate (XIII) in the presence of K_2CO_3 in THF to afford the *N,N'*-disubstituted piperazine (XIV). Finally, the resin-bound piperazine (XIV) is condensed with 2,4-dimethylthiophenol (II) (previously treated with NaH), and subsequently subjected to photolytic decomplexation, and further acidic cleavage from the resin (TFA/CH_2Cl_2), leading to the free base (VII) (6). Scheme 1.

BACKGROUND

The onset of major depressive disorder (MDD) and anxiety disorders occurs in childhood or adolescence and often persists into adulthood, with lifetime prevalence rates in the U.S. predicted to be 17% and 29%, respectively (7). Analysis of the World Health Organization's Global Burden of Disease project for data collected between 1990 and 2001 showed that depression was the leading cause of lifetime disability on a global scale, particularly in females (8). Monoaminergic signaling within the central nervous system (CNS) has long been known to play a central role in the control of mood, behavior and reward. The monoamine hypothesis of depression, which states that depletion of monoaminergic neurotransmitters at the synaptic level underlies a number of affective disorders, including MDD, was put forward when it was found that drugs that target components of these pathways, for example, the sodium-dependent serotonin transporter (5-HT transporter, 5HTT), had a positive effect in alleviating symptoms of depression (9). Serotonin (5-HT), dopamine (DA) and norepinephrine (NE) are three of the key neurotransmitters of monoaminergic signaling. Put simply, the rationale behind many of the treatments currently in use to treat affective disorders, such as bipolar disorder and major depression, as well as anxiety and mood disorders, is to increase the duration of action of these key neurotransmitters at the synaptic level.

5-HT is derived from tryptophan by the action of tryptophan hydroxylase (TPH) and amino acid decarboxylase (DDC), and acts as a classical neurotransmitter. When released from synaptic vesicles on the presynaptic neuron, it binds to receptors on postsynaptic neuron membranes (with the exception of the autoregulatory and inhibitory 5-HT_{1A} receptor, which is found on the presynaptic membrane) to elicit a response. 5-HT is also released extrasynaptically and can function as a neuromodulator regulating the release of other neurotransmitters, such as DA, NE, glutamate and GABA. In addition, 5-HT can also act as a neuroendocrine mediator, controlling the release of hormones such as vasopressin and cortisol. The family of 5-HT receptors is vast, accounting for its multifunctional role in many neurological and behavioral processes. The 5-HT receptors are largely composed of G protein-coupled receptors, with the exception of 5-HT_3, which acts as a ligand-gated ion channel. They are mostly excitatory receptors coupled to G_s to elicit increases in intracellular cAMP (5-HT_4, 5-HT_6, 5-HT_7), or to G_q to activate inositol-trisphosphate (IP_3) and diacylglycerol (DAG) (5-HT_2), with the exception of 5-HT_1 and 5-HT_5, which are coupled to G_i/G_o to inhibit cAMP formation and dampen excitability (10). Spatiotemporal regulation of 5-HT signaling is controlled by reuptake by the 5-HT transporter/5HTT located on the presynaptic membrane, and subsequent breakdown by intracellular monoamine oxidases (MAO).

Aberrant 5-HT signaling is a major focus for the treatment of affective disorders because patients typically display low levels of 5-HT, and animal models engineered to have malfunctioning 5-HT signaling display symptoms associated with mood disorders in behavioral tests. The 5-HT signaling system is one of the most widespread in the brain. 5-HT is produced in the neurons of the raphe nuclei in the midbrain. A single serotonergic neuron can have up to a million synaptic connections. Axon projections from the lower raphe nuclei terminate in the cerebellum and spinal cord (to mediate descending control of the CNS), while those from the upper raphe nuclei innervate brain regions thought to be involved in cognition and behavior, including the prefrontal cortex, the limbic system and the hypothalamus. The 5-HT system is also a major regulator of the hypothalamic–pituitary–adrenal (HPA) axis, the hyperactivity of which is believed to underlie many affective disorders, including depression and stress (11).

Therapies targeted to the 5-HT signaling systems to alleviate the symptoms of affective disorders have a number of modes of action, acting at all points in the serotonergic pathways, including blockade of 5-HT reuptake, increase in vesicular exocytosis, inhibition of 5-HT degradation, increase in 5-HT synthesis and activity as agonists/antagonists at 5-HT receptors. Many of the currently available treatments have broad-spectrum effects on the monoaminergic systems, for example, tricyclic antidepressants (TCAs) such as imipramine and serotonin–norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine, which affect both 5-HT and NE signaling by blocking transporters. Others have a more focused approach, for example, selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, citalopram and paroxetine, which act solely by blocking the reuptake of 5-HT by the 5HTT (12). MAO inhibitors (MAOIs), for example, moclobemide, work by preventing the degradation of 5-HT by MAOs following reuptake by the 5HTT (13). Drugs targeting receptors include those such as ipsapirone, which has partial agonist activity at the 5-HT_{1A} receptor, producing an antidepressant-like effect (14).

