CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204447Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	New NDA
Application Number	204447
Priority or Standard	Standard
Submit Date	10/01/2012
Received Date	10/02/2012
PDUFA V Goal Date	10/02/2013
Division/Office	DPP/ODE1
Reviewer Name	Jenn Sellers, MD, Ph.D.
Review Completion Date	06/04/2013
Established Name	Vortioxetine
Trade Name	Brintellix
Therapeutic Class	Selective Serotonin Transporter Inhibitor with Some Serotonin Receptor Activities
Applicant	Takeda
Formulations	Immediate-Release Tablets
Dosing Regimen	5, 10, 15 and 20 mg p.o. q.d.
Indication	Major Depressive Disorder
Intended Population	Adult

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, we recommend an approval with revisions to the proposed label of NDA 204447 Lu AA21004 (BRINTELLIX) for the treatment of Major Depressive Disorder (MDD) in adult patients.

1.2 Risk Benefit Assessment

Overall, the risk-benefit assessment is favorable for Lu AA21004 for the treatment of MDD in adult patients.

1.3 Recommendations for Post-market Risk Evaluation and Mitigation Strategies

We did not identify major risks that would merit a Risk Evaluation and Mitigation Strategy (REMS). However, a Medication Guide is required.

1.4 Recommendations for Post-market Requirements and Commitments

- MDD studies in children (7 to 12 years old) and adolescents (13 to 17 years old) are required as post-market requirements.

- A long-term relapse prevention study in US:
  In US, only Lu AA21004 20 mg demonstrated efficacy while Lu AA21004 5 – 15 mg did not separate from placebo in the MDD short-term studies. However, outside US, the MDD short-term studies demonstrated efficacy of Lu AA21004 5 – 20 mg and the long-term relapse prevention study demonstrated efficacy of Lu AA21004 5 – 10 mg. As a post-market commitment, we request a long-term relapse prevention study in US, which should provide helpful information regarding the dose of maintenance treatment and dose response in US.

2 Introduction and Regulatory Background

2.1 Product Information

United States Adopted Name (USAN): vortioxetine hydrobromide

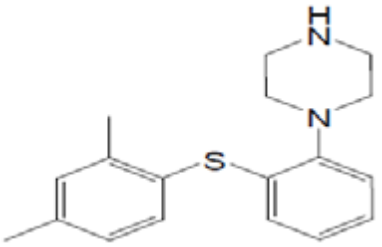
Proposed Trade Name: BRINTELLIX

Chemical Class: it belongs to a structural chemical group of vortioxetine hydrobromide and is formulated at 5, 10, 15 and 20 mg immediate-release film-coated tablets for oral administration.

Chemical name: 1-[2-(2, 4-486 Dimethyl-phenylsulfanyl)-phenyl]-piperazine, hydrobromide
Empirical formula: C18 H22 N2 S, HBr.

Molecular weight: 379.36 g/mol.

The structural formula (as free base):



Mechanism of Action: *In vitro* studies indicated that vortioxetine is an inhibitor of the 5-HT transporter, 5-hydroxytryptamine type 3 (5-HT3), 5-HT7, and 5-HT1D receptor antagonist, 5-HT1B receptor partial agonist, and 5-HT1A receptor agonist.

Proposed Indications: Treatment of Major Depressive Disorder (MDD)

Proposed Age Group: Adults

Proposed Dosage and Administration: The recommended starting dose is 5 mg - 20 mg, administered orally once daily (QD) without regard to meals.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 lists the antidepressant medications that are available for MDD treatment:

Table 1: Currently Available Antidepressant Medications

Tricyclic Antidepressants (TCA)	Imipramine, desipramine, amitryptiline, nortryptiline, doxepin, amoxapine, trimipramine, protryptiline, maprotiline.
Monoamine Oxidase Inhibitors (MAOI)	phenylzine, tranylcypromine, isocarboxazid, maprotiline, selegiline patch
Selective Serotonin Reuptake Inhibitors (SSRI)	fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, escitalopram, vilazodone
Serotonin and Norepinephrine Reuptake Inhibitors (SNRI)	venlafaxine, duloxetine, desvenlafaxine
Other Antidepressants	bupropion, trazadone, nefazodone, mirtazapine

Source: Self compiled.

Electroconvulsive therapy and transcranial magnetic stimulation are also available for the treatment of MDD.

2.3 Availability of Proposed Active Ingredient in the United States

This product is a new molecular entity (NME) under development for licensing by the applicant and is currently not marketed in the United States (US).

2.4 Important Safety Issues with Consideration to Related Drugs

Vortioxetine has an activity of selective serotonin reuptake inhibitor (SSRI) with additional serotonin receptor activities (antagonist at 5-HT3, 5-HT7, and 5-HT1D; partial agonist at 5-HT1B; agonist at 5-HT1A). SSRIs, as a class, have been associated with the following safety concerns:

- Suicidality
- Serotonin syndrome
- Seizures
- Abnormal bleeding
- Activation of mania or hypomania
- Hyponatremia
- Discontinuation syndrome

These issues are specifically addressed in Section 7, Review of Safety.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

Table 2 summarizes the highlights of regulatory interactions between the sponsor and FDA:

Table 2: Summary of Pre-submission Regulatory Activity Related to Submission

Type of Meeting/Correspondence (Meeting Date) [Correspondence Finalized]	FDA Recommendations/Comments
Initial IND 76,307 May proceed letter [6/12/2007]	DPP recommended the sponsor to characterize and monitor the safety signal of rash adequately given the number of events of rash that were reported in the clinical studies
IND 76,307 EOP2 Meeting (February 5, 2008) [02/13/2008]	For the long-term relapse prevention study, DPP recommended the sponsor to extend the open-label period to allow for patients to be stable responders for at least 12 weeks before randomization. The sponsor objected to the requirement for a 12 week

Type of Meeting/Correspondence (Meeting Date) [Correspondence Finalized]	FDA Recommendations/Comments
	period of stable "response" prior to randomization, arguing that the EMEA did not require such an extended responder phase. DPP advised the sponsor to consider fewer trials with more dose groups per trial to better understand dose response; and include older and younger patients in the same trial to allow for comparisons of safety and efficacy across the age spectrum. The sponsor maintained their preference for more studies with fewer dose arms per study and a separate study in elderly
IND 76,307 Type C meeting (March 30, 2010) [April 2, 2010]	DPP did not believe it was sufficient to assess discontinuation symptoms only at weekly intervals and recommended to assess discontinuation symptoms more frequently
IND 76,307 Pre-NDA (Pre-Submission) (June 22, 2012) [June 28, 2012]	The 120-day safety update is required as described in 21 CFR 314.50 (d) (5) (vi) (b).
IND 76,307 TESD Response [July 28, 2010]	DPP advised to define sexual dysfunction as an abnormal rating at least two consecutive visits and recommended the doses to be included in the pooled analysis should be limited to those doses shown to be effective.
IND 76,307 FDA Advise on Pediatric Plan [11/14/2011]	Recommended to assess subjects at every visit and also at the end of the study if subjects drop out. Complete C-SSRS assessment at every visit.

Source: 1.6.3: correspondence regarding meetings, 10/02/2013

2.6 Other Relevant Background Information

Change In Sponsor

H. Lundbeck A/S (Lundbeck) initially opened IND 76,307 on April 4, 2007. On February 11, 2008, Lundbeck informed FDA that the sponsorship of the IND was being transferred to Takeda Global Research & Development Center, Inc. (TGRD). TGRD is the current holder of IND 76,307. TGRD submitted NDA 204-447 for Vortioxetine (Lu AA21004) on behalf of Takeda Pharmaceuticals USA, Inc. (TPUSA).

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This reviewer audited adverse event (AE) safety data for accuracy in few samples (subjects with serious AEs: 0343/331, 0037/503, SK001/S1133, 0026/906) of submitted Case Report Forms (CRFs) and did not audit a certain proportion of them due to time constraints. The AEs from the CRFs for these subjects were compared to those in the narrative summary in the study body report. No deficiencies or discrepancies were noted.

However, some quality issues were identified during the normal course of reviewing the submission: the initial submission did not include some data we needed for review. The sponsor was able to submit the responses upon our requests at a timely fashion. For example, the sponsor did not include the follow-ups of the abnormal liver function test (LFT) results leading to discontinuations. Upon request, the sponsor submitted the narratives and follow-up lab results, which were acceptable. Another example is Subject 0350-303 in Study 303 had a low platelet count. Upon request, the sponsor provided the narrative and complete blood count (CBC) of this subject which indicated the subject had pancytopenia, but no corresponding AE was reported and no CBC was repeated, which was unsatisfactory. Furthermore, this reviewer identified some discrepancies between the integrated summary of safety (ISS) and the individual study reports. Upon request, the sponsor clarified the discrepancies. Refer to Section 9.4 for all the requests we made during the course of review.

Office of Scientific Investigations Inspections
Study Site Selection
Susan Leibenhaut, M.D. at Office of Scientific Investigations (OSI) recommended using the site selection tool to select 5 sites in 4 studies to be inspected by OSI. Therefore, we selected 5 sites in Study 305, 315, 316, and 11985A based on the analysis results of the site selection tool. Table 3 shows the rationale of site selection, which was based on mostly the total risk ranking, the total number of enrollment and ranking in individual study and other safety and efficacy information.

Table 3: Study Sites Selection Rationale (Based on Site Selection Tool)

Site ID	Investigator First Last Name	Site (City Country)	Total Risk Ranking in Individual Study	Enrollment Number (Enrollment Rank in Individual Study)	Other Rationales
Study 305 (Lu AA21004 1mg, 5mg, 10mg and placebo)					
88	Bettina Bergtholdt	Berlin Germany	1	32 (4th)	No death, SAE, or discontinuations or protocol deviations were reported
Study 315 (Lu AA21004 15mg, 20mg, Duloxetine 60mg and placebo)					

Site ID	Investigator First Last Name	Site (City Country)	Total Risk Ranking in Individual Study	Enrollment Number (Enrollment Rank in Individual Study)	Other Rationales
5009	Donald Garcia	Austin, TX, US	1	24 (3rd)	There were no deaths, or SAEs reported. One complaint was reported against Dr. Garcia.
5013	John Joyce	Jacksonville FL, US	3	28 (1st)	No deaths or SAEs reported. The protocol violation was reported as 0.4.
Study 316 (Lu AA21004 10mg, 20mg and placebo)					
6010	Lorena Wallhausser	Cincinnati, OH, US	2	30 (1st)	Large site-specific effect size of efficacy
Study 11985A (Long-Term Relapse-Prevention Study)					
BE003	Leo Ruelens	Tielt Belgium	1	20 (1st)	Large efficacy weighted on enrollment

Source: compiled from the site selection tool analysis result

Inspection Results

The OSI inspection consisted of auditing: (1) compliance with GCP regulations, (2) adequacy of financial disclosure, informed consent procedures, and IRB oversight, and (3) adherence to SOPs for the oversight of clinical study sites and contract research organizations, handling of protocol deviations, AE reporting, data management, and drug accountability.

OSI did not find any evidence of un-blinding or biased data collection. The reported protocol deviations were felt accurately reported in the NDA listings. Drug accountability records were felt adequate. The study data reported in the NDA were felt reliable. OSI concluded that the sponsor adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

Other Submission Quality and Integrity Issues

Concomitant Medications

This reviewer examined Table 34 in the clinical study report of Study 11492A (page 212-232) which listed concomitant medications either discontinued prior or at Baseline or continued at Baseline or started at or after Baseline and Panel 11 to 12 which listed the protocol deviations. It appeared that some subjects who took disallowed concomitant medications such as Escitalopram and benzodiazepine were not excluded from the Per-protocol set (PPS). We made requests and asked the sponsor to confirm the findings. The sponsor responded that the subject who used Escitalopram was

excluded from the PPS and most subjects only used benzodiazepine for a short period of time which was allowed. The response was satisfactory.

3.2 Compliance with Good Clinical Practices

The sponsor indicated that they conducted the clinical studies in accordance with International Conference on Harmonization (ICH) of Good Clinical Practice (GCP) and local ethical and legal requirements, and with the Declaration of Helsinki.

However, the sponsor indicated in the clinical study reports that the following sites were identified as not compliant with good clinical practices:

- AT002 in Study 11492A (Austria): The quality of the medical records was inadequate
- FR004 in Study 13267A (France): Non-compliance with the protocol, GCP, and applicable regulations
- BE002 (Belgium), KR002 (Republic of Korea), and IN005 (India) in Study 11985A: Non-compliance with the protocol, GCP, the Declaration of Helsinki, and /or other applicable regulations.

The sponsor mentioned that they analyzed the efficacy results without the subjects from those sites and the overall efficacy results were not affected.

3.3 Financial Disclosures

Form 3454 (version 10/09) "Certification: Financial Interests and Arrangements of Clinical Investigators" was included in the submission. The Sponsor indicated that they had not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21CFR54.2 (a).

The sponsor provided the financial disclosure information for all covered clinical studies. This reviewer focused the review of financial disclosure information on the 6 positive short-term studies and the positive long-term MDD relapse prevention study.

According to the submission, none of the investigators had anything to disclose except (b) (6) in Study (b) (4). (b) (6) declared that he received grants in excess of $25,000 for two investigator-initiated studies.

(b) (6) enrolled 4 subjects for Study (b) (4). Since a large number of subjects (429) were randomized in Study (b) (4) and the number of subjects enrolled by (b) (6) (b) (6) was small and since Study (b) (4) used a randomized, double-blind design, it seems unlikely that this financial arrangement would have biased the overall efficacy results of Study (b) (4)

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The chemistry, manufacturing and controls (CMC) data were reviewed by Chemist Wendy Wilson. CMC recommends a complete response action for Brintellix (vortioxetine) Tablets according to Dr. Wendy's review dated 05/29/2013 due to the deficiencies of drug substance Drug Master File (DMF).

4.2 Clinical Microbiology

No clinical microbiology study was conducted.

4.3 Preclinical Pharmacology/Toxicology

The pharmacology/toxicology data was reviewed by Antonia Dow, Ph.D. At the time this review was completed, the pharmacology/toxicology review was not available. The review team held many status meetings during the course of this NME review and the main concern was the finding of polypoid adenomas of the rectum in high dose females in the Rat Carcinogenicity Study. Our Pharmacology/Toxicology team met with executive Carcinogenicity Assessment Committee (CAC) and the Committee concurred that the polypoid adenomas of the rectum in high dose females were drug-related. CAC suggested including this finding in the product label.

4.4 Clinical Pharmacology

The clinical pharmacology data was reviewed by Andre Jackson, Ph.D. At the time this review was completed, the clinical pharmacology review was not available. The review team held many status meetings during the course of this NDA and few issues were identified by the clinical pharmacology reviewer.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Only studies involving human subjects are included in the following section. Please refer to pharmacology/toxicology and biopharmaceutics reviews for animal and *in vitro* studies.

The Completed Studies

- 10 MDD short-term placebo-controlled studies
- 1 MDD long-term placebo-controlled relapse-prevention study
- 4 GAD short-term placebo-controlled studies
- 1 GAD long-term placebo-controlled relapse-prevention study

- 3 MDD long-term open-label extension studies
- 31 clinical pharmacology studies

The On-Going Studies

- 7 ongoing clinical studies in MDD
- 3 MDD long-term open-label extension studies
- 6 clinical pharmacology studies

Table 4 lists the completed studies and the on-going studies in more detail (next page).

Table 4: Completed MDD Long-Term Relapse-Prevention Study

Study No./ Region	Study Design/ Duration	Diagnosis and Main Inclusion Criteria	Study Drug Doses (mg) (a)	No. of Subjects Treated
11985A Europe, Australia, Asia, South Africa	Open-label, flex ble dose/12-wk period, followed by a randomized, double-blind, placebo-controlled, fixed- dose relapse- prevention period/ 24- to 64-wks + 2 wks discontinuation period	MDD, 18-75 years, MADRS≥26, men and women. Subjects in remission (MADRS ≤10) at Wks 10 and 12 were randomized to placebo or Lu AA21004 in double-blind treatment period	Lu AA21004: 5 or 10 placebo	Open-label: 639 Randomized: Lu AA21004: 204 placebo: 192

Source: 2.7.4 Summary of Clinical Safety, page 16/183

Table 5: Completed MDD Long-Term Open-label Extension Studies

Study No./ Region	Study Design/ Duration	Diagnosis and Main Inclusion Criteria	Study Drug Doses (mg) (a)	No. of Subjects Treated
11492C Europe, Australia Canada	Open-label, flexible-dose, 1-year extension study (to Study 11492A)	Subjects from Study 11492A	Lu AA21004: 5 or 10	Open-label: 74 (b)
11984B Europe, Canada, Australia, Asia	Open-label, flexible- dose, 1-year extension study (to Study 11984A)	Subjects from Study 11984A	Lu AA21004: 2.5, 5, or 10	Open-label: 535 (c)
301 Europe, Australia, Asia, South Africa, US	Open-label, flexible- dose, 1-year extension study (to Studies 304 and 305)	Subjects from Studies 304 and 305	Lu AA21004: 2.5, 5, or 10	Open-label: 834 (d)

CGI-S=Clinical Global Impression-Severity of Illness, CSR=clinical study report, MADRS=Montgomery-Åsberg Depression Rating Scale, MDE=major depressive episode, Mos=months, N/A=not applicable, US=United States, wks=weeks.
(a) Route of administration was oral. (b) 39 of these subjects received placebo or venlafaxine in the lead-in study, Study 11492A.
(c) 246 of these subjects received placebo or duloxetine in the lead-in study, Study 11984A.
(d) 313 of these subjects received placebo or duloxetine in the lead-in studies, Studies 304 and 305.
Source: 2.7.4 Summary of Clinical Safety, page 17/183

Table 6: Completed Phase 2/3 Short-Term MDD Studies

Study No./ Region	Study Design/ Duration	Diagnosis and Main Inclusion Criteria	Study Drug Doses (mg) (a)	No. of Subjects Treated
Phase 2/3 Short-Term Studies				
11492A Europe, Australia, Canada, Asia	Randomized, double-blind, parallel-group, placebo-controlled, active-referenced (venlafaxine), fixed-dose/6 wks + 2 wks taper-down/discontinuation period	MDD, 18-65 years, MADRS ≥30, men and women	Lu AA21004: 5 or 10 venlafaxine: 225 placebo	Lu AA21004 5 mg: 108 Lu AA21004 10 mg: 100 Venlafaxine 225 mg: 113 placebo: 105
11984A Europe, Canada, Asia, Australia,	Randomized, double-blind, parallel-group, placebo-controlled, active-referenced (duloxetine), fixed-dose / 8 wks + 1 week taper-down (only duloxetine)	MDD, 18-75 years, MADRS ≥26, men and women	Lu AA21004: 2.5, 5, or 10 duloxetine: 60 placebo	Lu AA21004 2.5 mg: 155 Lu AA21004 5 mg: 157 Lu AA21004 10 mg: 151 duloxetine 60 mg: 155 placebo: 148
305 Europe, Asia, Australia, South Africa	Randomized, double-blind, placebo-controlled, parallel-group, fixed-dose/ 8-wks	MDD, 18-75 years, MADRS ≥26, men and women	Lu AA21004: 1, 5, or 10 placebo	Lu AA21004 1 mg: 140 Lu AA21004 5 mg: 140 Lu AA21004 10 mg: 139 placebo: 140
13267A Europe, South Africa	Randomized, double-blind, placebo-controlled, active-referenced (duloxetine), parallel-group, fixed-dose/ 8 wks + 2 wks discontinuation period	MDD, 18-75 years, MADRS ≥26 and CGI-S ≥4, men and women	Lu AA21004: 15 or 20 duloxetine: 60 placebo	Lu AA21004 15 mg: 152 Lu AA21004 20 mg: 151 duloxetine 60 mg: 147 placebo: 157
315 US	Randomized, double-blind, placebo-controlled, active-referenced (duloxetine), parallel-group, fixed-dose / 8 wks + 2 wks discontinuation period	MDD, 18-75 years, MADRS ≥26 and CGI-S≥4, men and women	Lu AA21004: 15 or 20 duloxetine: 60 placebo	Lu AA21004 15 mg: 147 Lu AA21004 20 mg: 154 duloxetine 60 mg : 152 placebo: 161
316 US	Randomized, double-blind, placebo-controlled, parallel-group, fixed-dose/ 8 wks + 2 wks discontinuation period	MDD, 18-75 years, MADRS ≥26 and CGI-S ≥4, men and women	Lu AA21004: 10 or 20 placebo	Lu AA21004 10 mg: 154 Lu AA21004 20 mg: 148 placebo: 155
317 US	Randomized, double-blind, placebo-controlled, parallel-group, fixed dose / 8 weeks	MDD, 18-75 years, MADRS ≥26 and CGI-S ≥4, men and women	Lu AA21004: 10 or 15 placebo	Lu AA21004 10 mg: 143 Lu AA21004 15 mg: 142 placebo: 149
303 US	Randomized, double-blind, placebo-controlled, parallel-group, fixed-dose/6 wks + 2 wks discontinuation period	MDD, 18-75 years, MADRS ≥30, men and women	Lu AA21004: 5 placebo	Lu AA21004 5 mg: 299 placebo: 298
304 US	Randomized, double-blind, placebo-controlled, parallel-group, active-referenced (duloxetine), fixed-dose/8 wks + 1 wk taper-down (only duloxetine)	MDD, 18-75 years, MADRS ≥22, men and women	Lu AA21004: 2.5 or 5 duloxetine: 60 placebo	Lu AA21004 2.5 mg: 153 Lu AA21004 5 mg: 153 duloxetine 60 mg: 152 placebo: 153
12541A Europe, Canada, US	Randomized, double-blind, parallel-group, placebo-controlled, active-referenced (duloxetine), fixed dose, in elderly subjects/ 8 wks + 1 wk taper- down (only duloxetine)	MDD, ≥65 years, MADRS ≥26, men and women	Lu AA21004: 5 duloxetine: 60 placebo	Lu AA21004 5 mg: 156 duloxetine 60 mg: 151 placebo: 145

Source: 2.7.4 Summary of Clinical Safety, page 15-16/183

Table 7: Completed Clinical Pharmacology Studies

Clinical Pharmacology Studies	Study No.
Single- and multiple-dose PK	10272, 10467, 13921A, 13138A, 13119A
Japanese single- and multiple-dose PK	CPH-001, CPH-002, CPH-003
Mass-balance	10477
Absolute and relative bioavailability	10982, 123, 106
Intrinsic factor(a)	111, 114, 112
Extrinsic factor(b)	117, 115, 103, 11862A,101, 102, 109, 113, 110,116, 118
Pharmacodynamic	104, 12689A, 10985,12260A, 124

Source: 2.5 Clinical overview, figure 1.a, page 11/78
BE= bioequivalence, MRI= magnetic resonance imaging, PD=pharmacodynamic(s), PK=pharmacokinetic(s).
(a) Effect of sex, age, race; renal impairment; hepatic impairment.
(b) Cytochrome P450 and other drug-drug interaction studies.

Table 8: Completed Clinical Studies in Generalized Anxiety Disorder (GAD)

Completed Clinical Studies in GAD	Study No.
Short-term, placebo controlled, fixed-dose	308, 309, 310, 311
Long-term, placebo controlled, relapse prevention	12473A

Source: 2.5 Clinical overview, figure 1.a, page 11/78

Table 9: Ongoing Clinical Studies in MDD

Ongoing Clinical Studies in MDD (c)	Study No.
Short-term, placebo controlled, fixed-dose	CCT-002, CCT-003, 14122A
Short-term, placebo controlled, flexible-dose	202
Short-term, active comparator, fixed dose	13926A
Short-term, active comparator, flexible dose	14178A, 318
Long-term, open-label, safety	13267B, 314, OCT-001

Source: 2.5 Clinical overview, figure 1.a, page 11/78. (c): As of 04 May 2012

Table 10: Ongoing Clinical Pharmacology Studies

Ongoing Clinical Pharmacology Studies (c)	Study No.
Japanese Food effect study	CPH-004
Polysomnographic study	14029A
Functional MRI	14137A
BE component	14520A
Pediatric PK tolerability	12708A
PK	14077A

Source: 2.5 Clinical overview, figure 1.a, page 11/78. (c): As of 04 May 2012

5.2 Review Strategy

The efficacy assessment will focus on 6 positive MDD short-term studies (11492A, 305, 13267A, 315, 316, 12541A) and one positive MDD long-term relapse-prevention study. Among the other 4 MDD short-term controlled clinical studies, 11984A was a failed

study (neither Lu AA21004 treatment groups nor duloxetine 60mg separated from placebo) and 3 others (Study 303, 304 and 317) were negative studies.

The MDD open label studies are not reviewed for the efficacy purpose due to the open-label design and lack of placebo control so that the efficacy cannot be readily established. However, the MDD open label studies together with studies in Generalized Anxiety Disorder (GAD) and phase 1 studies are used in the analysis of safety.

5.3 Discussion of Individual Studies/Clinical Trials

See Section 6.3 of the review.

6 Review of Efficacy

6.1 Efficacy Summary

This section summarizes the efficacy of the 10 MDD short-term studies and the long-term relapse prevention study that the sponsor submitted to support the efficacy of Lu AA21004 5 mg – 20 mg taken by mouth (p.o.) QD in the treatment of MDD.

The cumulative evidence from the MDD short-term studies and the long-term relapse prevention study demonstrated the efficacy of Lu AA21004 5 mg – 20 mg in the treatment of MDD in non-US subjects. However, in US short-term studies, only Lu AA21004 20 mg demonstrated efficacy. The reason of the regional treatment difference between US and non-US is unclear.

Efficacy Summary of MDD Short-Term Studies

This reviewer compiled Table 11 which lists the study number (Study No.), the region the study was conducted, main inclusion criteria, results of Lu AA21004 doses (only the proposed doses 5 mg – 20 mg are included), and the overall study results of the 10 short-term studies. Six out of 10 studies were positive.

Table 11: 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

Study No./ Region	Main Inclusion Criteria	Results of Study Drug Doses (mg) vs. PBO	Overall Study Results
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

NS - not significant

Table 12 summarizes the Least Squares Means (LS Means) change from Baseline in primary endpoint either MADRS or HAM-D24 total score at the Endpoint in the positive MDD short-term studies.

Table 12: Summary of LS Mean Change from Baseline in MADRS or HAM-D24 Total Score at the Endpoint in the Positive MDD Short-term Studies

Study Name (Study Sites)	Primary Endpoint	Placebo	Lu AA21004 (mg) QD				Dul	VEF
			5	10	15	20		
11492A (Non-US)	MADRS	-14.5	-20.4	-20.2				-20.9
13267A (Non-US)	MADRS	-11.7			-17.2	-18.8	-21.2	
315 (US)	MADRS	-12.8			-14.3*	-15.6	-16.9	
316 (US)	MADRS	-10.8		-13.0*		-14.4		
305 (Non-US)	HAM-D24	-11.3	-15.4*	-16.2				
12541A (US & Non US)	HAM-D24	-10.3	-13.7				-15.8	

Source: compiled from the results of individual studies, Dul: duloxetine 60 mg, VLF: Venlafaxine 225 mg,
*: not significant

Table 13 summarizes the LS Mean differences from placebo (the treatment effect size) in MADRS or HAM-D24 total score in the 6 positive short-term studies. A higher dose demonstrated a larger treatment effect in all studies except Study 11492A.

Table 13: Summary of LS Mean Change Differences from Placebo in MADRS or HAM-D24 Total Score at the Endpoint in the Positive MDD Short-term Studies

Study Name (Study Sites)	Primary Endpoint	Lu AA21004 (mg) QD				Dul	VLF
		5	10	15	20		
11492A (Non-US)	MADRS	-5.9	-5.7				-6.4
13267A (Non-US)	MADRS			-5.5	-7.1	-9.5	
315 (US)	MADRS			-1.5*	-2.8	-4.1	
316 (US)	MADRS		-2.2*		-3.6		
305 (Non-US)	HAM-D24	-4.1*	-4.9				
12541A (US & Non-US)	HAM-D24	-3.3				-5.5	

Source: compiled from the results of individual studies. Dul: duloxetine 60 mg, VLF: Venlafaxine 225 mg *: not significant

Efficacy Summary of Long-Term Relapse Prevention Study 11985A (Non-US)
Study 11985A was a MDD relapse-prevention study including a 12-week open-label flexible-dose period and a randomized, double-blind, placebo-controlled, and fixed-dose period of 24 to 64 weeks. The initial dose of Lu AA21004 was 5 mg, p.o., QD. The dose can be increased to 10 mg from Week 2 to Week 8 during the Open-label Period if clinically indicated and can be decreased back to 5 mg if subject could not tolerate the AEs. From Week 8, the dose was fixed. Subjects in remission (MADRS < 10) at both visits at Weeks 10 and 12 in the Open-label Period were randomized 1:1 to either Lu AA21004 or placebo in the Double-Blind Period. The primary efficacy variable was the time to relapse of major depressive episode (MDE) within the first 24 weeks of the Double-blind Period.

Subjects with MDE on Lu AA21004 (5 or 10 mg) experienced a statistically significantly longer time to relapse than those in placebo ($p < 0.005$).

Study 11985A demonstrated the efficacy of Lu AA21004 5 mg and 10 mg p.o. QD in the prevention of relapse of MDE.

6.2 Rationale for Selection of Studies for Review

The clinical review for efficacy focused primarily on 6 positive short-term controlled MDD studies and the positive MDD long-term efficacy relapse prevention study.

6.3 Study Summary of MDD Short-Term Studies

6.3.1 Method/Study Design/Analysis Plan of MDD Short-Term Studies

Overall Study Design
All of the 10 short-term MDD studies were randomized, double-blind, placebo-controlled, fixed-dose studies with the treatment duration of 6 or 8 weeks. Six studies had active controls (5 studies used duloxetine and 1 study used venlafaxine).

Eligible subjects were randomized equally to each treatment group including placebo, and fixed doses of Lu AA21004 1, 2.5, 5, 10, 15, or 20 mg QD; (the doses varied across

studies). Study 11492A had an active control of venlafaxine 225 mg/day and 5 other studies had an active control of Duloxetine 60 mg/day.

In Studies 315, 316, and 317, subject randomization was stratified by baseline sexual dysfunction (SD) status (normal or abnormal SD).

Dose and Administration
The study drug was taken by mouth (p.o.) once daily (QD).

The subjects who were randomized to Lu AA21004 1, 2.5, 5, or 10 mg started treatment on that dose, whereas the subjects who were randomized to Lu AA21004 15 or 20 mg were titrated up from 10 mg after 1st week.
The subjects who were randomized to duloxetine in Studies 11984A, 304, and 12541A started and stayed on 60 mg during the treatment period, whereas in Studies 13267A and 315 they were titrated up from 30 mg to 60 mg after the 1st week.

The active control venlafaxine in Study 11492A was titrated stepwise twice during the 1st week from 75 mg to 150 mg and then to the treatment dose of 225 mg QD.

Selection of Study Population
The study population included male and female subjects aged ≥18 years with a primary diagnosis of MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; Text Revision (DSM-IV-TR) criteria.

Key Inclusion Criteria:

The following table listed the key differences in the eligibility criteria for the 10 short-term MDD studies.

Table 14: Eligibility Requirements in Short-Term Studies

Eligibility Requirements	Study									
	11492A	**11984A**	**305**	**13267A**	**315**	**316**	**303**	**304**	**317**	**12541A**
MADRS total score	≥30	≥26	≥26	≥26	≥26	≥26	≥30	≥22	≥26	≥26
CGI-S total score	NR	NR	NR	≥4	≥4	≥4	NR	NR	≥4	NR
Duration of current MDE (months)	≥3-<12	≥3	≥3	>3	≥3	≥3	≥3	≥3	≥3	≥4 weeks
Prior MDE required	No	No	No	Yes	Yes	Yes	No	No	Yes	Yes (a)

(a) Subjects had to have had 1 MDE before age 60.
NR=not required.
Source: 2-7-3 Summary of Clinical Efficacy, Table 1.d, page 20/185

Key exclusion criteria:

- had any current psychiatric disorder other than MDD (the MINI or the SCID-I was used to assist in the exclusion of disallowed Axis I disorders); a history of manic

or hypomanic episode; schizophrenia; any other psychotic disorder; a mental disorder due to a general medical condition; any clinically significant neurological or neurodegenerative disorder; or any significant Axis II disorder.

- had a significant risk of suicide (as judged by the investigator; a score ≥5 on MADRS item 10 [suicidal thoughts] at the Screening and Baseline Visits; or a suicide attempt during the last 6 months)

- had clinically significant unstable illness

- had any substance-related disorder (except nicotine or caffeine) within the previous 6 months (within at least 2 years in Study 13267A); had a diagnosis of alcohol or substance abuse that was not in sustained full remission for at least 2 years prior to screening (Studies 315, 316, and 317)

- had treatment-resistant depression (defined as resistant to 2 adequate antidepressant treatments of ≥6 weeks' duration, as judged by the investigator)

- receiving formal cognitive, behavioral, or other systematic psychotherapy

- had received electroconvulsive therapy (or vagal nerve stimulation, or repetitive transcranial magnetic stimulation [Studies 13267A, 315, 316, and 317]) within 6 months prior to the Screening Visit

12541A was a study in the elderly aged ≥65 years with at least 1 MDE before the age of 60. Subjects with a Mini Mental State Examination (MMSE) score <24 were excluded in order to exclude the confounding effects of dementia.

The Primary and Secondary Efficacy Endpoints

The primary efficacy endpoint was the change from baseline to endpoint of either MADRS or HAM-D24 total score. CGI-S and CGI-I were measured in all 10 short-term studies as secondary efficacy endpoints.

Statistical Methods

The **Full Analysis Set (FAS)** included all subjects who took at least 1 dose of study drug and who had at least 1 valid post-baseline measurement of the primary efficacy variable.

The primary efficacy measurement - MADRS or HAM-D24 total score 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). Table 15 lists the primary efficacy analyses in 10 MDD short-term studies. For more details, please refer to the more comprehensive statistical review by Dr. George Kordzakhia.

Table 15: Primary Efficacy Analyses in the Short-Term Studies

Study	Endpoint	Comparison	Primary Statistical Methodology
11492A	Δ MADRS total score at Week 6	10 mg vs. PBO	ANCOVA (LOCF)
11984A	Δ MADRS total score at Week 8	5 mg vs. PBO 10 mg vs. PBO	ANCOVA (LOCF)
305	Δ HAM-D24 total score at Week 8	10 mg vs. PBO	MMRM
13267A	Δ MADRS total score at Week 8	15 mg vs. PBO 20 mg vs. PBO	MMRM
315	Δ MADRS total score at Week 8	15 mg vs. PBO 20 mg vs. PBO	MMRM
316	Δ MADRS total score at Week 8	10 mg vs. PBO 20 mg vs. PBO	MMRM
303	Δ HAM-D24 total score at Week 6	5 mg vs. PBO	ANCOVA (LOCF)
304	Δ HAM-D24 total score at Week 8	5 mg vs. PBO	ANCOVA (LOCF)
317	Δ MADRS total score at Week 8	10 mg vs. PBO 15 mg vs. PBO	MMRM
12541A	Δ HAM-D24 total score at Week 8	5 mg vs. PBO	ANCOVA (LOCF)

Δ=change from Baseline. All doses are QD.
Source: 2-7-3 Summary of Clinical Efficacy, Table 1.f, page 24/185

In each study, a hierarchically ordered testing strategy was defined in the statistical analysis plan (SAP) and comprised the primary efficacy endpoint and key secondary efficacy endpoints. The testing strategy comprised either 1 sequence, or 2 sequences tested in parallel. Formal testing stopped as soon as the hypothesis in the hierarchy could not be rejected.

6.3.2 The Results of Individual MDD Short-Term Studies

We examined the results of 6 positive studies carefully and presented the study results individually in this section.

6.3.2.1 - Study 11492A (Non-US)

Study Title
"Double-blind, randomized, placebo-controlled study comparing the efficacy and safety of two fixed dosages of a novel antidepressant compound to that of placebo in patients with Major Depressive Disorder"

Objectives
To evaluate the efficacy, safety, and tolerability of Lu AA21004 (5 or 10 mg) compared with placebo in the treatment of MDD subjects aged 18-65 years.

Study Conduct Dates: 08/2006 - 08/2007

Study Sites
49 sites in Austria, Australia, Canada, the Czech Republic, Finland, France, Italy, Malaysia, Slovakia, Spain, and Sweden

Demographics
Approximately 55% of the subjects in the venlafaxine group and 65% of the subjects in the placebo and Lu AA21004 groups were women. The mean age of the subjects was 43 years, ranging from 18 to 65 years, and the majority (92%) was Caucasian

The age, race, weight and BMI were roughly comparable among treatment groups.

The mean age (SD) at Baseline was 43 (12) years. 92% were Caucasian, 6.8% were Asian, and 0.5% were Black. The mean weight (SD) for male was 82 (16) kg and the BMI 26 (4.5). The mean weight (SD) for female was 69 (15) kg and the BMI 25 (5).

Baseline Disease Characteristics

The baseline disease characteristics which were measured by MADRS total score and CGI-S rating at Baseline were comparable among all the treatment groups (Table 16).

Table 16: Baseline Assessment Scores (FAS) - Study 11492A (Non-US)

Assessment	Mean (SD)				
	PBO N=105	Lu AA21004		Venlafaxine N=112	Total N=425
		5 mg N=108	10 mg N=100		
MADRS total score	33.9 (2.8)	34.1 (2.6)	34.0 (2.8)	34.2 (3.1)	34.0 (2.8)
HAM-D24 total	29.7 (5.0)	29.9 (5.4)	29.3 (5.6)	29.4 (5.0)	29.6 (5.2)
HAM-A total score	22.9 (5.9)	21.7 (6.2)	22.3 (5.6)	22.0 (5.5)	22.2 (5.8)
CGI-S score	5.1 (0.7)	5.2 (0.7)	5.1 (0.7)	5.2 (0.7)	5.2 (0.7)

MADRS total score ≥30 at Baseline was an inclusion criterion
Source: Table 2.b in page 40/183 of 2.7.4 Summary of Clinical Safety

Subject Disposition
A total of 429 subjects were randomized to this 6-week treatment trial. The completion rate at Endpoint was 82.9%, 90.7%, 82.0% and 82.3% for placebo, LU AA21004 5mg, LU AA21004 10mg, and Venlafaxine groups, respectively (Table 17).

The number of subjects who withdrew prematurely due to lack of efficacy in Lu AA21004 5mg group (5.6%) was almost as high as the placebo (5.7%). Venlafaxine group had the lowest rate of early termination due to lack of efficacy (1.8%).

Table 17: Subject Disposition - Study 11492A (Non-US)

	Number of Subjects (%)				
	Placebo	LuAA21004		Venlafaxine (a)	Total
		5 mg	10 mg		
Randomized	105	109	101	114	429
Treated (b)	105 (100)	108 (100)	100 (100)	113 (100)	426 (100)
Completed study	87 (82.9)	98 (90.7)	82 (82.0)	93 (82.3)	360 (84.5)
Early termination	18 (17.1)	10 (9.3)	18 (18.0)	20 (17.7)	66 (15.5)
Reasons for early termination					
Lack of efficacy	6 (5.7)	6 (5.6)	3 (3.0)	2 (1.8)	17 (4.0)
Noncompliance	0	0	0	1 (0.9)	1 (0.2)
Protocol deviations	0	1 (0.9)	2 (2.0)	0	3 (0.7)
Withdrawal of consent	4 (3.8)	0	4 (4.0)	1 (0.9)	9 (2.1)
Lost to follow-up	1 (1.0)	0	1 (1.0)	0	2 (0.5)
Other	3 (2.9)	0	1 (1.0)	0	4 (0.9)
FAS	105	108	100	112	425

IMP=investigational medicinal product, VLF=venlafaxine.
(a) Venlafaxine doses were 75 mg for 4 days, 150 mg for 3 days, then 225 mg for remainder of treatment period.
(b) Percentages are based on all treated subjects.
Source: Table 2.a, page 39/185 of 2.7.3 Summary of Clinical Efficacy

Concomitant Medication Use

This reviewer focused primarily on prohibited (disallowed) concomitant medication use that may have impacted study results – specifically the use of prohibited concomitant antidepressants, antipsychotic, and benzodiazepines and such.

This reviewer examined Table 34 in the clinical study report of Study 11492A (page 212-232) which listed concomitant medications either discontinued prior or at Baseline or continued at Baseline or started at or after Baseline. The following table summarizes the findings. All the disallowed concomitant antidepressants, antipsychotics and benzodiazepine listed below were started at or after Baseline.

Table 18: Disallowed Concomitant Medications Taken - Study 11492A (Non-US)

Concomitant Medications	Number (%)		
	Placebo (N=105)	Lu AA21004	
		5 mg (N=108)	10 mg (N=100)
Antidepressants			
Citalopram		1 (0.9)	
Escitalopram		1 (0.9)	
Antipsychotics			
Olanzapine			1 (1)
Benzodiazepine Derivatives			
Alprazolam		1 (0.9)	

Concomitant Medications	Number (%)		
	Placebo (N=105)	Lu AA21004	
		5 mg (N=108)	10 mg (N=100)
Diazepam		2 (1.9)	
Benzodiazepine Related Drugs			
Zolpidem	1 (1)	1 (0.9)	3 (3)
Zopiclone	2 (2)	2 (1.9)	

Source: compiled from Table 34 in 11492A Clinical Study Report, page 212/1107 to 232/1107

We requested the sponsor to confirm our findings on May 13, 2013 and the sponsor responded on May 17, 2013. They clarify that four of the subjects (subject 3011 on citalopram, subject 4402 on Escitalopram, subject 3739 on Diazepam and subject 3502 on Zolpidem) included in the Table above as starting disallowed concomitant medications after baseline in fact started those medications after their last visit in the double-blind treatment period of the study. The subject who took olanzapine in Lu AA21004 10mg group was not included in the Per-protocol set (PPS) according to sponsor.

In the response dated May 17, 2013, the sponsor submitted a line listing of all subjects who took disallowed concomitant antidepressants, antipsychotics, benzodiazepine derivatives, or benzodiazepine related drugs during the double-blind treatment period in Study 11492A. All subjects who were included in PPS took Zolpidem/Diazepam/Zopiclone for insomnia for a short period of duration (1-2 days), which would less likely have affected the overall efficacy results.

Protocol Deviations

The sponsor mentioned in the submission that after un-blinding the study, an audit was conducted at center AT002 and found that the quality of the medical records at this center was inadequate. They repeated the efficacy analyses without the data from center AT002 and they found that the results from these analyses were slightly more favorable for Lu AA21004. Therefore, they kept the 28 subjects randomized in this center in all the analyses.

This reviewer examined the inclusion/exclusion/withdrawal criteria deviations (Panel 11: clinical study report page 55-56) and procedural compliance deviations (Panel 12: page 57-58). The sponsor did not note here that the subject who took olanzapine in Lu AA21004 10mg group was excluded from the Per-protocol set (PPS), but they mentioned in the response dated May 17, 2013 that this subject was actually not included in PPS. Other deviations were minor and the handling of the deviations appeared to be appropriate.

Efficacy Findings

Primary Efficacy Endpoint

The primary efficacy endpoint, change from Baseline and the difference of change to placebo by week in MADRS total score are shown in the following table. In each treatment group, bigger changes were observed with longer treatment. Mean changes from Baseline MADRS total score are shown by study visit for all treatment groups in

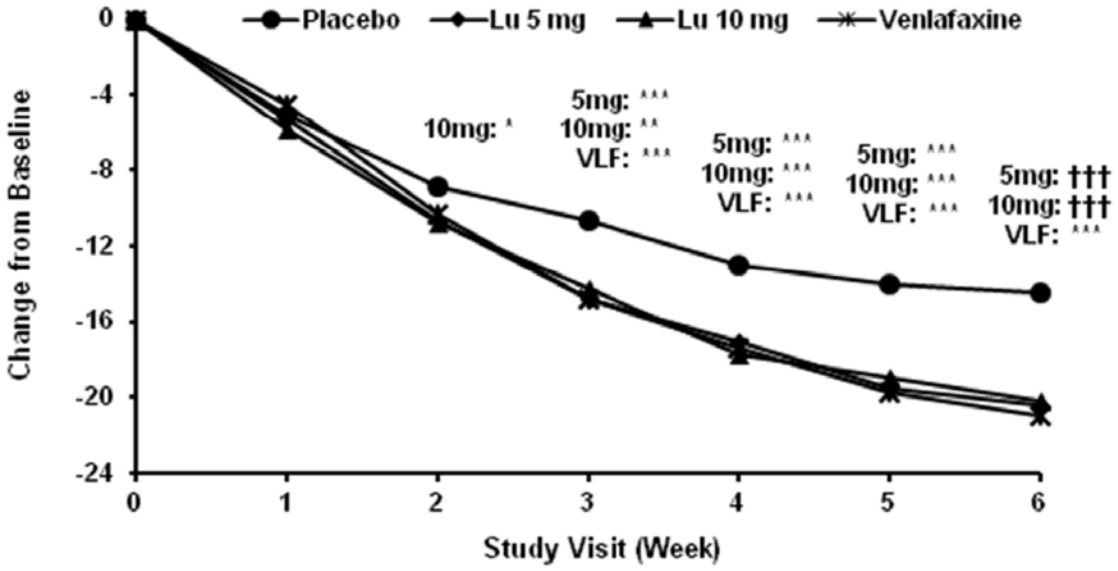
the following figure. Lu AA21004 10mg started to separate from placebo from Week 2 and 5mg from Week 3 onwards.

