CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204447Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 20, 2013

FROM: Jing Zhang, MD. PhD.
Medical Team Leader, Division of Psychiatry Products
HFD-130

SUBJECT: Cross Discipline Team Leader Review

NDA/Supp#: 204447/S001

Proprietary/ Established name: Vortioxetine (Brintellix)

Dosage forms/ Strength: Oral Immediate Release Tablets: 5, 10, 15 and 20 mg

Indication: Mono-therapy for Major Depressive Disorder in adults

Recommendation: Approval

1. Introduction and Background

Vortioxetine, Lu AA21004 (1-[2-(2, 4-dimethyl-phenylsulfanyl)-phenyl]-piperazine), is a New Molecule Entity discovered and patented by Lundbeck and is being co-developed with Takeda for the indication of Major Depressive Disorder in adult as mono-therapy. LuAA21004 belongs to a new chemical class of psychotropics, the bis-aryl-sulfanyl amines. The mechanism of action of Lu AA21004 is unknown. Lu AA21004 is a potent and selective inhibitor of the serotonin transporter, without significant activity at the norepinephrine and dopamine transporters. In addition, Lu AA21004 is a potent antagonist at 5-HT3 receptor, a moderate antagonist at 5-HT1D receptor, a moderate agonist at 5-HT1A receptor, a moderate to weak partial agonist at 5-HT1B, and a weak antagonist at 5-HT7 receptor.

Lu AA21004 is developed under IND 76,307 that was first submitted to FDA on 04 April 2007 for the indication of Major Depressive Disorder (MDD). Lu AA21004 was initially developed globally in MDD at doses up to 10 mg. The initial phase 2/3 program included 6

short-term studies (Studies 11492A, 11984A, 303, 304, 305, and 12541A [in the elderly]), 1 long-term relapse-prevention study (Study 11985A), and 3 open-label, long-term extension studies (Studies 11492C, 11984B and 301). The results of these studies did not demonstrate consistent efficacy at the 5 mg dose in the United States, therefore, a revised phase 3 program evaluating doses up to and including 20 mg once daily (QD) was initiated.

The Lu AA21004 MDD program consists of the following completed studies: 32 clinical pharmacology studies (one submitted during review cycle); 10 short-term, placebo-controlled studies (including a dedicated study in the elderly); 1 long-term, placebo-controlled, relapse-prevention study; 3 completed long-term, open label extension studies, and 2 ongoing long-term, extension studies. In addition, 4 short-term, placebo-controlled studies and 1 long-term, placebo-controlled, relapse-prevention study with Lu AA21004 in subjects with generalized anxiety disorder (GAD) provide supportive safety data.

Among the 10 short-term, placebo-controlled studies, 6 of them were considered as positive studies. One study (11984A) was considered as a failed study and the rest 3 were considered as negative studies. Therefore, the acute efficacy of Lu AA21004 in the treatment of MDD was demonstrated in the 6 short-term, placebo-controlled studies and the maintenance efficacy was demonstrated in a long-term relapse prevention study.

Takeda, Lundbeck and the Food and Drug Administration (FDA) have held 3 face-to-face meetings to discuss the Lu AA21004 clinical development program.

> An End-of-Phase 2 Meeting was held on 05 February 2008 mainly discussed the results of completed nonclinical and clinical phase 1 and phase 2 studies as well as the phase 3 clinical development plan.
>
> A Type C Meeting was held on 30 March 2010. The results of an initial phase 3 program with doses of Lu AA21004 up to 10 mg in which consistent efficacy was not demonstrated in the United States were reviewed. The main objectives of the meeting were to discuss a new phase 3 clinical program in MDD to study higher doses of Lu AA21004, to demonstrate efficacy in the US population, and to support an eventual NDA.
>
> A Pre-NDA Meeting was held on 22 June 2012. The content, organization and format of the NDA as well as issues related to implementation of the Prescription Drug User Fee Act (PDUFA) V were discussed.

This NDA was submitted on 01 October 2012.

2. Chemistry, Manufacturing and Controls (CMC)

Wendy Wilson-Lee, Ph.D., is the chemistry reviewer and Houda Mahayni, Ph.D., is the biopharmaceutics reviewer. Both of them recommended that Lu 21004 to be approved from the CMC perspective.

LuAA21004 is a new chemical class of psychotropics, the bis-aryl-sulfanyl amines. LuAA21004 (Vortioxetine HBr) is white to very slightly beige powder. (b) (4)

The (b) (4) (β-form) is the form that is developed. (b) (4)

Brintellix (Lu AA21004) Tablets are immediate-release, film-coated tablets for oral administration, formulated into four strengths, 5 mg, 10 mg, 15 mg, and 20 mg IR tablets differentiated by tablet color and debossed marking. Each tablet contains 6.355, 12.71, 19.065, or 25.42 mg of vortioxetine hydrobromide equivalent to 5, 10, 15, or 20 mg of vortioxetine, respectively. The drug product does not contain any novel excipients or excipients of human or animal origin.

Biopharmaceutics Review

Houda Mahayni, Ph.D., is the biopharmaceutics reviewer. His review dated April 8, 2013 focuses on the evaluation of: 1) The acceptability of the dissolution method and acceptance criterion; 2) Data supporting the acceptability of the 5 mg strength (biowaiver), 3) The acceptability of data supporting the bridging throughout the LuAA21004 clinical development, and 4) The acceptability of data supporting the bridging of the proposed manufacturing sites.

In his review he felt that the Applicant has submitted sufficient information to support the discriminating ability of the dissolution method. The proposed dissolution method and acceptance criterion are acceptable.

Biopharmaceutics initially assessed that the 5 mg strength does not qualify for a biovaiver because it is (b) (4) in its active and inactive ingredients to the corresponding highest strength product for which the BA/BE study was conducted, and Formulation IV (5 mg) strength was not used in clinical studies. FDA sent information request to the Applicant on February 28, 2013, regarding the biowaiver. The Applicant responded on March 7, 2013 that a bioequivalence study (Study 14520) was conducted comparing dose strengths of 5 mg and 20 mg. The bioequivalence study report was submitted and reviewed later by Office of Clinical Pharmacology (OCP). Therefore, a biowaiver assessment for the 5 mg strength is no longer needed.

Four different IR tablet formulations of Lu AA21004 were developed: Formulation I, II, III, and IV. PK studies including efficacy and safety of Lu AA21004 have been generated with Formulation I, III, and IV. Formulation II was not used in any clinical studies. The Applicant conducted two relative bioavailability studies (Study 106 and Study 123) to link formulation used throughout the different phases of drug development. These studies are being reviewed by OCP and were felt adequate. The commercial tablet formulation (Formulation IV, Colored-Almond) had minor modifications compared to the tablet used in Phase 3 studies (Formulation IV, White-Round). These changes are considered minor and will not affect tablet performance.

The sponsor proposed two manufacturing sites: Lundbeck (Denmark) and Takeda (Osaka, Japan). Only the registration stability batches manufactured at Lundbeck, were included in clinical studies. The dissolution testing results in three different media established the bridge between the manufacturing sites and confirmed that all differences in MgSt, film-coat, and debossing between the two sites are minor and do not affect the release of vortioxetine from the drug product. Therefore, it is acceptable to use Takeda, Japan site as an alternative site for commercial manufacturing.