Despite the widespread use of TCAs, SSRIs and SNRIs in treating depressive disorders, their efficacy is variable, and many patients do not respond favorably, with side effects including gastrointestinal complications, headache, tremor and, at worse, suicidal behavior. In addition, the mechanism(s) of their effectiveness, beyond the level of increasing available monoaminergic transmitters, is not fully understood. Lundbeck and Takeda have developed a new antidepressant and anxiolytic compound, Lu-AA-21004, for the treatment of depression and general anxiety, which has a novel mechanism of action. Lu-AA-21004 is multifunctional, acting as an antagonist at 5-HT_3 and 5-HT_7 receptors, an agonist at 5-HT_{1A} receptors, a partial agonist at 5-HT_{1B} receptors and an inhibitor of 5HTT, effectively elevating 5-HT concentrations in the synaptic cleft concomitant with an increase in postsynaptic activity (5, 15-17). Lu-AA-21004 is currently undergoing phase III clinical testing for major depressive disorder and general anxiety and is planned to be submitted for U.S. and European registration during 2012.

PRECLINICAL PHARMACOLOGY

The preclinical pharmacological profile of Lu-AA-21004 has been assessed in functional binding assays in vitro by cloning of rat (r) and human (h) 5-HT receptors and the 5HTT on cell membranes from CHO cells or rat brain synaptosomes and in whole cells. Antagonism of 5-HT-induced ion currents and radiolabeling displacement studies in these preparations showed that Lu-AA-21004 displayed high binding affinity for h5-HT_{3A} (K_i = 4.5 nM) and acted as a potent r5-HT_{3A} and h5-HT_{3A} receptor antagonist (IC_{50} = 0.2 and 20 nM, respectively), a h5-HT_{1A} receptor partial agonist (K_i = 15 nM; 80-96% intrinsic activity; EC_{50} = 200 nM) and a h5HTT (K_i = 1.6 nM) and r5HTT blocker (K_i = 5.4 nM; IC_{50} = 5.4 nM). The potency of Lu-AA-21004 at the r5-HT_{1A} (K_i = 670 nM) was considerably less than that

for the human receptor. Lu-AA-21004 also displayed affinity for the cloned h5-HT_{1B} (K_i = 36 nM) and h5-HT_7 (K_i = 19 nM) receptors (5, 15-19). The likelihood of off-target effects was assessed at a concentration of 1 μM, but Lu-AA-21004 did not show any significant activity when tested against more than 63 other receptors, enzymes, ion channels or transporters, displaying specific selectivity for the serotonergic system (17, 19).

In vivo microdialysis studies were used to quantify neurotransmitter levels following acute and subchronic administration of Lu-AA-21004 (2.5-10 mg/kg s.c. for 3 days) in rodents. Dose-dependent increases in extracellular levels of 5-HT, NA, DA and acetylcholine (ACh) where observed in the prefrontal cortex and ventral hippocampus. In addition, in animals receiving chronic treatment at a dose of 5 mg/kg/day, radioligand binding studies using [^{3}H]-MADAM, a 5-HT-specific tracer, showed increased 5-HT levels at low 5HTT occupancy (40%) (15, 16, 20, 21). More recently, similar increases in extracellular 5-HT, NA and DA have been recorded under steady-state conditions in rats after 3-day exposure to Lu-AA-21004 (19 and 28 mg/kg/day), with 5HTT occupancies of 89% and 98%, respectively. In addition, when compared to the effect of escitalopram (7.5 mg/kg/day), 5-HT release was significantly greater in Lu-AA-21004-treated animals despite similar transporter occupancies (92%). Moreover, acute challenge with Lu-AA-21004 (10 mg/kg) in rats that had received vehicle for 3 days prior produced a surge in 5-HT release. This acute challenge did not produce additional release in rats that had received the drug for 3 days prior (22).

The steady-state levels of distribution of Lu-AA-21004 (18 mg/kg/day) in plasma, brain and cerebrospinal fluid (CSF) have also been evaluated in rats. Tissue collection of samples began 24, 26 and 28 hours following implantation of osmotic minipumps containing the drug. Mean plasma exposure levels were recorded at 1872 ± 657, 2640 ± 1148 and 2813 ± 763 ng/mL, respectively, for 24, 26 and 28 hours. Mean brain exposure levels were recorded at 5925 ± 1855, 8089 ± 1640 and 9520 ± 2750 ng/mL, respectively, for 24, 26 and 28 hours, suggesting a steady-state brain to plasma ratio of 3:1. Ex vivo brain slice autoradiography was used to determine 5-HT_{1B} and 5-HT occupancy at these time points (5-HT_{1B}: 81 ± 6%, 81 ± 1% and 89 ± 1%, respectively; 5-HT: 48 ± 3%, 50 ± 5% and 73 ± 5%, respectively). CSF levels did not correspond to brain levels, suggesting an extended duration of occupancy at brain 5-HT_{1B} and 5-HT that warrants further study (23).