Table 19: Mean Change from Baseline in MADRS Total Score by Week (FAS, LOCF, ANCOVA) - Study 11492A (Non-US)

Treatment Group	Week	n	Least Squares Estimates		Difference to Placebo				
			Mean	SE	Mean	SE	95% CL Lower	95% CL Upper	p-value
PBO	1	105	-5.04	0.50					
	2	105	-8.87	0.70					
	3	105	-10.70	0.81					
	4	105	-13.06	0.89					
	5	105	-14.05	0.97					
	6	105	-14.50	1.03					
VLF	1	112	-4.50	0.48	0.54	0.67	-0.77	1.85	0.4142
	2	112	-10.31	0.67	-1.45	0.94	-3.29	0.39	0.1224
	3	112	-14.76	0.79	-4.06	1.09	-6.21	-1.92	0.0002
	4	112	-17.39	0.86	-4.32	1.19	-6.67	-1.98	0.0003
	5	112	-19.73	0.94	-5.68	1.31	-8.25	-3.11	<.0001
	6	112	-20.92	0.99	-6.42	1.38	-9.13	-3.72	<.0001
5mg	1	107	-5.26	0.49	-0.22	0.67	-1.54	1.11	0.7489
	2	108	-10.63	0.69	-1.77	0.94	-3.62	0.09	0.0619
	3	108	-14.86	0.80	-4.16	1.10	-6.33	-1.99	0.0002
	4	108	-17.11	0.88	-4.04	1.20	-6.41	-1.68	0.0009
	5	108	-19.55	0.96	-5.49	1.32	-8.08	-2.90	<.0001
	6	108	-20.40	1.01	-5.90	1.39	-8.64	-3.17	<.0001
10mg	1	99	-5.86	0.51	-0.82	0.69	-2.17	0.54	0.2377
	2	99	-10.77	0.71	-1.91	0.97	-3.81	-0.00	0.0497
	3	99	-14.24	0.83	-3.54	1.13	-5.77	-1.32	0.0019
	4	100	-17.71	0.90	-4.65	1.23	-7.07	-2.23	0.0002
	5	100	-18.91	0.99	-4.86	1.35	-7.51	-2.21	0.0004
	6	100	-20.20	1.04	-5.70	1.42	-8.49	-2.91	<.0001

Source: Clinical Study Report Table 42, page 241

Figure 1: Change From Baseline in MADRS Total Score (FAS, LOCF) - Study 11492A (Non-US)



Source: Study 11492A Table 42.
*=nominal p <0.05, **=nominal p <0.01, ***nominal p <0.001 versus placebo. †††=p <0.001, statistically significant by testing strategy.

The following table shows the mean change from baseline to endpoint and the effect size. The sponsor was able to demonstrate statistical significance using FAS, LOCF for both Lu AA21004 5mg and 10 mg (p<0.0001) compared to the placebo at the endpoint.

Table 20: Mean Change from Baseline at Endpoint (Week 6) in MADRS Total Score (FAS, LOCF, ANCOVA) - Study 11492A (Non-US)

	Placebo N=105	Lu AA21004		Venlafaxine N=112
		5 mg QD N=108	10 mg QD N=100	
Δ LS mean change from baseline (SE)	-14.50 (1.03)	-20.40 (1.01)	-20.20 (1.04)	-20.92 (0.99)
LS mean differences from placebo (SE)		-5.90 (1.39)	-5.70 (1.42)	-6.42 (1.38)
95% CI for differences (lower, upper)		-8.64, -3.17	-8.49, -2.91	-9.13, -3.72
p-value, treatment vs. placebo		<0.0001	<0.0001	<0.0001

Source: compiled from Table 42 from CSR 11492A, page 241/1107

The sponsor did not pre-specify any key secondary endpoints for this study.

6.3.2.2 - Study 305 (Non-US)

Study Title
"A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Fixed-Dose Study Comparing the Efficacy and Safety of 3 Doses of Lu AA21004 in Acute Treatment of Adults with Major Depressive Disorder"

Objectives
To evaluate the efficacy, safety, and tolerability of Lu AA21004 (1, 5 or 10 mg) compared with placebo in the 8-week treatment of MDD subjects aged 18-75 years.

Study Conduct Dates: 08/2008-08/2009

Study Sites
48 sites in Australia, Croatia, France, Germany, Latvia, Lithuania, Malaysia, Netherlands, Poland, Republic of Korea, Russia, South Africa, Taiwan, and Ukraine

Demographics
At baseline, the age, sex, race, weight, BMI, the baseline characteristics of smoking and alcohol consumption were comparable among treatment groups.

The mean age (SD) at Baseline was 46 (12) years. About 34%-39% of the subjects were male. 86% were Caucasian, 11% were Asian, and 2% were Black. The mean weight (SD) was 75 (16) kg and the BMI 26 (4.9). The baseline characteristics of smoking and alcohol consumption were comparable among treatment groups.

Baseline Disease Characteristics

The baseline disease characteristics which were demonstrated in Baseline MADRS total score and CGI-S rating were comparable among all the treatment groups. They were summarized in the following table.

Table 21: Baseline Assessment Scores (FAS) - Study 305 (Non-US)

Assessment	Mean (SD)				
	PBO N=139	Lu AA21004			Total N=556
		1 mg N=139	5 mg N=139	10 mg N=139	
MADRS total score	30.6 (2.9)	30.4 (3.0)	30.6 (2.8)	31.6 (3.8)	30.8 (3.2)
HAM-D24 total score	32.7 (4.4)	32.5 (5.1)	32.2 (5.0)	33.1 (4.8)	32.6 (4.8)
HAM-A total score	19.7 (7.1)	20.0 (6.4)	19.5 (6.8)	21.1 (7.4)	20.1 (6.9)
CGI-S score	4.8 (0.8)	4.7 (0.7)	4.8 (0.7)	4.9 (0.8)	4.8 (0.8)

Note: A MADRS total score ≥26 at Baseline was an inclusion criterion.
Source: Table 2.j, page 49/185 of 2.7.3 Summary of Clinical Efficacy

Subject Disposition

A total of 560 subjects were randomized to this 8-week treatment trial. The completion rate at Endpoint was 90.7%, 90.7%, 92.1% and 87.1% for placebo, LU AA21004 1 mg, 5 mg, and 10 mg groups, respectively.

As expected, the placebo group (5.7%) had the highest premature withdrawal due to lack of efficacy and Lu AA21004 10mg group (3.6%) had the highest premature withdrawal due to AEs.

Table 22: Subject Disposition - Study 305 (Non-US)

Category	Treatment n (%)				
	Placebo	Lu AA21004			Total
		1 mg	5 mg	10 mg	
Subjects randomized (a)	140 (100)	140 (100)	140 (100)	140 (100)	560 (100)
Subjects treated	140 (100)	140 (100)	140 (100)	139 (99.3)	559 (99.8)
Subjects completed	127 (90.7)	127 (90.7)	129 (92.1)	122 (87.1)	505 (90.2)
Subjects withdrawn	13 (9.3)	13 (9.3)	11 (7.9)	18 (12.9)	55 (9.8)
Primary reason for withdrawal					
Adverse event	2 (1.4)	3 (2.1)	1 (0.7)	5 (3.6)	11 (2.0)
Lack of efficacy	8 (5.7)	4 (2.9)	2 (1.4)	3 (2.1)	17 (3.0)
Noncompliance	0	0	1 (0.7)	0	1 (0.2)
Protocol deviations	1 (0.7)	2 (1.4)	1 (0.7)	1 (0.7)	5 (0.9)
Withdrawal of consent	1 (0.7)	3 (2.1)	5 (3.6)	7 (5.0) (b)	16 (2.9)
Lost to follow-up	0	1 (0.7)	1 (0.7)	1 (0.7)	3 (0.5)
Other	1 (0.7)	0	0	1 (0.7)	2 (0.4)
FAS	139	139	139	139	556

(a) Percentages are based on all randomized subjects.
Source: Table 2.i, page 48/185 of 2.7.3 Summary of Clinical Efficacy

Concomitant Medication Use

We requested this information on May 13, 2013 and the sponsor responded on May 17, 2013. The sponsor submitted the following table listing of all subjects who took disallowed concomitant antidepressants, antipsychotics, benzodiazepine derivatives, or benzodiazepine related drugs during the double-blind treatment period in Study 305. Since the protocols allowed occasional use of zopiclone, zolpidem or zaleplon for severe insomnia, many subjects had concomitant use of these medications.

Table 23: Summary of Disallowed Concomitant Medications in Study 305

Therapeutic Class Preferred Term	Placebo (N=140)	Lu AA21004 (mg)			Total (N=560)
		1 (N=140)	5 (N=140)	10 (N=140)	
Subjects with Disallowed Medications	3 (2.1)	6 (4.3)	10 (7.1)	5 (3.6)	24 (4.3)
Antidepressants	0	1 (0.7)	1 (0.7)	1 (0.7)	3 (0.5)
Cipralex	0	1 (0.7)	0	0	1 (0.2)
Duloxetine	0	0	1 (0.7)	0	1 (0.2)
Lerivon	0	0	0	1 (0.7)	1 (0.2)

Therapeutic Class Preferred Term	Placebo (N=140)	Lu AA21004 (mg)			Total (N=560)
		1 (N=140)	5 (N=140)	10 (N=140)	
Antipsychotics	0	1 (0.7)	0	0	1 (0.2)
Zyprexa	0	1 (0.7)	0	0	1 (0.2)
Benzodiazepine	0	0	0	1 (0.7)	1 (0.2)
Lorazepam	0	0	0	1 (0.7)	1 (0.2)
Benzodiazepine Related Drugs	3 (2.1)	4 (2.9)	9 (6.4)	3 (2.1)	19 (3.4)
Imovane	0	1(0.7)	0	0	1 (0.2)
Somnols	0	2	1(0.7)	0	3 (0.5)
Stilnox	0	0	4(2.9)	0	4 (0.7)
Zolpi	0	1(0.7)	0	0	1 (0.2)
Zolpidem	1(0.7)	1(0.7)	2(1.4)	1(0.7)	5 (0.9)
Zopiclon	1(0.7)	0	2(1.4)	1(0.7)	4 (0.7)
Zopiclone	1(0.7)	0	0	0	1 (0.2)
Zoplicone	0	0	0	1 (0.7)	1 (0.2)

Source: Table 305.1 in 2013-05-17-Request-for-Infomration-Con Meds.pdf

According to the sponsor's response dated on May 17, 2013, the subjects, who took Cipralex, Duloxetine, and Lerivon started their medications after the last dose of Lu AA21004 treatment. The subject who took Zyprexa was not included in the PPS. Therefore, the efficacy results would not have been affected.

Protocol Deviations

The percentage of subjects with at least 1 major protocol deviation was similar across all treatment groups: 5.7%, 4.3%, 5.7% and 4.3% in the Lu AA21004 1 mg, 5 mg, 10 mg and placebo, respectively. As mentioned earlier, the subject who took Zyprexa was not included in the PPS and therefore it would not have affected efficacy results.

Efficacy Findings

Primary and Secondary Efficacy Endpoint

The primary endpoint was the mean change from baseline to endpoint in HAM-D24 total score. It was analyzed by an LOCF ANCOVA. SDS and CGI-I were the secondary efficacy endpoint.

Table 24 shows the LS Mean (SE) change from Baseline by week in HAM-D-24 Total Score. In each treatment group, bigger changes were observed with longer treatment.

Table 24: LS Mean (SE) Change from Baseline by Week in HAM-D-24 Total Score (FAS, MMRM) - Study 305 (Non-US)

Week	Placebo	Lu AA21004		
		1mg	5mg	10mg
1	-3.5 (0.32)	-2.8 (0.32)	-3.2 (0.32)	-3.2 (0.32)
2	-5.7 (0.48)	-7.3 (0.48)	-7.3 (0.49)	-7.4 (0.49)
4	-8.4 (0.63)	-11.1 (0.64)	-11.0 (0.64)	-11.9 (0.65)
6	-10.2 (0.69)	-13.4 (0.70)	-13.7 (0.70)	-15.2 (0.71)
8	-11.3 (0.74)	-14.8 (0.75)	-15.4 (0.74)	-16.2 (0.76)

Source: End of Text Tables and Figures, Table 15.2.1.1.8 (pg. 159-160)

The sponsor was able to demonstrate statistical significance using MMRM for 10 mg dose ($p<0.001$) compared to the placebo. The following table shows the mean change from baseline to endpoint and the effect size.

Table 25: HAM-D24 Total Score Change From Baseline at Week 8 (FAS, MMRM) - Study 305 (Non-US)

	Placebo N=128	**Lu AA21004 10 mg QD N=122**
Δ LS mean change from baseline (SE)	-11.30 (0.738)	-16.23 (0.755)
LS mean differences from placebo (SE)		-4.93 (1.050)
95% CI for differences (lower, upper)		(-6.99, -2.86)
p-value, treatment vs. placebo		<0.001

Source: compiled from Table 11.a from Study 305 CSR page 63/118

Since Δ SDS total score at Lu AA21004 10mg was not significant (p= 0.135), the multiplicity controlled hierarchical testing stopped (see the following table for the pre-defined hierarchical testing strategies for Study 305). Therefore, none of the subsequent endpoints including Lu AA21004 5 mg were considered significant, according to the pre-defined hierarchical testing strategies for Study 305 shown in Table 26.

Table 26: Hierarchical Testing Strategies for Study 305 (MMRM) (Non-US)

Hierarchical testing in 1 sequence; α = 0.05 - at Week 8:
1. Δ HAM-D24 total score – 10 mg
2. Δ SDS total score – 10 mg
3. CGI-I score – 10 mg
4. Response – defined as a ≥50% reduction in HAM-D24 total score – 10 mg
5. Δ HAM-D24 total score in subjects with a HAM-A total score ≥ 20 at Baseline – 10 mg
6. Remission – defined as a MADRS total score ≤10 – 10 mg
7. Δ HAM-D24 total score – 5 mg
8. Δ SDS total score – 5 mg
9. CGI-I score – 5 mg
10. Response – defined as a ≥50% reduction in HAM-D24 total score – 5 mg
11. Δ HAM-D24 total score in subjects with a HAM-A total score ≥20 at Baseline – 5 mg
12. Remission – defined as a MADRS total score ≤10 – 5 mg

Source: Table 1.g, page 26/185 of 2.7.3 Summary of Clinical Efficacy

6.3.2.3 - Study 13267A (Non-US)

Study Title
"A randomized, double-blind, parallel-group, placebo-controlled, duloxetine-referenced, fixed-dose study evaluating the efficacy and safety of Lu AA21004 (15 and 20mg/day) in the acute treatment of adult subjects with Major Depressive Disorder"

Objectives
To evaluate the efficacy, safety, and tolerability of Lu AA21004 (15 or 20 mg) compared with placebo in the 8-week treatment of MDD subjects aged 18-75 years.

Study Conduct Dates: 05/2010-09/2011

Study Sites
72 sites in Belgium, Estonia, Finland, France, Germany, Latvia, Lithuania, Norway, Russian Federation, Slovakia, South Africa, Sweden, and Ukraine

Demographics
At baseline, Lu AA21004 20mg had more male subjects than placebo, Lu AA21004 15mg and Duloxetine group (40%, 30%, 31% and 36%, respectively).

The age, race, weight and BMI were roughly comparable among treatment groups.

The mean age (SD) at Baseline was 46 (14) years. 98% were Caucasian, 1.2% were Black and 0.2% were Asian. The mean weight (SD) was 75 (16) kg and the BMI 26 (5.2).

Baseline Disease Characteristics

The baseline disease characteristics which were demonstrated in Baseline MADRS total score and CGI-S rating were comparable across the treatment groups. They were summarized in Table 27.

Table 27: Baseline Assessment Scores (FAS) - Study 13267A (Non-US)

Assessment	Mean (SD)				
	PBO N=158	Lu AA21004		Duloxetine N=146	Total N=604
		15 mg N=149	20 mg N=151		
MADRS total	31.5 (3.6)	31.8 (3.4)	31.2 (3.4)	31.2 (3.5)	31.4 (3.5)
CGI-S score	4.9 (0.7)	4.9 (0.6)	4.8 (0.7)	4.8 (0.7)	4.8 (0.7)

Note: A MADRS total score ≥26 and a CGI-S score ≥4 at Baseline were inclusion criterion.
Source: Table 2.n, page 53/185 of 2.7.3 Summary of Clinical Efficacy

Subject Disposition
A total of 608 subjects were randomized to this 8-week treatment trial. The completion rate at Endpoint was 84.2%, 77.5%, 82.8% and 89.1% for placebo, Lu AA21004 15 mg, 20 mg, and Duloxetine groups, respectively (Table 28).

Surprisingly, Lu AA21004 15 mg had the highest rate of withdrawal due to lack of efficacy (more than placebo). Lu AA21004 20 mg had the highest rate of withdrawal due to AEs, which was expected.

Table 28: Subject Disposition - Study 13267A (Non-US)

	Treatment n (%)				
	Placebo	Lu AA21004		Duloxetine 60 mg	Total
		15 mg	20 mg		
Subjects randomized	158	152	151	147	608
Subjects treated (a)	158 (100)	151 (100)	151 (100)	147 (100)	607 (100)
Subjects completed	133 (84.2)	117 (77.5)	125 (82.8)	131 (89.1)	506 (83.4)
Subjects withdrawn	25 (15.8)	34 (22.5)	26 (17.2)	16 (10.9)	101 (16.6)
Primary reason for withdrawal					
Adverse event	7 (4.4)	10 (6.6)	17 (11.3)	7 (4.8)	41 (6.8)
Lack of efficacy	6 (3.8)	8 (5.3)	2 (1.3)	1 (0.7)	17 (2.8)
Noncompliance	0	1 (0.7)	0	1 (0.7)	2 (0.3)
Protocol violation	5 (3.2)	3 (2.0)	2 (1.3)	1 (0.7)	11 (1.8)
Withdrawal of consent	6 (3.8)	6 (4.0)	2 (1.3)	2 (1.4)	16 (2.6)
Lost to follow-up	1 (0.6)	1 (0.7)	0	2 (1.4)	4 (0.7)
Other	0	5 (3.3)	3 (2.0)	2 (1.4)	10 (1.6)
FAS	158	149	151	146	604

(a) Percentages are based on all treated subjects.
Source: Table 2.m, page 53/185 of 2.7.3 Summary of Clinical Efficacy

Concomitant Medication Use

We requested this information on May 13, 2013 and the sponsor responded on May 17, 2013. The sponsor submitted the following table listing of all subjects who took disallowed concomitant antidepressants, antipsychotics, benzodiazepine derivatives, or benzodiazepine related drugs during the double-blind treatment period in Study 13267A.

According to the sponsor's response dated on May 17, 2013, the subjects who took Venlafaxine started it after the last dose of Lu AA21004 treatment. Therefore, the efficacy results would not have been affected by concomitant venlafaxine.

Table 29: Summary of Disallowed Concomitant Medications in Study 13267A

Therapeutic Class	Placebo (N=158)	Lu AA21004 (mg)		Duloxetine (N=147)	Total (N=608)
		15 (N=152)	20 (N=151)		
Subjects with Disallowed Medications	10(6.3)	5(3.3)	4(2.6)	8(5.4)	27(4.4)
Antidepressants	0	1(0.7)	0	0	1(0.2)
Venlafaxine Hydrochloride	0	1(0.7)	0	0	1(0.2)
Benzodiazepine Related Drugs	10(6.3)	4(2.6)	4(2.6)	8(5.4)	26(4.3)
Zolpidem	1(0.6)	1(0.7)	1(0.7)	2(1.4)	5(0.8)
Zolpidem Tartrate	2(1.3)	1(0.7)	0	3(2.0)	6(1.0)
Zopiclone	7(4.4)	2 1.3)	3(2.0)	3(2.0)	15(2.5)

Source: Table 305.1 in 2013-05-17-Request-for-Infomration-Con Meds.pdf

Few subjects took insomnia medications chronically, which were protocol violations, and might have confounded the evaluation of efficacy. Table 30 lists the subjects with the chronic use (disallowed) of Zopiclone for insomnia.

Table 30: Subjects with the Chronic Use (Disallowed) of Zopiclone for Insomnia in Study 13267A

Site No./ Subject No./ First Dose Date/ Last Dose Date	Medication Name (a)/ Generic Name/ Indication	Dates (Study Day) (b)		Included in PPS
		Start	On-going?	
FR011/S1630/01JUN2011/ 21JUN2011 in Lu AA21004 15mg	Imovane/Zopiclone/insomnia due to depression	11MAY2011 (-22)	Yes	Yes
FR011/S1630/01JUN2011/21JUN2011 in Lu AA21004 15mg	Imovane/ Zopiclone/insomnia	23MAY2011 (-9)	Yes	Yes
FR002/S1331/18FEB2011/14APR2011 in Lu AA21004 20 mg	Imovane/ Zopiclone/insomnia due to depression	02FEB2010 (-381)	Yes	Yes
FR002/S1447/06APR2011/31MAY2011 in Lu AA21004 20mg	Imovane/ Zopiclone/insomnia due to depression	15FEB2011 (-50)	Yes	Yes
FR002/S1514/21APR2011/15JUN2011 in Lu AA21004 20mg	Imovane/ Zopiclone/insomnia	04APR2011 (-17)	Yes	Yes

Source: Table 305.1 in 2013-05-17-Request-for-Infomration-Con Meds.pdf

Protocol Deviations

According to the submission, site FR004 was identified as non-compliance with the protocol, GCP, and applicable regulations. Only 1 subject was randomized and this person completed the study.

This reviewer examined the Inclusion/Exclusion/Withdrawal Criteria Deviations (Panels 14), Procedural Compliance Deviations (Panels 15) and Exclusions from Analysis Sets (Panels 16) in the clinical study report and found them adequate.

Efficacy Findings

Primary Efficacy Endpoint

The change from Baseline in MADRS total score and the difference to placebo at each week are shown in the following table. In each treatment group, bigger changes were observed with longer treatment.

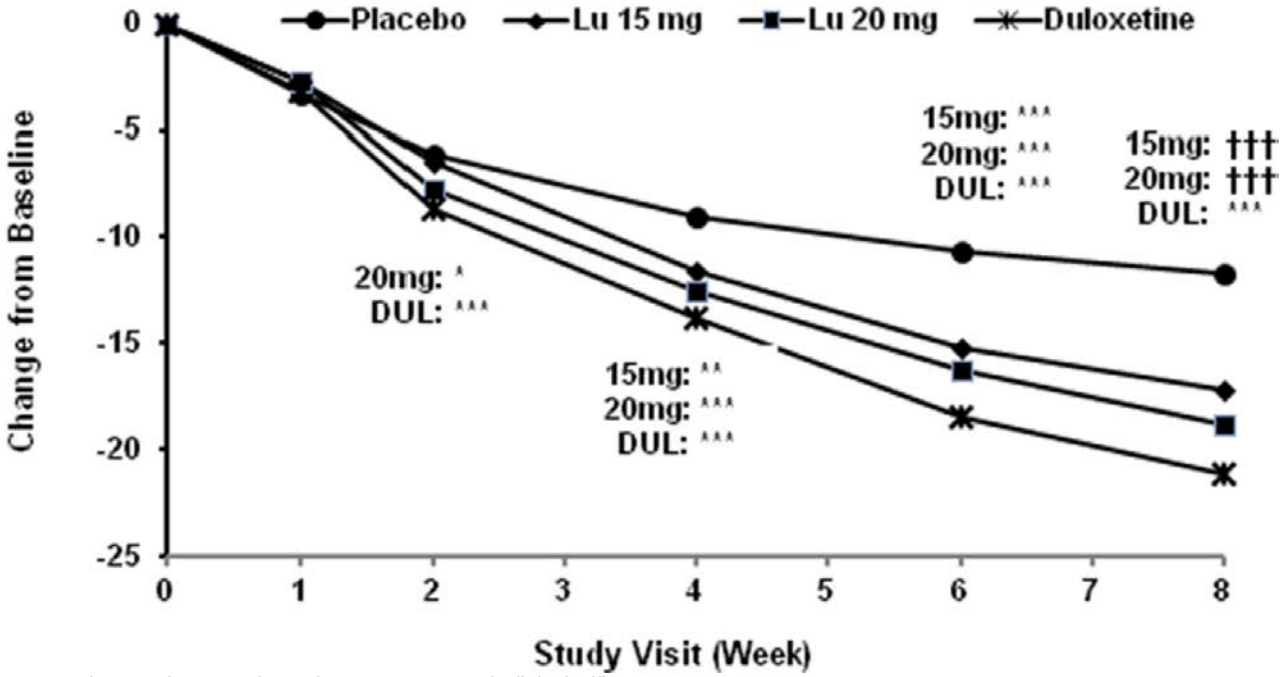
Table 31: Adjusted Changes from Baseline in MADRS Total Score by Week (FAS, MMRM) - Study 13267A (Non-US)

Treatment Group	Week	N	Mean	SE	Difference to Placebo				
					Mean	SE	95% CI		p-value
							Lower	Upper	
PBO	1	157	-3.28	0.31					
	2	152	-6.13	0.48					
	4	146	-9.02	0.60					
	6	135	-10.63	0.71					
	8	130	-11.70	0.76					
DUL	1	145	-3.22	0.33	0.06	0.44	-0.80	0.92	0.8880
	2	143	-8.71	0.50	-2.58	0.69	-3.93	-1.23	0.0002
	4	141	-13.80	0.62	-4.78	0.85	-6.46	-3.11	<.0001
	6	135	-18.43	0.72	-7.80	1.01	-9.78	-5.81	<.0001
	8	131	-21.15	0.77	-9.45	1.07	-11.55	-7.35	<.0001
Lu AA21004 15mg	1	148	-2.76	0.33	0.52	0.43	-0.33	1.37	0.2328
	2	148	-6.45	0.50	-0.32	0.68	-1.66	1.02	0.6407
	4	136	-11.64	0.62	-2.62	0.86	-4.30	-0.94	0.0023
	6	123	-15.20	0.74	-4.57	1.02	-6.57	-2.56	<.0001
	8	118	-17.23	0.79	-5.53	1.09	-7.66	-3.40	<.0001
Lu AA21004 20mg	1	150	-2.71	0.32	0.57	0.43	-0.28	1.42	0.1879
	2	141	-7.78	0.50	-1.65	0.69	-3.00	-0.31	0.0162
	4	135	-12.55	0.63	-3.53	0.86	-5.22	-1.85	<.0001
	6	127	-16.21	0.74	-5.58	1.02	-7.58	-3.58	<.0001
	8	125	-18.79	0.78	-7.09	1.08	-9.21	-4.97	<.0001

Source: Table 30 from Study 13267A CSR page 265/955

The LS mean changes from Baseline in MADRS total score are shown by study visit for all treatment groups in the following figure. Lu AA21004 20mg separated from placebo from Week 2 and 15mg from Week 4 onwards.

Figure 2: Change From Baseline in MADRS by Week (FAS, MMRM) - Study 13267A (Non-US)



Source: Figure 2.d page 55/185 of 2.7.3 Summary of Clinical Efficacy.
*=nominal p <0.050, **= nominal p <0.010, ***= nominal p <0.001 versus placebo. †††= p <0.001 versus placebo, statistically significant by hierarchical testing strategy.

The following table shows the change from baseline to endpoint and the effect size. The primary efficacy endpoint, the mean changes from baseline to Week 8 (endpoint) in MADRS total score were -17.2, -18.8, and -11.7 in the Lu AA21004 15mg, Lu AA21004 20mg, and placebo groups, respectively. Both Lu AA21004 15 and 20mg separated from placebo.

Table 32: Adjusted Changes from Baseline in MADRS Total Score at Week 8 (FAS, MMRM) - Study 13267A (Non-US)

	Placebo N=130	Lu AA21004		Duloxetine N=131
		15 mg QD N=118	20 mg QD N=125	
Δ LS mean change from baseline (SE)	-11.70 (0.76)	-17.23 (0.79)	-18.79 (0.78)	-21.15 (0.77)
LS mean differences from placebo (SE)		-5.53 (1.09)	-7.09 (1.08)	-9.45 (1.07)
95% CI for differences (lower, upper)		(-7.66, -3.40)	(-9.21, -4.97)	(-11.55, -7.35)
p-value, treatment vs. placebo		<0.0001	<0.0001	<0.0001

Source: compiled from Table 30 from Study 13267A CSR page 265/955

Secondary Efficacy Endpoints
The key secondary efficacy endpoints are shown in the following table. Both doses separated from placebo in change from baseline in total SDS score and in mean CGI-I.

Table 33: Change From Baseline in SDS Total Score and the Mean CGI-I Score at Week 8, Difference from Placebo (FAS) - Study 13267A (Non-US)

Endpoint (Week 8)	Difference From Placebo, P-value	
	Lu AA21004	
	15 mg	20 mg
Δ SDS total score	-3.2 ± 1.2, p=0.005	-3.9 ± 1.1, p<0.001
CGI-I score	-0.7 ± 0.1, p<0.001	-1.0 ± 0.1 p<0.001

Source: Table 2.o, page 54/185 of 2.7.3 Summary of Clinical Efficacy

6.3.2.4 - Study 315 (US)

Study Title
"A Phase 3, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Duloxetine-Referenced, Fixed-Dose Study Comparing the Efficacy and Safety of 2 Doses (15 and 20 mg) of Lu AA21004 in Acute Treatment of Adults with Major Depressive Disorder"

Objectives
To evaluate the efficacy, safety, and tolerability of Lu AA21004 (15 or 20 mg) compared with placebo in the 8-week treatment of MDD subjects aged 18-75 years.

Study Conduct Dates: 06/2010-02/2012

Study Sites
58 sites in the United States

Demographics
At baseline, the age, sex, race, weight, BMI, the baseline characteristics of smoking and alcohol consumption were comparable among treatment groups.

Twenty six percent (26%) of subjects were male. The mean age (SD) was 43 (12) years. 76.5% were Caucasian, 22.1% were Black and 1.1% were Asian. The mean weight (SD) was 88 (24) kg and the BMI 31 (9).

Baseline Disease Characteristics

The baseline disease characteristics which were demonstrated in Baseline MADRS total score and CGI-S rating were comparable among all the treatment groups (Table 34).

Table 34: Baseline Assessment Scores (FAS) - Study 315 (US)

Assessment	Mean (SD)				
	Placebo N=153	Lu AA21004		Duloxetine N=146	Total N=591
		15 mg N=145	20 mg N=147		
MADRS total	31.5 (4.2)	31.9 (4.1)	32.0 (4.4)	32.8 (4.3)	32.1 (4.3)
HAM-A total	17.0 (5.2)	17.5 (5.3)	17.7 (5.5)	18.2 (5.6)	17.6 (5.4)
CGI-S score	4.6 (0.6)	4.5 (0.6)	4.5 (0.6)	4.5 (0.6)	4.5 (0.6)

Source: Table 2.r, page 57/185 of 2.7.3 Summary of Clinical Efficacy

Subject Disposition

A total of 614 subjects were randomized to this 8-week treatment trial. The completion rate at Endpoint was 80.1%, 76.9%, 73.4% and 75.7% for placebo, LU AA21004 15 mg, 20 mg, and Duloxetine groups, respectively.

As expected, the number of subjects who withdrew prematurely due to lack of efficacy was higher in the placebo group and the number of subjects who withdrew prematurely due to AEs was higher in the LU AA21004 treatment group.

Table 35: Subject Disposition - Study 315 (US)

	Treatment n (%)				
	Placebo	LuAA21004		Duloxetine 60 mg	Total
		15 mg	20 mg		
Randomized (a)	161 (100)	147 (100)	154 (100)	152 (100)	614 (100)
Treated	159 (98.8)	147 (100)	154 (100)	150 (98.7)	610 (99.3)
Completed study	129 (80.1)	113 (76.9)	113 (73.4)	115 (75.7)	470 (76.5)
Early termination	32 (19.9)	34 (23.1)	41 (26.6)	37 (24.3)	144 (23.5)
Primary reasons for early termination					
Adverse events	4 (2.5)	14 (9.5)	14 (9.1)	10 (6.6)	42 (6.8)
Lack of efficacy	9 (5.6)	0	2 (1.3)	1 (0.7)	12 (2.0)
Noncompliance	1 (0.6)	3 (2.0)	4 (2.6)	1 (0.7)	9 (1.5)
Protocol deviations	4 (2.5)	3 (2.0)	3 (1.9)	2 (1.3)	12 (2.0)
Withdrawal of consent	5 (3.1)	5 (3.4)	4 (2.6)	6 (3.9)	20 (3.3)
Lost to follow-up	8 (5.0)	8 (5.4)	11 (7.1)	15 (9.9)	42 (6.8)
Other	1 (0.6)	1 (0.7)	3 (1.9)	2 (1.3)	7 (1.1)
FAS	153	145	147	146	591

Source: Table 2.q, page 57/185 of 2.7.3 Summary of Clinical Efficacy
(a) Percentages are based on all randomized subjects.

Concomitant Medication Use

Overall, 4.3% in placebo and 4.1% in Lu AA21004 15 mg and 1.9% in Lu AA21004 20 mg group took disallowed concomitant medications according to sponsor's response dated on May 17, 2013.

One point two percent (1.2%) in placebo and 0.7% in Lu AA21004 15 mg and 0% in Lu AA21004 20 mg group took antidepressants (fluoxetine hydrochloride and/or trazadone) during the double-blind treatment period.

Protocol Deviations

In the clinical study report, the Sponsor indicated that 11 subjects (6.8%) in placebo, 20 subjects (13.6%) in Lu AA21004 15 mg, and 19 subjects (12.3%) in Lu AA21004 20mg, and 18 subjects (11.8%) in Duloxetine group had at least 1 major protocol violation.

Twelve subjects (2.0%) had protocol deviations as the primary reason leading to study discontinuation: 4 subjects (2.5%) in placebo, 3 subjects (2.0%) in Lu AA21004 15 mg, 3 subjects (1.9%) in Lu AA21004 20 mg and 2 subjects (1.3%) in duloxetine 60 mg.

Efficacy Findings

Primary Efficacy Endpoint

The change from Baseline in MADRS total score at each Week is shown in the following table. In each treatment group, bigger changes were observed with longer treatment.

Table 36: LS Mean (SE) Change from Baseline by Week in MADRS Total Score (FAS, MMRM) - Study 315 (US)

Week	Placebo	Lu AA21004		Duloxetine 60mg
		15mg	20mg	
1	-4.3 (0.47)	-4.7 (0.48)	-4.9 (0.47)	-5.2 (047)
2	-7.1 (0.59)	-9.0 (0.62)	-8.9 (0.61)	-9.2 (0.62)
4	-10.6 (0.72)	-12.0 (0.76)	-12.5 (0.75)	-12.1 (0.76)
6	-11.5 (0.78)	-13.1 (0.83)	-14.8 (0.82)	-14.6 (0.82)
8	-12.8 (0.83)	-14.3 (0.89)	-15.6 (0.88)	-16.9 (0.88)

Source: End of Text Tables and Figures, Table 15.2.1.1.5 (pg. 198-199)

The primary efficacy endpoint, change from Baseline in MADRS total score at Week 8 is shown Table 37. Only Lu AA21004 20 mg separated from placebo at the endpoint with LS Mean difference from placebo of -2.8 points.

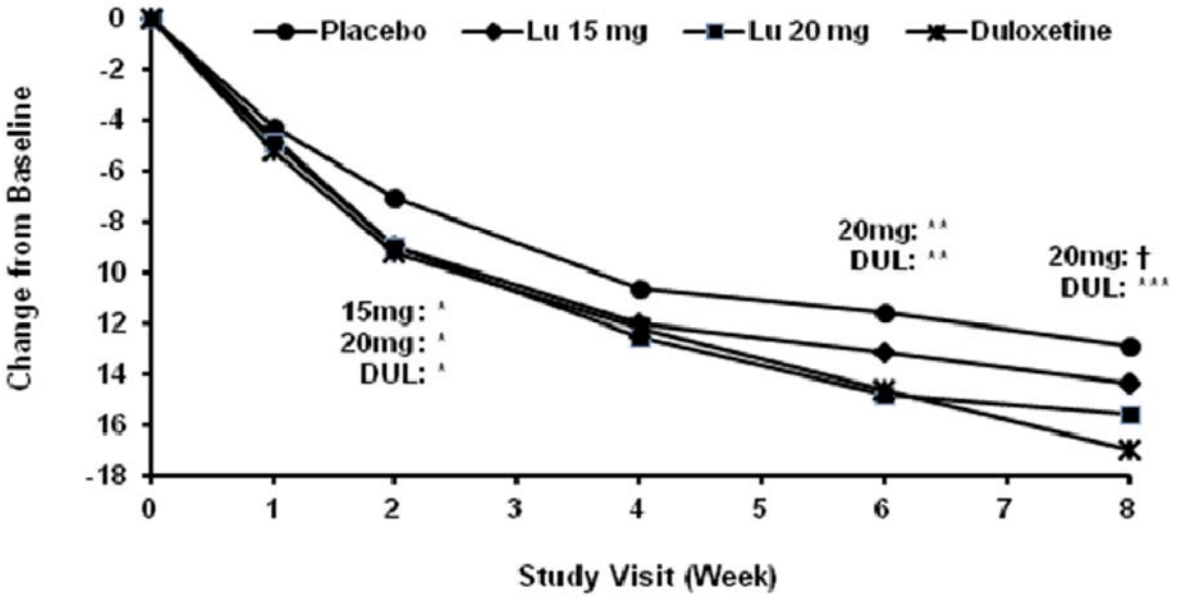
Table 37: Change From Baseline in MADRS Total Score at Week 8 (FAS, MMRM) - Study 315 (US)

	Placebo N=153	Lu AA21004		Duloxetine 60 mg N=146
		15 mg QD N=145	20 mg QD N=147	
Δ LS mean change from baseline (SE)	-12.83 (0.834)	-14.30 (0.890)	-15.57 (0.880)	-16.90 (0.884)
LS mean differences from placebo (SE)		-1.5 (1.21)	-2.8 (1.21)	-4.1 (1.21)
95% CI for differences		(-3.86, 0.91)	(-5.12, -0.38)	(-6.46, -1.69)
p-value, treatment vs. placebo		0.224	0.023 (<0.05)	<0.001

Source: compiled from table 11.f, Study 315 clinical study report, page 81/128

The LS mean changes from Baseline MADRS total score by study visit are shown in the following figure. Lu AA21004 20mg separated from placebo at Week 6 and onwards.

Figure 3: Change From Baseline in MADRS Total Score by Week (FAS, MMRM) - Study 315 (US)



Source: Figure 2.e page 59/185 of 2.7.3 Summary of Clinical Efficacy
*=nominal p <0.050, **= nominal p <0.010, ***= nominal p <0.001 versus placebo. †= p <0.025 versus placebo, statistically significant based on testing strategy.

The Key Secondary Efficacy Endpoint
Neither CGI-I nor change from baseline in SDS total score separated from placebo at Lu AA21004 15 or 20 mg dose.

Table 38: Change From Baseline in SDS Total Score and the Mean CGI-I Score at Week 8, Difference from Placebo (FAS, MMRM) - Study 315 (US)

	Difference From Placebo, P-value	
	Lu AA21004	
Endpoint (Week 8)	**15 mg**	**20 mg**
Δ SDS total score	-0.1 ± 1.11, p=0.962	-0.9 ± 1.10, p=0.427
CGI-I score	-0.1 ± 0.14, p=0.400	-0.2 ± 0.14, p=0.177

Source: Table 2.s, page 58/185 of 2.7.3 Summary of Clinical Efficacy

6.3.2.5 - Study 316 (US)

Study Title
"A Phase 3, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Fixed-Dose Study Comparing the Efficacy and Safety of 2 Doses (10 and 20 mg) of Lu AA21004 in Acute Treatment of Adults with Major Depressive Disorder"

Objectives
To evaluate the efficacy, safety, and tolerability of Lu AA21004 (10 mg and 20 mg) compared with placebo in the 8-week treatment of MDD subjects aged 18-75 years.

Study Conduct Dates: 07/2010-01/2012

Study Sites
37 sites in the United States

Demographics
At baseline, the age, sex, ethnicity, race, BMI and the duration of current MDD episode were roughly comparable among treatment groups.

The mean age (SD) at Baseline was 43 (12) years. 27% of the subjects were male and 73% female. The majority of the subjects were Caucasian (70%), 28% were Black, and <1% were Asian. The BMI (SD) was 30 (8) with 53% of subjects had BMI ≥ 30. 60% had the duration of current MDD episode ≥ 24 weeks.

Baseline Disease Characteristics

The baseline disease characteristics which were demonstrated in Baseline MADRS total score and CGI-S rating were comparable among all the treatment groups (Table 39).

Table 39: Baseline Assessment Scores (FAS) - Study 316 (US)

Assessment	Mean (SD)			
	PBO N=155	Lu AA21004		Total N=457
		10 mg N=154	20 mg N=148	
MADRS total score	32.0 (4.0)	32.2 (4.5)	32.5 (4.3)	32.2 (4.3)
HAM-A total score	17.6 (5.3)	18.5 (5.3)	19.0 (5.7)	18.4 (5.4)
CGI-S score	4.5 (0.6)	4.5 (0.6)	4.5 (0.5)	4.5 (0.6)

Source: Table 2.v, page 61/185 of 2.7.3 Summary of Clinical Efficacy
Note: A MADRS total score ≥26 and a CGI-S score ≥4 were inclusion criteria.

Subject Disposition
A total of 462 subjects were randomized to this 8-week treatment trial. The completion rate at Endpoint was 88.5%, 80.0%, and 81.3% for placebo, Lu AA21004 10 mg, and 20 mg groups, respectively.

Surprisingly, LU AA21004 10 mg group had the highest withdrawal due to both AEs and lack of efficacy.

Table 40: Subject Disposition - Study 316 (US)

	Treatment n (%)			
	Placebo	LuAA21004		Total
		10 mg	20 mg	
Randomized (a)	157 (100)	155 (100)	150 (100)	462 (100)
Treated	157 (100)	155 (100)	150 (100)	462 (100)
Completed study	139 (88.5)	124 (80.0)	122 (81.3)	385 (83.3)
Early termination	18 (11.5)	31 (20.0)	28 (18.7)	77 (16.7)
Reasons for early termination				
Adverse events (b)	2 (1.3)	9 (5.8)	7 (4.7)	18 (3.9)
Lack of efficacy	1 (0.6)	3 (1.9)	1 (0.7)	5 (1.1)
Noncompliance with IMP	0	2 (1.3)	0	2 (0.4)
Protocol deviations	2 (1.3)	2 (1.3)	5 (3.3)	9 (1.9)
Withdrawal of consent	5 (3.2)	7 (4.5)	3 (2.0)	15 (3.2)
Lost to follow-up	7 (4.5)	7 (4.5)	10 (6.7)	24 (5.2)
Other	1 (0.6)	1 (0.6)	2 (1.3)	4 (0.9)
FAS	155	154	148	457

Source: Table 2.u, page 61/185 of 2.7.3 Summary of Clinical Efficacy

Concomitant Medication Use

One subject in each of Lu AA21004 10 mg (0.6%), 20 mg (0.7%), and placebo (0.6%) group took antidepressants during the double blind treatment period according to the sponsor's response dated May 17, 2013.

No subjects in treatment group took antipsychotics that would have affected the overall efficacy results. Some subjects in placebo and Lu AA21004 treatment group used benzodiazepine derivatives and benzodiazepine related drugs for insomnia and most used for a short period of time, which was acceptable.

Protocol Deviations

In the clinical study report, the Sponsor indicated that 10 subjects (6.4%) in placebo, 16 subjects (10.3%) in Lu AA21004 10 mg, 14 subjects (9.3%) in Lu AA21004 20 mg group had at least 1 major protocol violation.

A total of 9 subjects (1.9%) had protocol deviations as the primary reason leading to study discontinuation: 2 subjects (1.3%) in placebo, 2 subjects (1.3%) Lu AA21004 10 mg and 5 subjects (3.3%) in Lu AA21004 20 mg

Efficacy Findings

Primary Efficacy Endpoint

The change from Baseline in MADRS total score at each week is shown in the following table. In each treatment group, bigger changes were observed with longer treatment.

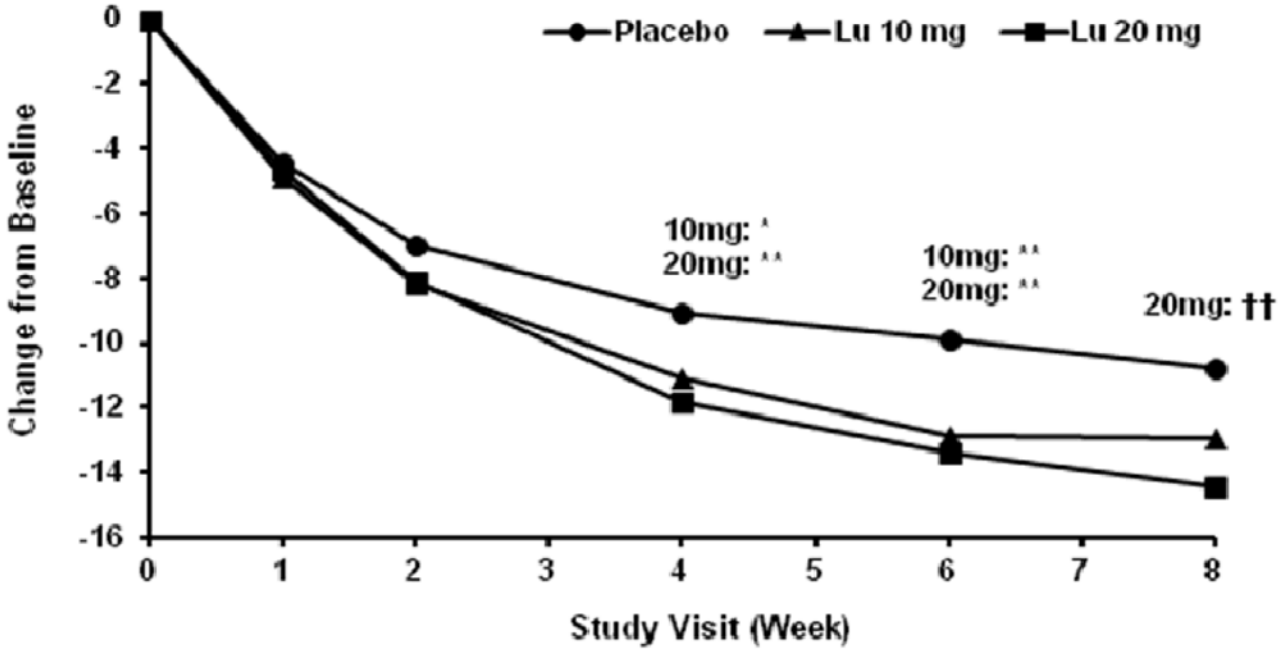
Table 41: LS Mean (SE) Change from Baseline by Week in MADRS Total Score (FAS, MMRM) - Study 316 (US)

Week	Placebo	Lu AA21004	
		10mg	20mg
1	-4.4 (0.50)	-4.8 (0.50)	-4.7 (0.51)
2	-6.9 (0.61)	-8.2 (0.61)	-8.1 (0.63)
4	-9.1 (0.71)	-11.1 0(.72)	-11.8 (0.74)
6	-9.9 (0.75)	-12.9 (0.77)	-13.4 (0.78)
8	-10.8 (0.81)	-13.0 (0.83)	-14.4 (0.85)

Source: Study 316: End of Text Tables and Figures, Table 15.2.1.1.5 (pg. 178-180)

The LS mean change from Baseline in MADRS total score by study visit is shown in the following figure. Lu AA21004 20 mg separated from placebo at Week 4 and onwards.