On April 8, 2013 and June 20, 3013 the sponsor submitted a comparability protocol for the proposed additional maufaturing site, Oranienburg. The ONDQA-Biopharmaceutics team reviewed submission. In the addendum review of Houda Mahayni, PhD, he concluded that the proposed dissolution documentation according to Case B is acceptable in support of adding the Oranienburg manufacturing site as described in the comparability protocol and the comparability protocol for additional manufacturing site is acceptable.

Chemistry Review

Wendy Wilson-Lee, Ph.D., did the quality review of this submission.

The proposed drug substance regulatory specification controls the appearance (visual); identification (FTIR, HPLC); assay (HPLC); (b) (4) (titration); impurities (HPLC, GC); (b) (4) (ICP-OES); residual solvents (GC); heavy metals; residue on ignition; particle size distribution (laser diffraction); and microbiological contamination. All drug substance analytical methods are appropriate and validated for their intended use. (b) (4)

Brintellix manufacturing (b) (4): (b) (4) The proposed regulatory drug product specification controls the appearance (visual); identification (UV and HPLC); degradation products (HPLC); content uniformity; dissolution (paddle method with HPLC); and assay (HPLC) of the drug product. All analytical methods are appropriate and validated for their intended use.

The applicant proposed three commercial packaging configurations and two physician sample configurations. They were reviewed and were acceptable.

Takeda proposes a 36 month drug product expiration dating period for all tablet strengths of Brintellix Tablets when stored in the commercial or sample packaging configurations. The reviewer agreed with their proposal based on the stability data and in accordance with ICH Q1E.

Pre-approval Inspection of Facilities and Quality Issues Observed

The facilities inspection has been completed. The Office of Compliance has determined that the drug substance, drug product, and packaging facilities are adequate.

There are no unresolved CMC approvable issues.

3. Nonclinical Pharmacology/Toxicology

Antonia Dow, Ph.D., is the Pharmacology/Toxicology reviewer. In her review, she recommended that vortioxetine can be approved if the genotoxic impurity, (b) (4), is limited during this review cycle so that the maximum daily clinical dose does not exceed (b) (4). The following is a brief summary of her review.

Lu AA21004 is a potent and selective inhibitor of the serotonin transporter, without significant activity at the norepinephrine and dopamine transporters. In addition, Lu AA21004 is a potent antagonist at 5-HT3 receptor, a moderate antagonist at 5-HT1D receptor, a moderate agonist at 5-HT1A receptor, a moderate to weak partial agonist at 5-HT1B, and a weak antagonist at 5-HT7 receptor. Lu AA21004 had mixed results demonstrating antidepressant-like activity in behavioral animal models.

General toxicology studies in two species (rat and dog) were conducted to support chronic use of Lu AA21004. General toxicities seen in rat or dog that might have clinical relevance are convulsions, kidney and liver pathology, and pupillary dilation. Convulsions were noted after acute dosing in rats and dogs at 195 and 16 times, respectively, the maximum recommended human dose (MRHD) of 20 mg on a mg/m2 basis; however, no convulsions were seen in chronic rat and dog studies at doses 39 and 12 times, respectively, the MRHD. In rat, kidney and liver pathology related to the presence of vortioxetine metabolite crystals was noted at doses 38 times the MRHD, but not at 7 times the MRHD. In dog, pupillary dilation occurred at doses 8 times the MRHD, but not at 6 times the MRHD.

Lu AA21004 was not genotoxic or teratogenic in animal studies.

In the review of Antonia Dow, she concluded that the only Pharmacology/Toxicology issue that could prevent approval of this NDA is a genotoxic impurity, (b) (4). This impurity issue was adequately addressed by the sponsor in the later review cycle and there were no unresolved pharm/tox issues.

The pharm/tox team has made a number of recommendations for labeling that we have incorporated.

4. Clinical Pharmacology/Bio-pharmaceutics

The clinical development program consisted of 32 clinical pharmacology studies (one was submitted during the review cycle). Twenty eight studies related to this formulation were review by Andre Jackson, Ph.D. our clinical pharmacology reviewer. Li Zhang, Ph.D., is

the pharmacometric reviewer. Both of them recommended an approval action on this NDA submission.

Lu AA21004 exhibits dose-proportional pharmacokinetics with an absolute bioavailability of 75%. No food effect is identified. Plasma protein binding is about 98%. Lu AA21004 is extensively metabolized through oxidation via multiple cytochrome P450 enzymes, primarily by CYP2D6, and followed by subsequent glucuronic acid conjugation. Specific dose recommendations in patients who also take strong CYP2D6 inhibitors and strong CYP inducers have been recommended by the clinical pharm team and incorporated into the label. Only negligible amount of unchanged Lu AA21004 is eliminated. The half-life of Lu AA21004 is 66 hours. A 5-time accumulation at steady state is expected following a once daily dosing. The presence of hepatic impairment (mild to moderate) and renal impairment (mild to end stage) does not appear to affect the apparent clearance of Lu AA21004.

Lu AA21004 does not prolong QTc interval. At the dose of 10 mg, Lu AA21004 does not seem to change International Normalized Ratio (INR) and prothrombin time significantly when adding stable doses of warfarin (1-10 mg). In addition, no apparent change in platelet aggregation was observed in patients receiving 150 mg aspirin and 10 mg of Lu AA21004 as compared to aspirin alone. Furthermore, 10 mg Lu AA21004 does not interfere with driving performance significantly as measured using the standard deviation of lateral position (SDLP) during an on-the-road driving test.

Office of Scientific Inspection (OSI) Inspection:

OSI identified misconducts and deficiencies of the bioassays conducted (b) (4) for pharmacokinetic samples collected in a total of 12 clinical trials. The affected trials include 1 relative BA and food effect study (Study 106), 4 extrinsic factor studies (Study 101, 102, 103, and 11826A), 2 PET scan studies (Study 10985 and 12260A), and 5 Phase 2/3 studies (Study 11492A, 11984A, 11985A, 11492C, 11984B). OSI inspection focused on the relative BA and food effect study and 4 extrinsic factor studies, which contain key clinical pharmacology information for Lu AA21004 and its metabolites and identified more issues as reflected in the 483 form issued on May 17, 2013. At present, OCP decided to exclude the pharmacokinetic information from the 12 trials in the current review until further remedial actions by the firm are discussed and accepted by OSI.

5. Clinical/Statistical

Jenn Sellers, MD. PhD., is the medical reviewer and George Kordzakhia, PhD., is the statistical reviewer for this submission. Please refer to their reviews for details.

The phase 2/3 clinical development program for Lu AA21004 was initiated in 2006 and has been jointly conducted by Takeda and Lundbeck. The efficacy of Lu AA21004 in the treatment of MDD has been evaluated in 10 short-term placebo-controlled studies (9 in adults and 1 in elderly subjects) and 1 long-term placebo-controlled relapse-prevention study. Three long-term, open-label, flexible-dose extensions studies have been completed

and 2 are ongoing. Out of 10 short-term studies, 5 studies were conducted exclusively in the United States (303, 304, 315, 316 and 317), 2 studies were multiregional trials including Canada (11492A and 11984A), 2 studies were multiregional trials conducted outside North America (305 and 13267A), and 1 trial (12541A) was multiregional and included both, US and Canada. The relapse prevention study (11985A) is a multiregional study including Canada.