The effect of Lu-AA-21004 on the 5-HT-producing neurons of the raphe nuclei was examined by electrophysiological extracellular single cell recording in Sprague-Dawley rats and compared to the action of the SSRI fluoxetine. A single administration of Lu-AA-21004 (250-1250 μg/kg i.v.) elicited dose-dependent but reversible inhibition of neuronal firing (ED_{50} = 548 μg/kg i.v.) at a much more potent level than fluoxetine (ED_{50} = 1.6 mg/kg i.v.). The therapeutic effects of inhibited neuronal activity (due to 5-HT_{3A} receptor blockade) with Lu-AA-21004 (5 mg/kg/day for 5 or 10 hours or 1, 3, 7 or 14 days) displayed rapid recovery 1 day after treatment cessation compared to those treated with fluoxetine (10 mg/kg/day s.c. for 7, 14 or 21 days), in which the recovery rate was 14 days. Furthermore, pretreatment with Lu-AA-21004 for 3 days followed by a 1-day wash out significantly affected dose-dependent inhibition of neuronal firing by flesinoxan (delta ED_{50} = +267 μg/kg) (24).

Behavioral studies in mice and rats treated with Lu-AA-21044 have revealed its antidepressant and anxiolytic potential in the mouse forced swim test (minimal effective dose [MED] = 15.8 mg/kg s.c.), tail suspension test (17 mg/kg), marble burying test (3.9 mg/kg), rat conditioned fear test (MED = 3.9 mg/kg s.c.), mouse conditioned fear test (MED = 10 mg/kg) and social interaction assay (MED = 1-1.9 mg/kg s.c.) (15, 16, 21). By comparison, other drugs such as the SNRI duloxetine and the 5-HT_3 receptor antagonist ondansetron were inactive in all tests of anxiolytic activity, whereas the SSRI paroxetine was inactive in the conditioned fear test (16, 25).

PHARMACOKINETICS AND METABOLISM

In an assessment of the pharmacokinetic/pharmacodynamic (PK/PD) profile of Lu-AA-21004, 6 healthy males received a single dose of radioactively labeled [^{14}C]-Lu-AA-21004 and biological sample collections were made over 360 hours. The majority of radioactivity was recovered in the urine (59%) or feces (26%). The maximum plasma concentration (C_{max}) of the drug or its metabolites was seen at 6 hours after dosing. The oral clearance of the drug was 45.7 L/h, with a volume of distribution (V_d) of 3789 L and a half-life ($t_{1/2}$) of 60 hours for the drug and its primary metabolite. The drug gave six metabolites at varying concentrations and accounting for 100% of the radioactivity by 4 hours after dosing, and the dose was well tolerated by all patients, with no adverse events (AEs) (18).

CLINICAL STUDIES

Lu-AA-21004 is currently in phase III clinical trials for MDD and anxiety. Two formulations of Lu-AA-21004 exist, a lactose-based formulation that was used in clinical studies prior to 2007 and a calcium hydrogen phosphate anhydrous-based formulation used after 2007. It has been determined that both compounds have similar PK/PD profiles and are considered bioequivalent to one another (26). A number of phase III trials investigating Lu-AA-21004 in the treatment of MDD and generalized anxiety disorder have reached completion but only some of those have associated published data.

A randomized, double-blind, parallel-group, fixed-dose study evaluating the efficacy and safety of three doses of Lu-AA-21004 (2.5, 5 and 10 mg/day p.o.) in the acute treatment of MDD was completed in April 2009 (27). Duloxetine (60 mg/day p.o.) was used as an active comparator. Patients suffering from moderate to severe depression with major depressive episodes (MDE) lasting for a duration of 3 months were enrolled (N = 776; 18-75 years of age; both sexes). The primary outcome measure was to evaluate the efficacy of the three fixed doses of Lu-AA-21004 versus placebo after 8 weeks of treatment. Secondary outcome measures included the evaluation of safety, tolerability and sustained response after 8 weeks compared to placebo (measured as a > 50% decrease in the Montgomery Asberg Depression Rating Scale [MADRS] total score from baseline compared to week 1). There were no differences in the primary endpoint between the higher concentrations of Lu-AA-21004 and placebo or between duloxetine and the lowest dose of Lu-AA-21004. At higher doses, Lu-AA-21004 demonstrated efficacy in the secondary analysis of depression and anxiety ($P < 0.05$). Treatment with Lu-AA-21004 was well tolerated, with mild AEs such as nausea, headache, dizziness and dry mouth leading to withdrawal of 72 patients (6%, 8%, 9%, 11% and 12%, respectively, in the 2.5 mg, placebo, 10 mg, 5 mg and duloxetine groups) (28).

A similar randomized, double-blind, parallel-group, fixed-dose study evaluating the efficacy and safety of three doses of Lu-AA-21004 has also been completed (July 2009) in adults with MDD, with an MDE of at least 3 months and an MADRS > 26 (29). Patients (N = 560; mean age of 46.4 years) received 1, 5 or 10 mg Lu-AA-21004 or placebo control for 8 weeks. The primary outcome measure evaluated the least squares mean change from baseline on the 24-item Hamilton Depression Scale (HAM-D). At week 8, patients receiving 10 mg Lu-AA-21004 showed a significant reduction in HAM-D score ($P < 0.001$). Response rates (equal to a 50% reduction in HAM-D score) at week 8 were 47.5%, 45.3% and 49.6%, respectively, for the 1-, 5- and 10-mg groups, compared with 23.0% for the placebo group ($P < 0.001$). Remission rates (MADRS score = 10) at week 8 were 25.9% ($P = 0.062$), 28.8% ($P = 0.015$) and 26.6% ($P = 0.026$), respectively, for the Lu-AA-21004 1-, 5- and 10-mg groups compared with 16.5% for the placebo group. Any AEs reported were considered to be moderate and included nausea, headache and dizziness (30).