Figure 4: Change From Baseline in MADRS by Week (FAS, OC, MMRM) - Study 316 (US)



Source: Figure 2.f page 63/185 of 2.7.3 Summary of Clinical Efficacy
††=statistically significant versus placebo by hierarchical testing strategy (p=0.002).
*=nominal p <0.050, **= nominal p <0.010 versus placebo.

The primary efficacy endpoint, change from Baseline in MADRS total score at Week 8 is shown in the following table. Only Lu AA21004 20 mg separated from placebo at the endpoint with a mean difference from placebo of -3.6 points.

Table 42: Change From Baseline in MADRS Total Score at Week 8 (FAS, MMRM) – Study 316 (US)

	Placebo N=155	Lu AA21004	
		10 mg QD N=154	20 mg QD N=148
Δ LS mean Change from Baseline (SE)	-10.77 (0.807)	-12.96 (0.832)	-14.41 (0.845)
LS mean differences from placebo (SE)		-2.19 (1.151)	-3.64 (1.161)
95% CI for differences (lower, upper)		(-4.45, - 0.08)	(-5.92, -1.35)
p-value, treatment vs. placebo		0.058	0.002 (<0.05)

Source: compiled from Study 316 clinical study report, table 11.f, page 77/131

Key Secondary Efficacy Endpoint
Lu AA21004 20 mg separated from placebo in both the change from Baseline in SDS total score and CGI-I score. Lu AA21004 10 mg did not separate from placebo in either secondary endpoint.

Table 43: Change From Baseline in SDS total score and the Mean CGI-I score at Week 8 (FAS, MMRM) - Study 316 (US)

	Difference From Placebo, P-value	
	Lu AA21004	
Endpoint (Week 8)	10 mg	20 mg
Δ SDS total score	-1.39 ± 1.04, p=0.183	-2.4 ± 1.07, p=0.025
Mean CGI-I score	-0.2 ± 0.13, p=0.119	-0.3 ± 0.13, p=0.024

Source: compiled from Table 2.w, page 62/185 of 2.7.3 Summary of Clinical Efficacy

6.3.2.6 - Study 12541A (Elderly, US and Non-US)

Study Title
"Randomized, double-blind, parallel-group, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in acute treatment of Major Depressive Disorder in elderly patients"

Primary Objective
To evaluate the efficacy, safety, and tolerability of Lu AA21004 (5 mg) compared with placebo in the 8-week treatment of MDD subjects aged ≥65 years.

Study Conduct Dates: 01/2009 - 02/2010

Study Sites
81 sites in Canada, Finland, France, Germany, Sweden, Ukraine, and the United States

Demographics
At baseline, the sex, age, race profile, weight and BMI were roughly comparable among treatment groups.

About 1/3 of each group were male subjects. The mean age (SD) at Baseline was 71 (5) years. Most subjects (93% to 96%) were Caucasian, which was consistent with the race profile in the study regions.

At Baseline, for male, the mean weight (SD) was 85 (15) kg and the BMI 28 (5). For female, the mean weight (SD) was 73 (15) kg and the BMI 28 (5). The mean BMI in US subjects was 29 kg/m^2 compared with 27 kg/m^2 in non-US subjects.

Baseline Disease Characteristics

The baseline disease characteristics which were demonstrated in Baseline MADRS total score and CGI-S rating were comparable among all the treatment groups (Table 44).

Table 44: Baseline Assessment Scores (FAS) - Study 12541A (Elderly, US and Non-US)

Variable Mean (SD)	Placebo N=145	Lu AA21004 5 mg N=155	Duloxetine N=148
MADRS total score (a)	30.3 (3.2)	30.7 (3.6)	30.4 (3.1)
HAM-D24	29.4 (5.1)	29.2 (5.0)	28.5 (4.9)
HAM-A	19.5 (5.7)	19.9 (5.8)	19.2 (6.5)
CGI-S	4.7 (0.7)	4.8 (0.7)	4.7 (0.8)

(a) A MADRS total score ≥26 at Baseline was an inclusion criterion.
Source: Table 2.ll, page 78/185 of 2.7.3 Summary of Clinical Efficacy

Subject Disposition

A total of 453 subjects were randomized to this 8-week treatment trial. The completion rate at Endpoint was 88.3%, 87.2%, and 84.8% for placebo, LU AA21004 5 mg, and Duloxetine group, respectively.

As expected, the placebo group had the highest premature withdrawal due to lack of efficacy and the LU AA21004 5 mg treatment group had more premature withdrawal due to AEs compared to placebo.

Table 45: Subject Disposition - Study 12541A (Elderly, US and Non-US)

	Treatment n (%)			
	Placebo	Lu AA21004 5 mg	Duloxetine	Total
Subjects randomized	145	157	151	453
Subjects treated (a)	145 (100)	156 (100)	151 (100)	452 (100)
Subjects completed	128 (88.3)	136 (87.2)	128 (84.8)	392 (86.7)
Subjects withdrawn	17 (11.7)	20 (12.8)	23 (15.2)	60 (13.3)
Reason for withdrawal				
Adverse event	6 (4.1)	10 (6.4)	15 (9.9)	31 (6.9)
Lack of efficacy	7 (4.8)	2 (1.3)	0	9 (2.0)
Protocol deviations	3 (2.1)	3 (1.9)	2 (1.3)	8 (1.8)

	Treatment n (%)			
	Placebo	Lu AA21004 5 mg	Duloxetine	Total
Withdrawal of consent	1 (0.7)	2 (1.3)	2 (1.3)	5 (1.1)
Lost to follow-up	0	0	2 (1.3)	2 (0.4)
Other	0	3 (1.9)	2 (1.3)	5 (1.1)
FAS	145	155	148	448

(a) Percentages are based on all treated subjects.
Source: Table 2.kk, page 77/185 of 2.7.3 Summary of Clinical Efficacy

Concomitant Medication Use

No subjects in treatment group took antidepressants or antipsychotics that would have affected the overall efficacy results. 6.2% in placebo and 8.3% in Lu AA21004 5 mg used disallowed concomitant benzodiazepine derivatives and benzodiazepine related drugs for insomnia.

Protocol Deviations

This reviewer examined the Inclusion/Exclusion/Withdrawal Criteria Deviations (Panels 15), Procedural Compliance Deviations (Panels 16) and Exclusions from Analysis Sets (Panels 17) in the clinical study report and found the handling of the deviations adequate.

Efficacy Findings

Primary Efficacy Endpoint

The change from Baseline in HAM-D-24 total score at each Week is shown in the following table. In each treatment group, more changes were observed with longer treatment.

Table 46: Mean Change from Baseline in HAM-D-24 Total Score by Week (FAS, LOCF, ANCOVA) - Study 12541A (Elderly, US and Non-US)

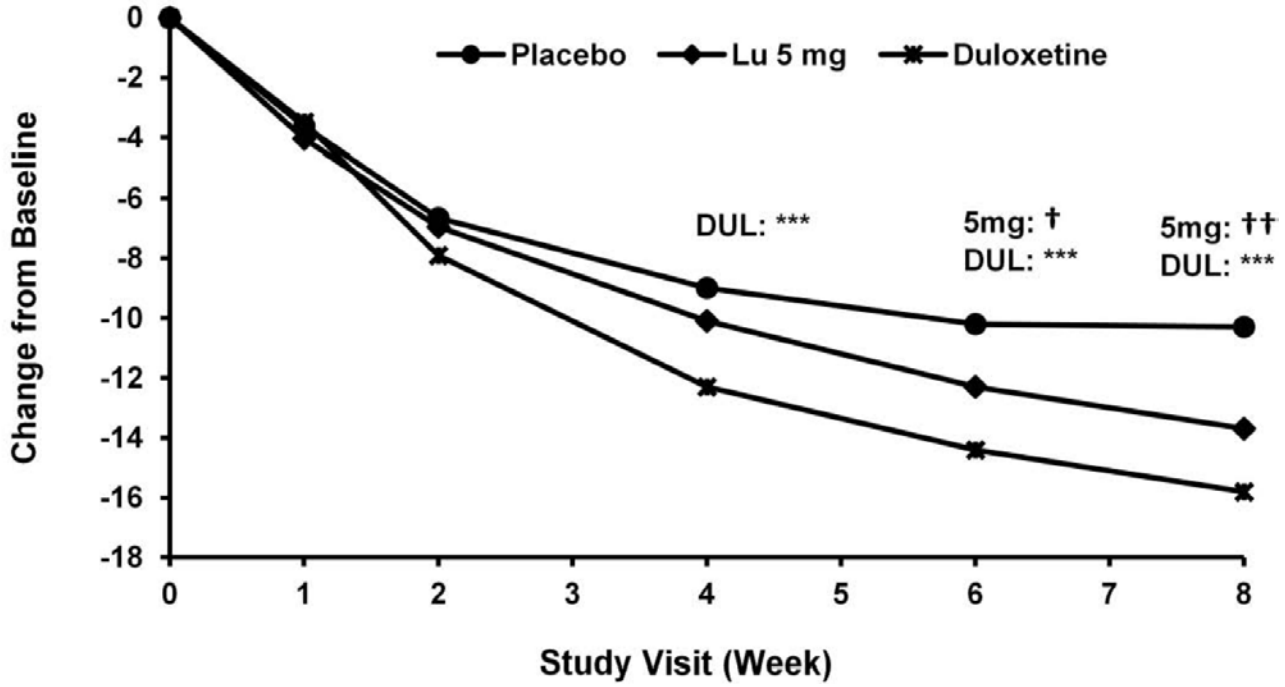
Treatment Group	Week	N	Mean	SE	Difference to Placebo				
					Mean	SE	95% CI		p-value
							Lower	Upper	
PBO	1	145	-3.62	0.41					
	2	145	-6.66	0.53					
	4	145	-8.99	0.64					
	6	145	-10.2	0.71					
	8	145	-10.3	0.76					
DUL	1	147	-3.48	0.41	0.14	0.56	-0.95	1.24	0.7971
	2	148	-7.91	0.52	-1.25	0.72	-2.65	0.16	0.0827
	4	148	-12.3	0.63	-3.30	0.86	-4.99	-1.60	0.0002
	6	148	-14.4	0.70	-4.22	0.96	-6.10	-2.34	<.0001
	8	148	-15.8	0.75	-5.48	1.03	-7.50	-3.46	<.0001

Treatment Group	Week	N	Mean	SE	Difference to Placebo				
					Mean	SE	95% CI		p-value
							Lower	Upper	
5mg	1	154	-4.04	0.40	-0.42	0.55	-1.49	0.66	0.4482
	2	155	-6.95	0.51	-0.28	0.70	-1.67	1.10	0.6879
	4	155	-10.1	0.62	-1.06	0.85	-2.72	0.61	0.2134
	6	155	-12.3	0.69	-2.13	0.94	-3.98	-0.28	0.0240
	8	155	-13.7	0.74	-3.32	1.01	-5.31	-1.34	0.0011

Source: Study 12541A Clinical Study Report Table 34 (pg. 231)

The LS mean changes from Baseline HAM-D24 total score by study visit are shown in the following figure. Lu AA21004 5mg separated from placebo at Week 6 and onwards.

Figure 5: Change From Baseline in HAM-D24 by Study Visit (FAS, LOCF, ANCOVA) - Study 12541A (Elderly, US and Non-US)



Source: Figure 2.j page 80/185 of 2.7.3 Summary of Clinical Efficacy
†=p <0.05, ††=p <0.010 versus placebo, statistically significant by testing strategy.
***=nominal p <0.001 versus placebo.

The primary endpoint was the mean change from baseline to endpoint (Week 8) on the HAM-D24 total score. The pre-defined statistical method was analysis of covariance (ANCOVA), with treatment and center as fixed factors, baseline HAM-D24 total score as covariate, and using last observation carried forward (LOCF) technique. Lu AA21004 5 mg separated from placebo. The effect size was -3.3, which was statistically significant.

Table 47: Mean Change from Baseline in HAM-D-24 Total Score at Week 8 (FAS, LOCF, ANCOVA) - Study 12541A (Elderly, US and Non-US)

	Placebo N=145	Lu AA21004 5 mg QD N=155	Duloxetine N=148
Δ LS mean change from baseline (SE)	-10.3 (0.76)	-13.7 (0.74)	-15.8 (0.75)
LS mean differences from placebo (SE)		-3.32 (1.01)	-5.48 (1.03)
95% CI for differences (lower, upper)		(-5.31, -1.34)	(-7.50, -3.46)
p-value, treatment vs. placebo		0.0011	<0.0001

Source: compiled from Table 34 in Study 12541A clinical study report, page 232/885

Secondary Efficacy Analysis Results

The results of MMRM and ANCOVA, LOCF analyses of the secondary efficacy variables were statistically significant for Lu AA21004 5 mg.

Table 48: Secondary Efficacy Analyses at Week 8, Difference From Placebo (FAS) - Study 12541A (Elderly, US and Non-US)

Variable LS Mean	ANCOVA, LOCF	
	Lu AA21004 5 mg N=155	Duloxetine N=148
ΔCGI-S score, p-value	-0.6, p <0.001	-1.0, p <0.001
CGI-I score, p-value	-0.6, p <0.001	-0.8, p <0.001

Source: compiled from Table 2.nn, page 80/185 of 2.7.3 Summary of Clinical Efficacy
***=nominal p <0.001 vs. placebo.

Approximately one-third of the subjects (171/448) in this study were enrolled in the United States. The results of regional analyses by ANCOVA, LOCF and MMRM methods are summarized in the following table. The effect size of Lu AA21004 5 mg was very small in US region based on HAM-D24 total score (-0.7 by ANCOVA, LOCF and -1.9 by MMRM) compared to -4.9 and -5.0 in non-US regions.

Table 49: Primary and Secondary Efficacy Analyses by Region, Difference from Placebo at Endpoint (FAS) - Study 12541A (Elderly, US and Non-US)

Analysis Method Efficacy Variable	US			Non-US		
	PBO (a) N=54	Difference From PBO LS Mean		PBO (a) N=91	Difference From PBO LS Mean	
		Lu AA21004 5 mg N=57	DUL N=60		Lu AA21004 5 mg N=98	DUL N=88
ANCOVA, LOCF						
Δ HAM-D24 total score	-10.1	-0.7	-2.8	-10.5	-4.9***	-7.1***
Δ CGI-S score	-0.9	-0.4	-0.7**	-1.1	-0.8**	-1.2***
CGI-I score (b)	2.9	-0.4	-0.8**	2.9	-0.7***	-0.9***
MMRM						
Δ HAM-D24 total score	-10.5	-1.9	-3.5*	-11.1	-5.0***	-7.7***
Δ CGI-S score	-0.9	-0.5*	-0.9**	-1.3	-0.7***	-1.3***
CGI-I score (b)	2.9	-0.5*	-0.9***	2.8	-0.6***	-1.0***

Source: compiled from Table 2.oo, page 81/185 of 2.7.3 Summary of Clinical Efficacy

PBO: placebo, DUL: Duloxetine.
*=nominal p <0.05; **=nominal p<0.01; ***=nominal p<0.001 versus placebo.
(a) LS mean change from Baseline, except for CGI-I.
(b) Mean CGI-I score at Week 8.
ANCOVA, LOCF was the pre-defined statistical method to analyze the efficacy.

6.3.3 Conclusions of MDD Short-Term Studies

Six (6) out of 10 MDD short-term studies were positive, which included 2 US studies, 3 non-US studies and one study (12541A, elderly) that was conducted in both US and non-US.

The sponsor demonstrated the efficacy of Lu AA21004 20 mg in US and Lu AA21004 5-20 mg in Non-US subjects with MDD.

6.4 Crosscutting Issues of MDD Short-Term Studies

6.4.1 Subgroup Analyses

This section presents the subgroup analyses of the pooled data of positive studies.

The sponsor conducted the subgroup analyses in the categories of demographic, disease characteristic and geographic region, as shown in the following table.

Table 50: Categories for Subgroup Analyses

Characteristic	Subgroups
Demographic	
Age	<65, ≥65 years
Sex	male, female
Race	White, Black, Asian, Other
BMI	<25, 25-<30, ≥30 kg/m^2
Disease Characteristic	
Baseline MADRS	<30, 30-33, ≥34
Baseline HAM-A	<20, ≥20
Duration of current MDE	<24, ≥24 weeks
Geographic region	US, non-US

BMI=body mass index
Source: 2-7-3 Summary of Clinical Efficacy, Table 1.I, page 37/185

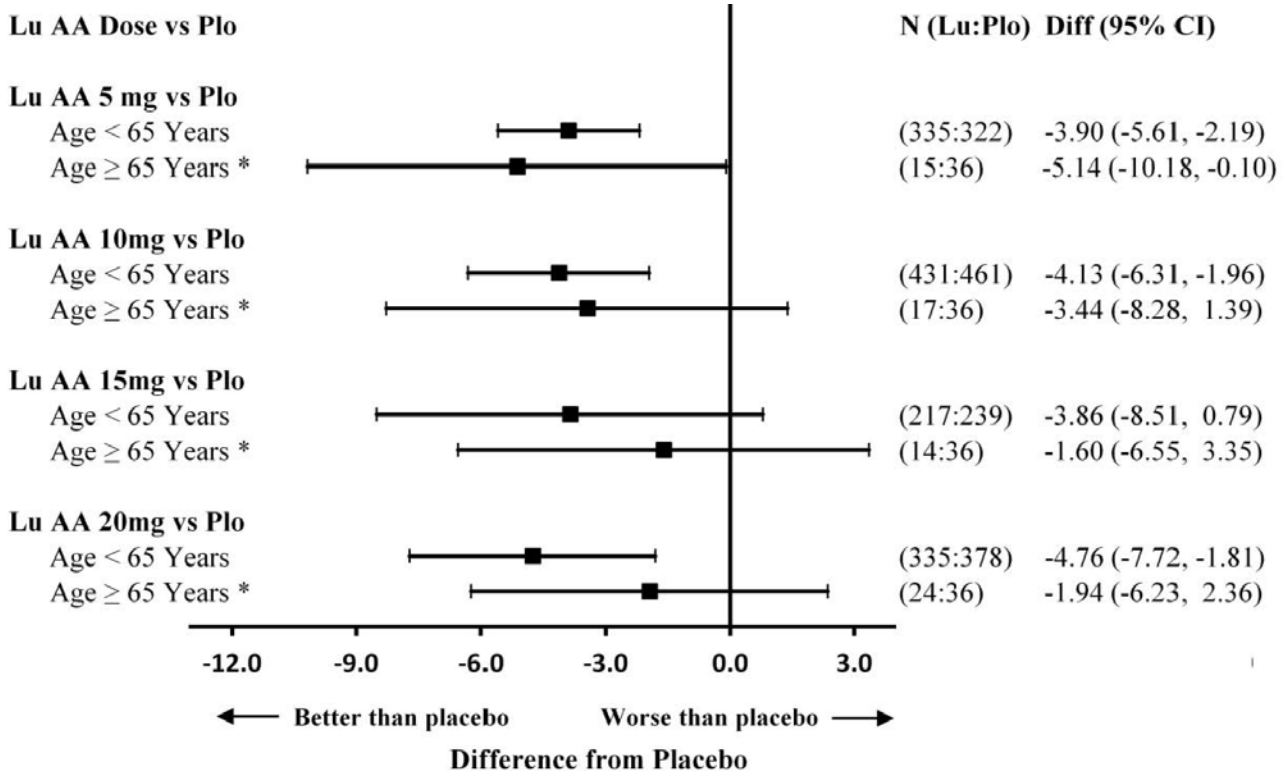
Demographic

Age

The sponsor provided the following figure to show the treatment effects on change from Baseline in MADRS Total Score at Week 6/8 by age from the positive/supportive studies in adults (FAS, MMRM). The results from the elderly study were not included in this analysis.

Age ≥ 65 appeared to have a smaller treatment effect in all Lu AA21004 doses except 5mg.

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

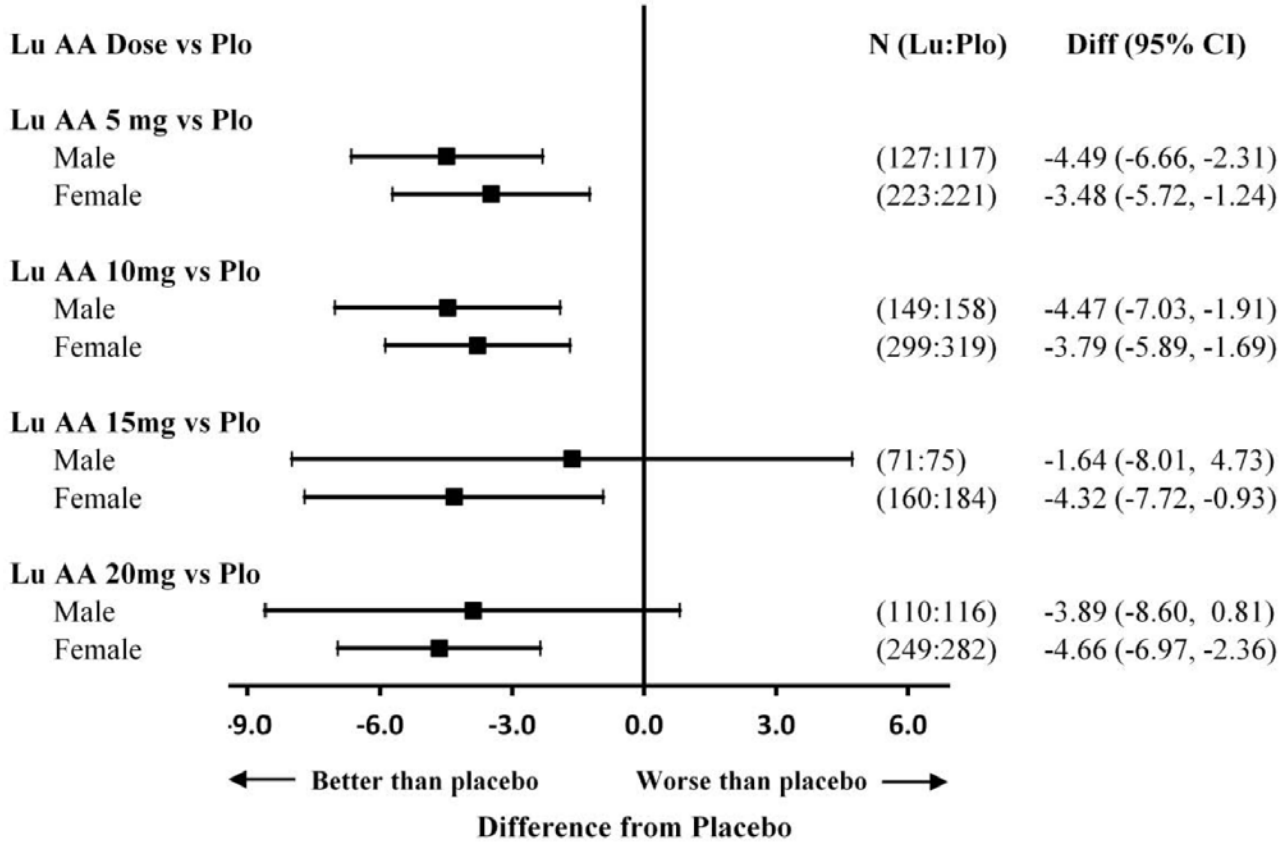


Source: Figure 3.k, page 122/185 of 2-7-3 Summary of Clinical Efficacy
*: based on Pooled ANCOVA analysis due to small number of subjects among the treatment groups.

Sex

Female subjects appeared to have smaller treatment effects in smaller doses (5 and 10 mg), and larger treatment effects in larger doses (15 and 20 mg) compared to male subjects.

Figure 7: Treatment Effect on Change from Baseline in MADRS Total Score at Week 6/8 by Sex, Positive/Supportive Studies in Adults (FAS, MMRM)

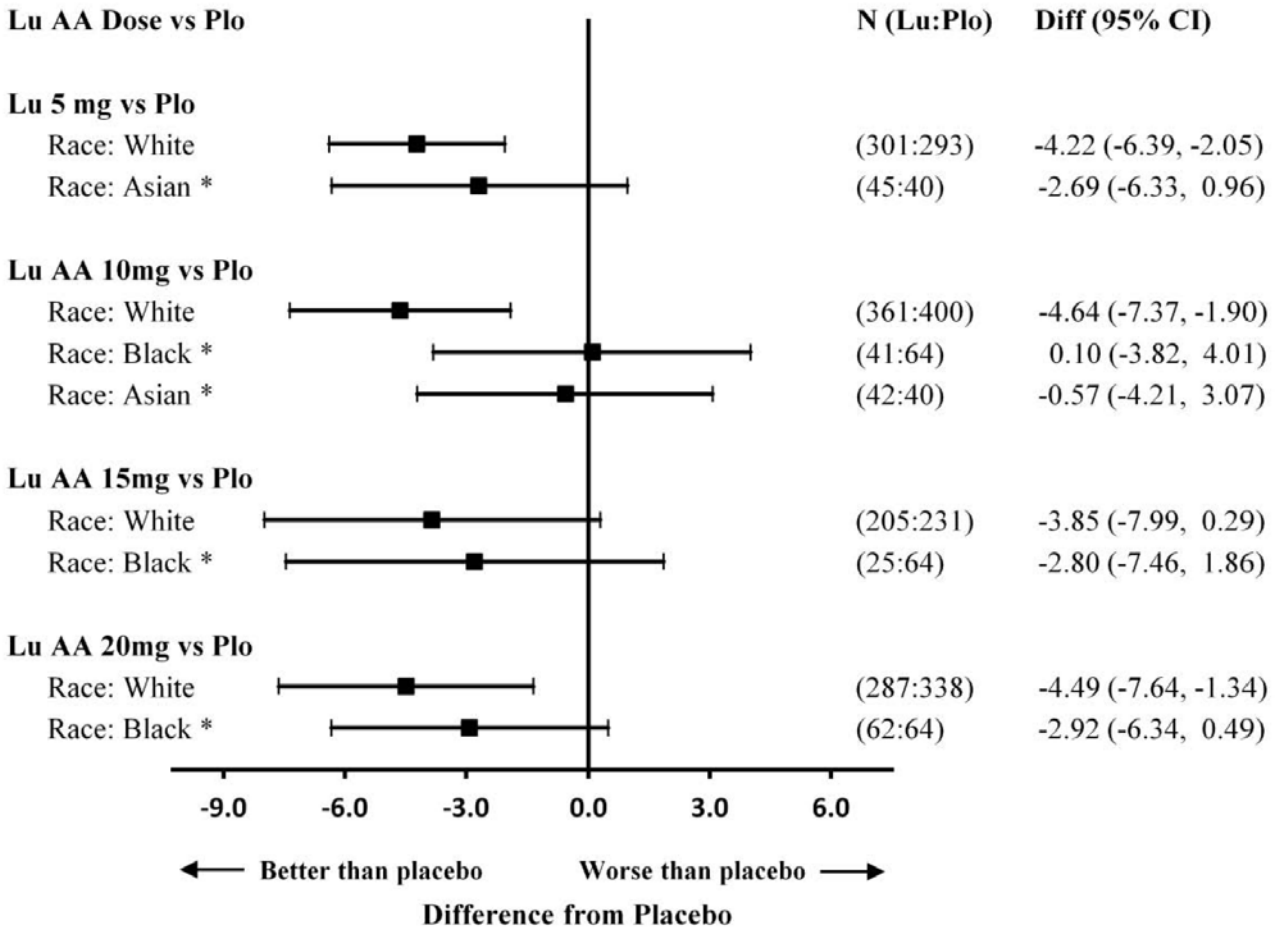


Source: Figure 3.l, page 123/185 of 2-7-3 Summary of Clinical Efficacy

Race

White appeared to have better treatment effects in all doses studied compared to Black or Asian.

Figure 8: Treatment Effect on Change from Baseline in MADRS Total Score at Week 6/8 by Race, Positive/Supportive Studies in Adults (FAS)



Source: Figure 3.m, page 125/185 of 2-7-3 Summary of Clinical Efficacy
*: based on Pooled ANCOVA analysis due to small number of subjects among the treatment groups.

BMI

Overweight subjects did better than normal weight and obesity in treatment effects across treatment groups.

We observed that US subjects were heavier (BMI: 30-31, obese) compared to non-US subjects (BMI: 25-25, overweight). In the elderly study, the weight difference was small: the BMI was 28.9 and 27 in North America and non-North America. Our statistician Dr. George Kordzakhia summarizes the weight and BMI of the 6 positive short-term studies in Table 51 (next page).

We speculated that the BMI difference among US and non-US subjects might contribute to the regional treatment effect difference and might explain why lower doses (5-15 mg) did not work in US. However, the analyses of treatment effects and BMI did not support.

Table 51: Mean Weight and BMI of the 6 Positive Short-Term Studies

Weight (kg) BMI	Placebo	Lu AA21004 (mg)				Duloxetine 60mg
		5	10	15	20	
11492A (non-US)						
Weight	75.2	72.9	71.7			
BMI	26	25.2	24.8			
305 (outside North America)						
Weight	75.2	75.4	74.6			
BMI	26.4	26.4	26.2			
13267A (outside North America)						
Weight	77.1			73.1	74.4	74.8
BMI	27.0			25.7	25.8	26.3
315 (US)						
Weight	88.6			87.4	87.4	87.2
BMI	31.1			31.3	31.0	31.5
316 (US)						
Weight	88.3		89.0		87.1	
BMI	31.3		31.9		30.8	
12541A (elderly, US and non-US)						
Weight (US)	81.0	81				81.2
Weight (non-US)	74.4	76.0				73.8
BMI (US)	28.9	28.9				29.2
BMI (non-US)	27.0	27.1				26.7

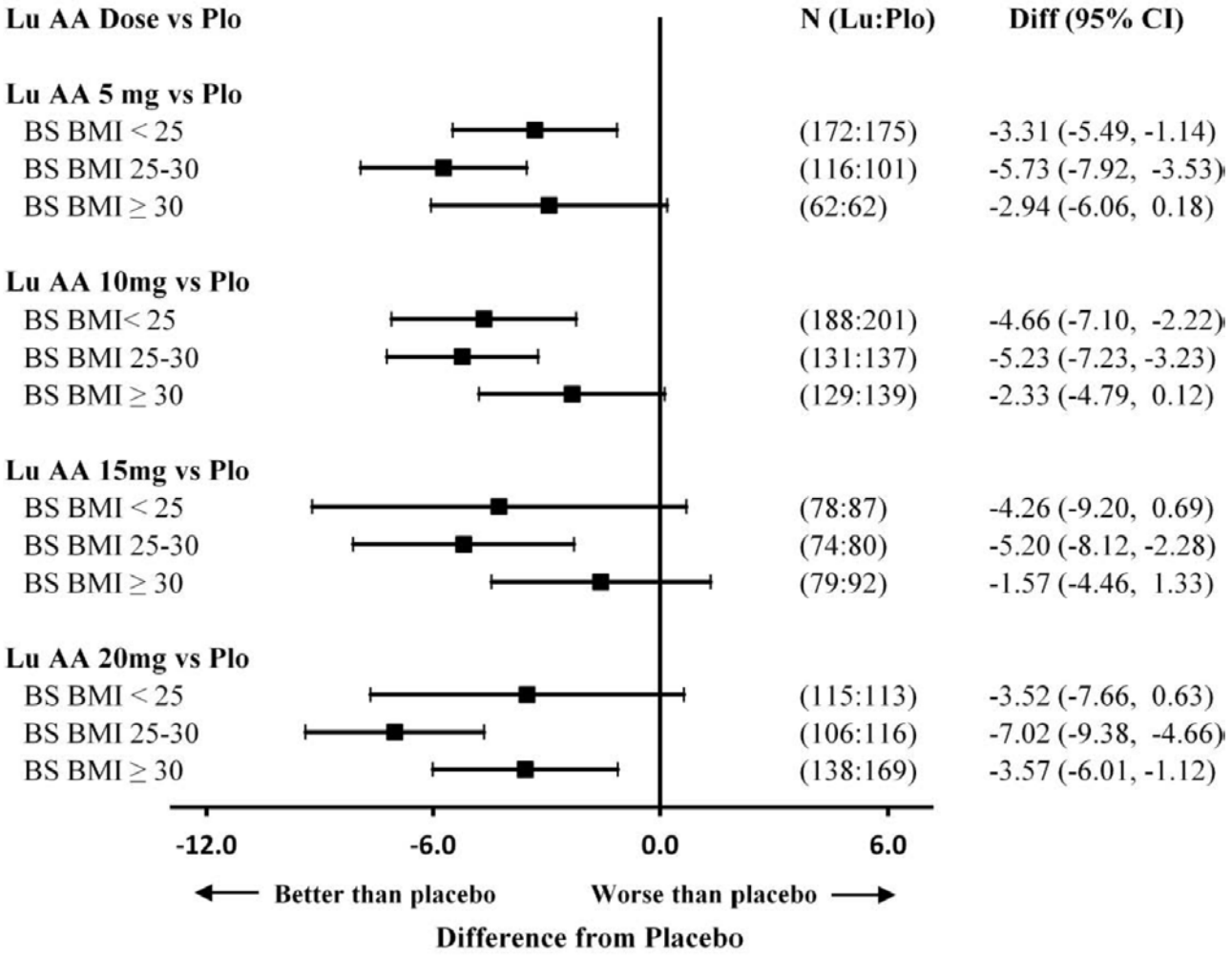
Source: summarized by FDA statistician Dr. George Kordzakhia

The sponsor analyzed the results of positive studies by dose and BMI category shown in Figure 10.

It appears that in each dose group, overweight subjects (BMI 25-30) did better than normal weight (BMI < 25) and obese subjects (BMI ≥ 30). In 20 mg dose, normal weight and obese group did equally worse than overweight group. This finding did not support the speculation that lower doses did not work in US because US subjects were more obese.

In addition, in the elderly study (12541A), the minimal BMI difference among US and non-US (28.9 vs. 27.1) could not explain the big treatment effect among US and non-US region (-0.7 vs. -4.9).

Figure 9: Treatment Effect on Change from Baseline in MADRS Total Score at Week 6/8 by BMI, Positive/Supportive Studies in Adults (FAS, MMRM)



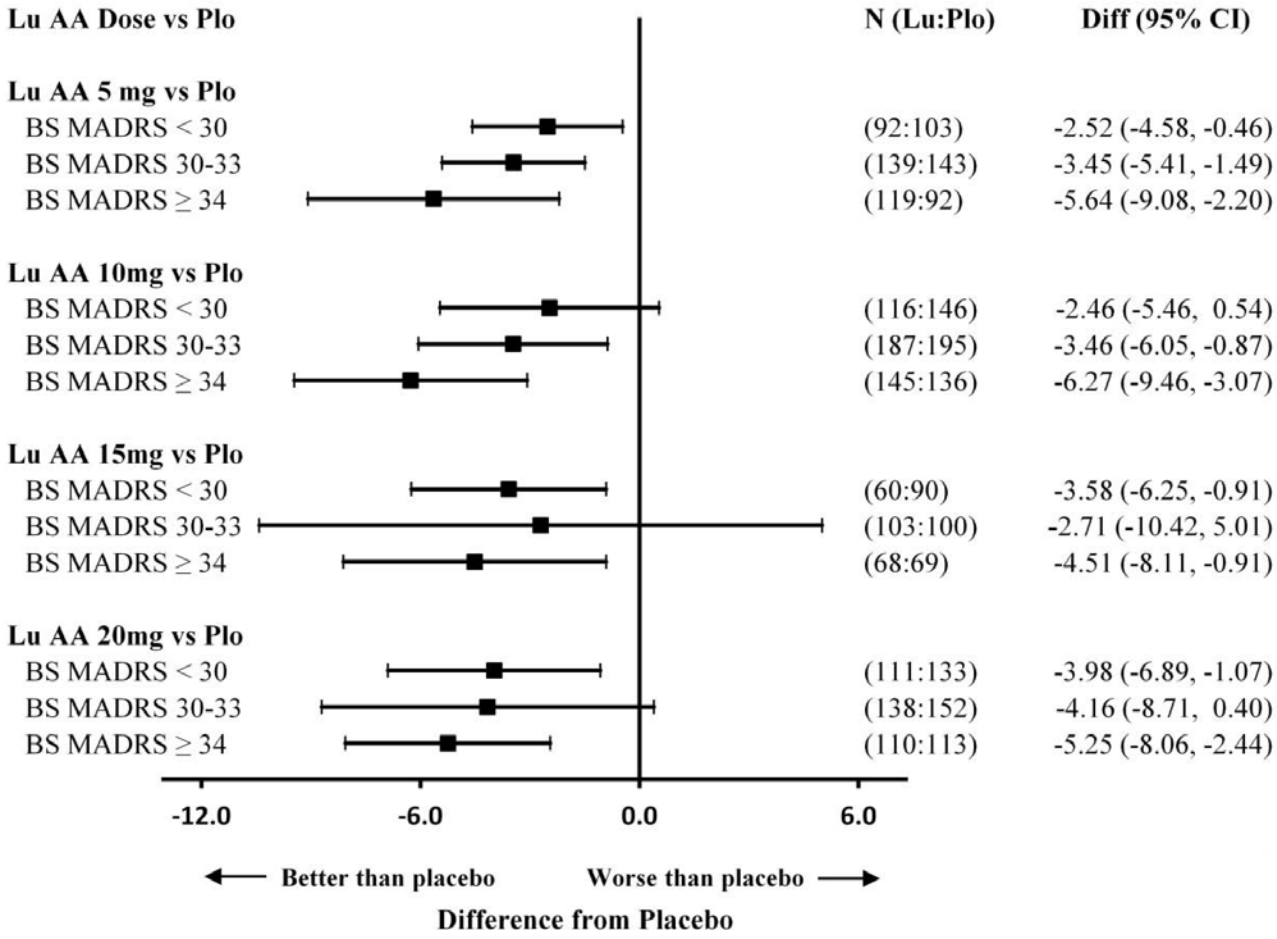
Source: Figure 3.n, page 126/185 of 2-7-3 Summary of Clinical Efficacy

Disease Characteristics

Symptom Severity

In each dose group, MADRS ≥34 (most severe) had the best treatment effect compared to subjects with less severe symptoms (MADRS 30-33 or MADRS<30) (Figure 11).

Figure 10: Treatment Effect on Change from Baseline in MADRS Total Score at Week 6/8 by Baseline MADRS Score (<30, 30-33, ≥34), Positive/Supportive Studies in Adults (FAS, MMRM)

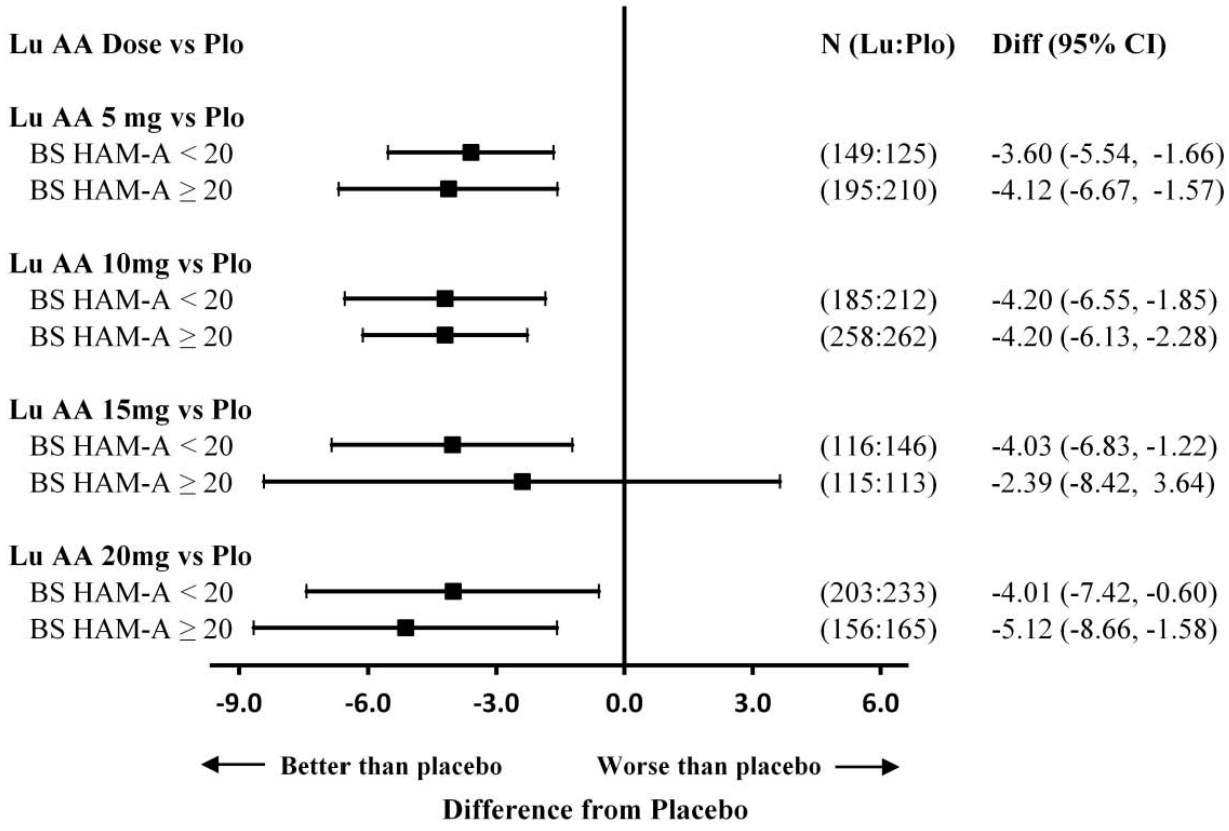


Source: Figure 3.o, page 127/185 of 2-7-3 Summary of Clinical Efficacy

Severity of Anxiety Symptoms in Depression

There were no consistent findings in severity of anxiety symptoms and treatment effects across treatment groups.

Figure 11: Treatment Effect on Change from Baseline in MADRS Total Score at Week 6/8 by Baseline HAM-A Score (<20, ≥20), Positive/Supportive Studies in Adults (FAS, MMRM)

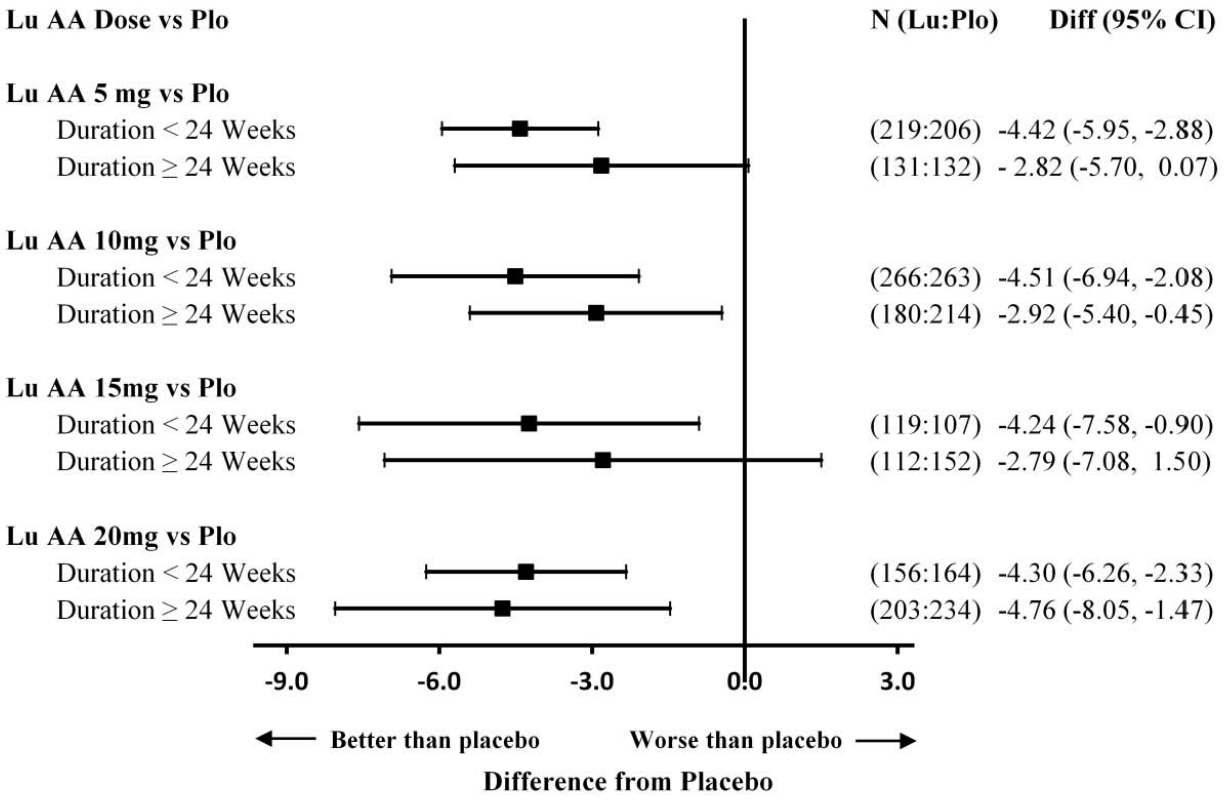


Source: Figure 3.p, page 129/185 of 2-7-3 Summary of Clinical Efficacy

Duration of the Current MDE

Overall, the subjects with shorter duration of current MDE did better except the subjects in 20 mg group, which subjects with longer duration (≥24 weeks) did slightly better than those with shorter duration (<24 weeks).