5.1 Efficacy

5.1.1 Clinical studies essential to regulatory decision (design, analytic features, and results)

Among the 10 short-term studies, six studies (11492, 305, 13267A, 315, 316 and 11985A) were considered as positive studies and one study (11984A) was considered as a failed study because the active control, duloxetine 60 mg, did not show statistically significant efficacy compared to placebo. The rest 3 studies (303, 304, and 317) were considered as negative studies. Therefore, the acute efficacy of LU AA21004 in the treatment of MDD was demonstrated in the 6 short-term, placebo-controlled studies and the maintenance efficacy was demonstrated in a long-term relapse prevention study. The following review will only focus on the 7 positively studies.

Studies 11492A, 11984A, 305, 13267A, 12541A, and 11985A were conducted at sites in 1 or more of the following areas: Asia, Australia, Canada, Europe, and South Africa. Study 12541A also included sites in the United States. Studies 303, 304, 315, 316, and 317 were conducted exclusively in the United States.

Table 1 is a brief summary of the 10 short-term studies.

Table1: Summary of Results of 10 MDD Short-Term Studies

Study No./ Region	Main Inclusion Criteria	Results of Study Drug Doses (mg) vs. PBO	Overall Study Results
11492A/Europe, Australia, Canada Asia	18-65 years MADRS ≥30	Lu AA21004 5 mg vs. PBO - p<0.001 Lu AA21004 10 mg vs. PBO - p<0.001 Venlafaxine 225 mg vs. PBO - p<0.001	Positive
305/Europe, Asia, Australia, South Africa	18-75 years, MADRS ≥26	Lu AA21004 5 mg vs. PBO - NS Lu AA21004 10 mg vs. PBO - p<0.001	Positive
13267A/Europe, South Africa	18-75 years, MADRS ≥26 and CGI-S ≥4	Lu AA21004 15 mg vs. PBO - p<0.0001 Lu AA21004 20 mg vs. PBO - p<0.0001 duloxetine 60 mg vs. PBO - p<0.0001	Positive
315/US	18-75 years, MADRS ≥26 and CGI-S≥4	Lu AA21004 15 mg vs. PBO - p=0.224 Lu AA21004 20 mg vs. PBO - p=0.023 duloxetine 60 mg vs. PBO - p<0.001	Positive
316/US	18-75 years, MADRS ≥26 and CGI-S ≥4	Lu AA21004 10 mg vs. PBO - p=0.058 Lu AA21004 20 mg vs. PBO - p=0.002	Positive
12541A (Elderly) /Europe, Canada, US	≥65 years, MADRS ≥26	Lu AA21004 5 mg vs. PBO - p=0.0011 duloxetine 60 mg vs. PBO - p<0.001	Positive

11984A/Europe, Canada, Asia, Australia	18-75 years, MADRS ≥26	Lu AA21004 5 mg vs. PBO - NS Lu AA21004 10 mg vs. PBO - NS duloxetine 60 mg vs. PBO - NS	Failed
317/US	18-75 years, MADRS ≥26	Lu AA21004 10 mg vs. PBO - NS Lu AA21004 15 mg vs. PBO - NS	Negative
303/US	18-75 years, MADRS ≥30	Lu AA21004 5 mg vs. PBO - NS	Negative
304/US	18-75 years, MADRS ≥22	Lu AA21004 5 mg vs. PBO - NS duloxetine 60 mg vs. PBO - p<0.05	Negative

Source: Jenn Seller review

Short-Term Efficacy

The short-term studies were randomized, double-blind, placebo-controlled, fixed-dose studies of 6- or 8-weeks' duration in adult subjects with DSM-IV TR diagnosis of MDD. Study 12541A was conducted in elderly subjects aged ≥65 years (no upper age limit).

Eligible subjects were randomized equally to each treatment group with placebo, a fixed dose of Lu AA21004 (1, 2.5, 5, 10, 15, or 20 mg QD; the doses varied across studies). For all doses, except 15 and 20 mg, subjects were started directly on the dose to which they had been randomized. Subjects randomized to 15 or 20 mg started with Lu AA21004 10 mg for 1 week. In Studies 315, 316, and 317, subject randomization was stratified by baseline sexual dysfunction status (normal or abnormal). Four out of the 6 positive trials have an active control arm. Study 11492A had an active control of venlafaxine 225 mg/day and the 3 other studies (13267A, 315, and 12541A) had an active control of Duloxetine 60 mg/day.

The primary efficacy endpoint was the change from baseline to endpoint of either MADRS (study11492A, 13267A, 315 and 316), or HAM-D24 (study 305 and 12541A). The primary efficacy variable was analyzed by either a mixed model repeated measures (MMRM) analysis using observed cases (OC), or an analysis of covariance (ANCOVA) using the last observation carried forward (LOCF). The sponsor also proposed multiple key secondary endpoints varying from study to study. The list of key secondary endpoints includes change from baseline in SDS, CGI-I, HAM-D24 response rate, MADRS remission rate, and change from baseline in HAM-D24 in subjects with baseline HAM-A ≥20.

Table 2 summarized the primary efficacy outcome from the 6 short-term studies. * indicate the dose is statistically significantly superior to placebo.

Table 2: Primary Efficacy Results of 6 Short-term Trials

Study No. [Primary Measure]	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
11492A [MADRS] Non-US study	BRINTELLIX (5 mg/day)*	34.1 (2.6)	-20.4 (1.0)	-5.9 (-8.6, -3.2)
	BRINTELLIX (10 mg/day)*	34.0 (2.8)	-20.2 (1.0)	-5.7 (-8.5, -2.9)
	Venlafaxine (225mg)*[b]	34.2 (3.1)	-20.9 (1.0)	-6.4 (-9.1, -3.7)
	Placebo	33.9 (2.7)	-14.5 (1.0)	--