A randomized, multicenter, double-blind, fixed-dose study evaluating the efficacy and safety of Lu-AA-21004 (5 or 10 mg/day for 6 weeks) in the acute treatment of patients with MDD (N = 429), with an MDE of at least 3 months' duration and an MARDS score of 30, was completed in August 2007 (31). Venlafaxine XR (75 mg/day for 4 days, 150 mg/day for the following 3 days and 225 mg/day thereafter) was employed as an active comparator. Six weeks following the onset of treatment, both Lu-AA-21004 groups showed similar marked improvement in MARDS scores, as did the active comparator (5.9 and 5.7 difference from placebo, respectively, for 5 and 10 mg Lu-AA-21004; $P < 0.0001$). Hamilton Anxiety Depression Rating (HAM-A) scores at 6 weeks showed a significant difference, as did the active comparator (3.3 and 3.0 difference from placebo, respectively, for 5 and 10 mg Lu-AA-21004; $P < 0.01$). Treatments were well tolerated, with mild AEs reported including nausea, headache, dizziness and dry mouth (32).

The efficacy and safety of Lu-AA-21004 (5 mg vs. placebo) in treating adults with MDD (N = 600; mean age 42.4 years), with an MDE of at least 3 months' duration and an MADRS score of 30, were evaluated in a multicenter, randomized, double-blind study completed in October 2008 (33). Patients were treated for 6 weeks followed by discontinuation. Efficacy (change in HAM-D score from baseline), response (measured as a > 50% reduction in HAM-D score) and remission (measured as an MADRS score < 10) between the Lu-AA-21004 and placebo groups were not significantly different at any time point throughout the study. Lu-AA-21004 was well tolerated and AEs were mild, including nausea, headache, dizziness, diarrhea and dry mouth (34).

The long-term efficacy and tolerability of Lu-AA-21004 (5 or 10 mg/day for 12 weeks) in a relapse prevention study of patients with MDD (N = 639) and an MADRS score > 26 were evaluated in a randomized, multicenter, open-label study completed in September 2009 (35). The primary efficacy endpoint was assessed in remitters (those with an MARDS score < 10 at weeks 10-12) as the time to relapse (defined as an MADRS score > 22) within the first 24 weeks of the double-blind period (up to 64 weeks). At the 10- to 12-week stage, patients were randomized to placebo (n = 194) or Lu-AA-21004 (n = 206). Relapse rates were lower in the Lu-AA-21004 group compared to the placebo group, with a hazard ratio (HR) of 2.01 (95% confidence interval [CI]: 1.26-3.21; $P = 0.0035$). In the placebo group, 26% of patients relapsed compared to 13% of the Lu-AA-21004-treated patients. The treatment was well tolerated, with mild AEs leading to the withdrawal of 54 patients in the open-label period and 21 patients in the double-blind period (approximately 15 patients treated with Lu-AA-21004) (36).

The results of other completed phase III studies have yet to be reported and include those evaluating the safety, tolerability and efficacy in adults with MDD (37-40), elderly patients with MDD (41) and generalized anxiety disorder (42-45). A study investigating the effectiveness of Lu-AA-21004 in preventing relapse in general anxiety disorder has also been performed, although no data have been published to date (46). A number of phase III studies are in the recruitment phase, including those evaluating Lu-AA-210044 in MDD (47-53) and another investigating the effect of Lu-AA-21004 on concentrations of neurotransmitters in healthy males (54). An open-label, extension study to assess the safety and tolerability of Lu-AA-21004 is currently enrolling by invitation (55), and a final phase III study examining the effect of Lu-AA-21004 versus escitalopram on sexual function in patients with MDD is planned but not yet recruiting (56).

DRUG INTERACTIONS

A study conducted by Wang et al. using Indiana cocktail (caffeine 200 mg, tolbutamide 500 mg, dextromethorphan 30 mg and midazolam 4 mg) to induce CYP450 isoforms found that multiple doses of Lu-AA-21004 (10 mg) in 24 healthy adults did not have any effect on the PK/PD profile of the probe substrates CYP1A2, CYP2D6, CYP2CP or CYP3A4 (57). In a similar study, Buchbjerg et al. assessed the potential for an interaction with CYP2C19 because of the potential for affecting the metabolism of other marketed drugs. Both Lu-AA-21004 and metabolite 2 can act as inhibitors of CYP2C19, which is strongly involved in the metabolism of other commercial drugs, such as the gastric proton pump inhibitor omerprazole. In agreement with SIMCYP computer stimulations, this study found no significant effect for Lu-AA-21004 (10 mg) administration on the PK/PD profile of omeprazole or its metabolites and vice versa (58).