Figure 12: Treatment Effect on Change from Baseline in MADRS Total Score at Week 6/8 by Duration of Current MDE (<24, ≥24 Weeks), Positive/Supportive Studies in Adults (FAS, MMRM)

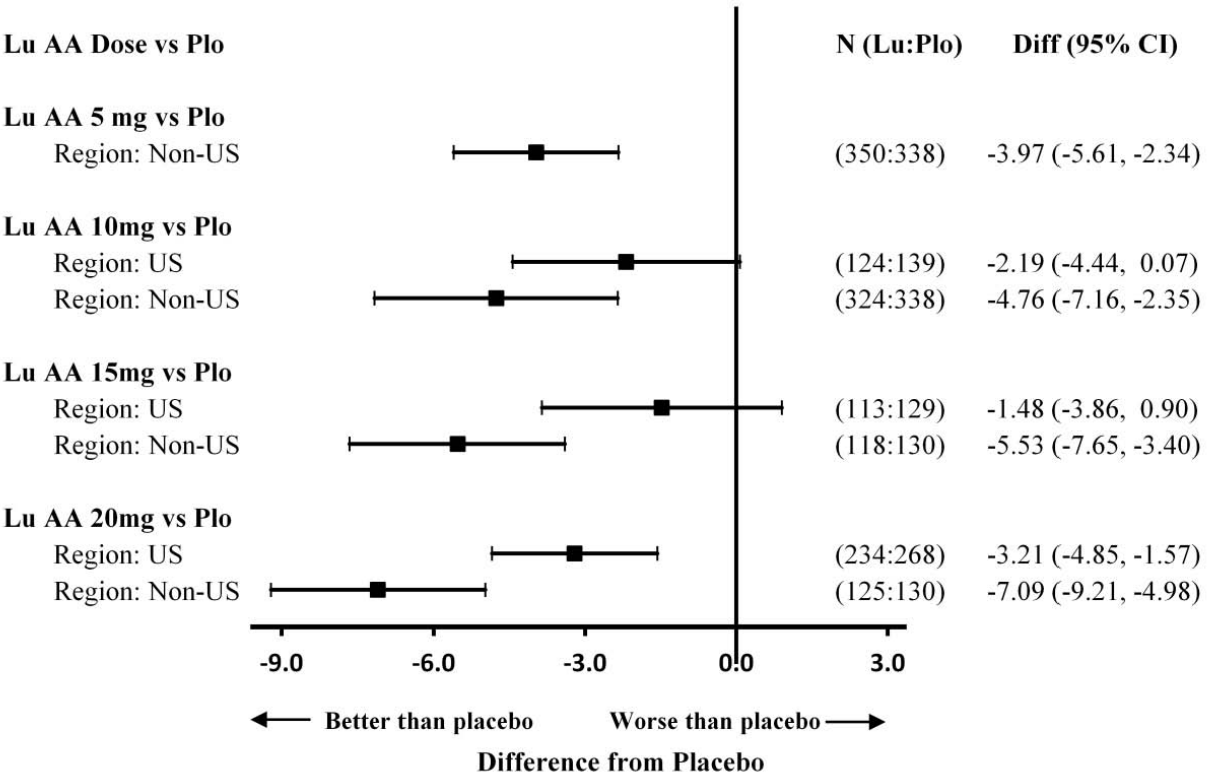


Source: Figure 3.q, page 130/185 of 2-7-3 Summary of Clinical Efficacy

Geographic Region

US subjects did worse than non-US subjects across treatment groups.

Figure 13: 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)



Source: Figure 3.r, page 131/185 of 2-7-3 Summary of Clinical Efficacy

6.4.2 Dose Response

In study 13267A, 305, 315 and 316, the larger dose appeared to have greater LS Mean Change from Baseline in primary endpoint either MADRS or HAM-D24 total score. Study 11492A did not demonstrate dose response. Refer to Efficacy Summary.

6.4.3 Effect Size

The effect size varied from -2.75 (Lu AA21004 20 mg in Study 315) to -7.18 (Lu AA21004 10 mg in Study 11492A). Refer to Table 13 in Efficacy Summary.

6.5 Long-Term Efficacy MDD Relapse Prevention Study (11985A, Non-US)

Objectives
To evaluate the efficacy of Lu AA21004 (doses of 5 mg or 10 mg) in the prevention of relapse of MDE

Study Conduct Dates: 12/2007 to 09/2009

Study Sites
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.

6.5.1 Method/Study Design/Analysis Plan of Study 11985A

Overall Study Design
Study 11985A was a MDD relapse-prevention study, which started with a 12-week open-label, flexible-dose period with Lu AA21004 (Open-label Period) and then followed by a randomized, double-blind, placebo-controlled, fixed-dose period (Double-blind Period) of 24 to 64 weeks.

The initial dose of Lu AA21004 was 5 mg, po, QD. The dose can be increased to 10mg from Week 2 to Week 8 during the Open-label Period if clinically indicated and can be decreased back to 5mg if subject could not tolerate the AEs. From Week 8, the dose was fixed.

Subjects in remission, which was defined as MADRS total score <10 at both Weeks 10 and 12, were randomized to the double-blind, placebo-controlled, fixed-dose treatment period (Double-blind Period). Subjects were randomized 1:1 to placebo or Lu AA21004 treatment group. Subjects randomized to Lu AA21004 continued the dose that was fixed from Week 8. Subjects randomized to placebo discontinued Lu AA21004 and started placebo.

The primary efficacy variable was the time to relapse of 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. Subjects who relapsed were withdrawn from the study.

Efficacy and safety data were collected at 2-week intervals in the Open-label Period and at Weeks 1, 2, and 4 and then at 4-week intervals in the Double-blind Period.

A safety follow-up contact was scheduled for 4 weeks after completion of the study or after withdrawal from the study.

The reviewer's comment: according to EOP_2 meeting dated February 13, 2008, the Division advised the sponsor to extend the open-label period to allow subjects to stay in remission for at least 12 weeks before randomization but the sponsor did not follow the advice arguing that the EMEA did not require such an extended responder phase. At the meeting, the Division indicated that we would accept a reasonably flexible definition of "stable responder, "e.g., it would be permissible for subjects to have slight excursions outside threshold criteria.

Selection of Study Population

Main Inclusion Criteria

- MADRS total score ≥26 at screening and at Baseline I (entry into the Open-label Period)
- were ≥18 and ≤75 years of age
- had had the current episode of MDE for ≥4 weeks
- had had at least one other MDE before the current episode

Main exclusion Criteria

- any current psychiatric disorder other than MDD as defined in the DSM-IV-TR
- presence or history of a clinically significant neurological disorder (including epilepsy) or neurodegenerative disorder
- The current depressive symptoms of the patient are considered by the investigator to have been resistant to two adequate antidepressant treatments of at least 6 weeks duration

The Primary and Secondary Efficacy Endpoints

The primary efficacy variable was the time to relapse of MDE within the first 24 weeks of the Double-blind Period.

Statistical Methods

Baseline I – beginning of the Open-label Period (that is, Visit 2 at Week 0)
Baseline II – beginning of the Double-blind Period (defined as the last visit [that is, Visit 8 at Week 12] in the Open-label Period) when subjects were randomized to double-blind treatment.

All-patients-treated set (APTS) – all patients who took at least one dose of IMP in the Open-label Period.

All-patients-randomized set (APRS) – all patients who completed the Open-label Period and were randomized to double-blind treatment

Full-analysis set (FAS) – all patients in the APRS who took at least one dose of study drug in the Double-blind Period.

Per-protocol set (PPS) – all patients in the FAS who did not have any major protocol violations.

The APTS was used for the evaluation of all data in the Open-label Period; the FAS was used for the evaluation of all data in the Double-blind Period. The primary efficacy analysis in the Double-blind Period was repeated on the PPS.

6.5.2 Results of Study 11985A

Demographics
At the Baseline I (start of the Open-Label Period), the mean age (SD) was 45 (12) years, 38% subjects were male. 78% were Caucasian, 19% were Asian and 2% were Black. The sex and race were similar at Baseline II.

Baseline Disease Characteristics
The disease characteristics at Baseline I and Week 12 of the Open-Label Period, and Baseline II were summarized in the following table.

The mean MADRS total score at Baseline I was 32, indicating that the subjects had severe MDD and the mean CGI-S score was 4.8, indicating that the subjects were moderately to markedly ill. Subjects at Week 12 and Baseline II had MADRS total score < 10 which met the criteria of remission.

Table 52: Mean Efficacy Scores (OC) - Study 11985A

Efficacy Variable	Mean Score (SD)		
	Open-Label Period		Double-Blind Period
	Baseline I (APTS) N=639	Week 12 (APTS) N=492	Baseline II (FAS) N=396
MADRS total score	32.3 (4.1)	7.0 (6.4)	4.8 (3.1)
CGI-S score	4.8 (0.7)	1.8 (1.0)	1.6 (0.7)
CGI-I score	NA	1.5 (0.7)	1.2 (0.4)

APTS=all patient treated set.
Note: Of the 492 subjects who completed the 12-week Open-Label Period, 400 enrolled in the Double-Blind Period and of these, 396 were treated.
Source: compiled from Table 2.qq page 84/185 of 2.7.3 Summary of Clinical Efficacy

Subject Disposition
Seventy seven (77%) subjects completed the 12-week treatment in the Open-Label Period. 57% subjects completed the study in the Double-Blind Period. A total of 492 subjects completed the 12-week Open-Label period. However, 92 of these subjects did not enroll in the Double-Blind Period because they were not in remission at both Weeks 10 and 12 (49 subjects), had an adverse event (5 subjects), lack of efficacy (24 subjects), or for an unspecified disqualifying reason (14 subjects). Of the 400 subjects randomized into the Double-Blind Period, 4 subjects were not treated.

Table 53: Subject Disposition - Study 11985A

	Number of Subjects (%)			
	Open-Label Period	Double-Blind Period		
		Placebo	Lu AA21004	Total
Subjects randomized	NA	194	206	400
Subjects treated	639 (100)	192	204	396 (a)
Subjects completed	492 (77.0)	104 (53.6)	125 (60.7)	229 (57.3)
Subjects withdrawn	147 (23.0)	90 (46.4)	81 (39.3)	171 (42.8)
Primary reasons for withdrawal				
Adverse event	54 (8.5)	5 (2.6)	16 (7.8)	21 (5.3)
Lack of efficacy	57 (8.92)	52 (27.1)	28 (13.7)	80 (20.2)
Not fulfilling randomization criteria	59 (9.2)	NA	NA	NA
Noncompliance	7 (1.1)	3 (1.6)	4 (2.0)	7 (1.8)
Protocol violation	15 (2.3)	11 (5.7)	8 (3.9)	19 (4.8)
Withdrawal of consent	11 (1.7)	7 (3.6)	3 (1.5)	10 (2.5)
Lost to follow-up	10 (1.6)	0	2 (1.0)	2 (0.5)
Other	26 (4.1)	10 (5.2)	18 (8.8)	28 (7.1)
FAS	NA	192	204	396

Source: Table 2.pp, page 83/185 of 2.7.3 Summary of Clinical Efficacy
(a) Two subjects each in the placebo and Lu AA21004 groups were randomized into the double-blind period but were not treated.

Concomitant Medication Use

The following table is from the sponsor's response dated May 17, 2013. 1.5% of subjects in both Lu AA21004 and placebo group used disallowed antidepressants during the study period. The subject who took Quetiapine was not included in the PPS according to sponsor.

Most subjects used benzodiazepine derivatives and benzodiazepine related drugs only for 1-2 days for insomnia, which was allowed by protocol.

Table 54: Summary of Disallowed Concomitant Medications in Study 11985A

Therapeutic Class Preferred Term	Placebo (N=194)	Lu AA21004 (N=206)	Total (N=400)
Subjects with Disallowed Medications	17(8.8)	18(8.7)	35(8.8)
Antidepressants	3(1.5)	3(1.5)	6(1.5)
Amitriptyline	1(0.5)	0	1(0.3)
Citalopram	1(0.5)	0	1 0.3)
Duloxetine Hydrochloride	0	2 (1.0)	2(0.5)
Mirtazapine	1(0.5)	0	1(0.3)
Trazodone	0	1(0.5)	1(0.3)
Antipsychotics	0	2(1.0)	2(0.5)
Quetiapine Fumarate	0	2(1.0)	2(0.5)
Benzodiazepine Derivatives	1(0.5)	6(2.9)	7(1.8)
Alprazolam	1(0.5)	2(1.0)	3(0.8)

Therapeutic Class Preferred Term	Placebo (N=194)	Lu AA21004 (N=206)	Total (N=400)
Bromazepam	0	1(0.5)	1(0.3)
Clorazepate Dipotassium	0	1(0.5)	1(0.3)
Diazepam	0	1(0.5)	1(0.3)
Lorazepam	0	1(0.5)	1(0.3)
Prazepam	0	1(0.5)	1(0.3)
Benzodiazepine Related Drugs	14(7.2)	12(5.8)	26(6.5)
Zolpidem	4(2.1)	6(2.9)	10(2.5)
Zolpidem Tartrate	5(2.6)	4(1.9)	9(2.3)
Zopiclone	7(3.6)	2(1.0)	9(2.3)

Source: Table 305.1 in 2013-05-17-Request-for-Infomration-Con Meds.pdf

Protocol Deviations

The sponsor stated in the clinical study report that Centers BE002, KR002, and IN005 were identified as non-compliance with the protocol, GCP, the Declaration of Helsinki, and /or other applicable regulations. Directed audits conducted at Centers BE002, KR002, and IN005 questioned whether the efficacy ratings had been conducted according to the protocol and the instructions given; furthermore, the auditors found that the quality of the medical records was inadequate.

All subjects from BE002 (12 subjects were enrolled in the Open-label Period and 10 were randomized to double-blind treatment) were excluded from the PPS. The data from KR002 and IN005 were kept in all the analyses. The primary efficacy analyses were repeated without the data from KR002 and IN005 and did not show differences.

Efficacy Findings

Primary Efficacy Endpoint

The primary efficacy analysis showed a statistically significantly superior effect of Lu AA21004 relative to placebo on the time to relapse of MDE during the first 24 weeks of the Double-blind Period (FAS; Cox proportional hazard model, 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.

Table 55: Time to Relapse Within 24 Weeks of Double-Blind Period (FAS) – Study 11985A

	Subject	Relapse	Relapse Rate	Cox Proportional Hazard		Log-rank
				Hazard Ratio	p-value	p-value
Placebo	192	50	26 %			
LuAA21004	204	27	13.2%	2.01	0.0035	0.003

Source: this table is provided by statistician reviewer Dr. George Kordzakhia based on Clinical Study Report of Study 11985A Panel 28 page 87/1659.

Since the sponsor did not follow FDA advice regarding extending the stabilization period, the statistical analysis team Dr. Peiling Yang and Dr. George Kordzakhia and we requested the sponsor to explore the actual stabilization durations for each subject and

the relapse results. The following is the response from the sponsor, which shows the weeks of stabilization of subjects in Lu AA21004 and placebo group.

Table 56: Summary of Subjects in Lu AA21004 and Placebo Group Based on Stabilization Duration in Study 11985A

	Number (%)				
	Stabilization Duration (Weeks)				
	≥ 2	≥ 4	≥ 6	≥ 8	≥ 10
Placebo (N=192)	191 (99.5%)	115 (59.9%)	69 (35.9%)	34 (17.7%)	5 (2.6%)
LuAA21004 (N=204)	202 (99.0%)	126 (61.8%)	78 (38.2%)	26 (12.7%)	8 (3.9%)

Source: Sponsor's Response to FDA Request for Information, Table 1.1 (\\Cdsesub1\evsprod\NDA204447\0022)

The sponsor also provided the relapse rates and the hazard ratio in the remission duration subgroups shown in the following table. In all subgroups of stabilization duration, the Lu AA21004 treated subjects had significantly less risk of relapse of MDE.

Table 57: Relapse Rates in Subgroups Based on Stabilization Duration - Study 11985A

	Relapse Number (Relapse Rate)					
		Stabilization Duration (Weeks)				
	Overall	≥ 2	≥ 4	≥ 6	≥ 8	≥ 10
Placebo	50/192 (26%)	50/191 (26%)	28/115 (24%)	18/69 (26%)	13/34(38 %)	1/5 (20%)
LuAA21004	27/204 (13%)	26/202 (13%)	14/126 (11%)	9/78 (12%)	2/26 (8%)	0/8 (0%)
Hazard Ratio	2.01	2.07	2.29	2.49	6.08	N/A
p-value	0.0035	0.0026	0.0114	0.0256	0.0176	N/A

Source: Sponsor's Response to FDA Request for Information, Table 1.1 (\\Cdsesub1\evsprod\NDA204447\0022)

6.5.3 Conclusions of Study 11985A

The long-term MDD relapse-prevention Study 11985A demonstrated the efficacy of Lu AA21004 5 and 10 mg QD in the prevention of relapse of MDE.

6.6 Pediatric Development

All studies with Lu AA21004 including completed or ongoing are adult studies. The Division will request pediatric studies (children and adolescents) as post-marketing requirements (PMR). The Division will take these requests to the Pediatric Review Committee (PeRC). The meeting with PeRC is scheduled on September 4, 2013.

6.7 Efficacy Conclusion

MDD Short-Term Studies
Lu AA21004 5 mg to 20 mg demonstrated the efficacy in the treatment of MDD in non-US subjects. However, in US only Lu AA21004 20mg demonstrated efficacy.

MDD Long-Term Efficacy Relapse-Prevention Study 11985A (Non-US)
Study 11985A demonstrated the efficacy of Lu AA21004 5 mg and 10 mg in the prevention of relapse of MDE.

Subgroups
The reason of the regional treatment difference between US and non-US was unclear.

7. Review of Safety

7.1 Safety Summery

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.

Deaths
In the clinical program, all 6 deaths occurred in the Lu AA21004 treatment group. The causes of death included 2 cancers, 1 suicide, 1 morphine toxicity, 1 road traffic accident, and 1 accidental death. For morphine toxicity and accidental death (an accidental fall from a balcony), suicide could not be ruled out as a cause, according to the sponsor, due to limited information available. All deaths were considered by the investigators as unrelated to Lu AA21004 treatment.

Nonfatal Serious Adverse Events (SAEs)

- The incidences of SAEs of Lu AA21004 Total group in the MDD and MDD/GAD short-term pool were low (1.0% and 0.9%, respectively) and comparable to placebo and Duloxetine. No dose relationship was observed across the Lu AA21004 dose groups. The following 4 SAEs were experienced by at least 2 subjects in Lu AA21004 treatment groups: depression (4 subjects), suicide attempt (3 subjects), suicidal ideation (3 subjects) and convulsion (2 subjects). Two cases of convulsion were related to traumatic brain injury.

- In the MDD relapse prevention Study 11985A, the incidence of SAEs of Lu AA21004 Total during the Open-Label Period was 2.2%. The incidence of SAEs

of Lu AA21004 Total was slightly higher than placebo in the Double-Blind Phase (3.4% and 2.1%, respectively).

- In the GAD relapse prevention Study 12473A, the incidence of SAEs of Lu AA21004 Total during the Open-Label Period was 1.5%. The incidence of SAEs of Lu AA21004 Total was higher than placebo in the Double-Blind phase (1.3% and 0.4%, respectively).

Dropouts and/or Discontinuations

- The discontinuation rate of LU AA21004 Total group due to TEAEs was greater than placebo but less than Duloxetine in both MDD and MDD/GAD short-term pools. The discontinuations due to TEAEs were dose-related.

- Nausea was the most common TEAE leading to discontinuation in all study pools except Phase 1 Study Pool.

- In Phase 1 Study Pool, the most common TEAEs leading to discontinuations were skin reactions and vomiting, all of which occurred in Lu AA21004 treated subjects. Eight subjects had the TEAEs related to drug hypersensitivity, which included urticaria (4 subjects); angioedema (2 subjects) and rash (2 subjects). Seven (7) subjects had vomiting. Discontinuations due to nausea occurred in 2 subjects treated with Lu AA21004.

The most common TEAEs in MDD/GAD Short-Term Pool: nausea (22% – 32%), vomiting (3% - 7%), and constipation (3% - 6%) for Lu AA21004 5 mg – 20 mg.

Significant AEs/AEs of Special Interest

QT Prolongation

Thorough QT study was negative.

Sexual Dysfunction (SD)

- Overall, the incidences of treatment-emergent sexual dysfunction (TESD) in Lu AA21004 groups were higher than placebo and appeared to be dose-related.

- In MDD/GAD Short-Term Pool, for both male and female subjects without sexual dysfunction (SD) at Baseline, the TESD incidence at two consecutive post-baseline visits in Lu AA21004 20 mg group (29%) were higher than both Duloxetine (26%) and placebo (14%).

- The overall incidence of worsening SD for subjects with baseline sexual dysfunction was dose-related for Lu AA21004 treated groups.

- There were 3 discontinuations due to TESD in Lu AA21004 treated groups but none in either Placebo or Duloxetine group in the MDD Short-Term Pool.

- There were 4 discontinuations due to TESD in Lu AA21004 treated group and none in Placebo and 1 in Duloxetine group in the MDD/GAD Short-Term Pool.

Discontinuation-Emergent Signs and Symptoms (DESS)

- A statistically significant difference in the mean number of discontinuation-emergent symptoms was observed for subjects discontinuing Lu AA21004 15 mg and 20 mg compared with placebo in the 1st week of discontinuation according to the assessment of the pooled data from US Studies 315, 316, and non-US Study 13267A by DESS scale.

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

Hyponatremia

Two cases of hyponatremia were identified. One had serum sodium 108 mmol/L and had TEAEs of nausea and abdominal pain reported, which were felt to be related to hyponatremia. The other had serum sodium 126 mmol/L.

Nausea

- The incidence of nausea in Lu AA21004 was significantly higher than placebo and was dose-related.

- 15-20% subjects experienced nausea in the first 1-2 days of Lu AA21004 treatment. Approximate 10% subjects in Lu AA21004 10 mg – 20 mg experienced nausea throughout the 8 week study period.

- The median time to first nausea event was similar to Duloxetine but shorter in Lu AA21004 groups than placebo (1-2 days vs. 3 days).

- The event of nausea lasted longer in Lu AA21004 group than placebo and Duloxetine during the entire treatment period.

- The incidence of nausea leading to discontinuation was dose-related and higher than placebo. The incidences of nausea leading to discontinuations in Lu AA21004 15 mg and 20 mg groups were higher than Duloxetine.

Dose-response

The following demonstrated a dose-response pattern across Lu AA21004 dose 5 – 20 mg:

1. Overall TEAEs
2. The discontinuations due to TEAEs
3. The most common TEAEs of nausea and constipation
4. Treatment-emergent sexual dysfunction (TESD)

Vitals
Lu AA21004 20mg group was associated with mean increases of 0.8 mm Hg in standing systolic blood pressure (SBP) and 0.5 mm Hg in supine SBP compared to a mean decrease of 0.8 mm Hg in standing SBP and a mean decrease of 1.0 mm Hg in supine SBP in placebo in MDD short-term pool. Similar findings were also seen in MDD/GAD short-term pool.

The proportions of subjects with at least 1 post-baseline potentially clinically significant (PCS) value of ≥180 mm Hg or increase ≥ 20 mm Hg for standing and supine SBP and ≥105 mm Hg or increase ≥ 15 mm Hg for standing and supine DBP in Lu AA21004 20mg group were slightly higher than placebo and Duloxetine.

Liver Function Test
We did not identify any Hy's law cases. Few subjects discontinued studies due to elevated liver enzymes of unknown causes.

Others
There were no significant findings in weight, hematology, urinalysis and EKG.

7.2 Methods

The safety evaluation of LU AA21004 consisted of a review of the deaths, serious adverse events (SAEs), adverse events (AEs) that led to early discontinuation, common adverse events, suicidal ideation and behaviors, sexual dysfunction, discontinuation symptoms, vitals, weight, clinical laboratory results, ECG findings, and other safety findings specifically related to antidepressants from phase 2 and phase 3 short term efficacy studies for both MDD and GAD indication. For phase 1 studies and open label studies, the safety review focused on the SAEs.

7.2.1 Studies/Clinical Trials Used to Evaluate Safety

The following data were used to evaluate safety profile of Lu AA21004 to support the indication of MDD in adult:

- 10 MDD short-term placebo controlled Phase 2 and 3 studies
- 4 GAD short-term placebo-controlled studies
- 1 MDD long-term relapse-prevention study (11985A)
- 1 GAD long-term relapse-prevention study (12473A)
- MDD long-term open-label studies (3 completed Studies: 11492C, 11984B, and 301 and 2 ongoing Studies: 314 and 13267B)
- 31 clinical pharmacology studies

7.2.2 Categorization of Adverse Events

An AE was defined as any new untoward medical occurrence or worsening of a preexisting medical condition regardless of causal relationship with treatment. An AE could be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational or marketed) product, whether or not considered related to the medicinal (investigational or marketed) product.

A SAE was any untoward medical occurrence at any dose that:

- Results in death
- Is life-threatening (defined as an event in which the subject or patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a cancer
- Is a congenital anomaly/birth defect
- Results in the development of drug dependency or drug abuse
- Is an important medical event (including pregnancy or overdose)

Due to time constraints, this reviewer did not audit the sponsor's coding of verbatim AE terms to MedDRA preferred term (PT) by examining ae.xpt in the dataset.

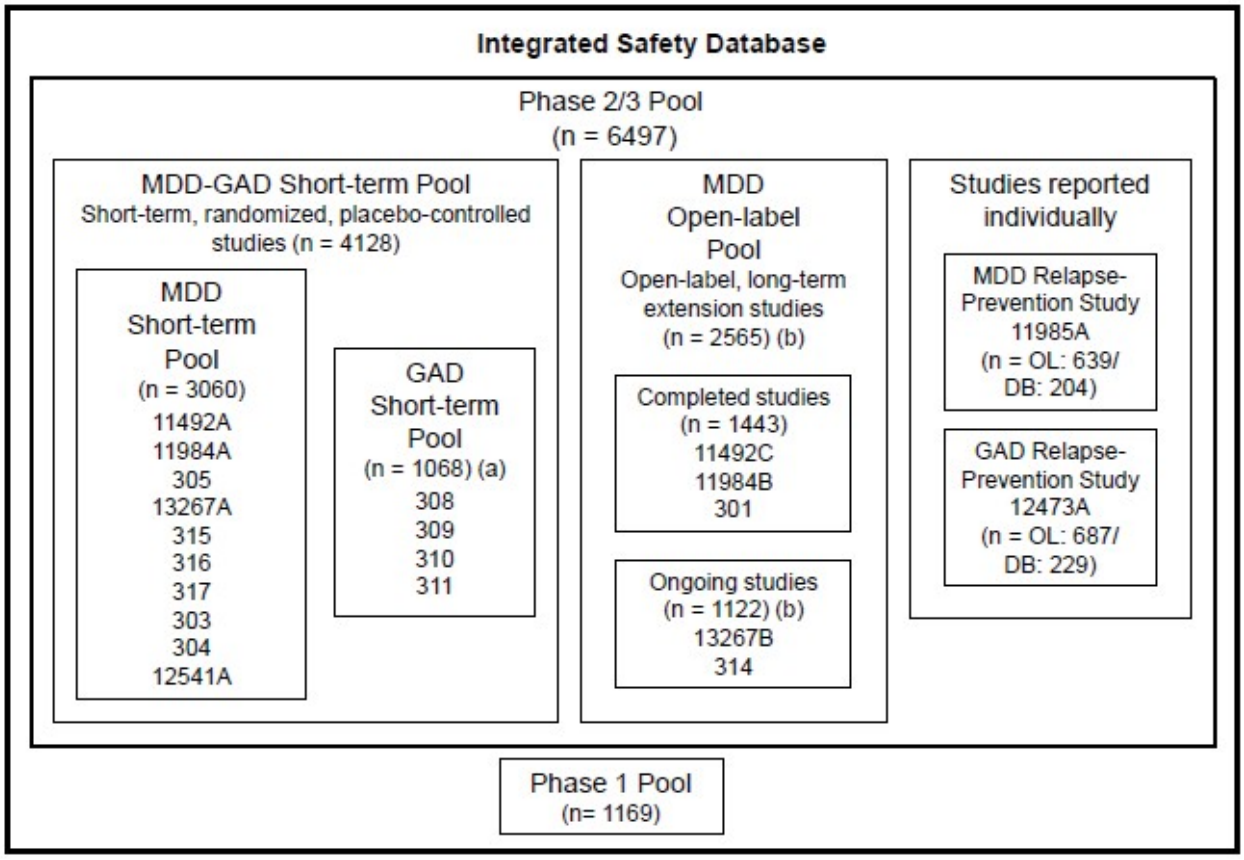
7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

The sponsor pooled the studies for the safety review in the following 5 categories shown in the following figure:

1. **MDD Short-Term Pool**
2. **GAD Short-Term Pool**
3. **MDD/GAD Short-Term Pool**
4. **MDD Open-Label Long-Term Pool**
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.

Figure 14: Overview of Pooled Data Sets and Un-pooled Studies for Safety Analyses



Source: 2-7-4-summary-clinical-safety, page 25/183
OL=Open-label, DB=Double-blind.
(a) GAD short-term studies did not assess Lu AA21004 15 mg and 20 mg doses.
(b) Totals include interim data in the clinical database as of 04 May 2012 for 2 ongoing, pooled studies: 13267B and314.
Note 1: Counts are for Lu AA21004 exposures.
Note 2: Ongoing un-pooled studies are specified in Table 1.b (ongoing phase 2 and 3 studies in MDD) and Table 1.e (ongoing phase 1 studies).

7.3 Adequacy of Safety Assessments

7.3.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

7.3.1.1 Overall Exposure in all clinical studies (Phase 1, 2, and 3)

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.

7.3.1.2 Overall Exposure in all Phase 2 and 3 Studies Combined

Table 58 summarizes the study drug exposure by dose and duration in all phase 2 and 3 studies combined. 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.

Table 58: Study Drug Exposure in All Phase 2 and 3 Studies Combined

Duration (Days)	Placebo N=2652 PY=500.7	Lu AA21004 (mg)							Duloxetine N=907 PY=120.2
		1 N=140 PY=20.2	2.5 N=773 PY=158.0	5 N=3853 PY=870.	10 N=3627 PY=1105.	15 N=1226 PY=215.	20 N=1090 PY=341.	Total N=6497 PY=2711.	
Mean	69.0	52.7	74.6	82.5	111.3	64.3	114.4	152.4	48.4
SD	62.94	10.02	78.97	108.79	127.83	79.71	105.56	142.18	16.97
Median	56.0	56.0	56.0	43.0	56.0	49.0	61.0	82.0	56.0
Min-Max	1-448	5-63	1-414	1-513	1-498	1-420	1-422	1-532	1-75
Cumulative exposure, N (%)									
≥1 day	2652 (100.0)	140 (100.0)	773 (100.0)	3853 (100.0)	3627 (100.0)	1226 (100.0)	1090 (100.0)	6497 (100.0)	907 (100.0)
≥4 wks	2399 (90.5)	132 (94.3)	663 (85.8)	2482 (64.4)	2452 (67.6)	709 (57.8)	936 (85.9)	5850 (90.0)	771 (85.0)
≥8 wks	1438 (54.2)	87 (62.1)	466 (60.3)	1595 (41.4)	1990 (54.9)	530 (43.2)	718 (65.9)	4560 (70.2)	542 (59.8)
≥12 wks	328 (12.4)	0	105 (13.6)	877 (22.8)	1247 (34.4)	230 (18.8)	463 (42.5)	3189 (49.1)	0
≥24 wks	269 (10.1)	0	73 (9.4)	528 (13.7)	874 (24.1)	126 (10.3)	263 (24.1)	2045 (31.5)	0
≥36 wks	95 (3.6)	0	53 (6.9)	441 (11.4)	704 (19.4)	62 (5.1)	149 (13.7)	1674 (25.8)	0
≥48 wks	30 (1.1)	0	33 (4.3)	329 (8.5)	484 (13.3)	36 (2.9)	87 (8.0)	1309 (20.1)	0
≥52 wks	24 (0.9)	0	6 (0.8)	246 (6.4)	179 (4.9)	7 (0.6)	28 (2.6)	1131 (17.4)	0

Source: ISS Table 1.m, page 53/410.
Max=maximum, Min=minimum, SD=standard deviation, wks=weeks.
Studies included: MDD (303, 304, 305, 315, 316, 317, 11492A, 11984A, 12541A and 13267A), GAD (308, 309, 310, and 311), MDD Open-Label (301, 314, 11492C, 11984B and 13267B), MDD relapse prevention (11985A), and GAD relapse prevention (12473A).

Note 1: Subjects may have received more than 1 dose within or across studies and are counted once for each dose received. The Lu AA21004 Total column summarizes exposure regardless of dose and is not necessarily the sum of the counts in the individual dose columns.

7.3.1.3 Overall Exposure in the MDD Short-Term Pool

Table 59 summarizes the exposure in the MDD Short-Term Pool, which included 10 studies: 303, 304, 305, 315, 316, 317, 11492A, 11984A, 12541A, and 13267A. A total of 3060 subjects were exposed to Lu AA21004 in this Pool. Of these, a total of 1013, 699, 449, and 455 subjects were exposed to Lu AA21004 5mg, 10mg, 15mg, and 20mg respectively. The mean duration of exposure in the Lu AA21004 Total was 48.5 days.

Table 59: Study Drug Exposure in the MDD Short-Term Pool

Duration (Days)	Placebo N=1621 PY=213.4	Lu AA21004 (mg)					Duloxetine N=753 PY=101.4
		5 N=1013 PY=128.7	10 N=699 PY=93.7	15 N=449 PY=60.7	20 N=455 PY=61.7	Total (a) N=3060 PY=406.3	
N	1621	1013	699	449	455	3060	753
Mean	48.1	46.4	48.9	49.4	49.5	48.5	49.2
SD	13.42	13.04	14.44	14.98	15.33	14.18	16.24
Median	55.0	51.0	56.0	56.0	56.0	56.0	56.0
Min-Max	1-75	1-71	1-66	1-63	1-72	1-72	1-75
Cumulative exposure, N (%)							
≥ 1 day	1621 (100.0)	1013 (100.0)	699 (100.0)	449 (100.0)	455 (100.0)	3060 (100.0)	753 (100.0)
≥ 2 wks	1556 (96.0)	972 (96.0)	652 (93.3)	418 (93.1)	422 (92.7)	2887 (94.3)	687 (91.2)
≥ 4 wks	1470 (90.7)	921 (90.9)	624 (89.3)	391 (87.1)	400 (87.9)	2735 (89.4)	652 (86.6)
≥ 6 wks	1337 (82.5)	806 (79.6)	583 (83.4)	373 (83.1)	380 (83.5)	2520 (82.4)	627 (83.3)
≥ 8 wks	743 (45.8)	378 (37.3)	365 (52.2)	256 (57.0)	259 (56.9)	1539 (50.3)	465 (61.8)

Source: ISS Table 1.n page 55/410.
(a) Lu AA21004 Total also includes 1 and 2.5 mg doses.
Note 1: Exposure duration was based on the double-blind treatment period.

7.3.1.4 Study Drug Exposure in the MDD/GAD Short-Term Pool

The GAD Short-Term Pool included subjects who were exposed to Lu AA21004 5 mg and 10 mg only. The mean duration of exposure in the Lu AA21004 Total in the MDD/GAD pool was similar to that of MDD short-term pool.

Table 60: Study Drug Exposure in the MDD/GAD Short-Term Pool

Duration (Days)	Placebo N=2230 PY=296.7	Lu AA21004 (mg)					Duloxetine N=907 PY=120.2
		5 N=1466 PY=191.2	10 N=1007 PY=134.4	15 N=449 PY=60.7	20 N=455 PY=61.7	Total N=4128 PY=550.4	
Mean	48.6	47.6	48.7	49.4	49.5	48.7	48.4
SD	13.58	13.47	14.68	14.98	15.33	14.33	16.97
Median	55.0	55.0	56.0	56.0	56.0	56.0	56.0
Min-Max	1-75	1-71	1-66	1-63	1-72	1-99	1-75
Cumulative exposure, N (%)							
≥1 day	2230 (100.0)	1466 (100.0)	1007 (100.0)	449 (100.0)	455 (100.0)	4128 (100.0)	907 (100.0)
≥2 wks	2139 (95.9)	1402 (95.6)	944 (93.7)	418 (93.1)	422 (92.7)	3902 (94.5)	820 (90.4)
≥4 wks	2015 (90.4)	1325 (90.4)	888 (88.2)	391 (87.1)	400 (87.9)	3669 (88.9)	771 (85.0)

Duration (Days)	Placebo N=2230 PY=296.7	Lu AA21004 (mg)					Duloxetine N=907 PY=120.2
		5 N=1466 PY=191.2	10 N=1007 PY=134.4	15 N=449 PY=60.7	20 N=455 PY=61.7	Total N=4128 PY=550.4	
Mean	48.6	47.6	48.7	49.4	49.5	48.7	48.4
SD	13.58	13.47	14.68	14.98	15.33	14.33	16.97
Median	55.0	55.0	56.0	56.0	56.0	56.0	56.0
Min-Max	1-75	1-71	1-66	1-63	1-72	1-99	1-75
Cumulative exposure, N (%)							
≥6 wks	1849 (82.9)	1192 (81.3)	828 (82.2)	373 (83.1)	380 (83.5)	3403 (82.4)	740 (81.6)
≥8 wks	1080 (48.4)	639 (43.6)	525 (52.1)	256 (57.0)	259 (56.9)	2117 (51.3)	542 (59.8)

Source: ISS Table 1.o page 57/410.
(a) Lu AA21004 Total also includes 1 and 2.5 mg doses.
Note 1: Exposure duration was based on the double-blind treatment period.

7.3.1.5 Overall Exposure in Relapse-Prevention Studies

In the Open-Label Period of the MDD long-term relapse-prevention study (Study 11985A), 639 subjects were exposed to at least 1 dose of Lu AA21004, and the mean duration of exposure was 73 days. In the Double-Blind Period, 204 subjects were exposed to Lu AA21004, and the mean duration of exposure was 211 days.

In the Open-Label Period of the GAD relapse-prevention study (Study 12473A), 687 subjects were exposed to at least 1 dose of Lu AA21004, and the mean duration of exposure was 119 days. In the Double-Blind Period, 229 subjects were exposed to at least 1 dose of Lu AA21004, and the mean duration of exposure was 196 days.

7.3.1.6 Exposure in the MDD Open-Label Long-Term Pool

The MDD Open-Label Long-Term Pool included completed Studies 11492C, 11984B, and 301 and ongoing Studies 314 and 13267B (Table 61).

The mean duration of exposure was 224.1 days. A total of 1505 subjects (58.7%) completed at least 24 weeks and 795 subjects (31.0%) completed at least 52 weeks of treatment on any dose of Lu AA21004.

Table 61: Study Drug Exposure in the MDD Open-Label Long-Term Pool

Duration (Days)	Studies 11492C/11984B/ 301	Studies 314/13267B N=1122 PY=476.2	Lu AA21004 Total N=2565
Mean	277.8	155.0	224.1
SD	127.20	116.31	136.83
Median	363.0	124.0	246.0
Min-Max	1-422	2-381	1-422
Cumulative exposure, N (%)			

Duration (Days)	Studies 11492C/11984B/ 301	Studies 314/13267B N=1122 PY=476.2	Lu AA21004 Total N=2565
≥1 day	1443 (100.0)	1122 (100.0)	2565 (100.0)
≥4 wks	1386 (96.0)	1035 (92.2)	2421 (94.4)
≥8 wks	1310 (90.8)	849 (75.7)	2159 (84.2)
≥12 wks	1237 (85.7)	693 (61.8)	1930 (75.2)
≥24 wks	1072 (74.3)	433 (38.6)	1505 (58.7)
≥36 wks	991 (68.7)	272 (24.2)	1263 (49.2)
≥48 wks	919 (63.7)	159 (14.2)	1078 (42.0)
≥52 wks	674 (46.7)	121 (10.8)	795 (31.0)

Source: ISS Table 1.p page 59/410
Studies included: 11492C/11984B/301 (2.5 to 10 mg) and 314/13267B (10 to 20 mg).
Note 1: Subjects in open-label studies may have received more than one dose and are counted once for each dose.
The Lu AA21004 Total column summarizes exposure regardless of dose and is not necessarily the sum of the counts in the individual dose columns.

7.3.2 Explorations for Dose Response

Summary
The following demonstrated a dose-related pattern across Lu AA21004 doses 5 - 20mg:

- Overall TEAEs
- The discontinuations due to TEAEs
- The most common TEAEs: nausea and constipation
- Treatment-emergent sexual dysfunction (TESD)

The detailed dose response is discussed in the corresponding safety sections of this review.

7.3.3 Special Animal and/or In Vitro Testing

Refer to the comprehensive review by Pharmacology/Toxicology.

7.3.4 Routine Clinical Testing

Routine clinical testing includes deaths, adverse events (AEs) which include serious AEs and common AEs, TESD, safety laboratory tests (hematology, clinical chemistry, urinalysis and serum beta HCG pregnancy test for females), vital signs including systolic blood pressure (SBP) and diastolic blood pressure (DBP), body weight, height and EKG. These routine clinical testing was felt to be adequate.

7.3.5 Metabolic, Clearance, and Interaction Workup

Refer to the comprehensive review by Clinical Pharmacology

7.3.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

In general, the monitoring for important AEs such as suicidal ideation and behavior, serotonin syndrome, seizure, activation of mania, hyponatremia and SD was felt adequate.

7.4 Major Safety Results

7.4.1 Overview of Treatment-Emergent Adverse Events (TEAEs)

Summary
In both MDD and MDD/GAD Short-Term Pools, the incidences of the total number of TEAEs in Lu AA21004 groups were higher than placebo but lower than duloxetine group. There was a dose-related increase in the total number of TEAEs across Lu AA21004 doses 5 – 20 mg. However, the serious TEAEs did not demonstrate such pattern.

In the Open Label Period of the MDD and GAD relapse prevention studies, the incidences of any TEAEs, serious TEAEs and the TEAEs leading to discontinuation were higher in Lu AA21004 group than those in the same dose groups (5 mg and 10 mg) in the short-term pools.

In the Double-Blind Period of the MDD and GAD relapse prevention studies, the incidences of TEAEs were similar in the Lu AA21004 group and placebo. However, the incidences of serious TEAEs and the TEAEs leading to discontinuation were higher in Lu AA21004 group than placebo.

7.4.1.1 Overview of TEAEs in the MDD Short-Term Pool

Table 62 shows the overview of TEAEs in the MDD Short-Term Pool dosing 5 - 20 mg. The doses of 1 - 2.5 mg were included in the group of Lu AA21004 Total.

The incidences of any TEAEs in the groups of 5 mg, 10 mg, 15 mg, 20 mg and Total were higher than placebo but lower than duloxetine group. There was a dose-related increase in any TEAEs across the doses 5 – 20 mg. However, the serious TEAEs did not demonstrate such dose response. One death was reported in each of the Lu AA21004 2.5 mg and 5 mg groups and these 2 cases are further described in Section 7.3.2 – Deaths

Table 62: Overview of TEAEs in the MDD Short-Term Pool

	Number of Events or Subjects (%)													
			Lu AA21004 (mg)											
	Placebo N=1621		5 N=1013		10 N=699		15 N=449		20 N=455		Total (a) N=3060		Duloxetine N=753	
	AEs	Subs	AEs	Subs	AEs	Subs	AEs	Subs	AEs	Subs	AEs	Subs	AEs	Subs
Any TEAEs	2654	1002 (61.8)	1779	672 (66.3)	1433	465 (66.5)	1005	316 (70.4)	990	331 (72.7)	5763	2029 (66.3)	2082	583 (77.4)
Related	1795	783 (48.3)	1290	543 (53.6)	1056	398 (56.9)	760	279 (62.1)	759	284 (62.4)	4260	1697 (55.5)	1748	539 (71.6)
Not related	859	219 (13.5)	489	129 (12.7)	377	67 (9.6)	245	37 (8.2)	231	47 (10.3)	1503	332 (10.8)	334	44 (5.8)
Mild	1533	412 (25.4)	967	263 (26.0)	837	192 (27.5)	609	125 (27.8)	585	126 (27.7)	3317	822 (26.9)	1151	208 (27.6)
Moderate	1005	495 (30.5)	705	325 (32.1)	525	222 (31.8)	365	167 (37.2)	365	173 (38.0)	2160	991 (32.4)	839	306 (40.6)
Severe	116	95 (5.9)	107	84 (8.3)	71	51 (7.3)	31	24 (5.3)	40	32 (7.0)	286	216 (7.1)	92	69 (9.2)
Leading to discontinuatio		62 (3.8)		53 (5.2)		42 (6.0)		36 (8.0)		38 (8.4)		191 (6.2)		68 (9.0)
Serious TEAEs	15	15 (0.9)	17	15 (1.5)	9	9 (1.3)	2	2 (0.4)	3	2 (0.4)	34	31 (1.0)	9	8 (1.1)
Related	2	2	3	3 (0.3)	4	4 (0.6)	0	0	2	1 (0.2)	9	8 (0.3)	2	2 (0.3)
Not related	13	13	14	12	5	5 (0.7)	2	2 (0.4)	1	1 (0.2)	25	23	7	6 (0.8)
Leading to discontinuatio		5 (0.3)		10 (1.0)		9 (1.3)		1 (0.2)		0		22 (0.7)		4 (0.5)
Deaths		0		1 (<0.1)		0		0		0		2 (<0.1)		0

Source: ISS Table 2.a page 81/410
AEs: Adverse events
Subs: Subjects
Studies included: MDD (303, 304, 305, 315, 316, 317, 11492A, 11984A, 12541A and 13267A)
(a) Lu AA21004 Total also includes 1 and 2.5 mg doses.