305 [HAMD-24] Non-US study	BRINTELLIX (1 mg/day)	32.5 (5.2)	-14.8 (0.8)	-3.5 (-5.6, -1.5)
	BRINTELLIX (5 mg/day)	32.2 (5.0)	-15.4 (0.7)	-4.1 (-6.2, -2.1)
	BRINTELLIX (10 mg/day)*	33.1 (4.8)	-16.2 (0.8)	-4.9 (-7.0, -2.9)
	Placebo	32.7 (4.4)	-11.3 (0.7)	--
13267A [MADRS] Non-US	BRINTELLIX (15 mg/day)*	31.8 (3.4)	-17.2 (0.8)	-5.5 (-7.7, -3.4)
	BRINTELLIX (20 mg/day)*	31.2 (3.4)	-18.8 (0.8)	-7.1 (-9.2, -5.0)
	Duloxetine (60mg)*[b]	31.2 (3.5)	-21.2 (0.8)	-9.5 (-11.6,-7.4)
	Placebo	31.5 (3.6)	-11.7 (0.8)	--
315 [MADRS] US study	BRINTELLIX (15 mg/day)	31.9 (4.1)	-14.3 (0.9)	-1.5 (-3.9, 0.9)
	BRINTELLIX (20 mg/day)*	32.0 (4.4)	-15.6 (0.9)	-2.8 (-5.1, -0.4)
	Duloxetine (60mg)* [b]	32.8 (4.3)	-16.9 (0.9)	-4.1 (-6.5, -1.7)
	Placebo	31.5 (4.2)	-12.8 (0.8)	--
316 [MADRS] US study	BRINTELLIX (10 mg/day)	32.3 (4.5)	-13.0 (0.8)	-2.2 (-4.5, -0.1)
	BRINTELLIX (20 mg/day)*	32.4 (4.3)	-14.4 (0.9)	-3.6 (-6.0, -1.4)
	Placebo	32.0 (4.0)	-10.8 (0.8)	--
12541A [HAMD-24] US &Non-US	BRINTELLIX (5 mg/day)*	29.2 (5.0)	-13.7 (0.7)	-3.3 (-5.3, -1.3)
	Duloxetine (60mg)*[b]	28.5 (4.9)	-15.8 (0.8)	-5.5 (-7.5, -3.5)
	Placebo	29.4 (5.1)	-10.3 (0.8)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
* Doses that are statistically significantly superior to placebo.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
[b] Included in the trial as an active comparator
Source: Vortioxetine label

Our statistic reviewer, George Kordzakhia, Ph.D., confirmed the sponsor's analyses and study results. He agreed that the efficacy of Lu AA21004 in treatment of MDD has been demonstrated in 5mg, 10mg, 15mg, and 20mg doses. The only dose that did not have replication of the efficacy was 15mg. The following tables (Table 3) I cited from his review summarized the primary efficacy results from each doses and p values.

Table 43. Primary efficacy results for positive efficacy studies

Study Number	Primary Endpoint	Dose				
		1mg	5mg	10mg	15mg	20mg
11492A	MADRS	**Region**: non-US, multi-regional including Canada. **Study Conduct Dates:** 08/2006-08/2007				
LS mean difference (SE)			-5.9 (1.4)	-5.7 (1.4)		
p-value (unadjusted)			<0.001	<0.001		
Significance (MCP adjusted)			**Yes**	**Yes**		
305	HAMD-24	**Region**: outside North America. **Study Conduct Dates**: 08/2008-08/2009				
LS mean difference (SE)		-3.5 (1.0)	-4.1 (1.0)	-4.9 (1.0)		
p-value (unadjusted)		<0.001	<0.001	<0.001		
Significance (MCP adjusted)		**N/A**[#]	**No**[*]	**Yes**		
13267A	MADRS	**Region**: outside North America. **Study Conduct Dates**: 05/2010-09/2011				
LS mean difference (SE)					-5.5 (1.1)	-7.1 (1.1)
p-value (unadjusted)					<0.001	<0.001
Significance (MCP adjusted)					**Yes**	**Yes**
315	MADRS	**Region**:US. **Study Conduct Dates**: 06/2010-02/2012				
LS mean difference (SE)					-1.5 (1.21)	-2.8 (1.21)
p-value (unadjusted)					0.224	0.023
Significance (MCP adjusted)					**No**	**Yes**
316	MADRS	**Region**:US. **Study Conduct Dates:** 07/2010-01/2012				
LS mean difference (SE)				-2.2 (1.15)		-3.6 (1.16)
p-value (unadjusted)				0.058		0.002
Significance (MCP adjusted)				**No**		**Yes**
12541A (elderly)	HAMD-24	**Region**: multi-regional, including US and Canada. **Study Conduct Dates**: 01/2009-02/2010				
LS mean difference (SE)			-3.3			
p-value (unadjusted)			0.001			
Significance (MCP adjusted)			**Yes**			

Source: Reviewer's summary based on sponsor's clinical study reports
[*]Since 10mg dose was not statistically significantly different from placebo in the first key secondary variable in the testing sequence (SDS), the formal testing was stopped according to the pre-specified hierarchical multiple testing procedure. None of the subsequent null hypotheses (including hypotheses associated with 5mg dose) in the pre-specified testing hierarchy are considered statistically significantly different from placebo.
[#] 1mg arm was not formally tested against placebo.

Even though the totality of data across the dose range of 5-20 mg demonstrated efficacy in treatment of MDD. In the two positive studies conducted solely in US (studies 315 and 316) no dose lowers than 20 mg was shown statistically significantly better than placebo. However, in study 316, 10 mg separated from placebo on change from Baseline in MADRS Total Score at Week 4 (-2.0 points, $p<0.05$) and 6 (-3.0 points, $p<0.01$). Although separation was not statistically significant at Week 8 ($p=0.058$), the difference from placebo was -2.2 points.

Even though several key secondary endpoints were proposed by the sponsor, we clearly communicated to the sponsor in the FDA Advice Letter dated September 14, 2010, that we only acceptable either CGI-I or SDS as a key secondary endpoints. For a key secondary

endpoint to be described in the product labeling, it must be pre-specified and the positive findings have to be replicated. None of the doses that were shown effective in this clinical program met the aforementioned criteria.

Maintenance Efficacy

The longer-term efficacy of LuAA21004 was demonstrated in one relapse-prevention study, Study 11985A. This is a non-US study and was conducted in 66 sites in Australia, Austria, Belgium, Canada, Finland, France, Germany, India, the Republic of Korea, Norway, Poland, South Africa, Sweden, Taiwan, Thailand, Turkey, and the United Kingdom.

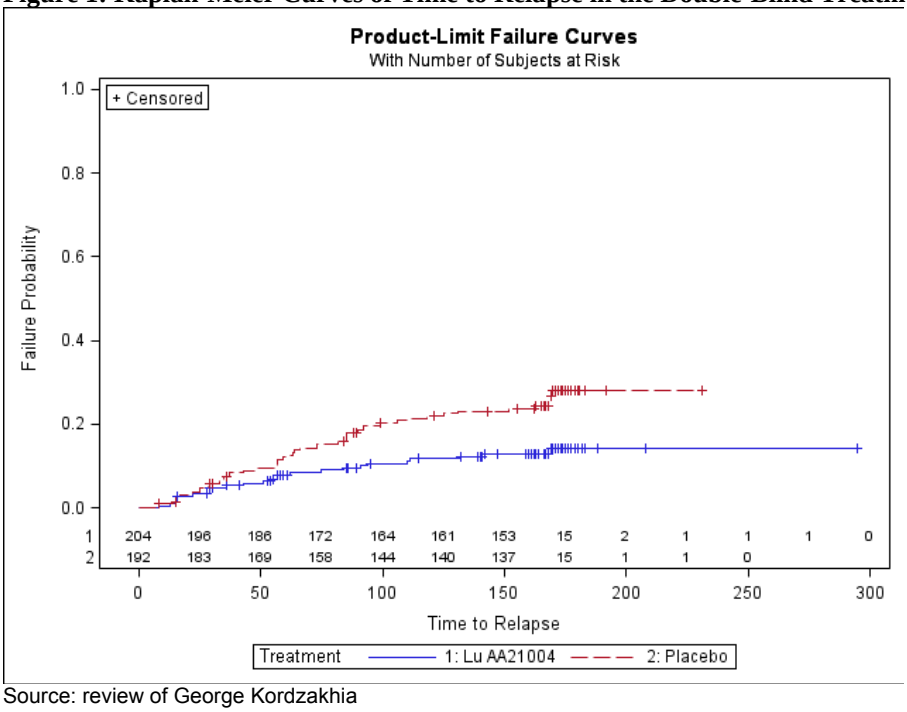
This was a relapse-prevention study, with a 12-week open-label, flexible-dose period, followed by a randomized, double-blind, placebo-controlled, fixed-dose period of at least 24 weeks (24 to 64 weeks). The initial dose of Lu AA21004 was 5 mg, po, QD. The dose can be increased to 10 mg from Week 2 to Week 8 during the Open-label or decreased back to 5mg based on clinical judgment. From Week 8, the dose was fixed.