Lu-AA-21004 (10 mg) was also found to have no effect on the concentration of female hormones in healthy female volunteers taking the oral contraceptives ethinyl estradiol (30 μg) or levonorgestrel (150 μg). In addition, the PK/PD profile of the contraceptives was not affected by Lu-AA-21004 (59).

The same group has recently investigated the effect of alcohol (ethanol) on the metabolism of Lu-AA-21004. Healthy volunteers received a single dose of either 20 or 40 mg of Lu-AA-21004 with ethanol (0.6 g/kg) or placebo control. Those individuals receiving combination treatment with the lower dose of Lu-AA-21004 showed significant differences in postural stability (LS mean = –7.32 at 1 hour post-ethanol; $P = 0.002$) and self-related awareness (6.32 at 2 hours post-ethanol; $P = 0.042$), compared to those who did not receive ethanol. In addition, the same group showed decreased digital vigilance speeds (32.89, 29.89 and 30.44, respectively, at 1, 2 and 4 hours post-ethanol) compared to those who received only Lu-AA-21004 (20 mg). In the group receiving 40 mg Lu-AA-21004 and ethanol, significant differences in postural stability (3.91 at 8 hours post-ethanol; $P = 0.030$) and self-related

awareness (–6.82 at 1 hour post-ethanol; $P = 0.021$) were seen and digital vigilance speeds decreased (35.76 and 31.84, respectively, at 1 and 2 hours post-ethanol; $P < 0.001$) compared to those who received Lu-AA-21004 alone. Ethanol did not affect the PK/PD profile of Lu-AA-21004 and vice versa, and none of the differences demonstrated clinical relevance (60).

Finally, one study investigated the effect of feeding on the PK/PD profile of Lu-AA-21004. Healthy adult volunteers (N = 24; mean age of 26.7 years) received a single oral dose of Lu-AA-21004 (10 mg) after overnight fasting (10 hours) or within 30 minutes of consuming a high-fat breakfast. The AUC and C_{max} values were unaffected by fasting or feeding, suggesting that Lu-AA-21004 can be taken with or without food (61).

Overall, Lu-AA-21004 appears to be effective in combination with a number of other drugs, does not affect oral contraceptives and can be taken in the absence or presence of food. It appears to be generally effective in the presence of other drugs, with the exception of the antibiotic rifampicin, suggesting that some drugs that do affect CYP450 isoforms may reduce the effectiveness of Lu-AA-21004 in the clinic. However, an investigation in patients with hepatic impairment found no effect on the kinetic profile of Lu-AA-21004 or its metabolites (62). Furthermore, Lu-AA-21004 (10 and 40 mg once daily for 2 weeks) demonstrated no effect on cardiac repolarization in healthy males (63).

CONCLUSIONS

Current therapies for the treatment of depression and anxiety disorder display similar efficacy but are associated with a high level of nonresponders and have undesirable side effects in many patients. The traditional TCAs have fewer side effects but a slower onset than newer therapies, such as SSRIs and SNRIs. In addition, MAOIs can have severe side effects and must be taken in line with a strict dietary regimen. More recently, 5-HT receptors have become an attractive target for many antidepressant and anxiolytic drugs. Lundbeck and Takeda developed Lu-AA-21004 as a multitargeted drug that acts upon multiple 5-HT receptors and the 5HTT to increase 5-HT levels, which are found at low concentrations in patients suffering from affective disorders. Lu-AA-21004 has been shown to increase 5-HT levels, as well as other mood-regulating neurotransmitters, and has proven effective in preliminary short-term phase III studies of 6-8 weeks in alleviating depression-like symptoms. The drug is generally well tolerated, with only mild AEs, has a fast onset of action, has few interactions with other common medications and outperforms some of the currently available treatments on the market. Further phase III testing in long-term studies of its efficacy in treating MDD and generalized anxiety is currently under way. Lundbeck envisages that Lu-AA-21004 will be submitted for U.S. and European registration during 2012.

SOURCES

H. Lundbeck A/S (DK); licensed to Takeda Pharmaceutical Co., Ltd. for codevelopment and comarketing in the U.S. and Japan.

DISCLOSURES

The author states no conflicts of interest.