7.4.1.2 Overview of TEAEs in the MDD/GAD Short-Term Pool

The findings of TEAEs in the MDD/GAD Short-Term Pool were similar to those in the MDD Short-Term Pool (Table 63).

Table 63: Overview of TEAEs in the MDD/GAD Short-Term Pool

	Number of Events or Subjects (%)						
	Placebo N=2230	Lu AA21004 (mg)					Duloxetine N=907
		5 N=1466	10 N=1007	15 N=449	20 N=455	Total (a) N=4128	
	Events/ Subjects	Events/ Subjects	Events/ Subjects	Events/ Subjects	Events/ Subjects	Events/ Subjects	Events/ Subjects
Any TEAEs	3499/ 1359 (60.9)	2596/ 974 (66.4)	2126/ 693 (68.8)	1005/ 316 (70.4)	990/ 331 (72.7)	7929/ 2775 (67.2)	2508/ 709 (78.2)
Related	2294/ 1033 (46.3)	1841/ 779 (53.1)	1567/ 593 (58.9)	760/ 279 (62.1)	759/ 284 (62.4)	5731/ 2284 (55.3)	2078/ 654 (72.1)
Not related	1205 326 (14.6)	755/ 195 (13.3)	559/ 100 (9.9)	245/ 37 (8.2)	231/ 47 (10.3)	2198/ 491 (11.9)	430/ 55 (6.1)
Mild	1999/ 577 (25.9)	1445/ 386 (26.3)	1277/ 291 (28.9)	609/ 125 (27.8)	585/ 126 (27.7)	4618/ 1128 (27.3)	1389/ 251 (27.7)
Moderate	1341/ 652 (29.2)	1003/ 477 (32.5)	737/ 325 (32.3)	365/ 167 (37.2)	365/ 173 (38.0)	2910/ 1356 (32.8)	1005/ 374 (41.2)
Severe	159/ 130 (5.8)	148/ 111 (7.6)	112/ 77 (7.6)	31/ 24 (5.3)	40/ 32 (7.0)	401/ 291 (7.0)	114/ 84 (9.3)
Leading to discontinuation	80 (3.6)	77 (5.3)	59 (5.9)	36 (8.0)	38 (8.4)	246 (6.0)	91 (10.0)
Serious TEAEs	20/20 (0.9)	18/16 (1.1)	11/11 (1.1)	2/2 (0.4)	3/2 (0.4)	40/37 (0.9)	12/11 (1.2)
Related	4/ 4 (0.2)	3/ 3 (0.2)	4/ 4 (0.4)	0/ 0	2/ 1 (0.2)	10/ 9 (0.2)	4/ 4 (0.4)
Not related	16/ 16 (0.7)	15/ 13 (0.9)	7/ 7 (0.7)	2/ 2 (0.4)	1/ 1 (0.2)	30/ 28 (0.7)	8/ 7 (0.8)
Leading to discontinuation	5 (0.2)	11 (0.8)	10 (1.0)	1 (0.2)	0	25 (0.6)	6 (0.7)
Deaths	0	2 (0.1)	0	0	0	3 (<0.1)	0

Source: ISS Table 2.b, page 83/410
Studies included: MDD (303, 304, 305, 315, 316, 317, 11492A, 11984A, 12541A and 13267A) and GAD (308, 309, 310, and 311)
(a) Lu AA21004 Total also includes 1 and 2.5 mg doses.

7.4.1.3 Overview of TEAEs in MDD Relapse Prevention Study 11985A

In the Open Label Period, the incidence of any TEAEs, serious TEAEs and the TEAEs leading to discontinuation were higher in Lu AA21004 group than those in the same dose groups (5mg and 10mg) in the short-term pools.

In the Double-Blind Period, the incidence of TEAEs was similar in the Lu AA21004 group and placebo. The incidence of serious TEAEs was slightly higher in Lu AA21004 group (3.4%) than placebo (2.1%). However, the incidence of TEAEs leading to discontinuation was significantly higher in the Lu AA21004 group (6.9%) than placebo (1.0%).

Table 64: Overview of TEAEs in the MDD Relapse-Prevention Study 11985A

Open-Label Treatment Period		
	Lu AA21004	
	Events	Subjects (%)
Subjects treated	N/A	639
TEAEs	1398	451 (70.6)
Serious TEAEs	16	14 (2.2)
Leading to study discontinuation	NC	55 (8.6)

Double-Blind Treatment Period				
	Placebo		Lu AA21004	
	Events	Subjects (%)	Events	Subjects (%)
Subjects treated	N/A	192	N/A	204
TEAEs	349	122 (63.5)	364	127 (62.3)
Serious TEAEs	7	4 (2.1)	7	7 (3.4)
Leading to study discontinuation	NC	2 (1.0)	NC	14 (6.9)

Source: ISS Table 2.c, page 84/410
N/A=not applicable, NC=not counted.

7.4.1.4 Overview of TEAEs in GAD Relapse-Prevention Study 12473A

In the Open Label Period, the incidence of any TEAEs, serious TEAEs and the TEAEs leading to discontinuation were higher in Lu AA21004 group than those in the same dose groups (5mg and 10mg) in the short-term pools.

In the Double-Blind period, compared to placebo, the incidence of any TEAEs was similar, but more serious TEAEs (1.3% vs. 0.4%) and discontinuations led by TEAEs (2.6% vs. 1.3%) were observed in Lu AA21004 group.

Table 65: Overview of TEAEs in the GAD Relapse-Prevention Study 12473A

Open-Label Treatment Period		
	Lu AA21004	
	Events	Subjects (%)
Subjects treated	N/A	687
TEAEs	1673	528 (76.9)
Serious TEAEs	10	10 (1.5)
Leading to study discontinuation	NC	61 (8.9)

Double-Blind Treatment Period				
	Placebo		Lu AA21004	
	Events	Subjects (%)	Events	Subjects (%)
Subjects treated	N/A	230	N/A	229
TEAEs	314	124 (53.9)	321	126 (55.0)
Serious TEAEs	1	1 (0.4)	3	3 (1.3)
Leading to study discontinuation	NC	3 (1.3)	NC	6 (2.6)

Source: ISS Table 2.d, page 85/410
N/A=not applicable, NC=not counted

7.4.1.5 Overview of TEAEs in the MDD Open-Label Long-Term Pool

The incidences of any TEAEs were similar between the completed studies (72.1% in Study 11492C/11984B/301) and the ongoing studies (73.1% in Study 314/13267B).

A total of 7.6% of subjects experienced TEAEs leading to study discontinuations.

The total incidence of serious TEAEs was low (2.7%). One death (UA004/S3116) was reported in this study pool. This case was discussed in **Section 7.3.2 Death**.

Table 66: Overview of TEAEs in the MDD Open-Label Long-Term Pool

	Number of Events or Subjects (%)					
	Studies 11492C/11984B/301 N=1443		Studies 314/13267B N=1122		Lu AA21004 Total N=2565	
	Events	Subjects	Events	Subjects	Events	Subjects
Any TEAEs	3780	1041 (72.1)	2628	820 (73.1)	6408	1861 (72.6)
Related	1952	749 (51.9)	1580	664 (59.2)	3532	1413 (55.1)
Not related	1828	292 (20.2)	1048	156 (13.9)	2876	448 (17.5)
Mild	1928	327 (22.7)	1426	288 (25.7)	3354	615 (24.0)
Moderate	1649	573 (39.7)	1105	455 (40.6)	2754	1028 (40.1)
Severe	203	141 (9.8)	97	77 (6.9)	300	218 (8.5)
Leading to discontinuation		96 (6.7)		98 (8.7)		194 (7.6)
Serious TEAEs	59	48 (3.3)	24	22 (2.0)	83	70 (2.7)
Related	15	15 (1.0)	4	3 (0.3)	19	18 (0.7)
Not related	44	33 (2.3)	20	19 (1.7)	64	52 (2.0)
Leading to study discontinuation		21 (1.5)		9 (0.8)		30 (1.2)
Deaths		1 (<0.1)		0		1 (<0.1)

Source: ISS Table 2.e, page 86/410
Studies included completed studies 11492C/11984B/301 (2.5 to 10 mg) and ongoing 314/13267B (10 to 20 mg).

7.4.1.6 Overview of TEAEs in the Phase 1 Study Pool

The incidence of any TEAEs was higher in Lu AA21004 group (63.2%) than placebo (47.4%). There were no deaths or serious TEAEs leading to discontinuations in the Phase 1 Study Pool. Two serious TEAEs (chest discomfort and dyspnea) in 1 subject were considered related to Lu AA21004 treatment by investigator.

Table 67: Overview of TEAEs in the Phase 1 Study Pool

	Number of Events or Subjects (%)					
	Placebo N=443		Lu AA21004 Total N=1169		Other Study Drugs N=421	
	Events	Subjects	Events	Subjects	Events	Subjects
Any TEAEs	461	210 (47.4)	2349	739 (63.2)	437	174 (41.3)
Related	241	113 (25.5)	1740	577 (49.4)	296	114 (27.1)
Not related	220	97 (21.9)	609	162 (13.9)	141	60 (14.3)
Mild	422	183 (41.3)	2090	591 (50.6)	389	140 (33.3)
Moderate	38	26 (5.9)	252	142 (12.1)	46	32 (7.6)
Severe	1	1 (0.2)	7	6 (0.5)	2	2 (0.5)
Leading to study discontinuation		6 (1.4)		37 (3.2)		4 (1.0)
Serious TEAEs	1	1 (0.2)	3	2 (0.2)	0	0
Related	0	0	2	1 (<0.1)	0	0
Not related	1	1 (0.2)	1	1 (<0.1)	0	0
Leading to study discontinuation		0		0		0
Deaths		0		0		0

Source: ISS Table 2.f, page 87/410. Studies included: Bioavailability studies (106, 10982, 123, 13119A, 13138A, and 13921A), pharmacokinetic studies (10272, 10467, CPH001, CPH002, and CPH003), mass balance study (10477), intrinsic factor studies

(111, 112, and 114), drug-drug interaction studies (101, 102, 103, 109, 110, 113, 115, 116, 117, 118, and 11826A), and pharmacodynamic studies (104, 12689A, 10985, 12260A, and 124).

7.4.2 Deaths

The sponsor reported a total of 6 deaths by the time of this submission, all of which occurred in Lu AA21004 treatment groups in the completed phase 2 and 3 clinical trials. No deaths were reported in the completed phase 1 clinical studies or in the 14 ongoing, un-pooled studies. All 6 deaths were assessed by the investigator as being unrelated to Lu AA21004 treatment.

The causes of death included 2 cancers, 1 suicide, 1 morphine toxicity, 1 road traffic accident, and 1 accidental death. The followings are the narratives.

Subject BG006/S3590
Subject, a 74 year old female on Lu AA21004 5 mg group, was diagnosed with gallbladder cancer on Study Day 39 and died on Study Day 47.

Subject CA204/S1129
Subject, a 46 year old male on Lu AA21004 10 mg group, died from pancreatic cancer on Study Day 280 (239 days after the last dose of study drug).

Subject FR011/S3103
Subject, a 58 year old male in the 12473A GAD relapse prevention study committed suicide two days after withdrawal from study due to erectile dysfunction. His medical history was hypothyroidism and was on levothyroxine. According to the CRF the subject consumed alcohol once a week and was a current smoker.

This subject received Lu AA21004 5 mg for 11 days and then the dose increased to 10 mg that he received for 17 days in the open-label period of the study. Subject started to experience erection difficulties 2 days after the dose increase to 10 mg.

Reportedly the subject set fire to himself two days after having received the last dose of LuAA21004 and two days after his wife asked him to leave the house. He was found dead in his car with some boxes of 12473A study drug. The case report stated that according to patient's journal the patient had problems with his marriage before and during the study. The investigator attributed his suicide to his marital problem.

Based on data from the CRF, the subject answered "no" to having suicidal thoughts in all visits on the C-SSRS and in the subject's MADRS item 10 (suicidal thoughts).

Subject 1009/008
Subject, a 49 year old female on Lu AA21004 5 mg group, was found dead on Study Day 3 in her apartment. The autopsy report stated the cause of death was morphine toxicity and manner of death was accidental. Autopsy external exam revealed needle sticks with surrounding ecchymosis on the antecubital fossae, and abrasions/needle sticks and scars on the forearms. Blood samples were positive for codeine and

morphine. Serum drug screen was positive for opiates, cocaine metabolites, and tricyclics. In this case, suicide could not be ruled out as a cause according to the sponsor.

Subject CA106/S3507
Subject, a 56 year old male on Lu AA21004 5 mg group, died in a motorcycle accident caused by another driver.

Subject UA004/S3116
Subject, a 63 year old male, received Lu AA21104 2.5 mg for 55 days in Study 11984A (MDD Short-Term Pool). His MADRS score was 30 at Baseline and was 15 at Final Visit. At the Baseline Visit for the open-label extension (Study 11984B), the subject received open-label study medication. Later that day, he was found dead having reportedly fallen from the fourth floor balcony. According to the investigator, the subject was not at risk of suicide and there were no signs of a suicidal act. On the day of the event, the subject's MADRS total score was 15 and his suicidal thought scored 0. The subject had no prior history of suicide attempts. No other AEs indicating that the subject was suffering from dizziness or blackouts were reported from Study 11984A. At the autopsy, there was no evidence of ethyl alcohol at judicial-toxicological examination of his body, blood, and urine. Study medication was returned to the site unopened. The investigator considered the event not related to study drug although suicide could not be ruled out as a cause according to the sponsor.

7.4.3 Nonfatal Serious Adverse Events (SAEs)

Summary

- The incidences of SAEs of Lu AA21004 Total group in the MDD and MDD/GAD short-term pool were low (1.0% and 0.9%, respectively) and comparable to placebo and Duloxetine. No dose relationship was observed across the Lu AA21004 dose groups. Four (4) SAEs were experienced by at least 2 subjects in Lu AA21004 treatment groups: depression (4 subjects), suicide attempt (3 subjects), suicidal ideation (3 subjects) and convulsion (2 subjects). Two cases of convulsion were related to traumatic brain injury.

- In the MDD relapse prevention Study 11985A, the incidence of SAEs of Lu AA21004 Total during the Open-Label Period was 2.2%. The incidence of SAEs of Lu AA21004 Total was slightly higher than placebo in the Double-Blind phase (3.4% and 2.1%, respectively).

- In the GAD relapse prevention Study 12473A, the incidence of SAEs of Lu AA21004 Total during the Open-Label Period was 1.5%. The incidence of SAEs of Lu AA21004 Total was higher than placebo in the Double-Blind phase (1.3% and 0.4%, respectively).

7.4.3.1 SAEs in the MDD Short-Term Pool

The MDD short-term pool included 10 Phase 2/3 Controlled Studies: Study 303, 304, 305, 315, 316, 317, 11492A, 11984A, 12541A and 13267A.

The incidence rate of SAEs of Lu AA21004 Total (1.0%) in the MDD Short-Term Pool was comparable to those of placebo (0.9%) and Duloxetine (1.1%). The incidences of SAEs of Lu AA21004 5mg, 10mg, 15mg and 20mg groups were not dose-related (1.5%, 1.3%, 0.4% and 0.4%, respectively).

Table 68: SAE Incidences in the MDD Short-Term Pool

n/N (%)							
MDD Short - Term Pool	**Placebo**	**Lu AA21004 (mg)**					**Duloxetine**
		5	**10**	**15**	**20**	**Total**	
	15/1621 (0.9)	15/1013 (1.5)	9/699 (1.3)	2/449 (0.4)	2/455 (0.4)	31/3060 (1.0)	8/753 (1.1)

Compiled from ISS Tables 2.i page 94/410
Lu AA21004 Total included 1mg and 2.5mg

Table 69 lists all treatment emergent SAEs by preferred term (PT) experienced by subjects in the MDD Short-Term Pool by treatment group, study number (Study No.), and subject number (Subject No.).

Table 69: Tabular Listing of Subjects with SAEs in MDD Short-Term Pool

LuAA21004 dose (mg) Once Daily	**Study No.**	**Subject No.**	**SAEs by Preferred Term**
LuAA21004 1 mg	T21004-305	0018/504	Hypertensive crisis
LuAA21004 2.5 mg	11984A	TW004/S3694	Suicidal ideation
LuAA21004 5 mg	11984A	FR008/S3455	Depression
		BG006/S3590	Jaundice cholestatic
		ES005/S3649	Suicide attempt
	12541A	S1071	Major depression
	T21004-303	0334/302	Drug hypersensitivity
		0311/303	Cerebrovascular accident
		0329/308	Renal cell carcinoma
		0309/312	Injury
		0320/313	Herpes zoster
		0340/317	Colon cancer
		0343/331	Convulsion
	T21004-304	0427/415	Coronary artery disease
		0441/433	Atrial fibrillation
		0428/454	Convulsion Head injury
	T21004-305	0016/516	Tachycardia
LuAA21004 10 mg	11492A	AT002/3002	Depression
		SE005/R1634	Varicella

LuAA21004 dose (mg) Once Daily	Study No.	Subject No.	SAEs by Preferred Term
	11984A	IN001/S3729	Depression
		FR007/S3805	Pelvic fracture
	T21004-305	0037/503	Pancreatitis
		0069/506	Suicide attempt
	T21004-316	6016/601	Kidney infection
		6042/613	Suicide attempt
	T21004-317	7051/706 (c)	Suicidal ideation
LuAA21004 15 mg	T21004-315	5045/503	Suicidal ideation
		5021/514	Stress fracture
LuAA21004 20 mg	13267A	SK001/S1133	Blood pressure decreased Dizziness
		FI003/S1396	Intentional self-injury

Compiled from Appendix B

This reviewer examined the SAEs in the MDD short-term pool and did not find any concerning safety signals.

Four (4) SAEs were experienced by ≥2 subjects in Lu AA21004 treatment groups: depression (4 subjects), suicide attempt (3 subjects), suicidal ideation (3 subjects) and convulsion (2 subjects). The SAEs of depression, suicidal attempt and suicidal ideation were most likely due to the underlying disease – MDD. In terms of the 2 cases of convulsion, one had past medical history of traumatic brain injury and seizure disorder; the other case of convulsion was caused by head trauma.

Other SAEs were experienced only by 1 subject. The cases described below appeared to be concerning, but after reviewing the case reports; we believe most were not related to the study drug. Only the case of pancreatitis and the case of blood pressure decreased did not identify any causes and therefore considered possibly related to the treatment of Lu AA21004.

0018/504 Hypertensive crisis

A 44 year old female subject with a relevant medical history of hypertension, manic episodes and kidney surgery in 1968 experienced a sudden episode of paraplegia on Study Day 8 of Lu AA21004 1mg and was admitted to hospital for overnight observation due to elevated blood pressure. Her BP was 146/102, 143/106 and 142/108 in Screening, Baseline and Visit 3. Her episode of elevated blood pressure was not considered to be related to the treatment of Lu AA21004 because of his past medical history of hypertension.

BG006/S3590 Cholestatic jaundice

See Death. Subject died of gallbladder cancer, which caused cholestatic jaundice.

0334/302 Drug hypersensitivity

This was a 50 year old African American female subject who was hospitalized for an allergic reaction. This event occurred 22 days after the last dose of Lu AA21004 5mg and 1 day after she took clindamycin for a dental abscess. The event was considered to be related to the use of clindamycin not Lu AA21004.

0343/331 Convulsion

48 year old African American male subject with a relevant medical history of traumatic brain injury (TBI) due to gunshot wound, seizure disorder, alcohol use, and recent seizure activity was randomized to LuAA21004 5 mg QD. He had one episode of generalized tonic-clonic activity on Day 26 of Lu AA21004 5mg treatment. Since the subject had history of TBI and seizure disorder, the event may not be related to Lu AA21004 treatment.

0037/503 Pancreatitis

A 55 year old female subject (0037-503) with no relevant medical history LuAA21004 10mg, 22 days after starting study drug, the subject experienced abdominal pain, nausea and poor appetite, a gastroenterologist was consulted and the subject was hospitalized. Pancreatitis was diagnosed. Amylase was 60 U/L. The investigator confirmed the subject does not drink alcohol, and does not have a history of gallstones or recent excessive intake of fatty foods. The outcome of the event of pancreatitis was reported as recovered. The study medication was considered possibly related to pancreatitis by the investigator and therefore the Lu AA21004 treatment was discontinued.

SK001/S1133 Blood pressure decreased

46-year-old female experienced dizziness and blood pressure decreased (70/50 mmHg) 2.5 hours after Lu AA21004 20mg taking. The event occurred 25 days after she started Lu AA21004 20mg treatment. She was treated in ER and recover in the same day. No other causalities were identified and the study drug was considered possibly related to the event.

7.4.3.2 SAEs in MDD/GAD Short-Term Pool

The MDD/GAD short-term pool included 4 additional GAD Phase 3 Controlled Studies: Study 308, 309, 310 and 311.

The overall incidence rate of SAEs of Lu AA21004 Total (0.9%) in the MDD/GAD Short-Term Pool was the same as that of Placebo (0.9%) but less than that of Duloxetine (1.2%).

Table 70: SAEs in the MDD/GAD Short-Term Pool

n/N (%)							
MDD/GAD Short-Term Pool	**Placebo**	**Lu AA21004 (mg)**					**Duloxetine**
		5	**10**	**15**	**20**	**Total**	
	20/2230 (0.9)	16/1466 (1.1)	11/1007 (1.1)	2/449 (0.4)	2/455 (0.4)	37/4128 (0.9)	11/907 (1.2)

Compiled from ISS Tables 2.i page 94/410, Lu AA21004 Total included 1mg and 2.5mg

The following table lists all SAEs experienced by subjects in the GAD Short-Term Pool by treatment group, Study No., and subject No.

Table 71: Tabular Listing of Subjects with SAEs in GAD Short-Term Pool

LuAA21004 dose (mg) Once Daily	Study No.	Subject No.	SAEs by Preferred Term
LuAA21004 2.5 mg	T21004-308	9045/806	Benign prostatic hyperplasia
	T21004-309	0027/903	Inguinal hernia
		0026/906	Pyrexia
LuAA21004 10 mg	T21004-308	9061/801	Abdominal hernia
	T21004-309	0020/909	Abortion spontaneous

Compiled from Appendix B

This reviewer examined every SAE in this GAD short-term pool. The case of pyrexia was considered by the investigator possibly related to the treatment of Lu AA21004 because no other causalities were identified.

0026/906 Pyrexia
36 year old Asian male subject developed 104 degree fever 21 days after initiation of Lu AA21004 2.5mg. The source of fever was not identified during the 2 week hospitalization. The event was considered possibly related to the use of Lu AA21004. CRF provided limited information about the hospitalization.

7.4.3.3 SAEs in MDD Relapse-Prevention Study 11985A

Twenty seven (27) subjects had SAEs in this MDD long-term relapse-prevention Study 11985A (including SAEs occurred in the Safety Follow-up Period, when Lu AA21004 treatment has completed).

In this Study, 14 subjects (2.2%) had treatment emergent SAEs during the Open-Label Period. 7 subjects (3.4%) in Lu AA21004 Total group and 4 subjects (2.1%) in placebo had SAEs during the Double-blind phase.

Table 72: SAEs in the MDD Long-Term Relapse-Prevention Study 11985A

	n/N (%)	
MDD Long-Term Relapse-Prevention Study 11985A	**Placebo**	**Lu AA21004 Total**
Open-Label Phase	--	14/639 (2.2)
Double-Blind Phase	4/192 (2.1)	7/204 (3.4)

Compiled from ISS Tables 2.j page 94/410

Table 73 lists all SAEs experienced by subjects in the MDD Long-Term Relapse-Prevention Study 11985A by treatment group, Study No., and Subject No.

Table 73: Tabular Listing of Subjects with SAEs in MDD Relapse-Prevention Study 11985A

LuAA21004 dose (mg) Once Daily	Study No.	Subject No.	SAEs by Preferred Term
LuAA21004 5 mg	11985A-OL	FI002/S1137	Sebaceous carcinoma
		FR005/S1159	Serotonin syndrome
		FR006/S1213	Intervertebral disc protrusion
		TH002/S1298	Bronchitis
			Cystitis
		BE002/S1302	Depression
		TW001/S1376	Accidental overdose
			Alcohol abuse
		BE003/S1486	Pneumonia
		BE003/S1798	Depression
	11985A-DB	FR002/S1022	Road traffic accident
		NO003/S1175	Streptococcal infection
		FR005/S1218	Road traffic accident
LuAA21004 10 mg	11985A-OL	BE003/S1102	Abdominal pain
		DE006/S1387	Hypoglycaemia (insulin overdose)
		PL003/S1483	Suicide attempt
		ZA006/S1582	Non-cardiac chest pain
		ZA004/S1605	Stress cardiomyopathy
	11985A-DB	BE003/S1059	Alcohol poisoning
		BE002/S1303	Social stay hospitalization
		IN002/S1630	Abortion incomplete
		AU003/S1734	Gastritis

Compiled from Submission Appendix B

This reviewer examined every SAE in MDD Relapse-Prevention Study 11985A. The case of Serotonin syndrome was described below:

FR005/S1159 Serotonin syndrome
39-year-old female subject had one episode of “migraine, insomnia and panic attack” after receiving Lu AA21004 5 mg once daily for 2 days in the open-label phase of Study 11985A. The event lasted 4 days. Her temperature was not measured during the episode. The investigator considered this event as serotonin syndrome and possibly related to Lu AA21004 treatment. This event led to study discontinuation.

7.4.3.4 SAEs in GAD Relapse-Prevention Study 12473A

Eighteen (18) subjects had SAEs during the GAD Long-Term Relapse-Prevention Study 12473A (including the SAEs occurred in Safety Follow-up Period, which Lu AA21004 treatment has completed).

In this study, 10 subjects (1.5%) had treatment emergent SAEs during the open label phase. 3 subjects (1.3%) in the Lu AA21004 Total group and 1 subject (0.4%) in placebo had SAEs during the Double-blind phase.

Table 74: SAEs in the GAD Long-Term Relapse-Prevention Study 12473A

	n/N (%)	
GAD Long-Term Relapse-Prevention Study 12473A	**Placebo**	**Lu AA21004 Total**
Open-Label Phase	--	10/687 (1.5)
Double-Blind Phase	1/230 (0.4)	3/229 (1.3)

Compiled from ISS Tables 2.j page 94/410

Table 75 lists all SAEs experienced by subjects in the GAD Long-Term Relapse-Prevention Study 12473A by treatment group, Study No., and Subject No.

Table 75: Tabular Listing of Subjects with SAEs in GAD Relapse-Prevention Study 12473A

LuAA21004 dose (mg) Once Daily	Study No.	Subject No.	SAEs by Preferred Term
LuAA21004 5 mg	12473A-OL	ZA002/S3093	Rhinitis allergic
		ZA002/S3111	Panic attack
		ZA002/S3184	Appendicitis
		FR004/S3396	Urethral stenosis
	12473A-DB	HU001/S3067	Major depression
		FI001/S3208	Anaphylactic reaction
		HU004/S3251	Nasal septal operation
LuAA21004 10 mg	12473A-OL	EE001/S3134	Atrial fibrillation
		ZA003/S3175	Nephrolithiasis
		ZA004/S3218	Migraine
		HU005/S3283	Cholelithiasis
		ZA011/S3352	Electrocardiogram QT prolonged
		ZA003/S3734	Depressive symptom
		AR015/S3806	Abortion spontaneous

Compiled from Appendix B

This reviewer examined every SAE in GAD Relapse-Prevention Study 12473A listed in the table above. The following described the cases that appeared to be concerning but none were considered to be related to Lu AA21004 treatment by the investigators.

FI001/S3208 Anaphylactic reaction

44 year old female was hospitalized for an anaphylactic allergic reaction after 10 month use of LUAA21004 5 mg and 1 day use of Nasolin (xylometazoline hydrochloride), a

Russian nasal spray. She recovered the 2nd day after the treatment. The event was considered to be related to Nasolin not Lu AA21004.

ZA011/S3352 Electrocardiogram QT prolonged
61-years-old female was hospitalized for an angiogram evaluation due to an episode of QTcF prolongation after receiving LU AA21004 5 mg/Day for 15 days and then 10 mg for 10 weeks in the open label period of GAD Relapse-Prevention Study. QTcF was 485 msec during hospitalization (Baseline QTcF = 424 msec). The angiogram was normal. She continued to receive Lu AA21004 10 mg for another 4 months and the QTcF was measured 404. The investigator considered the event not related to Lu AA21004 use.

7.4.3.5 SAEs in MDD Open-Label Long-Term Pool

Seventy (70) subjects (2.7%) in the completed and ongoing pooled studies combined had at least 1 SAE.

Table 76 lists all SAEs experienced by subjects in the MDD Open-Label Long-Term pool by treatment group, Study No., and Subject No.

Table 76: Tabular Listing of Subjects with SAEs in MDD Open-Label Long-Term Pool

LuAA21004 dose (mg) Once Daily	Study No.	Subject No.	SAEs by Preferred Term
LuAA21004 2.5 mg	11984B	UA001/S3115	Depression
		IN002/S3373	Suicidal ideation
	T21004-301	TW002/S3796	Adjustment disorder with mixed anxiety and depressed mood
		0196/101	Tachycardia paroxysmal
		0105/102	Ischemic stroke
LuAA21004 5 mg	11492C	FI006/3684	Thyroiditis
	11984B	FR007/S3439	Benign neoplasm of eye
			Benign salivary gland neoplasm
		BG004/S3465	Nephrolithiasis
		UA003/S3520	Pneumonia
		IN002/S3585	Menorrhagia
		CA107/S3625	Chest pain
		FR005/S3743	Appendicitis
		LT001/S3843	Dermatitis herpetiformis
	T21004-301	0187/102	Influenza
		0108/103	Arthritis
		0148/103	Influenza
		0159/104	Cholelithiasis
		0238/105	Pyrexia
		0149/107	Uterine hemorrhage

LuAA21004 dose (mg) Once Daily	Study No.	Subject No.	SAEs by Preferred Term
		0238/108	Myocardial infarction
		0244/110	Coronary artery disease
			Pulmonary hypertension
		0115/111	Hip fracture
		0132/111	Confusional state Headache Vomiting
LuAA21004 10 mg	11984B	FR003/S3107	Intentional overdose
		IN002/S3275	Suicidal ideation
		UA002/S3302	Depression
		UA003/S3328	Depression
		AU009/S3399	Back pain
			Muscle spasms
		AU003/S3629	Suicide attempt
		CA106/S3768	Suicidal ideation
	T21004-301	0131/101	Upper gastrointestinal hemorrhage
		0231/101	Suicidal ideation
		0133/102	Anemia Femur fracture Fibula fracture Tachycardia Tibia fracture
		0143/102	Appendicitis
		0115/103	Suicidal ideation Suicide attempt
		0114/104	Abortion induced
		0237/104	Major depression
		0174/106	Dupuytren's contracture
		0222/106	Depression
		0112/107	Diverticulitis
		0150/108	Abscess limb
		0174/109	Femoral neck fracture Edema peripheral
		0132/112	Supraventricular tachycardia
		0118/122	Atrial fibrillation
		0143/125	Umbilical hernia, obstructive
		0245/125	Alcohol abuse
		0244/128	Meniscus lesion
	T21004-314	4147/403	Suicide attempt
		4061/417	Breast cancer
LuAA21004 15 mg	T21004-314	4050/401	Suicidal ideation

LuAA21004 dose (mg) Once Daily	Study No.	Subject No.	SAEs by Preferred Term
		4112/401	Bone neoplasm malignant
		4146/401	Agitation
		4082/402	Asthma
		4151/405	Breast cancer
		4053/408	Malignant melanoma
LuAA21004 20 mg	13267B	FI003/S1343	Cholelithiasis
	T21004-314	4048/401	Breast cancer
		4012/403	Cholecystitis
		4022/403	Ankle fracture Wrist fracture
		4023/403	Phlebitis
		4060/403	Cerebral infarction
		4004/404	Abortion spontaneous
		4033/404	Pneumonia
		4074/404	Uterine leiomyoma
		4019/405	Periorbital cellulitis
		4092/408	Gastritis
		4053/409	Cholecystitis acute
		4061/410	Cholelithiasis
		4124/410	Anxiety Diabetes mellitus

Compiled from Appendix B

SAEs experienced by ≥2 subjects in either the completed studies (Studies 11492C, 11984B, and 301) with lower doses (2.5 to 10 mg) or the ongoing studies (Studies 314 and 13267B) with higher doses (10 to 20 mg) in the MDD open-label long-term pool are: cholelithiasis, appendicitis, influenza, pneumonia, breast cancer, suicidal ideation, depression and suicide attempt.

This reviewer examined every SAE in the MDD open-label long-term pool and did not find any new safety signals. The following described some SAEs that appeared to be concerning.

IN002/S3585 Menorrhagia

42-year-old female patient experienced intermittent menorrhagia 7 months after first dose of open label Lu AA21004 5mg. Subject had a uterine fibroid. She had laparoscopic hysterectomy. The investigator considered the SAEs of menorrhagia possibly related to Lu AA21004 treatment. Uterine fibroid could also be a contributing factor to menorrhagia.

0149/107 Uterine hemorrhage
49 year old, African American female subject had past medical history of intrauterine fibroids and increased intrauterine bleeding. 88 days after the initiation of open label study medication Lu AA21004, the subject experienced worsening of uterine bleeding which required hospitalization. She was diagnosed with iron deficiency anemia secondary to menorrhagia, secondary to fibroids and adenomyosis. Uterine hemorrhage was considered to be related to fibroids and adenomyosis but not Lu AA21004 treatment.

0131/101 Upper gastrointestinal hemorrhage
47 year old Caucasian male subject with a history of aspirin and other non-steroidal anti-inflammatory drugs had a SAE of upper gastrointestinal bleeding and was hospitalized 319 days after starting Lu AA21004. He took 650 mg of aspirin, 440 mg of Aleve, and 650 mg of Tylenol for a headache before the event. The SAE was considered to be related to the use of aspirin and Aleve but not Lu AA21004 use.

7.4.3.6 SAEs in Phase 1 Study Pool
Three (3) subjects in the Lu AA21004 treatment group had SAEs in the Phase 1 Study Pool. One SAE of spontaneous abortion in Phase 1 Study Pool was not listed in Appendix B of the submission.

Table 77: Tabular Listing of Subjects with SAEs in Phase 1 Study Pool

LuAA21004 dose (mg)	Study No.	Subject No.	SAEs by Preferred Term
LuAA21004 10 mg QD + Bupropion 150 mg BID	T21004-117	0001/052	Traumatic fracture
LuAA21004 10 mg QD + Microgynon QD	T21004-102	0001/033	Chest discomfort Dyspnea

Compiled from Appendix B

7.4.4 Dropouts and/or Discontinuations

Summary

- The discontinuation rate of LU AA21004 Total group due to TEAEs was greater than placebo but less than Duloxetine in both MDD and MDD/GAD short-term pools. The discontinuations due to TEAEs were dose-related.

- Nausea was the most common TEAE leading to discontinuation in all study pools except Phase 1 Study Pool.

- In Phase 1 Study Pool, the most common TEAEs leading to discontinuations were skin reactions and vomiting, all of which occurred in Lu AA21004 treated subjects. Eight subjects had the TEAEs related to drug hypersensitivity, which included urticaria (4 subjects); angioedema (2 subjects) and rash (2 subjects).

Seven (7 subjects) had vomiting. Nausea occurred in 2 subjects treated with Lu AA21004.

7.4.4.1 Discontinuations in the MDD Short-Term Pool and the MDD/GAD Short-Term Pool

In the MDD Short-Term Pool, the discontinuations of LU AA21004 Total group (6.2%) due to TEAEs was greater than placebo (3.8%) but less than active control Duloxetine group (9.0%). The same pattern was demonstrated in the MDD/GAD Short-Term Pool.

There was a dose-related increase in discontinuation rate due to TEAEs across Lu AA21004 groups: 5.2%, 6.0%, 8.0% and 8.4%, respectively in MDD short-term pool and 5.3%, 5.9%, 8.0% and 8.4%, respectively in MDD/GAD short-term pool for Lu AA21004 5 mg, 10 mg, 15 mg and 20 mg.

Table 78: Discontinuations Due to Treatment Emergent Adverse Events in the MDD Short-Term Pool and the MDD/GAD Short-Term Pool

Short-Term Pools	n/N (%)						
	Placebo	Lu AA21004 (mg)					Duloxetine
		5	10	15	20	Total(a)	
MDD Short-Term Pool	62/1621 (3.8)	53/1013 (5.2)	42/699 (6.0)	36/449 (8.0)	38/455 (8.4)	191/3060 (6.2)	68/753 (9.0)
MDD/GAD Short-Term Pool	80/2230 (3.6)	77/1466 (5.3)	59/1007 (5.9)	36/449 (8.0)	38/455 (8.4)	246/4128 (6.0)	91/907 (10.0)

Total (a): included doses 1mg and 2.5mg
Source: ISS: Table 2.o, page 103/410

The following table summarizes the TEAEs leading to discontinuations experienced by ≥1% subjects in any Lu AA21004 group in the MDD Short-Term Pool. Nausea was the most common TEAE leading to discontinuations across Lu AA21004 groups (dose-related) and Duloxetine.

Table 79: TEAEs Leading to Discontinuation in ≥1% Subjects in Any Lu AA21004 Group Based on Preferred Term in the MDD Short-Term Pool

	Number of Subjects (%)						
	Placebo N=1621	Lu AA21004 (mg)					Duloxetine N=753
		5 N=1013	10 N=699	15 N=449	20 N=455	Total N=3060	
TEAEs leading to discontinuation	62 (3.8)	53 (5.2)	42 (6.0)	36 (8.0)	38 (8.4)	191 (6.2)	68 (9.0)
Nausea	5 (0.3)	13 (1.3)	13 (1.9)	17 (3.8)	20 (4.4)	67 (2.2)	26 (3.5)
Vomiting	3 (0.2)	1 (<0.1)	5 (0.7)	2 (0.4)	2 (0.4)	13 (0.4)	4 (0.5)
Suicidal ideation	3 (0.2)	0	1 (0.1)	0	0	4 (0.1)	0

Compiled from ISS Table 2.q, page 105/410

The following table shows the TEAEs Leading to Discontinuation in MDD/GAD short-term pool.

The overall incidence of TEAEs leading to discontinuation in MDD/GAD short-term pool (6.0%) was similar to that of MDD Short Term Pool (6.2%). Nausea was the most common TEAEs leading to discontinuations across Lu AA21004 groups and was dose-related in MDD/GAD short-term pool, which was consistent with the findings in MDD Short-Term Pool.

Table 80: TEAEs Leading to Discontinuation in ≥1% of Subjects in Any Lu AA21004 Group Based on Preferred Term in the MDD/GAD Short-Term Pool

SOC Preferred Term	Number of Subjects (%)						
	Placebo N=2230	Lu AA21004 (mg)					Duloxetine N=907
		5 N=1466	10 N=1007	15 N=449	20 N=455	Total N=4128	
TEAEs leading to discontinuation	80 (3.6)	77 (5.3)	59 (5.9)	36 (8.0)	38 (8.4)	246 (6.0)	91 (10.0)
Nausea	6 (0.3)	18 (1.2)	18 (1.8)	17 (3.8)	20 (4.4)	81 (2.0)	33 (3.6)

Compiled from ISS Table 2.r, page 107/410

We examined Appendix B which listed all AEs leading to discontinuations in the MDD and GAD Short-Term Pool. This reviewer compiled Table 81 and Table 82, which list the AEs leading to discontinuations, which appeared to be concerning and we examined the cases in more details.

All the discontinuations due to abnormal labs (hematology, urine and Liver Function Test) are discussed in the Section of Laboratory.

All the discontinuations due to abnormal vitals are discussed in the Section of vital sign.

All the discontinuations due to weight changes are discussed in the Section of weight.

All the discontinuations due to abnormal EKGs are discussed in the EKG section.

Table 81: TEAEs Leading to Discontinuations in MDD Short-Term Pool

Lu AA21004 Doses (mg)	Study No.	Subject No.	AEs
2.5	11984A	TW001/S3094	Bradycardia
		KR001/S3241	Heart rate decreased
		UA002/S3867	White blood cell count decreased
	T21004-304	0411/401	Dizziness Headache
		0451/412	Breast discharge
5	11492A	SK002/3243	Electrocardiogram ST segment
	11984A	ES004/S3016	Chills Dry mouth Hyperhidrosis Tremor Vision blurred
		IN008/S3356	Tremor
		KR003/S3409	Chest discomfort
		UA002/S3608	Blood alkaline phosphatase increased Gamma-glutamyltransferase increased
	12541A	SE005/S1456	Dizziness
	T21004-303	0309/302	Dizziness
		0343/331	Convulsion
	T21004-304	0441/433	Atrial fibrillation
10	11492A	FR004/3502	Dizziness postural
	11984A	RO002/S3605	Chest pain
	T21004-305	0037/503	Pancreatitis
	T21004-317	7039/718	Blood pressure increased
		7044/721	Abdominal pain upper Arthralgia Dizziness Dry eye Headache Insomnia Nausea Vision blurred
15	13267A	LV005/S1351	Anxiety Tremor
20	13267A	BE001/S1511	Tension
	T21004-315	5049/506	Dizziness
	T21004-316	6058/601	Hypertension
		6042/621	Irritability

Compiled from Appendix B

Table 82: TEAEs Leading to Discontinuations in GAD Short-Term Pool

Lu AA21004 Doses (mg)	Study No.	Subject No.	AEs
2.5	T21004-308	9022/822	Syncope
	T21004-309	0020/904	Blood bilirubin increased
5	T21004-308	9076/802	Somnolence
	T21004-311	0070/209	Blood urine present
10	T21004-308	9058/818	Neutrophil count decreased

Compiled from Appendix B

7.4.4.2 Discontinuations due to TEAEs in the MDD Relapse-Prevention Study 11985A

In the Open-Label Period of the MDD Relapse-Prevention Study 11985A, 8.6% experienced TEAEs leading to discontinuations. Nausea (2.7%) and vomiting (1.3%) were the most common TEAEs leading to discontinuations.

In the Double-blind Period, the overall incidence of TEAEs leading to discontinuation was higher in the Lu AA21004 Total group (6.9%) than placebo (1.0%). Nausea (1.5%) was the most common TEAEs leading to discontinuations in the Lu AA21004 Total group.

Table 83: Discontinuations Due to TEAEs in the MDD Relapse-Prevention Study 11985A

Study 11985A	n/N (%)	
	Placebo	Lu AA21004 Total
Open-Label Period	--	55/639 (8.6)
Double-Blind Period	2/192 (1.0)	14/204 (6.9)

Source: ISS, page 103/410

This reviewer examined the Appendix B which listed all TEAEs leading to discontinuations especially the following cases which appeared to be of concerns and we examined these cases in more details.

Table 84: TEAEs Leading to Discontinuations in MDD Relapse-Prevention Study

LuAA21004 Doses (mg)	Study No.	Subject No.	AEs
5	11985A-OL	CA204/S1324	Alanine aminotransferase increased
		CA202/S1383	Alanine aminotransferase increased
		IN005/S1546	Electrocardiogram QT prolonged
		DE006/S1636	Sinus bradycardia
		DE006/S1779	Tachycardia
10	11985A-OL	DE004/S1257	Laboratory test abnormal
		ZA004/S1605	Stress cardiomyopathy
10	11985A-DB	CA202/S1353	Alanine aminotransferase increased

Compiled from Appendix B

The discontinuations due to abnormal labs are reviewed in the lab section.

7.4.4.3 Discontinuations due to TEAEs in the GAD Relapse-Prevention Study 12473A

In the Open-Label Period of the GAD Relapse-Prevention Study 12473A, 8.9% of subjects experienced TEAEs leading to discontinuations. The most common TEAE leading to discontinuation was nausea (2.9%).

During the Double-Blind Period, the overall incidence of TEAEs leading to discontinuation was higher in the Lu AA21004 group (2.6%) than in the placebo group (1.3%).

Table 85: Discontinuations Due to TEAEs in the GAD Relapse-Prevention Study 12473A

Study 12473A	n/N (%)	
	Placebo	Lu AA21004 Total
Open-Label Period	--	61/687 (8.9)
Double-Blind Period	3/230 (1.3)	6/229 (2.6)

Source: ISS, page 103/410

This reviewer examined the Appendix B which listed all AEs leading to discontinuations especially the following cases which appeared to be of concerns and we examined these cases in more details (Table 86).

Table 86: TEAEs Leading to Discontinuations in GAD Relapse-Prevention Study

LuAA21004 Doses (mg)	Study No.	Subject No.	AEs
5	12473A-OL	FI010/S3043	Ventricular tachycardia
		ZA010/S3234	Blood pressure increased
		HU005/S3326	Hypotension
		FI006/S3339	Electrocardiogram QT prolonged
5	12473A-DB	FI001/S3208	Anaphylactic reaction
		HU005/S3267	Respiratory failure
10	12473A-OL	FI012/S3493	Muscle rigidity, tremor

Compiled from Appendix B

7.4.4.4 Discontinuations due to TEAEs in the MDD Open-Label Long-Term Pool

TEAEs leading to discontinuation experienced by ≥1% subjects in either the completed studies (Studies 11492C, 11984B, and 301) with lower doses (2.5 to 10 mg) or ongoing studies (Studies 314 and 13267B) with higher doses (10 to 20 mg) in the MDD Open-Label Long-Term Pool are summarized in Table 87. Studies with higher doses had higher discontinuation rates due to TEAEs. Again, nausea was the most common TEAEs causing discontinuations and appeared to be dose-related.