Three hundred and ninety six subjects who were in remission (MADRS total score <10 at both Weeks 10 and 12) were randomized to 1:1 to either placebo or continuing Lu AA21004 treatment in the Double-blind Period. Subjects randomized to Lu AA21004 continued the dose that was fixed from Week 8. The primary efficacy variable was the time to relapse of major depressive episode (MDE) within the first 24 weeks of the Double-blind Period. The relapse criterion was a MADRS total score ≥ 22 or clinically worsening or lack of efficacy as judged by the investigator.

The primary efficacy analysis (Cox proportional model) showed that Lu AAS21004 was statistically significantly superior to placebo on the time to relapse of MDE during the first 24 weeks of the Double-blind Period (hazard ratio of placebo to drug: 2.01, p = 0.0035). The proportion of subjects who relapsed was lower in the LuAA21004 group (13%) than in the placebo group (26%). Placebo-treated subjects had two times the risk of relapse. Our statistical reviewer confirmed the sponsor's primary efficacy results.

The Kaplan-Meier curves for time to relapse support that the observed relapse rate was lower in the Lu AA21004 treatment group than in placebo treatment group during the entire double-blind period (see Figure 1).

Figure 1: Kaplan-Meier Curves of Time to Relapse in the Double-Blind Treatment



Source: review of George Kordzakhia

The protocol of this relapse prevention study was submitted to the Division after this non-US study was initiated. Per study protocol, the required duration of stability prior to randomization was only 2 weeks. At the End of Phase II Meeting (February 5, 2008) the Division pointed out that the stabilization period of 12 weeks was too short. We usually require that patients are fully stable for at least 12 weeks before the randomization. However, because the study already started at the time received FDA's comments, the comment was not been appropriately addressed.

Post hoc analysis showed that approximately 60% of patients in each treatment arm were stable for at least 4 weeks prior to randomization and less than 40% of the patients were stable for 6 weeks or more. Only a few patients in both treatment arms were stable for 10 weeks. However, the relapse rates and the hazard ratio were similar in the subgroup patients who were stable from ≥ 2 weeks to ≥ 6 weeks (relapse rates: 11% to 13%; hazard ratio: 2.07 to 2.49). Only a small numbers of patients who were stabilize for ≥ 8 weeks (8% in Lu AA21004 group), the efficacy results from this group is hardly interpretable. Even though the stabilization period of this study is not as long as we want, we still consider the results from this study acceptable.

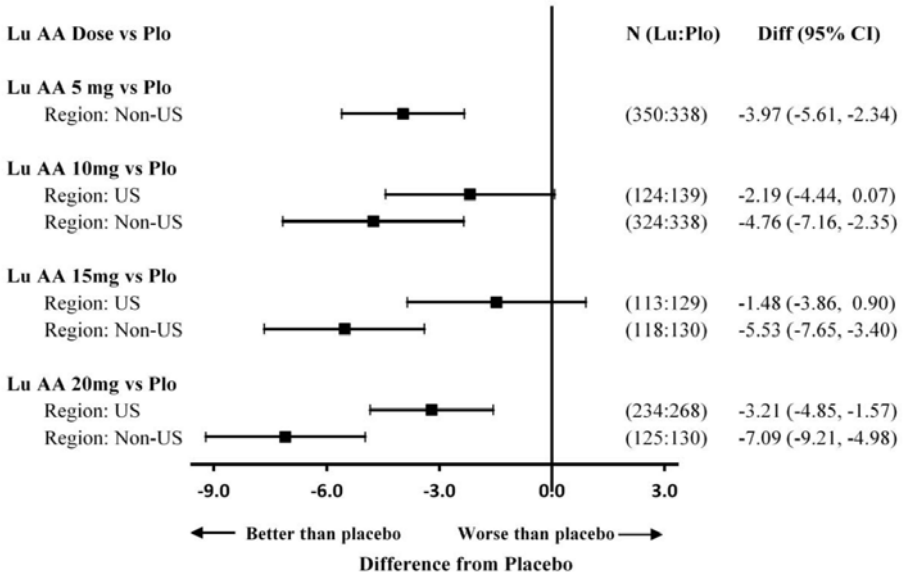
Subgroup Analysis

Subgroup analysis conducted by the sponsor found no clinically relevant treatment effect differences on MADRS total score observed by age, sex, race, BMI, severity of depression, severity of anxiety in subjects with depression, or duration of current MDE. No difference in efficacy response in these subgroups was observed except the regional effect. Treatment effect differences were observed between US and non-US populations.

The mean difference from placebo across the studies for adult subjects in the United States was statistically significant only at the 20 mg dose: -3.2 points (p <0.001); the 10 and 15 mg doses did not separate from placebo, although in Study 316, there was a difference from placebo of -2.2 points with the 10 mg dose (p=0.058).

A meta-analysis conducted by the sponsor using data from 6 short-term studies (11492A, 11984A, 305, 13267A, 315, and 316) by MMRM for the change from Baseline in MADRS total score at Week 6/8 by geographical region (US, non-US). The mean difference from placebo across the studies for adult subjects in the United States was statistically significant only at the 20 mg dose: -3.2 points (p <0.001); the 10 and 15 mg doses did not separate from placebo. Change from Baseline in MADRS total score difference from placebo (treatment effect) at endpoint was lower in the US than in non-US regions for all therapeutic doses (see figure 2). Placebo response across studies and regions varied and, therefore, this could not explain the observed difference in treatment effect between US and non-US studies.

Figure 2: Treatment Effect on Change from Baseline in MADRS Total Score at Week 6/8 by Region (US, non-US), Positive/Supportive Studies in Adults (FAS, MMRM)



In the elderly study (12541A), although the treatment efficacy of 5 mg was demonstrated overall based on HAM-D24 total score (-3.3 points, p< 0.0011, ANCOVA, LOCF), the effect size of Lu AA21004 5 mg was much smaller in US region consisted 38% of all subjects (-0.7 by ANCOVA, LOCF and -1.9 by MMRM) compared to the non-US regions (-4.9 by ANCOVA, LOCF and -5.0 by MMRM). The similar trend also been observed in active control arm (duloxetine 60 mg). The effect size of duloxetine in US region (-2.8 by ANCOVA, LOCF and -3.5 by MMRM) was only about half of that in non-US region (-7.1 by ANCOVA, LOCF and -7.7 by MMRM).