REFERENCES

1. Bang-Andersen, B., Faldt, A., Moerk, A. et al. (H. Lundbeck A/S). *1-[2-(2,4-Dimethylphenylsulfanyl)-phenyl]piperazine as a compound with combined serotonin reuptake, 5-HT3 and 5-HT1A activity for the treatment of cognitive impairment.* EP 2044043, JP 2009541216, JP 2010090165, US 2010297240, WO 2007144005.
2. Bang-Andersen, B., Ruhland, T., Smith, G. et al. *Discovery of Lu AA21004: A novel compound for the treatment of mood disorders.* 237th ACS Natl Meet (March 22-2, Salt Lake City) 2009, Abst MEDI 103.
3. Moore, N., Stensboel, T.B. (H. Lundbeck A/S). *1-[2-(2,4-Dimethylphenylsulfanyl)-phenyl]piperazine as a compound with combined serotonin reuptake, 5-HT3 and 5-HT1A activity for the treatment of pain or residual symptoms in depression relating to sleep and cognition.* CA 2684571, EP 2142193, JP 201052501, US 2011009422, WO 2008113359.
4. Nicolajsen, H.V., Lopez de Diego, H., Rock, M.H. (H. Lundbeck A/S). *Purification of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine*. WO 2010094285.
5. Bang-Andersen, B., Ruhland, T., Jorgensen, M. et al. *Discovery of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine (LU AA21004): A novel multimodal compound for the treatment of major depressive disorder.* J Med Chem 2011 54(9): 3206-21.
6. Smith, G.P., Pueschl, A., Moltzen, E.K., Ruhland, T., Bang-Andersen, B., Andersen, K. (H. Lundbeck A/S). *Phenyl-piperazine derivatives as serotonin reuptake inhibitors*. EP 1436271, EP 1749818, JP 2005505585, JP 2007031447, JP 2007051149, US 2006084662, US 2006089368, US 7138407, US 7144884, US 7148238, US 2007060574, US 7683053, US 2011009423, WO 2003029232.
7. Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K.R., Walters, E.E. *Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication*. Arch Gen Psychiatry 2005, 62(6): 593-602.
8. Lopez, A.D., Mathers,, C.D., Ezzati M., Jamison, D.T., Murray, C.J. *Global and regional burden of disease and risk factors, 2001: Systematic analysis of population health data*. Lancet 2006, 367(9524): 1747-57.
9. Zis, A.P., Goodwin, F.K. *Novel antidepressants and the biogenic amine hypothesis of depression. The case for iprindole and mianserin.* Arch Gen Psychiatry 1979, 36(10): 1097-107.
10. Gotlib, I.H., Joormann, J., Minor, K.L., Hallmayer, J. *HPA-axis reactivity: A mechanism underlying the associations among 5-HTTLPR, stress, and depression.* Biol Psychiatry 2008, 63(9): 847-51.
11. Nichols, D.E., Nichols, C.D. *Serotonin receptors.* Chem Rev 2008, 108(5): 1614-41.
12. Schloss, P., Williams, D.C. *The serotonin transporter: A primary target for antidepressants*. J Psychopharmacol 1998, 12(2): 115-21.
13. Lotufo-Neto, F., Trivedi, M., Thase, M.E. *Meta-analysis of the reversible inhibitors of monoamine oxidase type A moclobemide and brofaromine for the treatment of depression.* Neuropsychopharmacology 1999, 20(3): 226-47.
14. Carr, G.V., Lucki, I. *The role of serotonin receptor subtypes in treating depression: A review of animal studies.* Psychopharmacology 2011, 213(2-3): 265-87.
15. Moore, N., Bang-Andersen, B., Brennum, L. et al. *LU AA21004: A novel potential treatment for mood disorders*. Eur Neuropsychopharmacol [21st Congr Eur Coll Neuropsychopharmacol (ECNP) (Aug 30-Sept 3, Barcelona) 2008] 2008, 18(Suppl. 4): Abst P.2.b.015.
16. Mork, A., Brennum, L.T., Fallon, S.M. et al. *Pharmacological profile of LU AA21004, a novel multi-target drug for the treatment of mood disorders*. Eur Neuropsychopharmacol [22nd Congr Eur Coll Neuropsychopharma-

col (ECNP) (Sept 12-16, Istanbul) 2009] 2009, 19(Suppl. 3): Abst P.2.d.017.