Table 87: TEAEs Leading to Discontinuation in ≥1% of Subjects in Any LuA21004 Group Based on Preferred Term in the MDD Open-Label Long-Term Pool

	Number of Subjects (%)		
	Studies 11492C/11984B/301 Doses (2.5 - 10 mg) N=1443	**Studies 314/13267B Doses (10 – 20 mg) N=1122**	**Lu AA21004 Total N=2565**
TEAEs Leading to Discontinuations	96 (6.7)	98 (8.7)	194 (7.6)
Nausea	14 (1.0)	28 (2.5)	42 (1.6)

Compiled from ISS, Table 2.s page 109/410

This reviewer has examined the Appendix B in the submission which listed all AEs leading to discontinuations especially the following cases which appeared to be of concerns (Table 88).

Table 88: TEAEs Leading to Discontinuations in MDD Open-Label Long-Term Pool

LuAA21004 Doses (mg)	Study No.	Subject No.	AEs
2.5	11984B	BG003/S3531	Alanine aminotransferase increased
5	11984B	LT002/S3171	Neutrophil count decreased
		BG004/S3397	Electrocardiogram QT prolonged
		KR004/S3769	Gamma-glutamyltransferase increased
	T21004-301	0175/104	Visual impairment
		0196/110	White blood cell count decreased
		0114/112	Hallucination, auditory
		0115/112	Liver function test abnormal
		0245/134	Electrocardiogram QT prolonged
10	11984B	CA103/S3053	Gamma-glutamyltransferase increased
	T21004-301	0148/105	Hypertension
		0154/106	Blood pressure increased
		0118/122	Atrial fibrillation
15	T21004-314	4051/403	Hepatic enzyme increased
		4003/404	Atrial fibrillation
		4023/408	Blood creatinine increased
20	T21004-314	4161/402	Liver function test abnormal
		4128/409	Hepatic enzyme increased
		4061/410	Cholelithiasis
		4013/411	Alanine aminotransferase increased

Compiled from Appendix B

7.4.4.5 Discontinuations due to TEAEs in the Phase 1 Study Pool

The Lu AA21004 Total group had a higher incidence of TEAEs leading to discontinuations (37 subjects, 3.2%) than Placebo (6 subjects, 1.4%).

The most common TEAEs leading to discontinuations in the Phase 1 Study Pool were skin reactions and vomiting, which all occurred in Lu AA21004 treated subjects. Eight subjects had the TEAE related to hypersensitivity, which included urticaria (4 subjects); angioedema (2 subjects) and rash (2 subjects). Seven (7 subjects [0.6%]) had vomiting. Nausea occurred in 2 Lu AA21004 treated subjects. These TEAEs were considered to be related to the study drug.

This reviewer has examined the Appendix B which listed all AEs leading to discontinuations especially the following cases (Table 89).

Table 89: TEAEs Leading to Discontinuations in Phase 1 Study Pool

LuAA21004 Doses (mg)	Study No.	Subject No.	AEs
10	T21004-104	0001/432	Blood pressure increased Sinus tachycardia
		0001/519	Syncope
	T21004-111	0001/039	Angioedema
		0001/046	Angioedema
		0001/073	Blood pressure increased
		0001/111	Blood pressure increased
	T21004-114	0001/040	Syncope
	T21004-117	0001/006	Urticaria
10 +Bupropion 150 mg BID	T21004-117	0001/060	Urticaria
		0001/070	Urticaria
		0001/100	Urticaria
10 + Lithium 450 mg BID	T21004-118	0001/005	Syncope
		0001/013	Transaminases increased
20	12260A	LORCH/R0315	Blister Rash
	Lu AA21004_123	4001/082	Electrocardiogram PR prolongation
40	T21004-104	0001/032	Sinus tachycardia
	T21004-110	0001/092	Haematochezia
9	10982	001/S0121	Alanine aminotransferase increased

Source: Compiled from Appendix B

7.4.5 Significant Adverse Events/Adverse Events of Special Interest

7.4.5.1 Suicidal Ideation and Behavior

The sponsor used the Columbia-Suicide Severity Rating Scale (C-SSRS) to identify the suicidal ideation and behavior in the Lu AA21004 clinical program. They also

investigated the suicidal ideation and behavior based on TEAEs using the Standardized MedDRA Queries (SMQ) suicide/self-injury.

Suicidal Ideation and Behavior Based on the C-SSRS

The sponsor utilized C-SSRS in 18 completed and 2 ongoing studies: 3 clinical pharmacology studies (13921A, 123, and 124), 9 phase 3 studies in MDD (8 short-term studies [303, 304, 305, 13267A, 315, 316, 317, 12541A] and 1 open-label long-term study [301]), and 5 phase 3 studies in GAD (4 short-term [308, 309, 310, and 311] and 1 relapse-prevention study [12473A]), and the ongoing studies 314 and 13267B.

Suicide-related events based on C-SSRS in the MDD Short-Term Pool

Suicide-related events based on C-SSRS during the entire study for the MDD Short-Term Pool are shown in the following table. The incidences of suicidal ideation or behavior were similar among treatment groups. No completed suicide was reported in any studies for the MDD/GAD Short-Term Pool.

Table 90: Suicide-Related Events Based on C-SSRS during Entire Study - MDD Short-Term Studies

	Number of Subjects (%)						
	Placebo (N=1223)	Lu AA21004 (mg)					Duloxetine (N=447)
		5 (N=592)	10 (N=448)	15 (N=449)	20 (N=455)	Total (N=2233)	
Number of subjects	1199	586	446	445	447	2211	442
No suicidal ideation or behavior (0)	995 (83.0)	473 (80.7)	386 (86.5)	389 (87.4)	380 (85.0)	1874 (84.8)	392 (88.7)
Any suicidal ideation or behavior (1-9)	204 (17.0)	113 (19.3)	60 (13.5)	56 (12.6)	67 (15.0)	337 (15.2)	50 (11.3)
Suicidal ideation (1-5)	203 (16.9)	112 (19.1)	58 (13.0)	56 (12.6)	67 (15.0)	334 (15.1)	50 (11.3)
1-Wish to be dead	159 (13.3)	86 (14.7)	49	38 (8.5)	50 (11.2)	255 (11.5)	36 (8.1)
2-Nonspecific active suicidal thoughts	19 (1.6)	8 (1.4)	3 (0.7)	5 (1.1)	7 (1.6)	27 (1.2)	3 (0.7)
3-Active suicidal ideation with any methods (not plan) without intent to act	22 (1.8)	17 (2.9)	4 (0.9)	11 (2.5)	9 (2.0)	46 (2.1)	7 (1.6)
4-Active suicidal ideation with some intent to act, without specific plan	2 (0.2)	1 (0.2)	1 (0.2)	0	1 (0.2)	3 (0.1)	2 (0.5)
5-Active suicidal ideation with specific plan and intent	1 (<0.1)	0	1 (0.2)	2 (0.4)	0	3 (0.1)	2 (0.5)
Suicidal behavior (6-10)	1 (<0.1)	1 (0.2)	2 (0.4)	0	0	3 (0.1)	0
6-Preparatory acts or behavior	0	1 (0.2)	0	0	0	1 (<0.1)	0

	Number of Subjects (%)						
	Placebo (N=1223)	Lu AA21004 (mg)					Duloxetine (N=447)
		5 (N=592)	10 (N=448)	15 (N=449)	20 (N=455)	Total (N=2233)	
Number of subjects	1199	586	446	445	447	2211	442
7-Aborted attempt	1 (<0.1)	0	0	0	0	0	0
8-Interrupted attempt	0	0	0	0	0	0	0
9-Nonfatal suicide attempt	0	0	2 (0.4)	0	0	2 (<0.1)	0
10-Completed suicide	0	0	0	0	0	0	0
Non-suicidal self-injurious behavior	3 (0.3)	0	1 (0.2)	1 (0.2)	1 (0.2)	3 (0.1)	1 (0.2)

Lu AA21004 Total included doses 1mg and 2.5mg.
Source: ISS Table 2.jj, page 152/410
In column headings, N=number of subjects in the safety set.
Note 1: Subjects were counted once using the most severe event (behavior>ideation). Subjects could have also reported non-suicidal self-injurious behavior and these non-suicidal events were not included in the determination of the most severe event.

Suicide-related events based on C-SSRS in the MDD/GAD Short-Term Pool

Suicide-related events based on C-SSRS during the entire study for the MDD/GAD Short-Term Pool are shown in the following table. Lu AA21004 20mg has slightly higher percentage of any suicidal ideation or behavior (15% vs. 9-13% in others). No completed suicide was reported in any studies for the MDD/GAD Short-Term Pool.

Table 91: Suicide-Related Events Based on C-SSRS during Entire Study - MDD/GAD Short-Term Pool

	Number of Subjects (%)						
	Placebo (N=1832)	Lu AA21004 (mg)					Duloxetine (N=601)
		5 (N=1045)	10 (N=756)	15 (N=449)	20 (N=455)	Total (N=3301)	
Number of subjects	1796	1029	749	445	447	3256	592
No suicidal ideation or behavior (0)	1572 (87.5)	905 (87.9)	682 (91.1)	389 (87.4)	380 (85.0)	2892 (88.8)	539 (91.0)
Any suicidal ideation or behavior (1-9)	224 (12.5)	124 (12.1)	67 (8.9)	56 (12.6)	67 (15.0)	364 (11.2)	53 (9.0)
Suicidal ideation (1-5)	223 (12.4)	123 (12.0)	64 (8.5)	56 (12.6)	67 (15.0)	360 (11.1)	53 (9.0)
1-Wish to be dead	175 (9.7)	95 (9.2)	53 (7.1)	38 (8.5)	50 (11.2)	274 (8.4)	39 (6.6)
2-Nonspecific active suicidal thoughts	21 (1.2)	9 (0.9)	3 (0.4)	5 (1.1)	7 (1.6)	29 (0.9)	3 (0.5)
3-Active suicidal ideation with any methods (not plan) without intent to act	24 (1.3)	18 (1.7)	6 (0.8)	11 (2.5)	9 (2.0)	51 (1.6)	7 (1.2)
4-Active suicidal ideation with some intent to act, without specific plan	2 (0.1)	1 (<0.1)	1 (0.1)	0	1 (0.2)	3 (<0.1)	2 (0.3)

	Number of Subjects (%)						
	Placebo (N=1832)	Lu AA21004 (mg)					Duloxetine (N=601)
		5 (N=1045)	10 (N=756)	15 (N=449)	20 (N=455)	Total (N=3301)	
Number of subjects	1796	1029	749	445	447	3256	592
5-Active suicidal ideation with specific plan and intent	1 (<0.1)	0	1 (0.1)	2 (0.4)	0	3 (<0.1)	2 (0.3)
Suicidal behavior (6-10)	1 (<0.1)	1 (<0.1)	3 (0.4)	0	0	4 (0.1)	0
6-Preparatory acts or behavior	0	1 (<0.1)	1 (0.1)	0	0	2 (<0.1)	0
7-Aborted attempt	1 (<0.1)	0	0	0	0	0	0
8-Interrupted attempt	0	0	0	0	0	0	0
9-Nonfatal suicide attempt	0	0	2 (0.3)	0	0	2 (<0.1)	0
10-Completed suicide	0	0	0	0	0	0	0
Non-suicidal self-injurious behavior	3 (0.2)	1 (<0.1)	1 (0.1)	1 (0.2)	1 (0.2)	5 (0.2)	1 (0.2)

Source: ISS Table 2.gg, page 144/410
Lu AA21004 Total included doses 1mg and 2.5mg.
In column headings, N=number of subjects in the safety set.
Subjects were counted once using the most severe event (behavior>ideation). Subjects could have also reported non-suicidal self-injurious behavior and these non-suicidal events were not included in the determination of the most severe event.

Suicide-related events based on C-SSRS in the GAD Relapse-Prevention Study 12473A

In Study 12473A, during the Double-Blind Period, the incidences of suicidal ideation or behavior were 4.8% and 2.6% in placebo and Lu AA21004 Total respectively.

Suicidal Ideation and Behavior Based on TEAEs in the SMQ Suicide/Self-Injury
The sponsor performed the SMQ Suicide/Self-injury on reported TEAEs.

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 7 reported as SAEs in Lu AA21004 group (0.2%), 0 in placebo and 1 in Duloxetine (0.1%). There were 3 suicide attempt in Lu AA21004 group and none in either placebo or Duloxetine group.

Table 92: Suicide/Self-injury SMQ Overview and TEAEs by Preferred Term in the MDD Short-Term Pool

Medical Category	Number of Subjects (%)						
	Placebo N=1621	Lu AA21004 (mg)					Duloxetine N=753
		5 N=1013	10 N=699	15 N=449	20 N=455	Total N=3060	
Suicidal Ideation and Behavior	7 (0.4)	2 (0.2)	7 (1.0)	3 (0.7)	3 (0.7)	19 (0.6)	5 (0.7)
AEs Leading to Discontinuation	3 (0.2)	1 (<0.1)	3 (0.4)	0	0	7 (0.2)	0
SAEs	0	1 (<0.1)	3 (0.4)	1 (0.2)	1 (0.2)	7 (0.2)	1 (0.1)
Suicide/self-injury SMQ	7 (0.4)	2 (0.2)	7 (1.0)	3 (0.7)	3 (0.7)	19 (0.6)	5 (0.7)
Suicidal ideation	5 (0.3)	0	2 (0.3)	3 (0.7)	2 (0.4)	10 (0.3)	4 (0.5)
Intentional overdose	1 (<0.1)	1 (<0.1)	2 (0.3)	0	1 (0.2)	5 (0.2)	1 (0.1)
Suicide attempt	0	1 (<0.1)	2 (0.3)	0	0	3 (<0.1)	0
Intentional self-injury	0	1 (<0.1)	0	0	1 (0.2)	2 (<0.1)	0
Self-injurious behavior	1 (<0.1)	0	1 (0.1)	0	0	1 (<0.1)	1 (0.1)

Source: ISS table 2.tt page 167/410. Lu AA21004 Total included doses 1mg and 2.5mg.

The findings in MDD/GAD short-term pool were similar to those in MDD short-term pool.

Table 93: Suicide/Self-injury SMQ Overview and TEAEs by Preferred Term in the MDD/GAD Short-Term Pool

Medical Category	Number of Subjects (%)						
	Placebo N=2230	Lu AA21004 (mg)					Duloxetine N=907
		5 N=1466	10 N=1007	15 N=449	20 N=45	Total N=4128	
Suicidal Ideation and Behavior	9 (0.4)	3 (0.2)	9 (0.9)	3 (0.7)	3 (0.7)	25 (0.6)	5 (0.6)
AEs Leading to Discontinuation	3 (0.1)	1 (<0.1)	3 (0.3)	0	0	7 (0.2)	0
SAEs	0	1 (<0.1)	3 (0.3)	1 (0.2)	1 (0.2)	7 (0.2)	1 (0.1)
Suicide/self-injury SMQ	9 (0.4)	3 (0.2)	9 (0.9)	3 (0.7)	3 (0.7)	25 (0.6)	5 (0.6)
Suicidal ideation	7 (0.3)	0	4 (0.4)	3 (0.7)	2 (0.4)	14 (0.3)	4 (0.4)
Intentional overdose	1 (<0.1)	1 (<0.1)	2 (0.2)	0	1 (0.2)	5 (0.1)	1 (0.1)
Self-injurious behavior	1 (<0.1)	1 (<0.1)	1 (<0.1)	0	0	3 (<0.1)	1 (0.1)
Suicide attempt	0	1 (<0.1)	2 (0.2)	0	0	3 (<0.1)	0
Intentional self-injury	0	1 (<0.1)	0	0	1 (0.2)	2 (<0.1)	0

Source: ISS table 2.ss page 166/410. Lu AA21004 Total included doses 1mg and 2.5mg.

In the MDD Relapse-Prevention Study 11985A, 5 subjects (0.8%) in the open-label period and 1 subject (0.5%) in the placebo group in the double blind period had suicidal ideation and behavior (Table 94).

Table 94: Suicidal Ideation and Behavior Adverse Events by MedDRA Preferred Term in MDD Relapse-Prevention Study 11985A

Medical Category/ Medical Query/ Preferred Term	Number of Subjects (%)		
	Open-Label	Double-Blind	
	LuAA21004 Total (N=639)	Placebo (N=192)	LuAA21004 Total (N=204)
Suicidal Ideation and Behavior	5 (0.8)	1 (0.5)	0
Intentional overdose	3 (0.5)	1 (0.5)	0
Suicidal ideation	1 (0.2)	0	0
Suicide attempt	1 (0.2)	0	0

Source: compiled from Appendix F: Table 2.6.1.8 page 2527/26956

In the GAD Relapse-Prevention Study 12473A, 8 subjects (1.2%) in the open-label period and 5 subjects (2.2%) in the placebo in the double blind period had suicidal ideation and behavior (Table 95).

Table 95: Suicidal Ideation and Behavior Adverse Events by MedDRA Preferred Term in GAD Relapse-Prevention Study 12473A

Medical Category/ Medical Query/ Preferred Term	Number of Subjects (%)		
	Open-Label	Double-Blind	
	LuAA21004 Total (N=687)	Placebo (N=230)	LuAA21004 Total (N=229)
Suicidal Ideation and Behavior	8 (1.2)	5 (2.2)	0
Completed suicide	1 (0.1)	0	0
Intentional overdose	3 (0.4)	3 (1.3)	0
Suicidal ideation	4 (0.6)	2 (0.9)	0

Source: compiled from Appendix F: Table 2.7.1.8 page 2550/26956

Table 96: Suicidal Ideation and Behavior Adverse Events by MedDRA Preferred Term in MDD Open-Label Long-Term Pool

Medical Category/ Medical Query/ Preferred Term	Number of Subjects (%)		
	Studies 11492C/11984B/301 (N=1443)	Studies 314/13267B (N=1122)	LuAA21004 Total (N=2565)
Suicidal Ideation and Behavior	13 (0.9)	8 (0.7)	21 (0.8)
Suicidal ideation	7 (0.5)	6 (0.5)	13 (0.5)
Intentional overdose	4 (0.3)	0	4 (0.2)
Suicide attempt	2 (0.1)	1 (<0.1)	3 (0.1)
Self-injurious behavior	1 (<0.1)	0	1 (<0.1)
Self-injurious ideation	0	1 (<0.1)	1 (<0.1)

Source: compiled from Appendix F: Table 2.2.1.8.8 page 1928/26956

7.4.5.2 Serotonin Syndrome

The sponsor performed Lundbeck/Takeda-defined MedDRA Queries (LTMQ) search for the TEAEs of serotonin syndrome, which only revealed 1 SAE of serotonin syndrome after the first dose of open-label Lu AA21004 5 mg in the MDD long-term relapse-prevention Study 11985A, which resulted in discontinuation.

7.4.5.3 Abnormal Bleeding

Abnormal Bleeding on TEAEs in the SMQ Search

The sponsor performed SMQ search for the TEAEs related to abnormal bleeding.

In the MDD/GAD Short-Term Pool, abnormal bleeding SMQ overview and TEAEs by preferred term did not reveal any SAEs in Lu AA21004 group but 1 in Duloxetine. There were 3 discontinuations in Lu AA21004 groups (1 case of blood urine, menometrorrhagia and menorrhagia in each of 5 mg, 10 mg, and 15 mg group). The incidence of overall abnormal bleeding for Lu AA21004 Total was slightly higher than placebo and Duloxetine (1.7%, 1.2%, and 1.1% respectively) (Table 97). The SMQ search In the MDD Short-Term Pool had similar findings.

Table 97: Abnormal Bleeding SMQ Overview and TEAEs by Preferred Term in the MDD/GAD Short-Term Pool

Medical Category	Number of Subjects (%)						
	Placebo N=2230	Lu AA21004 (mg)					Duloxetine N=907
		5 N=1466	10 N=1007	15 N=449	20 N=455	Total N=4128	
Abnormal Bleeding	27 (1.2)	25 (1.7)	22 (2.2)	6 (1.3)	5 (1.1)	72 (1.7)	10 (1.1)
AEs Leading to Discontinuation	0	1 (<0.1)	1 (<0.1)	1 (0.2)	0	3 (<0.1)	0
SAEs	0	0	0	0	0	0	1 (0.1)

Source: compiled from Table 2.xx in ISS page 177/410

The SMQ search in the MDD and GAD Long-Term Relapse-Prevention Studies did not reveal any SAE of abnormal bleeding or discontinuations due to abnormal bleeding in Lu AA21004 groups.

In the MDD Open-Label Long-Term Pool, there were 3 subjects (0.1%) in the Lu AA21004 treatment group experienced SAEs (menorrhagia, uterine hemorrhage, and upper gastrointestinal hemorrhage) and no discontinuations due to abnormal bleeding. These 3 SAEs probably were not related to the use of Lu AA21004.

Clinical Pharmacology Studies 109 and 116

The sponsor conducted clinical pharmacology studies to assess the potential of Lu AA21004 to attenuate and/or enhance the anticoagulant effect of warfarin and aspirin.

Co-administration of Lu AA21004 10 mg for 14 days with multiple doses of warfarin did not have significant effects relative to placebo in prothrombin or plasma R- and S-warfarin values or international normalized ratio (INR) (Study 109).

Co-administration of Lu AA21004 10 mg for 14 days with multiple doses of aspirin for 6 days did not show synergetic effect on the ability of aspirin to inhibit platelet aggregation (Study 116).

For detailed information, please refer to the comprehensive review by clinical pharmacology.

7.4.5.4 Seizure

In the MDD/GAD Short-Term Pool, 2 subjects (0.1%) in the Lu AA21004 5 mg group had preferred terms of convulsion that were both SAEs, which were not related to Lu AA21004 treatment (refer to the SAE section). No convulsions occurred in the other pool or in the relapse-prevention studies.

7.4.5.5 Akathisia and Dyskinesia

Akathisia

In the MDD/GAD short-term pool, the incidence of Akathisia was 0.9%, 0.6% and 1.7% in Lu AA21004 Total, placebo and Duloxetine group, respectively. The incidence of Lu AA21004 5 mg, 10 mg, 15 mg and 20 mg was 0.8%, 1.3%, 0% and 1.1% and was not dose-related. There were no SAEs but had 4 subjects discontinued due to TEAE of Akathisia. The MDD short-term had similar findings.

In the MDD Long-Term Relapse-Prevention Study 11985A, the overall incidence of TEAEs captured in the SMQ Akathisia was 1.3% in the Open-Label Period; 1.0% for the Lu AA21004 Total group and 0 for placebo in the Double-Blind Period. There were no SAEs but 1 subject discontinued due to restlessness during the Open-Label Period.

In the GAD Long-Term Relapse-Prevention Study 12473A, the overall incidence of TEAEs captured in the SMQ Akathisia was 0.3% in the Open-Label Period; 0.4% for the Lu AA21004 Total group in the Double-Blind Period. There were no SAEs but 1 subject discontinued due to restlessness during the Open-Label Period.

In the MDD Open-Label Long-Term Pool, there were no SAEs or discontinuations due to AE of Akathisia.

Dyskinesia

Dyskinesia SMQ overview and TEAEs by preferred term did not reveal any SAEs or discontinuations in any pool data or individual studies.

7.4.5.6 Sexual Dysfunction (SD)

Summary

- Overall, the incidences of treatment-emergent sexual dysfunction (TESD) in Lu AA21004 groups were higher than placebo and appeared to be dose-related.

- In MDD/GAD Short-Term Pool, for both male and female subjects without sexual dysfunction (SD) at Baseline, the TESD incidence at two consecutive post-baseline visits in Lu AA21004 20 mg group (29%) were higher than Duloxetine (26%) and placebo (14%).

- The overall incidence of worsening SD for subjects with baseline sexual dysfunction was dose-related for Lu AA21004 treated groups.

- There were 3 discontinuations due to TESD in Lu AA21004 treated group and none in either Placebo or Duloxetine group in the MDD Short-Term Pool.

- There were 4 discontinuations due to TESD in Lu AA21004 treated group and none in Placebo and 1 in Duloxetine group in the MDD/GAD Short-Term Pool.

Background

The use of psychotropic medications including SSRIs has been reported to cause sexual dysfunction (SD) during treatment of MDD. The sponsor used the Arizona Sexual Experience Scale (ASEX) and collected data from voluntarily self-reported TEAEs related to SD to evaluate SD as TEAE related to Lu AA21004 treatment.

The sponsor used ASEX in 7 of the short-term clinical studies in MDD (Study 11984A, 13267A, 315, 316, 317, and 304) and 1 study in GAD (Study 308) to identify treatment-emergent sexual dysfunction (TESD). The ASEX scale is a 5-item rating scale that quantifies sex drive, arousal, vaginal lubrication/penile erection, ability to reach orgasm, and satisfaction from orgasm. Possible total scores range from 5 to 30, with the higher scores indicating more sexual dysfunction. The ASEX was assessed at Baseline and at each study visit in these studies. In addition, the sponsor collected data on voluntarily self-reported TEAEs related to SD in all MDD and GAD studies.

Our review focused on the assessment by ASEX rather than the voluntarily self-report of TESD because TESD is known to be under-reported by subjects and therefore is less reliable.

Results

Treatment-Emergent Sexual Dysfunction (TESD) Based on ASEX

The presence of sexual dysfunction based on ASEX scoring was defined at each visit using the following definition:

– An ASEX total score of ≥19, or
– A score of ≥5 on any item, or
– A score of ≥4 on any 3 items.

There were 2 definitions of TESD incidence: one was TESD occurred at any post-baseline visit during the double-blind phase (TESD Incidence 1) and the other was TESD occurred at least two consecutive post-baseline visits during the double-blind phase (TESD Incidence 2). We consider TESD Incidence 2 more reliable and more clinically meaningful because TESD Incidence 1 was more likely to be affected by other factors.

Table 98 shows the TESD incidences for the male subjects without sexual dysfunction at baseline in MDD/GAD Short-Term pool. In general, the TESD incidences of Lu AA21004 groups were higher than placebo and appeared to be dose-related. Compared to Duloxetine, all incidences were lower except TESD Incidence 2 for Lu AA21004 20 mg group.

Table 98: Incidence of Treatment-Emergent Sexual Dysfunction in Male Subjects without Sexual Dysfunction at Baseline in MDD/GAD Short-Term Pool

All studies	Placebo (N=348)	LuAA21004					Duloxetine 60 mg (N= 230)
		5 mg (N=156)	10mg (N=181)	15mg (N=141)	20mg (N=143)	Total (N=766)	
Baseline ASEX (a)	327	135	157	141	143	700	205
With BL Dysfunction	156	62	68	71	78	331	94
Without BL Dysfunction	169	72	89	70	65	368	111
TESD Incidence 1 (%) (b)	49/167 (29.3)	15/69 (21.7)	26/89 (29.2)	27/68 (39.7)	26/61 (42.6)	121/359 (33.7)	50/108 (46.3)
TESD Incidence 2 (%) (c)	22/162 (13.6)	11/67 (16.4)	17/86 (19.8)	13/67 (19.4)	17/59 (28.8)	73/346 (21.1)	26/99 (26.3)

Studies included: 304, 308, 315, 316, 317, 11984A and 13267A.
In column headings, N = number of subjects in the safety set. BL: baseline
Values measured more than 7 days after the last dose of double-blind study drug are not included in the analysis.
(a) Subjects with at least one ASEX question answered regardless of whether baseline dysfunction status could be determined.
(b) Incidence at any visit for subjects without sexual dysfunction at baseline who had at least one post-baseline visit.
(c) Incidence at two consecutive visits for subjects without sexual dysfunction at baseline who had at least two post-baseline visits.
Source: Compiled from Table 4.2 in 2013-03-05-Request-for-Information-TESD.pdf

Table 99 shows the TESD incidences for the female subjects without sexual dysfunction at baseline in MDD/GAD Short-Term pool. Female had slighter higher TESD incidence than male. The TESD incidences of Lu AA21004 groups were dose-related and higher than placebo except the TESD Incidence 1 for Lu AA21004 5 mg. Different from the findings in males, both the TESD Incidence 2 for Lu AA21004 15 mg and 20 mg were higher than Duloxetine.

Table 99: Incidence of Treatment-Emergent Sexual Dysfunction in Female Subjects without Sexual Dysfunction at Baseline in Phase 3 Controlled MDD/GAD Studies

All studies	Placebo (N=740)	LuAA21004					Duloxetine 60 mg (N= 526)
		5 mg (N=309)	10mg (N=435)	15mg (N=308)	20mg (N=312)	Total (N=1679)	
Baseline ASEX (a)	689	250	383	307	312	1512	470
With BL Dysfunction	542	180	279	248	243	1128	347
Without BL Dysfunction	147	69	104	59	69	382	119
TESD Incidence 1(%) (b)	50/142 (35.2)	20/67 (29.9)	41/101 (40.6)	27/58 (46.6)	33/67 (49.3)	158/372 (42.5)	59/118 (50.0)
TESD Incidence 2(%) (c)	27/135 (20.0)	14/65 (21.5)	22/94 (23.4)	19/57 (33.3)	23/67 (34.3)	95/357 (26.6)	31/109 (28.4)

Studies included: 304, 308, 315, 316, 317, 11984A and 13267A. BL: baseline
In column headings, N = number of subjects in the safety set.
Values measured more than 7 days after the last dose of double-blind study drug are not included in the analysis.

(a) Subjects with at least one ASEX question answered regardless of whether baseline dysfunction status could be determined.
(b) Incidence at any visit for subjects without sexual dysfunction at baseline who had at least one post-baseline visit.
(c) Incidence at two consecutive visits for subjects without sexual dysfunction at baseline who had at least two post-baseline visits

Source: Compiled from Table 4.3 in 2013-03-05-Request-for-Information-TESD.pdf

Worsening Sexual Dysfunction in Subjects with Sexual Dysfunction at Baseline

Subjects with SD at Baseline were evaluated for SD worsening using ASEX. The sponsor defined a shift as for each individual item on the ASEX if the item changed from ≤3 to >3 or from 4 to 5 or 6 or from 5 to 6 during the treatment period. They defined SD worsening as if the subject had ≥ 3 different items on the ASEX shift at the same evaluation visit.

The following table shows the incidence of worsening SD in subjects with SD at baseline at MDD/GAD Short-Term Pool. The overall incidence of worsening SD was dose-related for Lu AA21004 treated groups.

Table 100: Worsening Sexual Dysfunction in Subjects with Sexual Dysfunction at Baseline by Study at MDD/GAD Short-Term Pool

Study	Placebo (N=1088)	Lu AA21004					Duloxetine (N=756)
		5 mg (N=465)	10 mg (N=616)	15 mg (N=449)	20 mg (N=455)	Total (N=2445)	
MDD 11984A	14/37 (37.8)	17/37 (45.9)	16/36 (44.4)	--	--	44/108 (40.7)	16/32 (50.0)
MDD 304	25/86 (29.1)	18/88 (20.5)	--	--	--	36/165 (21.8)	27/75 (36.0)
GAD 308	9/61 (14.8)	12/70 (17.1)	16/63 (25.4)	--	--	45/196 (23.0)	20/66 (30.3)
MDD 13267A	28/82 (34.1)	--	--	26/71 (36.6)	27/83 (32.5)	53/154 (34.4)	24/66 (36.4)
MDD 315	26/83 (31.3)	--	--	18/82 (22.0)	33/90 (36.7)	51/172 (29.7)	28/76 (36.8)
MDD 316	21/83 (25.3)	--	27/90 (30.0)	--	27/84 (32.1)	54/174 (31.0)	--

Study	Placebo (N=1088)	Lu AA21004					Duloxetine (N=756)
		5 mg (N=465)	10 mg (N=616)	15 mg (N=449)	20 mg (N=455)	Total (N=2445)	
MDD 317	25/94 (26.6)	--	25/91 (27.5)	29/84 (34.5)	--	54/175 (30.9)	--
All Studies	148/526 (28.1)	47/195 (24.1)	84/280 (30.0)	73/237 (30.8)	87/257 (33.9)	337/1144 (29.5)	115/315 (36.5)

Source: compiled from Table 2.III in ISS. Page 207/410

Sexual Dysfunction by Preferred Term as TEAEs

In the MDD Short-Term Pool, the events of SD were non-serious. There were a total of 3 discontinuations in Lu AA21004 treated groups (1 in each of 5, 15 and 20mg group). There were no discontinuations due to SD in either placebo or Duloxetine group (refer to Table 2.ttt in ISS, page 223/410).

For the male subjects, the incidence of SD by preferred term as TEAEs was 3.1%, 4.1%, 3.5% and 4.9% in Lu AA21004 5, 10, 15 and 20mg treated while it was 1.7% in placebo and 12.1% in Duloxetine 60mg treated male subjects.

Table 101: Sexual Dysfunction by Preferred Term in Male Subjects in the MDD Short-Term Pool

Medical Category	Number of Subjects (%)						
	Placebo N=574	Lu AA21004 (mg)					Duloxetine N=239
		5 N=354	10 N=219	15 N=141	20 N=143	Total N=1002	
Subjects with sexual dysfunction TEAEs	10 (1.7)	11 (3.1)	9 (4.1)	5 (3.5)	7 (4.9)	36 (3.6)	29 (12.1)
Libido decreased	6 (1.0)	4 (1.1)	3 (1.4)	4 (2.8)	2 (1.4)	15 (1.5)	9 (3.8)
Orgasm abnormal	1 (0.2)	2 (0.6)	1 (0.5)	1 (0.7)	2 (1.4)	6 (0.6)	7 (2.9)
Anorgasmia	0	1 (0.3)	0	1 (0.7)	1 (0.7)	3 (0.3)	2 (0.8)
Ejaculation delayed	1 (0.2)	0	3 (1.4)	0	1 (0.7)	5 (0.5)	9 (3.8)
Erectile dysfunction	3 (0.5)	1 (0.3)	2 (0.9)	0	0	5 (0.5)	11 (4.6)
Loss of libido	0	2 (0.6)	1 (0.5)	0	0	3 (0.3)	0
Disturbance in sexual arousal	0	0	0	0	0	0	0
Ejaculation disorder	0	1 (0.3)	0	0	1 (0.7)	2 (0.2)	2 (0.8)
Sexual dysfunction	1 (0.2)	0	1 (0.5)	1 (0.7)	0	2 (0.2)	0
Orgasmic sensation decreased	0	0	0	0	0	0	0
Vulvovaginal dryness	0	0	0	0	0	0	0
Ejaculation failure	0	0	0	0	0	0	1 (0.4)

Source: compiled from Table 2.ttt in ISS. Page 223/410

For the female subjects, the incidence of SD by preferred term as TEAEs was 0.9%, 1.3%, 0.6% and 1.6% in Lu AA21004 5, 10, 15 and 20mg treated while it was 0.8% in placebo and 1.2% in Duloxetine treated subjects (Table 102).

Table 102: Sexual Dysfunction by Preferred Term in Female Subjects in the MDD Short-Term Pool

Medical Category	Number of Subjects (%)						
	Placebo N=1047	Lu AA21004 (mg)					Duloxetine N=514
		5 N=659	10 N=480	15 N=308	20 N=312	Total N=2058	
Subjects with sexual dysfunction TEAEs	8 (0.8)	6 (0.9)	6 (1.3)	2 (0.6)	5 (1.6)	22 (1.1)	6 (1.2)
Libido decreased	5 (0.5)	2 (0.3)	2 (0.4)	1 (0.3)	5 (1.6)	6 (0.3)	1 (0.2)
Orgasm abnormal	3 (0.3)	2 (0.3)	2 (0.4)	1 (0.3)	1(0.3)	6 (0.3)	2 (0.4)
Anorgasmia	0	1 (0.2)	2 (0.4)	0	1(0.3)	5 (0.2)	2 (0.4)
Ejaculation delayed	0	0	0	0	0	0	0
Erectile dysfunction	0	0	0	0	0	0	0
Loss of libido	0	1 (0.2)	1 (0.2)	0	0	2 (<0.1)	0
Disturbance in sexual arousal	0	1 (0.2)	0	0	0	2 (<0.1)	0
Ejaculation disorder	0	0	0	0	0	0	0
Sexual dysfunction	0	0	0	0	0	0	1 (0.2)
Orgasmic sensation decreased	1 (<0.1)	0	0	1 (0.3)	0	1 (<0.1)	0
Vulvovaginal dryness	0	0	1 (0.2)	0	0	1 (<0.1)	0
Ejaculation failure	0	0	0	0	0	0	0

Source: compiled from Table 2.ttt in ISS. Page 223/410

The findings of TESD in the MDD/GAD Short-Term Pool were similar to those of the MDD Short-Term Pool. The events of SD were non-serious. There were a total of 4 discontinuations in Lu AA21004 treated groups (2 in 5 mg, 1 in each of 15 and 20 mg). There was 1 discontinuation in Duloxetine group and none in placebo (refer to submission Table 2.sss in ISS, page 222/410).

For the male subjects, the incidence of SD by preferred term as TEAEs was 3.6%, 4.3%, 3.5% and 4.9% in Lu AA21004 5, 10, 15 and 20 mg treated while it was 1.6% in placebo and 14.2% in Duloxetine 60 mg treated subjects (refer to Table 2.sss in ISS, page 222/410).

For the female subjects, the incidence of SD by preferred term as TEAEs was 1.3%, 1.6%, 0.6% and 1.6% in Lu AA21004 5, 10, 15 and 20 mg treated while it was 0.7% in placebo and 1.9% in Duloxetine treated subjects (refer to Table 2.sss in ISS, page 222/410).

7.4.5.7 Discontinuation-Emergent Signs and Symptoms (DESS)

Summary

- A statistically significant difference in the mean number of discontinuation-emergent symptoms was observed for subjects discontinuing Lu AA21004 15 mg and 20 mg compared with placebo in the 1st week of discontinuation according to the assessment of the pooled data from US Studies 315, 316, and non-US Study 13267A by DESS scale.

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

- The results of self-reported AEs of discontinuation symptoms were not consistent with the findings of DESS assessment. First, the incidences of self-reported AEs were lower than those assessed by DESS scale. Second, there were no differences in self-reported AEs of discontinuation symptoms across the treatment groups in all studies.

- Since DESS scale is a direct form of inquiry administrated by clinicians which systematically evaluates discontinuation symptoms while self-reported AEs were based on subjects' spontaneous reports, we believe the data of discontinuation symptoms assessed by DESS scale were more reliable.

Recommendation
We recommend a dose decrease to 10 mg for 1 week before the complete discontinuation of Lu AA21004 15 and 20 mg.

Discontinuation Symptom Assessment by DESS instrument
Discontinuation symptoms were assessed by Discontinuation-Emergent Signs and Symptoms (DESS) instrument in Studies 13267A, 315, and 316.

At the Type C meeting dated March 30, 2010, the Division advised the sponsor to formally assess the discontinuation symptoms using a reliable tool, rather than relying on spontaneous reports from subjects. The sponsor added DESS scale to MDD Short-Term Studies 13267A, 315, and 316. We recommended a randomized withdrawal design to assess discontinuation symptoms because such a design would permit a distinction between symptoms related to drug discontinuation and symptoms occurring as part of the background in these subjects (refer to FDA Advice dated 09/14/2010). However, the sponsor did not take the advice.

The DESS is a clinician-rated checklist designed to evaluate possible discontinuation emergent events seen when subjects discontinue the antidepressant treatment. The DESS comprises 43 items (for example, agitation, insomnia, fatigue, and dizziness). An event was considered discontinuation emergent if it was reported for the first time (new symptom) or if a previously reported event worsened (old symptom but worse). In either case, the event scores 1 point on the checklist.

Data from the DESS scale was prospectively collected at Week 8 (end of the study), Week 9 (1st week of the Discontinuation Period), and Week 10 (2nd week of the Discontinuation Period) in Studies 315, 316, and 13267A. Comparisons between the different doses of Lu AA21004 and duloxetine to placebo for the DESS score changes at Week 9 and Week 10 were performed using an ANCOVA model.

For Studies 315, 316, and 13267A, during the 1st week of the Discontinuation Period (Weeks 9), subjects in Lu AA21004 10, 15, or 20 mg treatment groups discontinued Lu AA21004 treatment and received placebo, subjects in placebo group continued placebo, and subjects in duloxetine 60 mg group received duloxetine 30 mg. During the second week of the Discontinuation Period (Weeks 10), all subjects received placebo (Table 103).

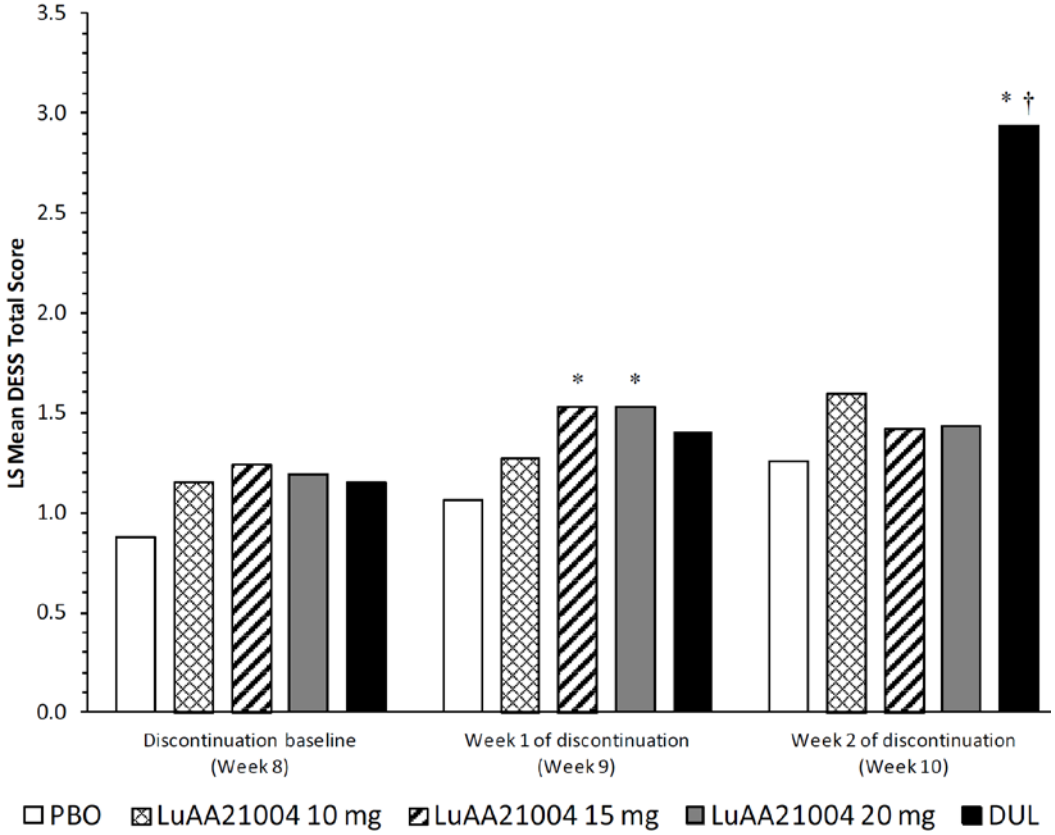
Table 103: Overview of Study 315, 316, and 13267A with a Discontinuation Period

Study	Duration of Treatment Period	Treatment Groups	Treatment in Discontinuation Period (a)	
			Week 9 (1st week of Discontinuation)	**Week 10** (2nd week of Discontinuation)
13267A (Europe, South Africa)	8 weeks	Placebo	Placebo	Placebo
		Lu AA21004 15 mg	Placebo	Placebo
		Lu AA21004 20 mg	Placebo	Placebo
		Duloxetine 60 mg	Duloxetine 30 mg	Placebo
315 (US)	8 weeks	Placebo	Placebo	Placebo
		Lu AA21004 15 mg	Placebo	Placebo
		Lu AA21004 20 mg	Placebo	Placebo
		Duloxetine 60 mg	Duloxetine 30 mg	Placebo
316 (US)	8 weeks	Placebo	Placebo	Placebo
		Lu AA21004 10 mg	Placebo	Placebo
		Lu AA21004 20 mg	Placebo	Placebo

(a) The collection of adverse events in the Discontinuation Period was captured at a study visit
Source: Table 1.h ISS page 36/410

The following figure presents a summary of the DESS total score at Weeks 8, 9, and 10.

Figure 15: DESS Total Score - Studies 315, 316, and 13267A



*Statistically significant versus placebo, p<0.05.
†Statistically significant versus each Lu AA21004 dose, p<0.05.
Note: Least squares (LS) means from the ANOVA (Week 8) and ANCOVA models (Weeks 9 and 10) are presented.
Source: ISS Figure 2.c, page 226/410

In 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 (LS mean DESS total score 1.06). No statistically significant changes were observed in subjects discontinuing Lu AA21004 10 mg (LS mean DESS total score 1.27) or tapering down on duloxetine from 60 mg to 30 mg (LS mean DESS total score 1.40).

At Week 10, no statistically significant differences were observed in the mean number of discontinuation-emergent symptoms in all 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).

Table 104 shows the DESS items occurred at > 5% and at a rate twice of placebo for Lu AA21004 15 mg and 20 mg at Week 9 in MDD Studies 315, 316, and 13267A: headache, muscle tension/stiffness, mood swings, and sudden outbursts of anger, dizziness/lightheadedness/vertigo, and nose runny during the first week of the Discontinuation Period (Weeks 9).