Even though we see the regional difference of efficacy in all doses, no single causative factor has been identified.

5.1.2 Discussion of primary reviewers' comments and conclusions

Both clinical reviewer, Jenn Sellers MD., and statistical reviewer, George Kordzakhia, PhD, concluded in their review that the efficacy data from 6 short-term studies have provided adequate evidence to support a claim that Lu AA 21004 is superior to placebo in acute treatment of MDD administered orally once per day at a dose range of 5 to 20 mg/day globally in adults with MDD. However, the short-term efficacy of Lu AA21004 was only established in 20 mg/d in the US. The maintenance efficacy of Lu AA21004 was demonstrated in one relapse prevention study at dose range of 5 to 10 mg/day. I agree with their conclusion.

5.1.3 Dose identification/selection and limitations

The efficacy of Lu AA21004 in treatment of MDD has been demonstrated in 5mg, 10mg, 15mg, and 20mg doses overall. The only dose that did not have replication of the efficacy was 15mg. Higher dose, 20 mg/d, showed better efficacy in the US trials. Even though 5 mg/d and 10 mg/d were not statistically significantly separated from placebo in the US studies, there was some supportive evidence to support an approval action on these two lower doses in the US. In study 316, 10 mg statistically separated from placebo on change from Baseline in MADRS Total Score up to Week 6 (-3.0 points, $p < 0.01$). Although separation was not statistically significant at Week 8, the difference from placebo was -2.2 points ($p=0.058$). In the elderly study 12541A, the US subgroup did not make the primary efficacy end point, HAM-D 24, based on pre-specified primary efficacy analysis, ANCOVA, LOCF. However, Lu AA21004 5 mg separated from placebo on the MADRS total score by -3.6 points ($p<0.05$) if using MMRM which is a preferred analysis by the division now.

The regional difference has been observed in many studies cross submissions. The effect size in the US tends to be smaller and the reason to cause this difference is not very clear. Based on Title 21 of the Code of Federal Regulations, Part 314.106, foreign data can be used to support a US marketing approval if the foreign data are applicable to the US population and US medical practice and if the studies have been performed by investigators of recognized competence. The OSI inspected 5 clinical sites in 4 studies. Two sites are foreign sites (Germany and Belgium). The inspection results are acceptable. Therefore, I feel that efficacy data obtained from non-US studies should be able to use to support an approval action in the US for doses lower than 20 mg/d. Additionally, we will ask the sponsor to conduct a US fixed-dose relapse prevention study covering dose range from 5 to 20 mg/d to future explore the dose-response relationship in the US and to answer the question of whether Lu AA21004 20 mg/day is necessary for maintenance treatment in the US. I recommend Lu AA21004 to be approved at dose range 5 to 20 mg/d with recommended starting dose of 10 mg/d.

5.1.4 Pediatric use/PREA waivers/deferrals

As a PREA requirement the sponsor will need to conduct two multi-center, double-blind, placebo-controlled pediatric studies in children and adolescents (7 to 17 years old) in the treatment of major depressive disorder. At least one of these studies must be a fixed-dose study. The sponsor has submitted a pediatric plan on August 26, 2011 under IND 76307. This plan included two pediatric studies: one in children ages 7 to 11 years old and the other in adolescents ages 12 to 17 years. Both studies are 12 weeks, double-blind, placebo-controlled, fixed dose, and placebo controlled and fluoxetine referenced studies. We feel that the proposed pediatric plan in general is acceptable because the final protocols have not been submitted yet. We had some comments on the pediatric plan and these comments had been conveyed to the sponsor. The final acceptance of their plan will ultimately depend on the decision of Pediatric Review Committee (PeCR). A PeCR meeting has been scheduled on Sept. 4, 2013.

5.2 Safety

5.2.1 General safety considerations

The safety evaluation of Lu AA21004 in the treatment of MDD are based on safety data obtained from 10 short-term, placebo-controlled MDD studies (including a study in elderly subjects treated with Lu AA21004 5 mg), 1 long-term, placebo-controlled, relapse-prevention study in MDD, and 5 (3 completed and 2 ongoing) long-term, open-label extension MDD studies, as well as phase 1 study data from 31 clinical pharmacology studies completed by Takeda or Lundbeck. The safety data obtained from the GAD clinical program including 5 completed studies (4 short-term, placebo-controlled studies and 1 long-term, placebo-controlled, relapse-prevention study) were also reviewed and used to support this submission.

The sponsor pooled all studies into 5 categories to facilitate review: 1. MDD Short-Term Pool; 2. GAD Short-Term Pool; 3. MDD/GAD Short-Term Pool; 4. MDD Open-Label Long-Term Pool; and 5. Phase 1 Pool. The relapse-prevention studies (Study 11985A in MDD) and (Study 12473A in GAD) were not pooled due to the different designs from the short-term studies. These studies were evaluated individually.

Deaths, Serious Adverse Events (SAEs) will be evaluated in considering all clinical studies. For common adverse events (AEs) the primary safety evaluation will mainly be focused on MDD Short-Term Pool (a pool of 10 short-term MDD studies), and MDD/GAD Short-Term Pool (a pool of 10 MDD short-term and 4 GAD short-term studies) because of the placebo controlled design.

Total Exposure
A total of 7666 subjects in all clinical studies (Phase 1, 2, and 3) were exposed to at least 1 dose of Lu AA21004 for a total of 2743.1 patient-years (PY). The doses used ranged from 1 to 75 mg in phase 1 studies, and 1 to 20 mg once daily (QD) in phase 2 and 3 studies. A total of 2045 subjects (31.5%) received ≥ 24 weeks (6 months) and 1131 subjects (17.4%)

received ≥ 52 weeks (1 year) of treatment with Lu AA21004 in all phase 2 and 3 studies combined.

5.2.2 Safety findings from submitted clinical trials – general discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests

Deaths

A total of 6 deaths have been reported in the completed phase 2 and 3 clinical studies with Lu AA21004, which all occurred in Lu AA21004 treatment groups. No deaths were reported in the completed phase 1 clinical studies, nor in the 14 ongoing studies. The causes of death included 2 cancers, 1 suicide, 1 morphine toxicity, 1 road traffic accident, and 1 accidental death (fall from a balcony). All deaths were considered by the investigators as unrelated to Lu AA21004 treatment.

Serious Adverse Events (SAEs)

In the MDD Short-Term Pool, the overall incidence of SAEs was similar in the Lu AA21004 group (1.0%) and the placebo group (0.9%), and no dose relationship was observed across the individual Lu AA21004 dose groups. The overall incidence of SAEs in the duloxetine group was 1.1%.

In the MDD Short-Term Pool, SAEs that occurred in ≥2 subjects in any Lu AA21004 treatment group by preferred term were as follows: convulsion (n = 2); depression (n = 3), and suicide attempt (n = 3). Two cases of convulsion were related to prior traumatic brain injury. No additional SAE were reported in the GAD short-term studies.

In the MDD relapse prevention study, 14 subjects (2.2%) had SAEs during the Open-Label Period. No SAE occurred in more than 1 subject, except for depression (n = 2). During the Double-Blind Period, 11 subjects had SAEs: 4 subjects (2.1%) in the placebo group and 7 subjects (3.4%) in the Lu AA21004 group. No SAE occurred in more than 1 subject in either treatment group, except for road traffic accident (2 in the Lu AA21004 group).