17. Mork, A., Fredriksen, K., Nielsen, S.M. et al. *LU AA21004, a novel antidepressant with multimodal activity exerted through serotonergic targets*. 10th World Cong Biol Psychiatry (May 29-June 2, Prague) 2011, P26-001.
18. Nilauseu, D., Hojer, A.M., Bendahl, L. *Absorption, metabolism, and excretion of an oral dose of [c-14]-LU AA21004 50 mg in healthy men.* J Clin Pharmacol [38th Annu Meet Am Coll Clin Pharmacol (ACCP) (Sept 13-15, San Antonio) 2009] 2009, 49(9): Abst 99.
19. Stensbol, T.B., Frederiksen, K., Zhong, H.L., Bang-Andersen, B. *The in vitro profile of LU AA21004, a novel multi-target drug for the treatment of mood disorders.* Biol Psychiatry [64th Annu Meet Soc Biol Psychiatry (SOBP) (May 14-16, Vancouver) 2009] 2009, 65(8, Suppl. 1): Abst 260.
20. Mork, A., Frederiksen, K., Moller, S.M. et al. *Pharmacological in vitro profile of LU AA21004, a novel multimodal drug for the treatment of mood disorders*. 164th Annu Meet Am Psychiatr Assoc (May 14-18, Honolulu) 2011, Abst NR04-49.
21. Mork, A., Brennum, L.T., Fallon, S.M. et al. *In vivo effects of the multi-target drug LU AA21004: A novel potential treatment for mood disorders*. Biol Psychiatry [64th Annu Meet Soc Biol Psychiatry (SOBP) (May 14-16, Vancouver) 2009] 2009, 65(8, Suppl. 1): Abst 239.
22. Sanchez, C., Cremers, T., Pehrson, A.L., Jorgensen, L.B., Madsen, M.M. *Effects of subchronic treatment with the multimodal antidepressant LU AA21004 on rat brain neurochemistry*. 164th Annu Meet Am Psychiatr Assoc (May 14-18, Honolulu) 2011, Abst NR04-59.
23. Chandrasena, G., Pehrson, A., Carnerup, M. et al. *Steady-state levels of the antidepressant Lu AA21004 in plasma, brain and CSF, and 5-HT target engagement in the rat.* 164th Annu Meet Am Psychiatr Assoc (May 14-18, Honolulu) 2011, Abst NR04-07.
24. Haddjeri, N., Etievant, A., Moore, N. et al. *Electrophysiological study of the effects of the novel antidepressant Lu AA21004 on the rat 5-HT neuronal activity*. Eur Neuropsychopharmacol [22nd Congr Eur Coll Neuropsychopharmacol (ECNP) (Sept 12-16, Istanbul) 2009] 2009, 19(Suppl. 3): S437.
25. Bisulco, S., Miller, S., Moore, N.A. et al. *LU AA21004, a novel multi-target drug, displays anxiolytic- and antidepressant-like effects in multiple preclinical assays*. Biol Psychiatry [64th Annu Meet Soc Biol Psychiatry (SOBP) (May 14-16, Vancouver) 2009] 2009, 65(8, Suppl. 1): Abst 360.
26. Wang, Y., Wojtkowski, T., Agyemang, A., Homery, M.C., Karim, A. *Relative bioavailability of two formulations of LU AA21004.* J Clin Pharmacol [38th Annu Meet Am Coll Clin Pharmacol (ACCP) (Sept 13-15, San Antonio) 2009] 2009, 49(9): Abst 105.
27. *Efficacy and safety of Lu AA21004 in acute treatment of major depressive disorder (NCT00635219).* ClinicalTrials.gov Web site, August 4, 2011.
28. Baldwin, D., Loft, H., Dragheim, M. *A randomised, double-blind, placebo-controlled duloxetine-referenced, fixed dose study of three dosages of LU AA21004 in acute treatment of MDD*. 164th Annu Meet Am Psychiatr Assoc (May 14-18, Honolulu) 2011, Abst NR04-02.
29. *Efficacy and safety of Lu AA21004 in adults with major depressive disorder (NCT00735709).* ClinicalTrials.gov Web site, August 4, 2011.
30. Henigsberg, N., Mahableshwarkar, A.R., Jacobsen, P., Chen, Y., Thase, M.E. *Efficacy and tolerability of multiple doses of LU AA21004 in an 8-week treatment of adults with major depressive disorder*. 164th Annu Meet Am Psychiatr Assoc (May 14-18, Honolulu) 2011, Abst NR04-22.
31. *Efficacy and safety of Lu AA21004 in acute treatment of major depressive disorder (NCT00839423).* ClinicalTrials.gov Web site, August 4, 2011.
32. Artigas, F., Dragheim, M., Loft, H. et al. *A randomised, double-blind, placebo-controlled, active-referenced study of Lu AA21004 in patients with major depression.* Eur Neuropsychopharmacol [22nd Congr Eur Coll Neuropsychopharmacol (ECNP) (Sept 12-16, Istanbul) 2009] 2009, 19(Suppl. 3): Abst P.2.c.040.
33. *Efficacy and safety of Lu AA21004 in treating adult subjects with major depressive disorder (NCT00672958).* ClinicalTrials.gov Web site, August 4, 2011.
34. Jain, R., Mahableshwarkar, A.R., Jacobsen, P., Chen, Y. Thase, M.E. *Efficacy and tolerability of LU AA21004 5 mg in a 6-week treatment of adults with major depressive disorder.* 164th Annu Meet Am Psychiatr Assoc (May 14-18, Honolulu) 2011, Abst NR04-29.
35. *Efficacy of Lu AA21004 in the prevention of relapse of major depressive episodes (NCT00596817).* ClinicalTrials.gov Web site, August 4, 2011.
36. Dragheim, M., Boulenger, J-P., Loft, H., Florea, I. *A double-blind, randomized, placebo-controlled, relapse prevention study with LU AA21004 in patients with major depressive disorder.* 164th Annu Meet Am Psychiatr Assoc (May 14-18, Honolulu) 2011, Abst NR4-14.
37. *Safety and tolerability of Lu AA21004 in subjects with major depressive disorder (NCT00707980).* ClinicalTrials.gov Web site, August 4, 2011.
38. *Long-term study of Lu AA21004 in patients with major depressive disorder (NCT00761306).* ClinicalTrials.gov Web site, August 4, 2011.
39. *Efficacy and safety of Lu AA21004 in the treatment of subjects with major depressive disorder (NCT00672620).* ClinicalTrials.com Web site, August 4, 2011.
40. *Long-term safety study of Lu AA21004 in patients with major depressive disorder (NCT00694304).* ClinicalTrials.gov Web site, August 4, 2011.
41. *Efficacy and safety of Lu AA21004 in acute treatment of major depressive disorder in elderly patients (NCT00811252).* ClinicalTrials.gov Web site, August 4, 2011.
42. *An efficacy and safety study of Lu AA21004 in treating generalized anxiety disorder (NCT00734071).* ClinicalTrials.gov Web site, August 4, 2011.
43. *Efficacy and safety of Lu AA21004 for treatment of generalized anxiety disorder in adults (NCT00744627).* ClinicalTrials.gov Web site, August 4, 2011.
44. *Efficacy and safety of Lu AA21004 in treating generalized anxiety disorder (NCT00730691).* ClinicalTrials.gov Web site, August 4, 2011.
45. *Efficacy and safety of Lu AA21004 in treating generalized anxiety disorder (NCT00731120).* ClinicalTrials.gov Web site, August 4, 2011.
46. *Relapse-prevention study with Lu AA21004 in patients with generalized anxiety disorder (NCT00788034).* ClinicalTrials.gov Web site, August 4, 2011.
47. *Efficacy and safety of Lu AA21004 in adults with major depressive disorder (NCT01179516).* ClinicalTrials.gov Web site, August 4, 2011.
48. *Efficacy and safety of Lu AA21004 in acute treatment of major depressive disorder (NCT01140906).* ClinicalTrials.gov Web site, August 4, 2011.
49. *Efficacy and safety of Lu AA21004 for treatment of major depressive disorder (NCT01255787).* ClinicalTrials.gov Web site, August 4, 2011.
50. *A study of 15 and 20 mg of Lu AA21004 in major depressive disorder (NCT01323478).* ClinicalTrials.gov Web site, August 4, 2011.
51. *Efficacy and safety study of Lu AA21004 in adults with major depressive disorder (NCT01163266).* ClinicalTrials.gov Web site, August 4, 2011.
52. *Safety and efficacy of Lu AA21004 in adults with major depressive disorder (NCT01153009).* ClinicalTrials.gov Web site, August 4, 2011.
53. *Efficacy and safety of Lu AA21004 for treatment of major depressive disorder (NCT01355081).* ClinicalTrials.gov Web site, August 4, 2011.
54. *Efficacy of Lu AA21004 on the concentrations of selected neurotransmitters in healthy male subjects (NCT01299805).* ClinicalTrials.gov Web site, August 4, 2011.
55. *Safety and tolerability of Lu AA21004 - Open label extension study (NCT01152996).* ClinicalTrials.gov Web site, August 4, 2011.