Table 104: Incidence of DESS Items > 5% and Twice of Placebo Rate for Lu AA21004 15mg and 20mg at Week 9 in MDD Studies 315, 316, and 13267A

Item/Visit	Number of Subjects (%)				
	Placebo (N = 385)	LuAA21004			Duloxetine (N = 243)
		15 mg (N = 226)	20 mg (N = 354)	Total* (N = 701)	
Headache	15 (3.9)	18 (8.0)	25 (7.1)	55 (7.8)	18 (7.4)
New symptom	6 (1.6)	14 (6.2)	15 (4.2)	33 (4.7)	13 (5.3)
Old symptom but worse	9 (2.3)	4 (1.8)	10 (2.8)	22 (3.1)	5 (2.1)
Muscle Tension or Stiffness	9 (2.3)	14 (6.2)	9 (2.5)	27 (3.9)	18 (7.4)
New symptom	2 (0.5)	7 (3.1)	4 (1.1)	12 (1.7)	11 (4.5)
Old symptom but worse	7 (1.8)	7 (3.1)	5 (1.4)	15 (2.1)	7 (2.9)
Mood Swings	12 (3.1)	14 (6.2)	15 (4.2)	37 (5.3)	7 (2.9)
New symptom	8 (2.1)	10 (4.4)	11 (3.1)	24 (3.4)	6 (2.5)
Old symptom but worse	4 (1.0)	4 (1.8)	4 (1.1)	13 (1.9)	1 (0.4)
Sudden Outbursts of Anger	8 (2.1)	12 (5.3)	16 (4.5)	32 (4.6)	2 (0.8)
New symptom	5 (1.3)	9 (4.0)	11 (3.1)	23 (3.3)	2 (0.8)
Old symptom but worse	3 (0.8)	3 (1.3)	5 (1.4)	9 (1.3)	0
Dizziness, Lightheadedness, or Vertigo	8 (2.1)	12 (5.3)	12 (3.4)	29 (4.1)	8 (3.3)
New symptom	6 (1.6)	9 (4.0)	10 (2.8)	22 (3.1)	7 (2.9)
Old symptom but worse	2 (0.5)	3 (1.3)	2 (0.6)	7 (1.0)	1 (0.4)
Nose Runny	8 (2.1)	12 (5.3)	15 (4.2)	31 (4.4)	6 (2.5)
New symptom	4 (1.0)	12 (5.3)	12 (3.4)	28 (4.0)	4 (1.6)
Old symptom but worse	4 (1.0)	0	3 (0.8)	3 (0.4)	2 (0.8)

Total* includes Lu AA21004 10mg group
Source: compiled from Appendix F: Table 5.1.4.1: Incidence of DESS Items by Visit in MDD Studies 315, 316, and 13267A
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In additional to the DESS items listed above, the following DESS items occurred at ≥1% and at a rate twice of placebo at Week 9 or Week 10 in MDD Studies 315, 316, and 13267A: increased dreaming or nightmares, feeling unreal or detached, stomach cramps, nausea, restless feeling in legs, sudden panic or anxiety attacks, blurred vision, chills, unsteady gait/incoordination, shaking/trembling, increased saliva in mouth, shortness of breath/gasping for air, burning/numbness/tingling sensations, ringing/noises in the ears, elevated mood/feeling high, stomach bloating, fever, vomiting, unusual sensitivity to sound, unusual tastes or smells (refer to 2013-03-27-Req-for-Info-DESS.pdf).

Discontinuation Symptoms by Self-Reported AEs

Discontinuation symptoms were also assessed by collection of self-reported AEs in MDD short-term Studies 315, 316, and 13267A, 11492A, 303, and 308, and in the relapse-prevention studies, 11985A and 12473A.

The self-reported discontinuation AEs collected from Studies 315, 316, and 13267A were pooled during the first and second week of the Discontinuation Period. The discontinuation AEs from MDD short-term Studies 11492A, 303, 11985A, 308, and

12473A and the MDD/GAD relapse-prevention studies were not pooled and presented individually by the sponsor.

The overall incidences of self-reported AEs during the first and the second week of the Discontinuation Period in the Lu AA21004 treatment groups for MDD Studies 315, 316, and 13267A were low and similar to placebo.

Table 105: Self-Reported AEs (Incidence ≥1% in any Lu AA21004 Group) During the First Week of Discontinuation Period - MDD Studies 315, 316, and 13267A

MedDRA SOC/ Preferred Term	Number of Subjects (%)					
	Placebo (N=385)	Lu AA21004				Duloxetine (N=243)
		Lu AA21004 10 mg (N=121)	Lu AA21004 15 mg (N=226)	Lu AA21004 20 mg (N=354)	Lu AA21004 Total (N=701)	
Subjects with TEAEs	38 (9.9)	15 (12.4)	26 (11.5)	41 (11.6)	82 (11.7)	31 (12.8)
Nausea	1 (0.3)	2(1.7)	2(0.9)	3 (0.8)	7 (1.0)	3 (1.2)
Diarrhea	4 (1.0)	3 (2.5)	1 (0.4)	0	4 (0.6)	2 (0.8)
Headache	5 (1.3)	0	2 (0.9)	6 (1.7)	8 (1.1)	3 (1.2)
Dizziness	2 (0.5)	1 (0.8)	1 (0.4)	4 (1.1)	6 (0.9)	2 (0.8)
Insomnia	0	1 (0.8)	4 (1.8)	2 (0.6)	7 (1.0)	2 (0.8)

Source: compiled from ISS Table 2.uuu, page 230/410
In column headings, N=number of subjects in the safety set who completed the treatment period and participated in the Discontinuation Period.

Table 106: Self-Reported AEs (≥1% Incidence in any Lu AA21004 Group) during the Second Week of the Discontinuation Period - MDD Studies 315, 316, and 13267A

MedDRA SOC/ Preferred Term	Placebo (N=385)	Lu AA21004 10 mg (N=121)	Lu AA21004 15 mg (N=226)	Lu AA21004 20 mg (N=354)	Lu AA21004 Total (N=701)	Duloxetine (N=243)
Subjects with TEAEs	27 (7.0)	19 (15.7)	22 (9.7)	42 (11.9)	83 (11.8)	54 (22.2)
Nausea	1 (0.3)	2 (1.7)	2 (0.9)	2 (0.6)	6 (0.9)	10 (4.1)
Diarrhea	1 (0.3)	2 (1.7)	0	2 (0.6)	4 (0.6)	2 (0.8)
Constipation	0	2 (1.7)	0	1 (0.3)	3 (0.4)	0
Vomiting	1 (0.3)	2 (1.7)	0	1 (0.3)	3 (0.4)	1 (0.4)
Nasopharyngitis	2 (0.5)	2 (1.7)	0	2 (0.6)	4 (0.6)	4 (1.6)
Headache	1 (0.3)	1 (0.8)	4 (1.8)	5 (1.4)	10 (1.4)	6 (2.5)
Dizziness	0	0	3 (1.3)	3 (0.8)	6 (0.9)	20 (8.2)
Insomnia	0	0	0	4 (1.1)	4 (0.6)	2 (0.8)

Source: compiled from ISS Table 2.vvv, page 232/410
In column headings, N=number of subjects in the safety set who completed the treatment period and participated in the Discontinuation Period.

The overall incidences of self-reported AEs related to discontinuations did not show differences in Lu AA21004 treated groups and placebo in the MDD short-term Studies

11492A, 303, 11985A, 308, and 12473A and the MDD/GAD relapse-prevention studies according to the individual reports.

7.4.5.8 Overdose

Please refer to 7.7.4.

7.4.5.9 Abuse Liability

Please refer to 7.7.4.

7.4.5.10 Closed-angle Glaucoma

The most common glaucoma SMQ findings were vision blurred. The incidence of Lu AA21004 group was comparable to placebo.

7.4.5.11 Activation of Mania or Hypomania

In the MDD/GAD Short-Term Pool, the overall incidence of TEAEs captured in the SMQ Hostility/Aggression was similar in Lu AA21004 Total, placebo, and duloxetine groups (2.3%, 2.8%, and 3.3%, respectively). There was 1 SAE in Lu AA21004 5mg group. There was 1 Hypomania and 1 Impulsive behavior in Lu AA21004 10mg group but not in placebo and Duloxetine group. The MDD Short-Term Pool had similar findings.

In the MDD and GAD Long-Term Relapse-Prevention Studies, no events of mania or hypomania were captured. There were no SAEs or discontinuations due to the SMQ Hostility/Aggression events.

In the MDD Open-Label Long-Term Pool, one subject in the ongoing studies experienced mania that led to discontinuation; 2 subjects in the completed studies reported hypomania and 1 of these also led to discontinuation.

7.4.5.12 Hyponatremia

Two cases of hyponatremia were identified.

The sponsor performed searches for hyponatremia/SIADH using the SMQ.

The following table shows an overview of the hyponatremia SMQ by treatment group and preferred term in the MDD Short-Term Pool. One case in Lu AA21004 10 mg was reported as hyponatremia.

Table 107: Hyponatremia SMQ Overview and TEAEs by Preferred Term in the MDD Short-Term Pool

Medical Category	Number of Subjects (%)						
	Placebo N=1621	Lu AA21004 (mg)					Duloxetine N=753
		5 N=1013	10 N=699	15 N=449	20 N=455	Total N=3060	
Hyponatremia	0	0	1 (0.1)	0	0	1 (<0.1)	0
AEs Leading to Discontinuation	0	0	0	0	0	0	0
SAEs	0	0	0	0	0	0	0
Hyponatremia/SIADH SMQ	0	0	1 (0.1)	0	0	1 (<0.1)	0
Hyponatremia	0	0	1 (0.1)	0	0	1 (<0.1)	0

Source: compiled from ISS Table 2.fff, page 258/410

The overview of the hyponatremia SMQ by treatment group and preferred term in the MDD/GAD Short-Term Pool also showed the same case of hyponatremia in Lu AA21004 10mg group.

The sponsor described this case of hyponatremia as follows: A 42-year-old male subject in the Lu AA21004 10 mg group in MDD Short-Term Pool had hyponatremia with sodium 126 mmol/L (reference range: 132 to 147 mmol/L) on Day 41. The event occurred while the subject was hospitalized due to depression. No other signs or symptoms were reported for the subject in the Safety Follow-up Period (8 days after last dose of Lu AA21004). The event was considered possibly related to Lu AA21004 use.

No events were captured in the SMQ Hyponatremia/SIADH in the MDD or GAD Long-Term Relapse-Prevention studies or in the MDD Open-Label Long-Term Pool.

In addition to the case reported, a Lab data review showed that a 20 year-old Caucasian female subject in Lu AA21004 5 mg group had sodium108 mmol/L at the Final Visit Day 56. The investigator did not report the low lab value as an AE. The TEAEs of nausea and abdominal pain were reported. The subject was not receiving any concomitant medications at the time of the Final Visit and had noncontributing medical history. This event was possibly related to Lu AA21004 treatment.

7.4.5.13 Bone Fractures/Osteoporosis

The sponsor performed the Osteoporosis/Osteopenia SMQ search and did not capture any meaningful findings.

The overall incidence of TEAEs captured in the Osteoporosis/Osteopenia SMQ was similar in the Lu AA21004 Total, placebo, and duloxetine groups in the MDD/GAD Short-Term Pool.

In the MDD Open-Label Long-Term Pool, all fractures were considered not related to the use of Lu AA21004 by the investigators.

7.4.5.14 Insomnia and Sleep-related Disturbances

The sponsor performed the LTMQ of insomnia search and did not find any SAEs in MDD/GAD short-term pools. There were 9 discontinuations in Lu AA21004 groups (0.2%), 4 in placebo (0.2%) and 9 in Duloxetine (1.0%) due to insomnia. The incidence of TEAEs captured in the LTMQ Insomnia was similar in the Lu AA21004 Total and placebo (4.8% and 4.4%, respectively). The review of other pools and long-term relapse prevention studies showed similar findings to those of the MDD/GAD short-term pool.

7.4.6 Submission Specific Primary Safety Concerns

7.4.6.1 QT Prolongation

In addition to the thorough QT study, the sponsor performed the SMQ QT Prolongation/Torsade de Pointes search, which did not find SAEs or arrhythmias or torsade de pointes in the short-term pools and the MDD Open-Label Long-Term Pool.

In the MDD long-term relapse-prevention study, there was 1 discontinuation due to QT prolongation during the Open-Label Period.

In the GAD Long-Term Relapse-Prevention study, there was 1 SAE of QT prolongation, which also led to discontinuation and another SAE of ventricular tachycardia in the Open-Label Period.

7.4.6.2 Nausea

Summary

- The incidence of nausea in Lu AA21004 was significantly higher than placebo and was dose-related.

- 15-20% subjects experienced nausea in the first 1-2 days of Lu AA21004 treatment. Approximate 10% subjects in Lu AA21004 10 mg -20 mg experienced nausea throughout the 8 week study period.

- The median time to first nausea event was similar to Duloxetine but shorter in Lu AA21004 groups than placebo (1-2 days vs. 3 days).

- The event of nausea lasted longer in Lu AA21004 group than placebo and Duloxetine during the entire treatment period.

- The incidence of nausea leading to discontinuation was also dose-related and higher than placebo. The incidences of nausea leading to discontinuations in Lu AA21004 15 mg and 20 mg groups were higher than Duloxetine group.

Nausea was the most common TEAE in the Lu AA21004 clinical program and it was dose-related. The incidence of nausea in the MDD Short-Term Pool was 21% - 32% in Lu AA21004 5 mg – 20 mg groups, 9% in placebo, and 36% in duloxetine group. Subjects in the Lu AA 21004 Total group had higher relative risk for nausea (RR of 2.7; CI 2.3-3.2) than subjects in the placebo group. The analysis of the data from the MDD

Short-Term Pool also showed that female subjects reported nausea more frequently than male subjects in the Lu AA21004 Total group (27.3% vs. 18.4%, respectively).

Nausea was the most common TEAE leading to discontinuations in all pools (except Phase I study pool) and in both relapse prevention studies.

Table 108 shows the onset of new nausea cases by time intervals in the MDD Short-Term Pool. It shows most new nausea events occurred during the first week of treatment in all treatment groups in the MDD Short-Term Pool. It also shows that with the longer treatment, the incidences of new nausea events in Lu AA21004 groups were higher than Duloxetine group.

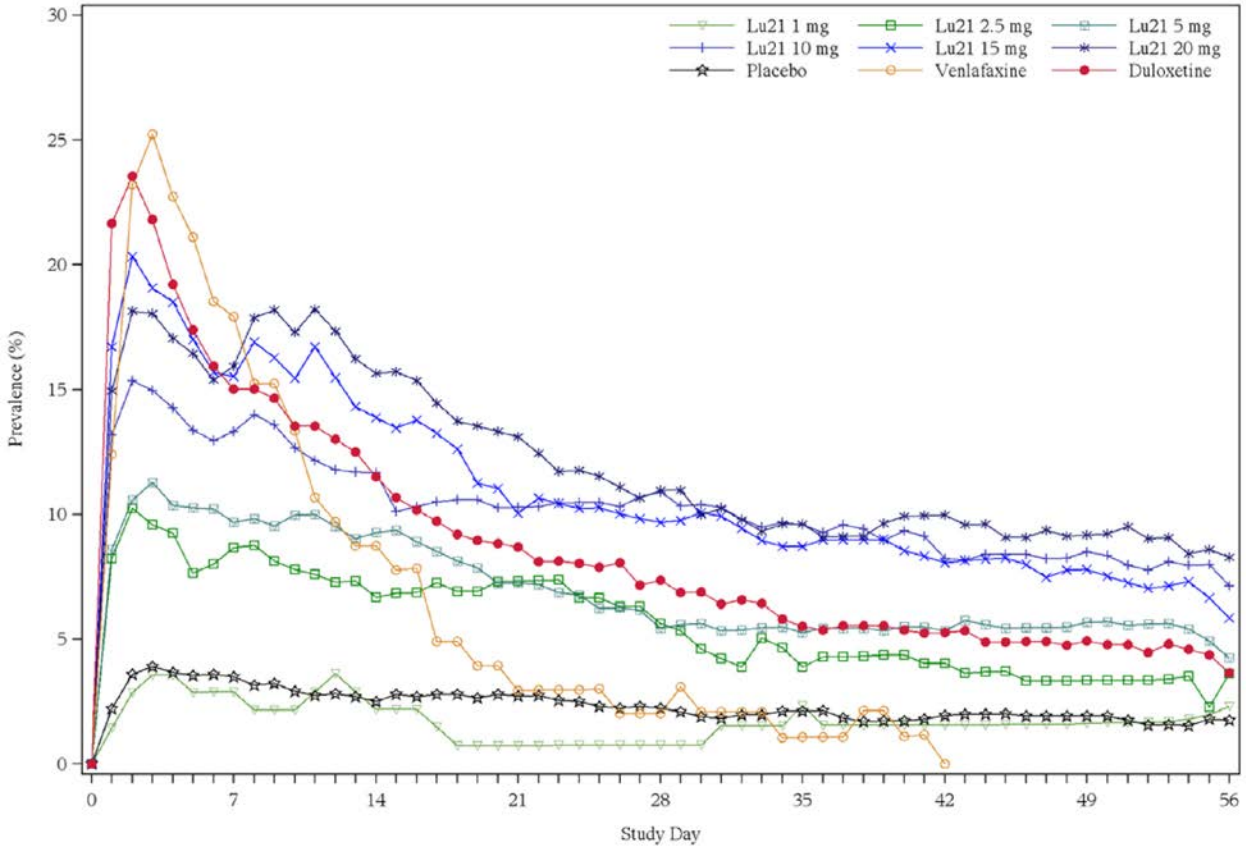
Table 108: New Nausea Events by Time Interval during the Treatment Period in the MDD Short-Term Pool

Treatment Groups	Time Interval			
	≤ 1 Week	>1 - 2 Weeks	>2 - 4 Weeks	>4 Weeks
	n/Number of subjects treated (%)			
Placebo	93/1621 (5.7)	16/1579 (1.0)	21/1536 (1.4)	15/1440 (1.0)
Lu AA21004 5 mg	157/1013 (15.5)	31/987 (3.1)	23/962 (2.4)	19/913 (2.1)
Lu AA21004 10 mg	128/699 (18.3)	28/679 (4.1)	22/643 (3.4)	22/619 (3.6)
Lu AA21004 15 mg	112/449 (24.9)	23/432 (5.3)	16/416 (3.8)	10/389 (2.6)
Lu AA21004 20 mg	104/455 (22.9)	25/431 (5.8)	13/420 (3.1)	16/390 (4.1)
Lu AA21004 Total	546/3060 (17.8)	116/2965 (3.9)	80/2857 (2.8)	76/2705 (2.8)
Duloxetine	220/753 (29.2)	28/699 (4.0)	17/684 (2.5)	12/640 (1.9)

Source: ISS: Table 2.oooo, page 276/410

Figure 18 shows the point prevalence of nausea on a given day during the treatment in the MDD short-term pool. The incidence of subjects with nausea was lower in Lu AA21004 treatment groups than duloxetine within the first week of treatment. However, as treatment continued, the prevalence of nausea in Lu AA21004 groups maintained relatively high while the prevalence of duloxetine and especially venlafaxine dropped significantly.

Figure 16: Point Prevalence of Nausea during the Treatment Period in the MDD Short-Term Pool



Source: ISS: Figure 2.g, page 275/410

Table 109 shows the total duration, time to first nausea event, and time to discontinuation due to the TEAE of nausea in the MDD Short-Term Pool.

The incidence of nausea in Lu AA21004 5 mg to 20 mg was higher than that of placebo and was dose-related. The median duration of nausea days for Lu AA21004 groups was longer than placebo (10 - 16 days for 5 mg – 20 mg vs. 7 days for placebo).The median time to first event was 1-2 days for Lu AA21004 groups vs. 3 days for placebo. The incidence of nausea leading to discontinuation was also dose-related (1.2%, 1.7%, 3.8% and 4.4% for 5 mg, 10 mg, 15 mg and 20 mg) and higher than placebo (0.3%).

Table 109: Nausea Events during the Treatment Period in the MDD Short-Term Pool

	Number of Subjects (%)						
		Lu AA21004 (mg)					
	Placebo N=1621	5 N=1013	10 N=699	15 N=449	20 N=455	Total* N=3060	Duloxetine N=753
Subjects with nausea, N (%)	140 (8.6)	212 (20.9)	176 (25.2)	140 (31.2)	141 (31.0)	730 (23.9)	257 (34.1)
Total duration (days)							
Median	7.0	10.0	13.0	10.5	16.0	12.0	7.0
Min-Max	1-76	1-74	1-81	1-63	1-70	1-81	1-73
Time to First Event (days)							
Median	3.0	2.0	1.0	1.0	2.0	2.0	1.0
Min-Max	1-55	1-53	1-56	1-43	1-59	1-59	1-53
Subjects with nausea leading discontinuation **N(%)**	5 (0.3)	12 (1.2)	12 (1.7)	17 (3.8)	20 (4.4)	65 (2.1)	26 (3.5)
Time to Discontinuation Due to Event (days)							
Median	2.0	1.0	5.0	1.0	2.5	1.0	1.0
Min-Max	1-18	1-15	1-44	1-17	1-14	1-44	1-45

Source: ISS: Table 2.pppp, page 277/410

7.4.6.3 Skin Reactions

Summary

No significant safety signals of skin reactions were identified in the Phase 2/3 studies.

Background

Data from Phase I studies demonstrated that hypersensitivity was the most common TEAEs leading to discontinuations, which all occurred in Lu AA21004 groups. Eight (8) subjects had the TEAEs related to hypersensitivity, which included urticaria (4 subjects); angioedema (2 subjects) and rash (2 subjects).

In 2007, the Division conducted the 30-day safety review for IND 76,307 (Lu AA21004) and recommended the sponsor to assess the nature and characteristics of rash and whether there were any systemic involvements. The sponsor therefore collected data related to skin reactions and performed standardized MedDRA queries (SMQ) for severe cutaneous adverse reactions.

Results

There were no SAEs or discontinuations in any pool except 1 discontinuation led by conjunctivitis in the MDD Open-Label Long-Term Pool.

Table 110 and Table 111 submitted by the sponsor show the overview of the severe cutaneous adverse reactions SMQ and the TEAEs by PT in the MDD Short-Term Pool and MDD/GAD Short-Term Pool, respectively.

Table 110: Severe Cutaneous Adverse Reactions SMQ Overview and TEAEs by Preferred Term in the MDD Short-Term Pool

Medical Category	Number of Subjects (%)								
	Placebo N=1621	Lu AA21004 (mg)							Duloxetine N=753
		1 N=140	2.5 N=304	5 N=1013	10 N=699	15 N=449	20 N=455	Total N=3060	
Severe Skin Reactions	4 (0.2)	0	0	3 (0.3)	0	1 (0.2)	1 (0.2)	5 (0.2)	1 (0.1)
AEs Leading to Discontinuation	2 (0.1)	0	0	0	0	0	0	0	0
SAEs	0	0	0	0	0	0	0	0	0
Severe cutaneous adverse reactions SMQ	4 (0.2)	0	0	3 (0.3)	0	1 (0.2)	1 (0.2)	5 (0.2)	1 (0.1)
Conjunctivitis	0	0	0	2 (0.2)	0	0	0	2 (<0.1)	0
Blister	0	0	0	1 (<0.1)	0	0	0	1 (<0.1)	0
Drug eruption	0	0	0	0	0	1 (0.2)	0	1 (<0.1)	0
Mouth ulceration	1 (<0.1)	0	0	0	0	0	1 (0.2)	1 (<0.1)	1 (0.1)
Dermatitis bullous	1 (<0.1)	0	0	0	0	0	0	0	0
Skin exfoliation	2 (0.1)	0	0	0	0	0	0	0	0

Source: ISS table 2.rrr, page 280/410

Table 111: Severe Cutaneous Adverse Reactions SMQ Overview and TEAEs by Preferred Term in the MDD/GAD Short-Term Pool

Medical Category	Placebo N=2230	1 N=140	2.5 N=611	5 N=1466	10 N=1007	15 N=449	20 N=455	Total N=4128	Duloxetine N=907
Severe Skin Reactions	4 (0.2)	0	1 (0.2)	5 (0.3)	0	1 (0.2)	1 (0.2)	8 (0.2)	2 (0.2)
AEs Leading to Discontinuation	2 (<0.1)	0	0	0	0	0	0	0	0
SAEs	0	0	0	0	0	0	0	0	0
Severe cutaneous adverse reactions SMQ	4 (0.2)	0	1 (0.2)	5 (0.3)	0	1 (0.2)	1 (0.2)	8 (0.2)	2 (0.2)
Conjunctivitis	0	0	0	3 (0.2)	0	0	0	3 (<0.1)	0
Blister	0	0	0	2 (0.1)	0	0	0	2 (<0.1)	0
Drug eruption	0	0	1 (0.2)	0	0	1 (0.2)	0	2 (<0.1)	1 (0.1)
Mouth ulceration	1 (<0.1)	0	0	0	0	0	1 (0.2)	1 (<0.1)	1 (0.1)
Dermatitis bullous	1 (<0.1)	0	0	0	0	0	0	0	0
Skin exfoliation	2 (<0.1)	0	0	0	0	0	0	0	0

Source: ISS table 2.qqq, page 279/410

7.5 Supportive Safety Results

7.5.1 Common Adverse Events

7.5.1.1 Common TEAEs in the MDD Short-Term Pool

The most common TEAEs (≥5% and at least twice placebo rate) in the MDD Short-Term Pool included nausea, vomiting, and constipation. Subjects in the Lu AA21004

Total group had higher relative risk (RR) for vomiting (RR of 2.9; CI 1.9-4.5), nausea (RR of 2.7; CI 2.3-3.2), and constipation (RR of 1.4; CI 1.0-1.9) than subjects in placebo group. The overall incidence of TEAEs as well as the incidences of nausea and constipation appeared to be dose-related.

Table 112: TEAEs Experienced by ≥5% Subjects in Any Lu AA21004 Treatment Group by Preferred Term and ≥ Twice of Placebo in the MDD Short-Term Pool

Preferred Term	Number of Subjects (%)						
	Placebo N=1621	Lu AA21004 (mg)					Duloxetine N=753
		5 N=1013	10 N=699	15 N=449	20 N=455	Total (a) N=3060	
Subjects with TEAEs	1002 (61.8)	672 (66.3)	465 (66.5)	316 (70.4)	331 (72.7)	2029 (66.3)	583 (77.4)
Nausea	149 (9)	216 (21)	180 (26)	144 (32)	144 (32)	745 (24)	268 (36)
Vomiting	22 (1)	29 (3)	33 (5)	29 (7)	26 (6)	124 (4)	31 (4)
Constipation	53 (3)	35 (4)	35 (5)	26 (6)	28 (6)	135 (4)	74 (10)

Compiled from ISS Table 2.1.1.3.1, Table 2.U page 114/410
(a) Lu AA21004 Total also includes 1 and 2.5 mg doses.

The common TEAEs occurring ≥2% in any Lu AA21004 groups and 2% greater than placebo are shown in Table 113.

There was a dose-related trend in TEAEs of nausea, constipation, vomiting, dizziness, abnormal dreams and pruritus.

Table 113: Incidence of TEAEs Occurred ≥2% in Subjects in Any Lu AA21004 Treatment Group and 2% Greater than Placebo by Preferred Term in the MDD Short-Term Pool

System Organ Class Preferred Term	Number of Subjects (%)				
	Placebo (N=1621)	Lu AA21004 (mg)			
		5 mg (N= 1013)	10 mg (N= 699)	15 mg (N= 449)	20 mg (N= 455)
Gastrointestinal Disorders					
Nausea	9	21	26	32	32
Diarrhea	6	7	7	10	7
Dry mouth	6	7	7	6	8
Constipation	3	4	5	6	6
Vomiting	1	3	5	6	6
Flatulence	1	1	3	2	1
Nervous System Disorders					
Dizziness	6	6	6	8	9
Psychiatric Disorders					
Abnormal dreams	1	<1	<1	2	3
Pruritus†	1	1	2	3	3

†includes pruritus generalized
Compiled from Table 2 in PI, Source: Appendix H, Table 2.1

7.5.1.2 Common TEAEs in the MDD/GAD Short-Term Pool

In the MDD/GAD Short-Term Pool, the patterns of TEAEs observed for Lu AA21004 were generally similar to that observed in the MDD Short-Term Pool, with the most common TEAEs (≥5% and at least twice placebo rate) being nausea, vomiting, and constipation. The overall incidence of TEAEs as well as the incidences of nausea and constipation was dose-related.

Table 114: TEAEs Experienced by ≥5% Subjects in Any Lu AA21004 Treatment Group by PT and ≥ Twice of Placebo in the MDD/GAD Short-Term Pool

Preferred Term	Placebo N=2230	Number of Subjects (%)					
		Lu AA21004 (mg)					Duloxetine N=907
		5 N=1466	10 N=1007	15 N=449	20 N=455	Total (a) N=4128	
Subjects with TEAEs	1359 (60.9)	974 (66.4)	693 (68.8)	316 (70.4)	331 (72.7)	2775 (67.2)	709 (78.2)
Nausea	205 (9.2)	316 (21.6)	270 (26.8)	144 (32.1)	144 (31.6)	985 (23.9)	325 (35.8)
Vomiting	38 (1.7)	39 (2.7)	50 (5.0)	29 (6.5)	26 (5.7)	159 (3.9)	41 (4.5)
Constipation	67 (3.0)	45 (3.1)	56 (5.6)	26 (5.8)	28 (6.2)	180 (4.4)	82 (9.0)

Compiled from Table 2.v in ISS page 120/410
(a) Lu AA21004 Total also includes 1 and 2.5 mg doses.

The common TEAEs occurring ≥2% in any Lu AA21004 groups and 2% greater than placebo are shown in the following table. Nausea, dizziness, constipation, and abnormal dreams were dose-related across Lu AA21004 groups.

Table 115: Incidence of TEAEs Occurred ≥2% and 2% Greater than Placebo in Subjects in Lu AA21004 Treatment Groups by Preferred Term in the MDD/GAD Short-Term Pool

Preferred Term	Number of Subjects (%)						
	Placebo N= 2230	Lu AA21004 (mg)					Duloxetine (N= 907)
		5 N= 1466	10 N= 1007	15 N= 449	20 N= 455	Total N= 4128	
Subjects with TEAEs	1033 (46.3)	779 (53.1)	593 (58.9)	279 (62.1)	284 (62.4)	2284 (55.3)	654 (72.1)
Nausea	183 (8.2)	306 (20.9)	262 (26.0)	140 (31.2)	141 (31.0)	953 (23.1)	316 (34.8)
Headache	246 (11.0)	178 (12.1)	124 (12.3)	62 (13.8)	60 (13.2)	498 (12.1)	122 (13.5)
Dry mouth	136 (6.1)	103 (7.0)	81 (8.0)	27 (6.0)	37 (8.1)	297 (7.2)	148 (16.3)
Dizziness	113 (5.1)	88 (6.0)	61 (6.1)	32 (7.1)	40 (8.8)	257 (6.2)	127 (14.0)
Diarrhea	106 (4.8)	80 (5.5)	73 (7.2)	37 (8.2)	32 (7.0)	256 (6.2)	66 (7.3)
Constipation	58 (2.6)	37 (2.5)	51 (5.1)	25 (5.6)	28 (6.2)	162 (3.9)	77 (8.5)
Vomiting	24 (1.1)	34 (2.3)	42 (4.2)	26 (5.8)	25 (5.5)	139 (3.4)	37 (4.1)

Compiled from ISS Table 2.4.1.3.2

Studies included: MDD (303, 304, 305, 315, 316, 317, 11492A, 11984A, 12541A and 13267A) and GAD (308, 309, 310, and 311).
Adverse events occurring on or after the first dose and within 30 days post dosing are included.
In column headings, N = number of subjects in the safety set.
Adverse events occurring on or after the first dose and within 30 days post dosing are included.

7.5.1.3 Common TEAEs in the MDD Relapse-Prevention Study 11985A

The most frequently reported (incidence ≥5% in any treatment group) TEAEs in the MDD Long-Term Relapse-Prevention Study 11985A are summarized in Table 116.

Nausea and headache were the most common TEAEs in the open-label period. The most common TEAE (≥5% and at least twice placebo rate) in the Double-Blind Period was again nausea. Dry mouth (2.0%) was only reported in the Lu AA21004 treated group not in placebo. The incidences of headache, dizziness, insomnia, and fatigue were less in the Double-Blind Period than those in the Open-Label Period. One explanation could be that subjects were used to the drug and therefore they reported less about these TEAEs or subjects have dropped out of the study because they could not tolerate these TEAEs.

Table 116: TEAEs Experienced by ≥5% Subjects in the Open-Label and Double-Blind Periods of the MDD Long-Term Relapse-Prevention Study 11985A by Preferred Term

Preferred Term	Number of Subjects (%)		
	Open-Label	Double-Blind	
	Lu AA21004 N=639	Placebo N=192	Lu AA21004 N=204
Subjects with TEAEs	451 (70.6)	122 (63.5)	127 (62.3)
Nausea	164 (25.7)	6 (3.1)	18 (8.8)
Headache	117 (18.3)	25 (13.0)	25 (12.3)
Nasopharyngitis	52 (8.1)	27 (14.1)	22 (10.8)
Dizziness	44 (6.9)	7 (3.6)	6 (2.9)
Dry mouth	41 (6.4)	0	4 (2.0)
Accidental overdose	37 (5.8)	15 (7.8)	16 (7.8)
Insomnia	36 (5.6)	3 (1.6)	5 (2.5)
Fatigue	32 (5.0)	4 (2.1)	4 (2.0)
Gastroenteritis	12 (1.9)	6 (3.1)	11 (5.4)
Influenza	7 (1.1)	10 (5.2)	14 (6.9)

Source: Table 2.w in ISS page 122/410

7.5.1.4 Common TEAEs in the GAD Relapse-Prevention Study 12473A

The most frequently reported (incidence ≥5% in any treatment group) TEAEs in the GAD Long-Term Relapse-Prevention Study 12473A are summarized in Table 117.

Study 12473A demonstrated the same pattern with MDD Long-Term Relapse-Prevention Study 11985A with nausea and headache being the most common TEAEs in the open-label period.

However, in the Double-Blind Period of Study 12473A, different from the Study 11985A; the most common TEAEs (≥5% and at least twice placebo rate) were influenza and accidental overdose. Influenza infection might not be drug-related. Again, other TEAEs were reported less in the Double-Blind Period either because subjects have tolerated those TEAEs or subjects have dropped out of the study due to those TEAEs.

Table 117: TEAEs Experienced by ≥5% Subjects in the Open-Label and Double-Blind Periods of the GAD Long-Term Relapse-Prevention Study 12473A by Preferred Term

Preferred Term	Number of Subjects (%)		
	Open-Label	Double-Blind	
	Lu AA21004 N=687	Placebo N=230	Lu AA21004 N=229
Subjects with TEAEs	528 (76.9)	124 (53.9)	126 (55.0)
Nausea	186 (27.1)	7 (3.0)	12 (5.2)
Headache	121 (17.6)	20 (8.7)	14 (6.1)
Influenza	52 (7.6)	14 (6.1)	28 (12.2)
Diarrhea	51 (7.4)	8 (3.5)	1 (0.4)
Accidental overdose	44 (6.4)	3 (1.3)	12 (5.2)
Dizziness	42 (6.1)	9 (3.9)	0
Insomnia	24 (3.5)	15 (6.5)	6 (2.6)

Source: Table 2.x in ISS page 123/410

7.5.2 Laboratory Findings

The following analyzes the mean changes, treatment emergent potentially clinically significant (PCS) changes, and dropouts due to abnormal labs for hematology, serum chemistry (liver function test, renal function test, basic chemistry, and lipid profile) and urinalysis.

For the mean and PCS changes of labs, our analyses focus on comparison of the Lu AA21004 groups and placebo in terms of the proportions of these subjects meeting those criteria.

7.5.2.1 Hematology

Summary of Hematology

We did not see any clinically meaningful mean changes from Baseline for the hematology variables.

For post-baseline potentially clinically significant changes, the overall incidences of post-baseline PCS values for selected hematology variables were similar across the treatment groups except platelets ≤75 $\times 10^9$/L which occurred in 3 subjects in Lu AA21004 groups (0.1%) but none in placebo or in Duloxetine group in MDD and MDD/GAD short-term pools. However, only 1 subject in the MDD Open-Label Long-Term Pool had platelet ≤75 $\times 10^9$/L, which is reassuring.

7.5.2.1.1 Mean Change of Selected Hematology Variables from Baseline

The mean changes from Baseline for the hematology variables (RBCs, WBCs basophils, eosinophils, hematocrit, hemoglobin, lymphocytes, monocytes, neutrophils, and platelets) generally were small and were not considered clinically meaningful.

7.5.2.1.2 Post-baseline PCS for Selected Hematology Variables

Post-baseline PCS for Selected Hematology Variables in the MDD Short-Term Pool

Post-baseline PCS values for selected hematology variables (hematocrit, hemoglobin, neutrophils, platelets, RBCs, WBCs) in the MDD Short-Term Pool are presented in the following table.

The overall incidences of post-baseline PCS values for selected hematology variables were similar across the treatment groups except platelets ≤75 $\times 10^9$/L which occurred in 3 subjects in Lu AA21004 groups (0.1%) but none in placebo or in Duloxetine group as shown in the following table. We requested the sponsor to provide narratives and/or lab follow-ups (email dated April 23, 2013). The sponsor responded on May 2, 2013. They noted that one subject in the venlafaxine group (11492A-CZ004-3326) also had platelets ≤75 $\times 10^9$/L.

Table 118: Post-baseline PCS Values for Selected Hematology Variables in the MDD Short-Term Pool (Lu AA21004 5 mg to 20 mg Doses)

Variable (units) Criteria	Number of Subjects (%)						
	Placebo N=1621	Lu AA21004 (mg)					Duloxetine N=753
		5 N=1013	10 N=699	15 N=449	20 N=455	Total (a) N=3060	
Hematocrit (fraction of 1)							
≤0.9×LLN	18/1534 (1.2)	19/969 (2.0)	9/671 (1.3)	3/413 (0.7)	3/414 (0.7)	40/2884 (1.4)	9/702 (1.3)
Hemoglobin (g/L)							
≤0.9×LLN	30/1535 (2.0)	24/969 (2.5)	13/672 (1.9)	9/415 (2.2)	3/418 (0.7)	58/2891 (2.0)	14/703 (2.0)
Neutrophils ($\times 10^9$/L)							
≤1.4	21/1246 (1.7)	14/658 (2.1)	8/522 (1.5)	3/414 (0.7)	2/415 (0.5)	31/2271 (1.4)	4/413 (1.0)
≥15.0	0/1246	2/658 (0.3)	0/522	1/414 (0.2)	0/415	3/2271 (0.1)	0/413
Platelets ($\times 10^9$/L)							
≤75	0/1530	1/963 (0.1)	0/672	1/414 (0.2)	1/417 (0.2)	3/2881 (0.1)	0/697
≥700	1/1530 (<0.1)	0/963	0/672	0/414	1/417 (0.2)	1/2881 (<0.1)	0/697
RBCs ($\times 10^{12}$/L)							
≤0.9×LLN	9/1535 (0.6)	13/969 (1.3)	0/672	4/415 (1.0)	2/418 (0.5)	21/2891 (0.7)	7/103 (1.0)

≥1.1×ULN	1/1535 (<0.1)	0/969	0/672	1/415 (0.2)	2/418 (0.5)	3/2891 (0.1)	2/703 (0.3)
WBCs (×10^9/L)							
≤2.8	7/1535 (0.5)	7/969 (0.7)	5/672 (0.7)	0/415	3/418 (0.7)	17/2891 (0.6)	1/703 (0.1)
≥16.0	7/1535 (0.5)	6/969 (0.6)	0/672	2/415 (0.5)	1/418 (0.2)	11/2891 (0.4)	0/703

Source: ISS Table 3.b page 295/410
Studies included: 303, 304, 305, 315, 316, 317, 11492A, 11984A, 12541A, and 13267A.
Lu AA21004 (a) Total also includes 1 and 2.5 mg doses.

Upon requests, the sponsor provided the following narratively and hematology follow-ups of the subjects who had low platelets on May 2, 2013:

Subject FI002-S1231 in Study 13267A
This was a 62-year old Caucasian male subject with a body mass index of 23.9 kg/m2 and an ongoing relevant medical history of low thrombocyte counts (November 2009) continued having low platelet count throughout the study. The investigator did not report this lab abnormality as an AE. The subject did not take any concomitant medications and received Lu AA21004 10-20 mg/day during study participation. The subject completed the trial as planned.

Study day	Hemoglobin (g/L)	Erythrocytes (x10^12/L)	Hematocrit	Leukocytes (x10^9/L)	Platelet (x10^9/L)
Baseline Day -8	143	4.40	0.430	4.10	--
Day 29	145	4.40	0.420	3.90 L (4.10)	56 L (140)
Day 35	146	4.30	0.410	4.80	78 L (140)
Day 41	146	4.40	0.420	4.90	73 L (140)
Day 55	139	4.30	0.420	3.70 L (4.10)	60 L (140)

L = below normal range, lower limit of normal in parentheses

Reviewer's comment:
It appeared that this case of low platelet was not related to Lu AA21004 treatment.

Subject UA010-S1452 in Study 13267A
This 71-year old Caucasian male subject with a body mass index of 23.6 kg/m2 and an ongoing relevant medical history of gout (1998) and dysmetabolic nephropathy (2004) experienced a low platelet count on Day 28, which was not reported as an AE by the investigator. The subject did not take any concomitant medications and received Lu AA21004 10-15 mg/day during study participation. The value returned to normal on Day 55 despite continuation of treatment with Lu AA21004. The subject completed the trial as planned.

Study day	Hemoglobin (g/L)	Erythrocytes (x10^12/L)	Hematocrit (fraction of 1)	Leukocytes (x10^9/L)	Platelet (x10^9/L)
Baseline Day -7	141	5.00	0.430	6.00	184
Day 28	201 H (177)	7.40 H (5.80)	0.630 H (0.500)	5.10	75 L (140)
Day 55	137	5.00	0.420	4.60	172

L = below normal range, lower limit of normal in parentheses.
H = above normal range, upper limit of normal in parentheses.

Reviewer's comment:
It appeared that this case of low platelet was not related to Lu AA21004 treatment.

Subject 0350-303 in Study 303
This 29-year old Caucasian male subject with a body mass index of 23.2 kg/m2 and no contributing medical or concomitant medications was withdrawn from the study on Day 21 due to lack of efficacy. The subject received Lu AA21004 5 mg/day during study participation. Laboratory results performed at the early termination visit on Day 21 were indicative of pancytopenia. No corresponding AE was reported because a hematologist and the investigator felt the original abnormal sample was most likely a lab error (possibly from the sample being in ambient status for too long a period of time resulting in instability of sample); the subject was completely healthy with no signs or symptoms that could be attributed to anemia or low leukocytes level. Therefore, instability of the sample was considered a possible explanation for the low hematology results. Previous study related hematology results for this subject, from samples collected at Screening and Baseline were within normal range. No repeat lab values were available for this subject. The subject did not report any adverse events at a safety follow-up visit on Day 42.

Study day	Hemoglobin (g/L)	Erythrocytes (x10^12/L)	Hematocrit	Leukocytes (x10^9/L)	Platelet (x10^9/L)
Screening Day -7	157	5.24	0.466	7.52	288
Baseline Day -1	154	5.21	0.470	6.94	227
Day 21	76 L (132)	2.58 L (4.20)	0.217 L (0.400)	0.93 L (3.50)	13 L (150)

L = below normal range, lower limit of normal in parentheses

Reviewer's comment:
This reviewer is very troubled by this response. If the investigators truly believed the finding of pancytopenia a lab error, they should have repeated the lab test to confirm it. However, there was no repeated hematology test at all, which was bothersome.

Post-baseline PCS for Selected Hematology Variables in the MDD/GAD Short-Term Pool

The findings of the Post-baseline PCS values for selected hematology variables in the MDD/GAD Short-Term Pool were similar to those in the MDD Short-Term Pool.

Table 119: Post-baseline PCS Values for Selected Hematology Variables in the MDD/GAD Short-Term Pool

Variable (units) Criteria	Number of Subjects (%)						
	Placebo N=2230	Lu AA21004 (mg)					Duloxetine N=907
		5 N=1466	10 N=1007	15 N=449	20 N=455	Total N=4128	
Hematocrit (fraction of 1)							
≤0.9×LLN	23/2098 (1.1)	24/1387 (1.7)	9/956 (0.9)	3/413 (0.7)	3/414 (0.7)	48/3862 (1.2)	12/841 (1.4)
Hemoglobin (g/L)							
≤0.9×LLN	41/2099 (2.0)	29/1387 (2.1)	15/957 (1.6)	9/415 (2.2)	3/418 (0.7)	72/3869 (1.9)	19/842 (2.3)

Variable (units) Criteria	Number of Subjects (%)						
	Placebo N=2230	Lu AA21004 (mg)					Duloxetine N=907
		5 N=1466	10 N=1007	15 N=449	20 N=455	Total N=4128	
Neutrophils (×10^9/L)							
≤1.4	27/1807 (1.5)	19/1075 (1.8)	13/807 (1.6)	3/414 (0.7)	2/415 (0.5)	46 (3248 (1.4)	8/552 (1.4)
≥15.0	0/1807	3/1075 (0.3)	0/807	1/414 (0.2)	0/415	4/3248 (0.1)	0/552
Platelets (×10^9/L)							
≤75	0/2092	1/1380 (<0.1)	0/957	1/414 (0.2)	1/417 (0.2)	3/3858 (<0.1)	0/835
≥700	2/2092 (<0.1)	0/1380	0/957	0/414	1/417 (0.2)	1/3858(<0.1)	0/835
RBCs (×10^{12}/L)							
≤0.9×LLN	11/2099 (0.5)	14/1387 (1.0)	1/957 (0.1)	4/415 (1.0)	2/418 (0.5)	26/3869 (0.7)	7/842 (0.8)
≥1.1×ULN	1/2099 (<0.1)	0/1387	0/957	1/415 (0.2)	2/418 (0.5)	4/3869 (0.1)	2/842 (0.2)
WBCs (×10^9/L)							
≤2.8	12/2099 (0.6)	12/1387 (0.9)	8/957 (0.8)	0/415	3/418 (0.7)	26/3869 (0.7)	1/842 (0.1)
≥16.0	8/2099 (0.4)	8/1387 (0.6)	1/957 (0.1)	2/415 (0.5)	1/418 (0.2)	16/3869 (0.4)	0/842

Source: ISS Table 3.c page 296/410
Studies included: MDD (303, 304, 305, 315, 316, 317, 11492A, 11984A, 12541A, and 13267A) and GAD (308, 309, 310, and 311).