Adverse Events Leading to Discontinuation

In the MDD Short-Term Pool, the overall incidence of Treatment Emergent Adverse Events (TEAEs) leading to discontinuation was higher in the Lu AA21004 Total group (6.2%) and the duloxetine group (9.0%) than in the placebo group (3.8%). A dose-related increase in the proportion of subjects who discontinued due to a TEAE was observed in the individual Lu AA21004 dose groups (2.1% [1 mg] to 8.4% [20 mg]).

The most common TEAE leading to discontinuation in the Lu AA21004 Total group was nausea. The incidence was higher in the Lu AA21004 Total group (2.2%) and the duloxetine group (3.5%) than in the placebo group (0.3%) and increased with increasing Lu AA21004 dose, 0.7% in 1 mg/d to 4.4% in 20 mg/d. Other TEAEs leading to discontinuation experienced by ≥1% subjects in any Lu AA21004 group were vomiting and suicidal ideation.

The overall incidence of TEAEs leading to discontinuation was similar in the MDD/GAD Short-Term Pool.

Treatment-Emergent Adverse Events

In the MDD Short-Term Pool, the most commonly observed TEAEs with Lu AA21004 (≥5% in the Lu AA21004 Total group and at least twice the rate of placebo) were nausea, constipation and vomiting. Nausea is the most commonly reported AE, occurred in 24.3% in Lu AA21004 and 9.2% in placebo group. Nausea occurred in 35.6% in the Duloxetine group.

Among the Lu AA21004 treatment groups, a dose-related trend was observed for the incidence of TEAEs of nausea, dizziness, constipation, and vomiting.

The majority of TEAEs reported in all treatment groups were mild to moderate in intensity in the Lu AA21004 treatment groups based on the sponsor's report. The TEAEs considered to be severe in intensity were observed at an incidence of ≤8.3% across Lu AA21004 treatment groups compared with 5.9% in the placebo group. The onset of events was generally highest in each treatment group (including placebo and duloxetine) during the first week of treatment. Nausea in some patients may last longer (throughout the 8 weeks study), especially when on high doses (10 or 20 mg/d).

In MDD/GAD Short-Term Pool the most commonly observed TEAEs with Lu AA21004 (≥5% in the Lu AA21004 Total group) were the same as those observed for MDD alone. In the Long-Term Relapse-Prevention Studies, the incidences of nausea and headache were higher in the Open-Label Periods compared with other TEAEs. During the Double-Blind Period, the incidence of nausea was higher in Lu AA21004 than in placebo.

Adverse Events of Special Interest

Suicidal Ideation and Behavior
Prospective suicidality assessment was performed by using Columbia-Suicide Severity Rating Scale (C-SSRS) and the Standardized MedDRA Queries (SMQ) suicide/self-injury.

C-SSRS
C-SSRS was conducted in 18 completed and 2 ongoing studies.

In the MDD/GAD Short-Term studies, the incidence of suicidal ideation and behavior was balanced across the placebo, Lu AA21004 Total, and duloxetine treatment groups during the studies. In the combined Lu AA21004 treatment groups 11.2% reported suicidal ideation or behavior during the studies compared to 12.5% in the placebo group. Based on the C-SSRS data, there was 1 (<0.1%) subject with suicidal behavior (aborted attempt) in the placebo group, and 4 (0.1%) subjects in the Lu AA21004 Total group. There were no completed suicides during the studies in the MDD/GAD Short-Term studies.

Overall, based on the C-SSRS assessment, Lu AA21004 did not exacerbate the risk of suicidal .ideation or behavior in the MDD/GAD Short-Term Pool.

SMQ Suicide/Self-injury
In the MDD short-term pool, the incidences of suicidal ideation and behavior of Lu AA21004 10-20 mg groups were slightly higher than placebo (1.0%, 0.7% and 0.7% for 10mg, 15mg and 20mg and 0.4% for placebo) and similar to Duloxetine (0.7%). There were 3 suicide attempt in Lu AA21004 group and none in either placebo or Duloxetine group. The findings in MDD/GAD short-term pool were similar to those in MDD short-term pool.

Sexual Dysfunction
The ASEX score was assessed in 7 short-term studies: MDD Studies 11984A, 13267A, 304, 315, 316, and 317 and in general anxiety disorder Study 308. In studies 315, 316, and 317, the subject randomization was stratified by baseline sexual dysfunction status.

The main analysis was to assess treatment-emergent sexual dysfunction (TESD) based on the subset of subjects who do not have dysfunction at baseline. The non-inferiority was to be established through comparing the upper bound of the two-sided 95% confidence interval for the difference of the incidence rates between Lu AA21004 and placebo in subjects who developed sexual dysfunction at any time during the study period with a margin of 10 percentage points.

For all MDD studies combined, approximately 30% of subjects with ASEX assessment at Baseline did not have sexual dysfunction at Baseline. This was consistent across all LuAA21004 dose groups, duloxetine group and placebo group. In the GAD Study 308, the percentage of patients without sexual dysfunction was approximately 50%.

In the dose range of 5 to 20 mg, the observed incidence of TESD for all studies combined increased with the dose from 25.7% (5 mg) to 46.1% (20 mg). For the lower dose of 2.5mg, the observed incidence rate of 42.4% was noted. The observed incidence rates for 2.5mg, 15mg and 20mg were larger than placebo by more than 10 percentage points. In the female subgroup the observed incidence rates were higher than in males by 5-10% in all treatment arms. The proportions of the males and females varied from arm to arm but on average were balanced among treatment arms.

Discontinuation Symptoms
Discontinuation symptoms were assessed by blinded administration of the DESS scale in a placebo-controlled manner in Studies 13267A, 315, and 316. In the first week of the Discontinuation Period (Week 9), a statistically significant difference ($p<0.05$) in the mean number of discontinuation-emergent symptoms was observed for subjects discontinuing Lu AA21004 15 mg (LS mean DESS total score 1.53) and Lu AA21004 20 mg (LS mean DESS total score 1.53) compared with placebo. At Week 10, the second week of the Discontinuation Period, no statistically significant differences were observed in the mean number of discontinuation-emergent symptoms in the Lu AA21004 treatment groups compared with placebo, while subjects discontinuing duloxetine experienced statistically

significantly more symptoms (LS mean DESS total score 2.94) compared to placebo (LS mean DESS total score 1.26).

The following DESS items had incidence of ≥ 5% and twice of placebo for subjects discontinuing Lu AA21004 15 mg at the end of the 1st week: headache, muscle tension/stiffness, mood swings, and sudden outburst of anger, dizziness, and nose runny. In 20 mg group, sudden outbursts of anger and nose runny occurred > 4% and twice of placebo.

There were no differences in self-reported AEs of discontinuation symptoms across the treatment groups in all studies.

Clinical Laboratory Evaluations

In general, no clinically significant effects of Lu AA21004 were noted on any chemistry or hematology laboratory parameters during the clinical development program.

Vital Signs, Weight, and ECG Findings

No clinical meaningful differences between Lu AA21004 and placebo treatment in vital signs, weight, and electrocardiogram (ECG) were observed in clinical studies.