56. *Effect of Lu AA21004 versus escitalopram on sexual functioning in adults with well-treated major depressive disorder (NCT01364649).* ClinicalTrials.gov Web site, August 4, 2011.

57. Wang, Y., Wojtkowski, T., Hanson, E., Harris, S., Karim, A. *An open-label, multiple-dose study in healthy adults to assess the drug interaction potential of LU AA21004 using the Indiana cocktail*. J Clin Pharmacol [38th Annu Meet Am Coll Clin Pharmacol (ACCP) (Sept 13-15, San Antonio) 2009] 2009, 49(9): Abst 103.

58. Buchbjerg, J.K., Hojer, A.M., Jensen, K.G., Sogaard, B. *Assessment of the CYP2C19 interaction potential of LU AA21004*. J Clin Pharmacol [38th Annu Meet Am Coll Clin Pharmacol (ACCP) (Sept 13-15, San Antonio) 2009] 2009, 49(9): Abst 123.

59. Wang, Y., Wojtkowski, T., Devoti, A., Priestley, A., Karim, A. *Effect of LU AA21004 on the pharmacokinetics and pharmacodynamics of ethinyl estradiol (30 MU G) and levonorgestrel (150 MU G) in healthy adult women.* J Clin Pharmacol [38th Annu Meet Am Coll Clin Pharmacol (ACCP) (Sept 13-15, San Antonio) 2009] 2009, 49(9): Abst 104.

60. Wang, Y., Munsaka, M., Serenko, M., Smith, S., Nomikos, G., Karim, A. *Evaluation of the pharmacodynamics and pharmacokinetics of the interaction of LU AA21004 and ethanol in healthy adult subjects.* Clin Pharmacol Ther 2011, 89(Suppl. 1): Abst PI-40.

61. Wang, Y., Wojtkowski, T., Agyemang, A. et al. *Effect of food on the pharmacokinetics of LU AA21004 in healthy volunteers*. J Clin Pharmacol [38th Annu Meet Am Coll Clin Pharmacol (ACCP) (Sept 13-15, San Antonio) 2009] 2009, 49(9): Abst 106.

62. Wang, Y., Munsaka, M., Serenko, M. et al. *Evaluation of the single-dose pharmacokinetics of LU AA21004 and its metabolites in subjects with and without hepatic impairment.* Clin Pharmacol Ther 2011, 89(Suppl. 1): Abst PIII-13.

63. Wang, Y., Munsaka, M., Serenko, M. et al. *Evaluation of the effects of LU AA21004 on cardiac repolarization in healthy adult male subjects.* Clin Pharmacol Ther 2011, 89(Suppl. 1): Abst PIII-14.