6 Labeling Recommendations

Physician labeling
There were extensive labeling revisions recommended by the primary review teams (including clinical, pharmacology/toxicology, clinical pharmacology, and CMC), the Division of Professional Promotion/Office of Prescription Drug Promotion (OPDP), the Pediatric Maternal Health Staff (PMHS) and the Patient Labeling Team under division of Medical Policy Program, DMPI. Their recommendations have been incorporated in the product labeling.

We are still negotiating the label with the sponsor at the time of completion of this review. The final product label will be attached to the approval letter if this product is granted an approval action.

7 The Office of Scientific Investigation (OSI) Audits

The Office of Scientific Investigation (OSI) inspected 4 clinical studies at 6 trial sites: five clinical study sites (see table 4) and the sponsor site (Takeda Pharmaceuticals USA). The clinical investigator (CI) sites were selected for inspection based on: (1) relatively large subject enrollment, (2) significant efficacy contribution, (3) potential SAE under reporting, and (4) no prior or recent (< 2 years) FDA inspection.

Table 4: Summary of Clinical Inspection Sites

	Inspected Entity	Studies, Sites, Subjects	Inspection Outcome
1	Donald Garcia, Jr., M.D. Austin, TX	Lu AA21004-315 Site 5009, 24 subjects	January 7 - 11, 2013 NAI
2	John M. Joyce, M.D. Jacksonville, FL	Lu AA21004-315 Site 5013, 28 subjects	December 17 -19, 2012 NAI
3	Lorena Wallhausser, M.D. Cincinnati, OH	Lu AA21004-316 Site 6010, 30 subjects	December 5 - 20, 2012 NAI
4	Bettina Bergtholdt, M.D. Berlin, Germany	Lu AA21004-305 Site 88, 32 subjects	February 11 - 15, 2013 Pending (preliminary NAI)
5	Leo Ruelens, M.D. Tielt, Belgium	11985A Site BE003, 20 subjects	February 2 - 8, 2013 VAI
6	Takeda Pharmaceuticals USA Deerfield, IL	Lu AA21004-305, Lu AA21004-315 Lu AA21004-316, and 11985A	January 9 - 28, 2013 NAI

NAI = no action indicated (no significant GCP deviations); VAI = voluntary action indicated (significant GCP deviations); OAI = official action indicated (serious GCP deviations and/or data unreliable)

Pending: Preliminary classification is based on information on Form FDA 483 and preliminary communication with the field investigator. The final establishment inspection report has not been received from the field office and OSI's complete review of the EIR remains pending as of this clinical inspection summary.

At all 6 inspections, no significant deficiencies were observed (Form FDA 483 not issued at 5 of 6 sites), and the clinical efficacy and safety data from all inspected sites appear reliable as reported in the NDA. The major observations for each inspected site were:

- Site 5009, Study Lu AA21004-315 (Donald Garcia, 4% of total study enrollment): Three blood samples for pharmacokinetic (PK) evaluation (Subjects 5009510, 5009512, and 5009513) were stored at 1 - 4 oC for two weeks (not stored frozen < -20 oC). The PK data from Subjects 5009510, 5009512, and 5009513 may not be reliable due to improper sample storage.

- Site 5013, Study Lu AA21004-315 (John Joyce, 5% of total study enrollment): (1) use of clonazepam (prohibited medication) in one subject in the emergency room in treating an anxiety attack, (2) unused study medication not recovered from one subject lost to follow up, (3) late informed consent in one subject, and (4) late reporting of protocol deviations.

- Site 6010, Study Lu AA21004-316 (Lorena Wallhausser, 6% of total study enrollment): Test article disposition was tracked at the level of the blister pack and not for the individual capsules.

- Site 88, Study Lu AA21004-305 (Bettina Bergtholdt, 6% of total study enrollment): (1) for Subject 526, a few AE data discrepancies between source documents and CRFs, and (2) Subject 503 apparently refused to self-administer SDS assessments (no documentation of subject refusal).

- Takeda Pharmaceuticals USA, Inc. (Sponsor): No significant deficiencies were observed. The sponsor's records indicated adequate control over the various aspects of the audited studies.

- Site BE003, Study 11985A (Leo Ruelens, 3% of total study enrollment): A Form FDA 483 was issued at this site for: (1) miscalculations on the drug inventory log for five subjects; and (2) improper practice in correcting errors on source documents.

Dr. John Lee, MD., is the reviewer for this NDA in OSI. He concluded that even though deficiencies were observed at all six sites inspected all deficiency observations (whether or not cited on Form FDA 483) appear to be minor, isolated, and unlikely to affect study outcome. All audited study data appear reliable as reported in the NDA and can be used to support this NDA submission.

8 Conclusions and Recommendations

8.1 Recommended regulatory action

After considering the conclusions and recommendations from all review teams, I recommend that the division take an approval action on this NDA. I agree that the 6 short-term studies and 1 maintenance MDD studies have provided adequate efficacy and safety evidence to support a claim that Lu AA21004 is superior to placebo as mono-therapy in the treatment of MDD, either as acute or maintenance treatment, in adults at doses of 5 to 20 mg/d, and the safety profile of Lu AA21004 is acceptable.

8.2 Safety concerns to be followed postmarketing

There are no specific safety concerns with Lu AA21004 that have become apparent from this clinical program that would require specific actions.

8.3 Risk Minimization Action Plan

Currently, I do not recommend any specific risk minimization actions.

8.4 Postmarketing studies required

OCP team requested the follow PMC studies:

1. An in vivo study in subjects with severe hepatic impairment compared to healthy subjects using the 5 mg dose.

2. In vitro determination of Lu AA21004 and its major metabolites as potential inhibitors of major transporters as recommended by the drug-drug interaction guidance.

Clinical team requests two pediatric studies which are PMR and 1 relapse prevention study which is a PMC.

3. Pediatric studies: as a PREA requirement the sponsor will need to conduct two multi-center, double-blind, placebo-controlled pediatric studies in children and adolescents (7 to 17 years old) in the treatment of major depressive disorder. At least one of these studies must be a fixed-dose study.

   The sponsor has submitted a pediatric plan on August 26, 2011 under IND 76307. In the pediatric plan two pediatric studies were proposed: one in children ages 7 to 11 years old and the other in adolescents ages 12 to 17 years. Both studies are 12 weeks, double blind, placebo controlled and fluoxetine referenced study. We consider that the proposed studies are acceptable. We will provide more comments after the protocols are submitted and reviewed.

4. A relapse prevention study in the US: since only Lu AA21004 20 mg/day demonstrated efficacy in the US and the relapse prevention study (11985A) was a non-US study and only covered dose range 5 to 10 mg/d, the sponsor will need to conduct a relapse prevention study to further characterize the dose response relationship of Lu AA21004 in the United States and to answer the question of whether Lu AA21004 20 mg/day is necessary for maintenance treatment in the US. This study should be a fixed dose study with a randomized withdrawal design and the dose choice should cover the approved dose range.

8.5 Comments to be conveyed to the applicant in the regulatory action letter

I do not have any comments to be conveyed to the applicant in the regulatory action letter.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JING ZHANG
08/20/2013