Post-baseline PCS for Selected Hematology Variables in the MDD Open-Label Long-Term Pool

The proportions of subjects with at least 1 post-baseline PCS value were low for each variable in the MDD Open-Label Long-Term Pool; the proportions generally were slightly higher in the completed than the ongoing studies, which are expected due to the longer duration of monitoring in the completed studies. Only 1 subject in this Open-Label Long-Term Pool had platelet ≤75 ×109/L.

Table 120: Post-baseline PCS Values for Selected Hematology Variables in the MDD Open-Label Long-Term Pool

Variable Criteria	Number of Subjects (%)		
	Completed Studies 11492C/11984B/301 N=1443	Ongoing Studies 314/13267B N=1122	Lu AA21004 Total N=2565
Hematocrit (fraction of 1)			
≤0.9×LLN	34/1402 (2.4)	8/1015 (0.8)	42/2417 (1.7)
Hemoglobin (g/L)			
≤0.9×LLN	57/1402 (4.1)	29/1015 (2.9)	86/2417 (3.6)
Neutrophils (×109/L)			

Variable Criteria	Number of Subjects (%)		
	Completed Studies 11492C/11984B/301 N=1443	Ongoing Studies 314/13267B N=1122	Lu AA21004 Total N=2565
≤1.4	28/887 (3.2)	13/1015 (1.3)	41/1902 (2.2)
≥15.0	2/887 (0.2)	0/1015	2/1902 (0.1)
Platelets ($\times 10^9$/L)			
≤75	1/1326 (<0.1)	0/1014	1/2340 (<0.1)
≥700	0/1326	0/1014	0/2340
RBCs ($\times 10^{12}$/L)			
≤0.9×LLN	21/1402 (1.5)	1/1015 (<0.1)	22/2417 (0.9)
≥1.1×ULN	2/ 1402 (0.1)	4/1015 (0.4)	6/2417 (0.2)
WBCs ($\times 10^9$/L)			
≤2.8	21/1402 (1.5)	5/1015 (0.5)	26/2417 (1.1)
≥16.0	9/1402 (0.6)	1/1015 (<0.1)	10/2417 (0.4)

Source: ISS Table 3.2.1.1.1. Table 3.d page 297/410
Studies included: 11492C/11984B/301 (2.5 to 10 mg) and 314/13267B (10 to 20 mg).

7.5.2.2 Liver Function Test (LFT)

Summary of LFT

Our review focused on the PCS of LFTs, any SAEs due to abnormal LFTs and the discontinuations due to abnormal LFTs. We did not find any Hy's law cases.

7.5.2.2.1 Mean Change of LFT from Baseline

The mean changes from Baseline for the LFT variables: alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT), total bilirubin generally were small and were not considered clinically meaningful in the MDD and MDD/GAD Short-Term Pool. In the MDD Long-Term Relapse-Prevention Study 11985A and GAD Long-Term Relapse-Prevention Study 12473A, the mean changes from Baseline II during the Double-Blind Period for the LFT variables were small and were similar between the Lu AA21004 and placebo groups in both studies.

7.5.2.2.2 PCS of LFT

The focus of this section is to review PCS of LFT to see whether there were any Drug-Induced Liver Injury (DILI) cases or Hy's law cases during the Lu AA21004 development.

For the LFT variables (AST, ALT, GGT, total bilirubin and ALP), the proportions of subjects with post-baseline PCS values are presented for the MDD Short-Term Pool, the MDD/GAD Short-Term Pool, the MDD Open-Label Long-Term Pool, and the individual relapse-prevention studies.

Elevated post-baseline Values for LFT Variables in the MDD Short-Term Pool
In the MDD Short-Term Pool, Subject (BG006/S3590) in the Lu AA21104 5 mg had AST≥3×ULN and total bilirubin >2×ULN concurrently due to gallbladder cancer.

Two subjects had AST and ALP >1.5×ULN concurrently. We requested the narrative and lab follow-ups of these 2 cases dated April 23, 2013. The sponsor responded on May 2, 2013. They noted that one subject (BG006/S3590) had gallbladder cancer and the other subject (0343-314) had medical history of hepatitis.

No subjects had ALT ≥10×Upper Limit of Normal (ULN); ALT ≥3×ULN and total bilirubin >2×ULN concurrently; ALT ≥3×ULN and ALP >1.5×ULN or >3×ULN concurrently; or AST ≥3×ULN and ALP >3×ULN concurrently in Lu AA21004 groups.

Table 121: Elevated Post-baseline Values for LFT Variables in the MDD Short-Term Pool

Variable Criteria	Number of Subjects (%)						
	Placebo N=1621	Lu AA21004 (mg)					Duloxetine N=753
		5 N=1013	10 N=699	15 N=449	20 N=455	Total (a) N=3060	
ALP							
>1.5×ULN	5/1539 (0.3)	5/971 (0.5)	3/673 (0.4)	1/418 (0.2)	2/424 (0.5)	11/2906 (0.4)	7/703 (1.0)
>3×ULN	0/1539	1/971 (0.1)	0/673	0/418	0/424	1/2906 (<0.1)	0/703
ALT							
≥3×ULN	9/1538 (0.6)	5/971 (0.5)	1/673 (0.1)	1/418 (0.2)	1/423 (0.2)	9/2905 (0.3)	4/703 (0.6)
≥5×ULN	0/1538	1/971 (0.1)	0/673	0/418	0/423	1/2905 (<0.1)	1/703 (0.1)
AST							
≥3×ULN	5/1538 (0.3)	8/971 (0.8)	2/673 (0.3)	1/418 (0.2)	2/423 (0.5)	14/2905 (0.5)	3/702 (0.4)
≥5×ULN	1/1538 (<0.1)	2/971 (0.2)	1/673 (0.1)	0/418	0/423	3/2905 (0.1)	1/702 (0.1)
≥10×ULN	0/1538	0/971	1/673 (0.1)	0/418	0/423	1/2905 (<0.1)	0/702
GGT							
≥3×ULN	18/886 (2.0)	8/310 (2.6)	15/439 (3.4)	6/418 (1.4)	7/425 (1.6)	38/1746 (2.2)	6/569 (1.1)
Total bilirubin							
≥34.2 µmol/L	3/1539 (0.2)	5/971 (0.5)	3/673 (0.4)	0/418	0/424	8/2906 (0.3)	3/703 (0.4)
>2×ULN	1/1539 (<0.1)	3/971 (0.3)	0/673	0/418	0/424	3/2906 (0.1)	3/703 (0.4)
ALT and AST concurrently							
Both ALT and AST ≥3×ULN	2/1538 (0.1)	3/971 (0.3)	1/673 (0.1)	0/418	1/423 (0.2)	5/2905 (0.2)	3/702 (0.4)
AST and total bilirubin >2×ULN concurrently							

Variable Criteria	Number of Subjects (%)						
	Placebo N=1621	Lu AA21004 (mg)					Duloxetine N=753
		5 N=1013	10 N=699	15 N=449	20 N=455	Total (a) N=3060	
AST ≥3×ULN	0/1538	1/971 (0.1)	0/673	0/418	0/423	1/2905 (<0.1)	0/702
ALT and ALP >1.5×ULN concurrently							
ALT ≥3×ULN	0/1538	0/971	0/673	0/418	0/423	0/2905	1/703 (0.1)
AST and ALP >1.5×ULN concurrently							
AST ≥3×ULN	0/1538	2/971 (0.2)	0/673	0/418	0/423	2/2905 (<0.1)	1/702 (0.1)

Source: ISS Tables 3.1.1.1.1 and 3.1.2.1: Table 3.f, page: 301/410 (a) Lu AA21004 Total also includes 1 and 2.5 mg doses.

Elevated post-baseline Values for LFT Variables in the MDD/GAD Short-Term Pool

Table 122: Elevated Post-baseline Values for LFT Variables in the MDD/GAD Short-Term Pool

Variable Criteria	Placebo N=2230	Number of Subjects (%) Lu AA21004 (mg)							Duloxetine N=907
		1 N=140	2.5 N=611	5 N=1466	10 N=1007	15 N=449	20 N=455	Total N=4128	
ALP									
>1.5×ULN	6/2106 (0.3)	0/138	0/559	6/1390 (0.4)	4/957 (0.4)	1/418 (0.2)	2/424 (0.5)	13/3886 (0.3)	8/842 (1.0)
>3×ULN	0/2106	0/138	0/559	1/1390 (<0.1)	0/957	0/418	0/424	1/3886 (<0.1)	0/842
ALT									
≥3×ULN	11/2105 (0.5)	1/138 (0.7)	0/560	6/1390 (0.4)	1/957 (0.1)	1/418 (0.2)	1/423 (0.2)	10/3886 (0.3)	5/842 (0.6)
≥5×ULN	0/2105	0/138	0/560	2/1390 (0.1)	0/957	0/418	0/423	2/3886 (<0.1)	2/842 (0.2)
≥10×ULN	0/2105	0/138	0/560	0/1390	0/957	0/418	0/423	0/3886	1/842 (0.1)
AST									
≥3×ULN	6/2105 (0.3)	0/138	1/560 (0.2)	9/1390 (0.6)	3/957 (0.3)	1/418 (0.2)	1/423 (0.5)	16/3886 (0.4)	4/841 (0.5)
≥5×ULN	1/2105 (<0.1)	0/138	0/560	3/1390 (0.2)	1/957 (0.1)	0/418	0/423	4/3886 (0.1)	2/841 (0.2)
≥10×ULN	0/2105	0/138	0/560	0/1390	1/957 (0.1)	0/418	0/423	1/3886 (<0.1)	1/841 (0.1)
GGT									
≥3×ULN	18/886 (2.0)	0/0	2/154 (1.3)	8/310 (2.6)	51/439 (3.4)	6/418 (1.4)	7/425 (1.6)	38/1746 (2.2)	6/569 (1.1)
Total bilirubin									
≥34.2 µmol/L	3/2106 (0.1)	0/138	1/559 (0.2)	7/1390 (0.5)	3/957 (0.3)	0/418	0/424	11/3886 (0.3)	3/842 (0.4)
>2×ULN	1/2106 (<0.1)	0/138	1/559 (0.2)	5/1390 (0.4)	0/957	0/418	0/424	6/3886 (0.2)	3/842 (0.4)
ALT and AST concurrently									
Both ALT and AST ≥3×ULN	2/2105 (<0.1)	0/138	0/560	4/1390 (0.3)	1/957 (0.1)	0/418	1/423 (0.2)	6/3886 (0.2)	4/841 (0.5)
AST and total bilirubin >2×ULN concurrently									
AST ≥3×ULN	0/2105	0/138	0/559	1/1390 (<0.1)	0/957	0/418	0/423	1/3885 (<0.1)	0/841
ALT and ALP >1.5×ULN concurrently									
ALT ≥3×ULN	0/2105	0/138	0/559	0/1390	0/957	0/418	0/423	0/3885	2/842 (0.2)
AST and ALP >1.5×ULN concurrently									
AST ≥3×ULN	0/2105	0/138	0/559	2/1390 (0.1)	0/957	0/418	0/423	2/3885 (<0.1)	2/841 (0.2)

Four (4) subjects in the MDD Short-Term Pool had elevated ALT and AST (≥5×ULN) without jaundice (normal bilirubin level) during Lu AA21004 treatment with normal baseline LFTs. Both ALT and AST returned to normal without changing or discontinuing the study drug. One subject in the GAD Short-Term Pool had elevated ALT and AST (≥5×ULN), which probably were related to alcohol drinking. Narratives for these cases are provided in Table 123.

Table 123: Narratives for Individual Lu AA21004-Treated Subjects with ALT and/or AST ≥ 5×ULN in the MDD/GAD Short-Term Pool

Study No. Site/Subject No. Sex/Age(yrs.)/Race	LuAA21004 Dose (mg) (a)	Narrative
MDD Short-Term Pool		
303 0343/314 M/52/Caucasian	5	At Baseline (Study Day -1), the subject's CK was 234 (reference range, 24-195 U/L), ALT was 16 (reference range, 0-47 U/L), AST was 25 (reference range, 0-37 U/L), and ALP was 154 (reference range, 40-135 U/L). On Study Day 27, the subject experienced AEs of elevated CK of 12,401 and elevated liver enzymes; his ALT was 82, AST was 245, and ALP was 213. On Study Day 29, his CK was 3,261, CK-MB was 5.3 (reference range, <4.8 ng/mL), ALT was 62, AST was 111, and ALP was 174. For 6 days before the AE onset, the subject reportedly did a workout with heavy lifting. AE symptoms included muscle soreness/aches since Study Day 26, attributed by the investigator to the recent workout. The subject denied having muscle weakness, generalized weakness, change in urine color, or other symptoms. He had hepatitis in 2000, but no other relevant medical history. He received no treatment for the AEs. The AE of elevated liver enzymes was considered resolved on Study Day 34 when the subject's ALT, AST, and ALP levels were 34, 38, and 170, respectively. The AE of elevated CK was considered resolved on Study Day 40 when he had a CK of 127. The subject was discontinued from the study due to the AE of elevated CK on Study Day 40; he took his last dose of study drug on Study Day 37.
317 7043/729 M/43/Black	10	At Baseline (Study Day -1), the subject's ALT was 21 (reference range, 0-47 U/L), AST was 23 (reference range, 0-37 U/L), and total bilirubin was 0.4 (reference range, 0-1.1 mg/dL). On Study Day 54, his ALT was 234, AST was 408, and total bilirubin was 0.3. On repeat testing on Study Day 58, these values were 101, 51, and 0.3, respectively. The subject was not an alcohol consumer and had a history of hypertension. Concomitant mediations taken by this subject were hydrochlorothiazide and atenolol. No AEs were reported for this subject. The subject completed the study; his Final Visit took place on October 03, 2011.
11984A IN002/S3276 M/36/Asian	5	At Baseline (Study Day -9), the subject's ALT and AST were 56 U/L and 39 U/L, respectively. On Study Day 18, the subject experienced an AE of elevation of liver function tests, assessed by the investigator as probably related to

Study No. Site/Subject No. Sex/Age(yrs.)/Race	LuAA21004 Dose (mg) (a)	Narrative
		study drug; his ALT and AST were 255 U/L and 170 U/L, respectively. The AE was considered resolved on Study Day 26, and the subject was not discontinued from the study. His ALT and AST were 97 U/L and 50 U/L, respectively, on Study Day 26, and 58 U/L and 38 U/L, respectively, on Study Day 63. He also experienced AEs of breathlessness, cough, and body ache.
11984A IN002/S3658 M/26/Caucasian	5	At Baseline (Study Day -8), the subject's ALT and AST were 11 U/L and 16 U/L, respectively. On Study Day 26, the subject experienced AEs of elevated ALT and AST, assessed by the investigator as probably related to study drug; his ALT and AST were 160 U/L and 241 U/L, respectively. Study drug was continued unchanged and the AE resolved on Study Day 55; his ALT and AST were 9 U/L and 17 U/L, respectively, on Study Day 54.
GAD Short-Term Pool		
310 1010/004 F/52/Caucasian	5	At Baseline (Study Day -1), the subject's ALT was 25 (reference range, 0-47 U/L) and AST was 28 (reference range, 0-37 U/L). On Study Day 27, the subject experienced an AE of elevated LFTs, assessed by the investigator as possibly related to study drug; her ALT was 136 and AST was 242. The subject had been consuming alcohol regularly. According to the investigator, in July 2008, the subject was consuming alcohol socially, at an unspecified time her monthly consumption increased to 18 cans of beer, and in August 2008 she was consuming 8 cans of beer per day. Two weeks before the AE, she was consuming approximately 1/4 pint of vodka per day. After the elevated LFT results, the subject stated she no longer drank alcohol. On Study Day 44, her ALT and AST were 292 and 314, respectively. On Study Day 112, the subject's ALT and AST returned to normal, being 29 and 32, respectively. The AE was considered resolved on Study Day 118. There was no change to study drug as a result this AE; however, the date of the subject's last dose is unknown. The subject was last dispensed study drug on Study Day 44. The subject did not complete the study as planned, rather she was withdrawn on Study Day 112 due to lack of compliance with study drug.

Elevated Post-baseline Values for LFT Variables in the MDD Long-Term Relapse-Prevention Study 11985A

Table 124 shows that there were no cases of ALP > 3 x ULN; or AST/ALT ≥ 3 x ULN and Total Bilirubin (> 2xULN) concurrently, or AST/ALT and Alkaline Phosphatase ≥3xULN concurrently.

Table 124: Elevated Post-baseline Values for LFT Variables in the MDD Relapse-Prevention Study 11985A

Laboratory Test(s) Criteria	Number of Subjects (%)		
	Open Label	Double Blind	
	Lu AA21004 Total (N=639)	Placebo (N=192)	Lu AA21004 Total (N=204)
ALT			
≥ 3 x ULN	5/615 (0.8)	2/181 (1.1)	1/189 (0.5)
≥ 5 x ULN	2/615 (0.3)	0/181	1/189 (0.5)
≥ 10 x ULN	1/615 (0.2)	0/181	0/189
AST			
≥ 3 x ULN	2/614 (0.3)	0/181	1/189 (0.5)
≥ 5 x ULN	1/614 (0.2)	0/181	1/189 (0.5)
≥ 10 x ULN	0/614	0/181	0/189
ALT and AST Concurrently			
Both ALT & AST ≥3xULN	1/613 (0.2)	0/181	1/189 (0.5)
Total Bilirubin			
> 2 x ULN	0/ 615	1/ 182 (0.5)	0/ 188
ALP			
> 1.5 x ULN	8/615 (1.3)	2/182 (1.1)	2/189 (1.1)
ALT and ALP (> 1.5xULN) Concurrently			
ALT ≥ 3 x ULN	3/ 615(0.5)	0/ 181	1/ 189(0.5)
AST and ALP (> 1.5xULN) Concurrently			
AST ≥ 3 x ULN	1/ 614(0.2)	0/ 181	1/ 189(0.5)

Source: 2013-02-05 Request for information LFT 11985 and 12473.pdf.

ALT ≥3×ULN and ALP (> 1.5xULN) concurrently occurred in 3 subjects in the Open-label and 1 subject in the Double Blind phase. The sponsor responded our request on May 2, 2013 and provided 2 narratives in the following:

Subject CA204/S1129 had pancreatic cancer.

Subject: IN001-S1765
This was a 22-year old Asian male subject with a body mass index of 17.9 kg/m2 and no contributing medical history or concomitant medications experienced an increase in hepatic enzymes which was not reported as an AE by the investigator. The subject received LuAA21004 5 mg/day during the open-label and placebo during double-blind portions of the trial. The subject was prematurely discontinued from the study due to lack of efficacy; last dose of study medication was taken on Day 55 of the double-blind period.

Reviewer's comment:
From the labs the sponsor provided, this subject's total bilirubin stayed normal throughout the treatment which made it less likely a Hy's case even though AST, ALT, GGT and ALP were all elevated for unknown reasons.

Subject FR006-S1343 and Subject FI001/S1151 had AST ≥3×ULN and ALT ≥3×ULN and ALP (> 1.5xULN) concurrently. From the response provided by the sponsor, these subjects had normal total bilirubin.

The following 3 subjects had elevated LFTs (≥5×ULN):
Subject FI001/S1151 had elevated ALT and AST which probably were related to cytomegalovirus (CMV) infection.

Subject FR006/S1343 had elevated ALT and AST (≥5×ULN) during Lu AA21004 treatment with normal baseline LFTs. Both ALT and AST returned to normal without changing or discontinuing the study drug.

Subject CA204/S1129 had elevated LFTs due to pancreatic cancer.

The narratives for these 3 subjects with elevated LFTs are included in Table 125.

Table 125: The Narratives for the Subjects with LFTs Elevated (≥5×ULN) in the MDD Relapse-Prevention Study 11985A

Study No. Site/Subject No. Sex/Age(yrs.)/Race	LuAA21004 Dose (mg) (a)	Narrative
11985A FI001/S1151 F/56/Caucasian	DB Lu AA21004 10	At Screening (Study Day -8), the subject's ALT was 14 (reference range, 6-37 U/L) and AST was 22 (reference range, 10-36 U/L). On Study Days 14, 28, 56, 84, and 167, her ALT ranged from 9 to 15 and AST ranged from 15 to 19. On Study Days 216 and 225, her ALT was elevated at 239 and 398, respectively, and her AST was 227 and 232, respectively. The laboratory elevations were not reported as AEs. The subject experienced AEs of acute respiratory infection on Study Day 165 and cytomegalovirus on Study Day 197.
11985A FR006/S1343 F/31/Caucasian	OL Lu AA21004 5	At Screening (Study Day -4), the subject's ALT was 34 (reference range, 6-37 U/L) and AST was 28 (reference range, 10-36 U/L). On Study Days 10, 27, and 31, her ALT ranged from 12 to 29 and her AST from 8 to 24. On Study Day 81, she experienced an AE of hepatic enzyme increased, assessed by the investigator as possibly related to study drug; on Study Day 80 her ALT was 196 and AST was 207. Study drug was continued unchanged and the AE was considered resolved on Study Day 120; the subject's ALT was 15 and AST was 16 on Study Day 119.
11985A CA204/S1129 (b) M/46/Caucasian	OL Lu AA21004 10	At Screening (Study Day -7), the subject's ALT was 27 (reference range, 6-48 U/L) and GGT was 21 (reference range, 7-51 U/L). On Study Day 26, the subject's ALT was 120 and GGT was 154, and he was experiencing fatigue, exhaustion, nausea, vomiting and a progressive increase in right-sided back pain; he was subsequently diagnosed with pancreatic cancer. On Study Day 40, his ALT increased to 769 and GGT to 1006. On Study Day 42, the subject took his last dose of study drug and was withdrawn from the study; his ALT was 798 and GGT was 1080. On Study Day

Study No. Site/Subject No. Sex/Age(yrs.)/Race	LuAA21004 Dose (mg) (a)	Narrative
		280 (239 days after the last dose of study drug), the subject died from pancreatic cancer. See Section 2.2 for additional details.

Source: compiled from Table 3.i in ISS.

Elevated Post-baseline Values for LFT Variables in the GAD Long-Term Relapse-Prevention Study 12473A

Table 126 shows the elevated post-baseline LFT in Study 12473A.

Table 126: Elevated Post-baseline Values for LFT Variables in the GAD Relapse-Prevention Study 12473A

Laboratory Test(s) Criteria	Number of Subjects (%)		
	Open Label	Double Blind	
	Lu AA21004 Total (N=687)	Placebo (N=230)	Lu AA21004 Total (N=229)
ALT			
≥ 3 x ULN	9/675 (1.3)	3/211 (1.4)	3/216 (1.4)
≥ 5 x ULN	2/675 (0.3)	0/211	1/216 (0.5)
≥ 10 x ULN	0/675	0/211	0/216
AST			
≥ 3 x ULN	3/675(0.4)	0/211	1/216 (0.5)
≥ 5 x ULN	1/675(0.1)	0/211	0/216
≥ 10 x ULN	0/675	0/211	0/216
ALT and AST Concurrently			
Both ALT & AST ≥3xULN	2/675 (0.3)	0/211	1/216 (0.5)
Total Bilirubin			
> 2 x ULN	3/675 (0.4)	0/211	0/216
ALP			
> 1.5 x ULN	5/675 (0.7)	0/211	4/216 (1.9)
> 3 x ULN	0/675	0/211	1/216 (0.5)
ALT and ALP (> 1.5xULN) Concurrently			
ALT ≥ 3 x ULN	1/ 675(0.1)	0/211	2/ 216(0.9)
ALT and ALP (> 3xULN) Concurrently			
ALT ≥ 3 x ULN	0/675	0/211	1/216 (0.5)
AST and ALP (> 1.5xULN) Concurrently			
AST ≥ 3 x ULN	0/675	0/211	1/216 (0.5)
AST and ALP (> 3xULN) Concurrently			
AST ≥ 3 x ULN	0/675	0/211	1/216 (0.5)

Source: 2013-02-05 Request for information LFT 11985 and 12473.pdf.

There were no cases of ALT ≥ 3 x ULN or AST ≥ 3 x ULN and Total Bilirubin > 2xULN concurrently.

The sponsor provided the following response on May 2, 2013 upon request:

ALT ≥3×ULN and ALP (> 1.5xULN) concurrently:

Subject FR005-S3304 had elevated liver enzymes but AST/ALT and ALP returned normal despite continuation of treatment with LuAA21004. Her Total Bilirubin was normal throughout the Lu AA21004 treatment.

Subject AR012-S3559 received LuAA21004 5-10 mg/day during the open-label portion of the trial and 10 mg/day during the double blind period. She had elevated ALT, AST, ALP and GGT at Day 80 while Total Bilirubin stayed normal throughout the treatment duration. The subject was prematurely discontinued from the study due to lack of efficacy; last dose of study medication was taken on Day 78 of the double-blind period. No lab follow-ups were available.

Three subjects (Subject EE002-S3151, Subject FR016-S3389 and Subject ZA006-S3247) had elevated bilirubin (> 2xULN) in the open label period of GAD Relapse-Prevention Study 12473A, but the AEs were not reported as serious and did not cause discontinuations.

Another 2 subjects (Subject HU004-S3096, Subject RU001-S3537) had both ALT & AST ≥ 3xULN. Subject RU001-S3537 dropped out in the double blind period of Study 12473A due to AEs of TYPE II diabetes mellitus and upper respiratory tract infection.

Another 3 subjects had at least 1 ALT value and/or at least 1 AST value ≥5×ULN, but ALT, AST values returned to normal without changing or discontinuing the study drug. The narratives for these 3 subjects are included in Table 127.

Table 127: The Narratives for the Subjects with LFTs Elevated (≥5×ULN) in the GAD Relapse-Prevention Study 12473A

Study No. Site/Subject No. Sex/Age(yrs.)/Race	LuAA21004 Dose (mg) (a)	Narrative
12473A AR009/S3737 F/54/Caucasian	OL Lu AA21004 5	At Screening (Study Day -7) and Study Day 6, the subject's ALT values were 26 and 25, respectively (reference range, 6-37 U/L). On Study Day 27, the subject experienced an AE of increase of ALT, assessed by the investigator as probably related to study drug; her ALT was 364. Study drug was continued unchanged and the AE was considered resolved on Study Day 49; her ALT was 22 on Study Day 55. She also experienced AEs moderate increase of GGT. According the response provided by the sponsor dated on May 2, 2013, her total bilirubin remained normal except on Day 2 of the double-blind phase, bilirubin was 22 (normal < 21umol/L) but it returned to 10 (normal) on Day 61.
12473A HU004/S3096 M/41/Caucasian	OL Lu AA21004 5	At Screening (Study Day -7), the subject's ALT was 25 (reference range, 6-48 U/L), AST was 25 (reference range, 10-45 U/L), and GGT was 26 (reference range, 7-51 U/L).

Study No. Site/Subject No. Sex/Age(yrs.)/Race	LuAA21004 Dose (mg) (a)	Narrative
		On Study Day 7, the subject experienced AEs of increased ALT, AST, and GGT assessed by the investigator as possibly related to study drug; his ALT was 251, AST 264, and GGT 233. No action was taken with study drug. On Study Day 21, the AE was considered resolved. On Study Day 23, the subject's ALT was 32, AST was 20, and GGT was 51.
12473A EE001/S3121 M/23/Caucasian	DB Lu AA21004 5	At Screening (Study Day -3), the subject's ALT was 42 and on Study Days 8, 28, 83, 140, and 224, his ALT ranged from 33 to 80 U/L. On Study Day 308, he experienced an AE of increase of ALT, reason unknown, assessed by the investigator as not related to study drug; his ALT was 255 U/L. Study drug was continued unchanged and on Study Day 392, the AE was considered resolved; his ALT was 22 U/L and remained within the reference range for the duration of his participation in the study. He also experienced AEs of common viral flu, decrease of neutrophils, and increase of lymphocytes due to common flu.

Source: compiled from Table 3.i in ISS page 308/410.

Elevated Post-baseline Values for Liver Function Test Variables in the MDD Open-Label Long-Term Pool

Table 128: Elevated Post-baseline Values for Liver Function Test Variables in the MDD Open-Label Long-Term Pool

Number of Subjects (%)			
Variable **Criteria**	**Completed Studies 11492C/11984B/301** **N=1443**	**Ongoing Studies 314/13267B** **N=1122**	**Lu AA21004 Total** **N=2565**
ALP			
>1.5×ULN	9/1405 (0.6)	3/1016 (0.3)	12/2421 (0.5)
>3×ULN	0/1405	1/1016 (<0.1)	1/2421 (<0.1)
ALT			
≥3×ULN	9/1405 (0.6)	9/1017 (0.9)	18/2422 (0.7)
≥5×ULN	2/1405 (0.1)	4/1017 (0.4)	6/2422 (0.2)
AST			
≥3×ULN	11/1405 (0.8)	7/1016 (0.7)	18/2421 (0.7)
≥5×ULN	2/1405 (0.1)	3/1016 (0.3)	5/2421 (0.2)
≥10×ULN	1/1405 (<0.1)	0/1016	1/2421 (<0.1)
GGT			
≥3×ULN	11/517 (2.1)	28/1017 (2.8)	39/1534 (2.5)
Total bilirubin			
≥34.2 µmol/L	4/1405 (0.3)	2/1017 (0.2)	6/2422 (0.2)
>2×ULN	3/1405 (0.2)	0/1017	3/2422 (0.1)
ALT and AST Concurrently			

Number of Subjects (%)			
Variable Criteria	**Completed Studies 11492C/11984B/301 N=1443**	**Ongoing Studies 314/13267B N=1122**	**Lu AA21004 Total N=2565**
Both ALT and AST ≥3×ULN	3/1405 (0.2)	5/1016 (0.5)	8/2421 (0.3)

Source: ISS Table 3.h Page: 305/410

Table 129 includes narratives for subjects treated with any dose of Lu AA21004 had at least 1 ALT value and/or at least 1 AST value ≥5×ULN.

Table 129: The Narratives for the Subjects with LFTs Elevated (≥5×ULN) in the MDD Open-Label Long-Term Pool

Study No. Site/Subject No. Sex/Age(yrs.)/Race	LuAA21004 Dose (mg) (a)	Narrative
Completed Open-Label Long-Term Studies in MDD		
11492C CZ001/3315 F/26/Caucasian	Lu AA21004 10	At Baseline (Study Day -1), the subject's ALT, AST, and total bilirubin were 19 (reference range, 6-37 U/L), 24 (reference range, 10-36 U/L), and 0.8 (reference range, 0.18-1.23 µmol/L), respectively. On Study Day 28, the subject experienced an AE of transaminases increased, assessed by the investigator as not related to study drug; her ALT, AST, and total bilirubin were 63, 70, and 1.3, respectively. The increased ALT, AST, and total bilirubin persisted and then peaked on Study Day 275 at 199, 207, and 1.7, respectively. The investigator reported on an unspecified date the subject had started consuming 1 to 1.5 liters of wine per day and alcohol abuse was provided as an alternative etiology for the AE. The subject reported her alcohol abuse was related to major stress as she was the victim of sexual abuse by her boyfriend and had withdrawn from school. The subject was later withdrawn from the study at Lundbeck's recommendation due to possible relapse of depressive symptoms (MADRS total score=22) and alcohol abuse.
301 0228/107 F/53/Asian	OL Lu AA21004 5	At Baseline (Study Day 1), the subject's ALT was 11 (reference range: 0-47 U/L), AST was 20 (reference range, 0-37 U/L), and total bilirubin was 0.2 (reference range, 0-19 µmol/L). On Study Day 144, the subject experienced AEs of AST elevation and ALT elevation; her ALT was 295, AST was 1487, and total bilirubin was 0.5. The subject denied taking alcohol or any concomitant medications at the time of the AEs. The subject had a history of alcohol abuse from 1998 to 2008. Her last reported drinking episode was 03 March 2009, determined impulsive and not abusive by the investigator. On Study Day 150, laboratory testing performed by a non-protocol designated laboratory revealed that the subject's AST was 63 (reference range, 5-40 U/L) and ALT was 61 (reference range, 0-40 U/L); the AEs were considered resolved that same day. The subject was asymptomatic and continued in the study; her study drug dose was not changed.
Ongoing Open-Label Long-Term Studies in MDD		
314	OL	At Baseline (Study Day -1), the subject's ALT was 78

Study No. Site/Subject No. Sex/Age(yrs.)/Race	LuAA21004 Dose (mg) (a)	Narrative
4013/411 (b) F/40/Caucasian	Lu AA21004 20	(reference range, 0-47 U/L), AST was 49 (reference range, 0-37 U/L), and total bilirubin was 0.4 (reference range, 0-1.1 mg/dL). On Study Day 140, the subject experienced an AE of elevated ALT of 200; her AST was 102 and total bilirubin was 0.5 at that time. The subject was not an alcohol consumer and had a history of obesity and nonalcoholic fatty liver disease. Concomitant medications taken by this subject were Claritin, amoxicillin, fluconazole, and orthotricycline. Other AEs experienced were numbness in left foot and hand, tingling in toes and fingers, viral upper respiratory infection, pruritus, and sinusitis. The elevated ALT was assessed as possibly related to study drug and was ongoing at study end. The subject was discontinued from the study due to the AE of elevated ALT. Her Early Termination Visit took place on Study Day 258 when her ALT was 459, AST was 280, and total bilirubin was 0.5. These values peaked on Study Day 272 when her ALT was 766, AST was 367, and total bilirubin was 0.8. Repeat testing continued until Study Day 314, when her ALT was 42, AST was 30, and total bilirubin was 0.4 (all values within references ranges).
314 4128/409 (b) F/57/Caucasian	OL Lu AA21004 20	At Baseline (Study Day -1), the subject's ALT was 12 (reference range, 0-47 U/L), AST was 17 (reference range, 0-37 U/L), and total bilirubin was 0.8 (reference range, 0-1.1 mg/dL). On Study Days 144 and 145, the subject took an accidental overdose of Nyquil, a concomitant medication, which was considered an AE. On Study Day 149, she experienced an AE of elevated liver enzymes, when her ALT was 279, AST was 264, and total bilirubin was 0.3; the investigator assessed the AE as not related to study drug and provided an alternative causality of Nyquil overdose. The subject was discontinued from the study due to the elevated liver enzymes. Her Early Termination Visit took place on Study Day 161, when her ALT was 55, AST was 27, and total bilirubin was 0.6; the AE of elevated liver enzymes was considered resolved on that same day.
314 4133/401 M/31/Caucasian	OL Lu AA21004 15	At Baseline (Study Day 1), the subject's ALT was 32 (reference range 0-47 U/L), AST was 28 (reference range 0-37 U/L), and total bilirubin was 0.4 (reference range 0-1.1 mg/dL). Between Visit 4 and Visit 11, his ALT ranged from 31 to 54, AST from 25 to 49, and total bilirubin from 0.4 to 1.2. The subject was a smoker, consumed alcohol daily, and had a history of being overweight and of elevated GGT >3×ULN, nausea, fatigue, diarrhea, and hypertriglyceridemia. Concomitant medications taken by this subject were Ambien and multivitamins. He experienced an AE of elevated transaminases beginning on Study Day 311, assessed as possibly related to study drug; his ALT was 259, AST was 199, and total bilirubin was 0.7. Other AEs experienced were lightheadedness and worsening hypertriglyceridemia. The subject was discontinued from the study due to a concurrent medical condition of fatigue. Repeat laboratory testing on Study Day 317 revealed that

Study No. Site/Subject No. Sex/Age(yrs.)/Race	LuAA21004 Dose (mg) (a)	Narrative
		his ALT was 82, AST was 47, and total bilirubin was 0.4; the AE of elevated transaminases was considered resolved that same day.
314 4059/402 F/42/Caucasian	OL Lu AA21004 20	At Baseline (Study Day 1), the subject's ALT was 51 (reference range, 0-47 U/L), AST was 32 (reference range, 0-37 U/L), and total bilirubin was 0.4 (reference range, 0-1.1 mg/dL). On Study Day 29, her ALT was 283, AST was 127, and total bilirubin was 0.3; however, the elevated ALT and AST were not considered an AE. The subject consumed alcohol 2 to 6 times weekly, had a BMI of 31.6 kg/m2 at Baseline, and had no relevant medical history. Concomitant medications taken by the subject were Claritin, Aleve, multivitamins, calcium, Robitussin DM, Robitussin AC, Tylenol, and Mucinex. She experienced an AE of flu from Study Day 11 to Study Day 43. From Study Day 36 to Study Day 367 (Final Visit), her ALT ranged from 39 to 89, AST from 24 to 45, and total bilirubin from 0.2 to 0.6.

Source: compiled from Table 3.i in ISS.

7.5.2.2.3. Dropouts due to Elevated LFTs

This reviewer examined all the AEs leading to discontinuations in Appendix B in submission and compiled Table 130, which lists all the discontinuations/dropouts (15 subjects) due to elevated LFTs in the Lu AA21004 development. The GAD Relapse-Prevention Study Pool did not have dropouts due to elevated LFTs. Therefore, it is not listed.

Table 130: Discontinuations Due to Elevated LFTs

Lu AA21004 Doses (mg)	Study No.	Subject No.	AEs
MDD Short-Term Pool			
5	11984A	UA002/S3608	Gamma-glutamyltransferase increased
GAD Short-Term Pool			
2.5	T21004-309	0020/904	Blood bilirubin increased
MDD Relapse-Prevention Study Pool			
5	OL	CA204/S1324	Alanine aminotransferase increased
		CA202/S1383	Alanine aminotransferase increased
10	DB	CA202/S1353	Alanine aminotransferase increased
MDD Open-Label Long-Term Pool			
2.5	11984B	BG003/S3531	Alanine aminotransferase increased
5	11984B	KR004/S3769	Gamma-glutamyltransferase increased
	T21004-301	0115/112	Liver function test abnormal
10	11984B	CA103/S3053	Gamma-glutamyltransferase increased
15	T21004-314	4051/403	Hepatic enzyme increased
20	T21004-314	4161/402	Liver function test abnormal
		4128/409	Hepatic enzyme increased
		4013/411	Alanine aminotransferase increased

Lu AA21004 Doses (mg)	Study No.	Subject No.	AEs
Phase 1 Study Pool			
10 + Lithium 450 mg BID	T21004-118	0001/013	Transaminases increased
9	10982	001/S0121	Alanine aminotransferase increased

Compiled from Appendix B page 10/52 to 52/52

This reviewer has examined the narratives of these discontinuations listed above due to Elevated LFTs in Appendix B and realized that some narratives did not have LFT values. We requested the sponsor to provide the narratives of all discontinuations due to abnormal lab values and the outcomes on February 5, 2013 and we received the response on February 18, 2013.

This reviewer reviewed the sponsor's response and found it acceptable. Among these 15 subjects, 14 had elevated ALT/AST without concurrent hyperbilirubinemia. Follow up ALT/AST of these 14 subjects were normal. One subject (0020/904) receiving LuAA21004 2.5 mg had elevated bilirubin to 2.4 mg/dL (reference range 0.2-1.2 mg/dL) on Day 4 of treatment but he had elevated bilirubin at Baseline (2.0 mg/dL). His bilirubin was 2.3 mg/dL on Day 8 and he was withdrawn from the study. His AST and AKP values were normal. His ALTs were slightly elevated with the highest being 57 U/L (ULN: 47 U/L).

Table 131 summarizes the findings of the discontinuations due to Elevated LFTs according to sponsor's response.

Table 131: Findings of Discontinuations Due to Elevated LFTs

Tx. (mg)	Study No.	Subject No.	AEs (MedDRA Preferred Term)	Possible cause
MDD Short-Term Pool				
5	11984A	UA002/S3608	Blood ALP ↑ (no alcohol or other illness) GGT ↑ (no alcohol or other illness)	Possibly related
GAD short-term Pool				
2.5	309	0020/904	Blood bilirubin↑	Blood bilirubin ↑ baseline
MDD Relapse-Prevention Study Pool				
5	11985A-OL	CA204/S1324	ALT ↑ Blood bilirubin increased Day -7 (1.4) and Day 14 (1.3) [normal 0.2-1.2mg/dL]. ALT/AST ↑ on Day 22 (normal bili), withdrew Day 24	Blood bilirubin ↑ at baseline
5	11985A-OL	CA202/S1383	ALT ↑	↑at baseline
10	11985A-DB	CA202/S1353	ALT ↑	↑at baseline
MDD Open-Label Long-Term Pool				
2.5	11984B	BG003/S3531	ALT, AST, ALP, GGT ↑	Possibly related
5	11984B	KR004/S3769	GGT ↑	Possibly related

Tx. (mg)	Study No.	Subject No.	AEs (MedDRA Preferred Term)	Possible cause
5	301	0115/112	ALT, AST↑	↑at baseline
10	11984B	CA103/S3053	GGT ↑	Possibly related
10	314	4128/406 (b)	ALT, AST, ALP ↑	Possibly related
15	314	4051/403	ALT, AST↑	Possibly related
15	314	4073/401 (b)	ALT, AST, ALP ↑	Possibly related
15	314	4078/405 (b)	ALT, AST↑	Possibly related
20	314	4161/402	ALT, AST↑	H/O Hepatitis C
20	314	4128/409	ALT, AST↑	Nyquil overdose
20	314	4013/411	ALT, AST↑	↑at baseline
Phase 1 Study Pool				
10 *	118	0001/013	ALT, AST↑	Possibly related
9	10982	001/S0121	ALT, AST↑	Possibly related

10 * included Lu AA21004 10mg and Lithium 450 mg BID, Tx: treatment
Source: Clinical response dated 2/19/2013.

7.5.2.3 Renal Function Test

7.5.2.3.1 Mean Changes of Renal Function Test Variables from Baseline

The mean changes from Baseline for the renal function test variables (BUN, serum creatinine) generally were small and not considered clinically meaningful at each visit and the mean changes were similar in the Lu AA21004 Total and placebo groups.

7.5.2.3.2 PCS Values for Renal Function Test Variables

Post-baseline PCS values for the renal function test variables (BUN, serum creatinine) in the MDD Short-Term Pool and the MDD/GAD Short-Term Pool are presented in the following tables. The proportions of subjects with at least 1 post-baseline PCS values of BUN and Creatinine were low and similar in the Lu AA21004 Total and placebo groups in both pools.

Table 132: Post-baseline PCS Values for Renal Function Test Variables in MDD Short-Term Pool

Variable (units) Criteria	Number of Subjects (%)						
	Placebo N=1621	Lu AA21004 (mg)					Duloxetine N=753
		5 N=1013	10 N=699	15 N=449	20 N=455	Total (a) N=3060	
BUN (mg/dL) ≥24	2/1146 (0.2)	0/553	0/425	1/418 (0.2)	2/425 (0.5)	3/2087 (0.1)	1/411 (0.2)
Creatinine (mg/dL) ≥2	2/1539 (0.1)	2/971 (0.2)	0/673	1/418 (0.2)	0/424	4/2906 (0.1)	0/703

Source: ISS Table 3.j
BUN 11.1mmol/L=24mg/dL
Creatinine 177 (µmol/L) = 2 mg/dL

Table 133: Post-baseline PCS Values for Renal Function Test Variables in MDD/GAD Short-Term Pool

Variable (units) Criteria	Number of Subjects (%)						
		Lu AA21004 (mg)					
	Placebo	5	10	15	20	Total (a)	Duloxetine
BUN (mg/dL) ≥24	3/1713 (0.2)	0/972	0/709	1/418 (0.2)	2/425 (0.5)	3/3067 (<0.1)	1/550 (0.2)
Creatinine (mg/dL) ≥2	3/2106 (0.1)	2/1390 (0.1)	0/957	1/418 (0.2)	0/424	4/3886 (0.1)	0/842

Source: ISS Table 3.k
BUN 11.1mmol/L=24mg/dL
Creatinine 177 (µmol/L) = 2 mg/dL

7.5.2.4 Electrolyte Variables

7.5.2.4.1 Mean Changes and Shifts from Baseline for Electrolyte Variables

The mean changes from Baseline for the renal function test variables (BUN, serum creatinine) generally were small and not considered clinically meaningful at each visit and the mean changes were similar in the Lu AA21004 Total and placebo groups.

7.5.2.4.2 PCS Values for Electrolyte Variables

Post-baseline PCS values for clinically meaningful electrolyte variables (calcium, potassium, sodium) in the MDD Short-Term Pool and MDD/GAD Short-Term Pool are listed in the following tables. The proportions of subjects with at least 1 post-baseline PCS value were low for each variable in the Lu AA21004 Total, placebo, and duloxetine groups. The proportions were similar in the Lu AA21004 Total and placebo groups in both pools.

Table 134: Post-baseline PCS Values for Electrolyte Variables in the MDD Short-Term Pool

Variable (units) Criteria	Number of Subjects (%)						
		Lu AA21004 (mg)					
	Placebo N=1621	5 N=1013	10 N=699	15 N=449	20 N=455	Total (a)	Duloxetine N=753
Calcium (mg/dL)							
≤7	3/1539 (0.2)	0/971	0/673	1/418 (0.2)	0/424	1/2906 (<0.1)	0/703
≥12	0/1539	1/971 (0.1)	1/673 (0.1)	0/418	0/424	2/2906 (<0.1)	0/703
Potassium (mmol/L)							
≤3.0	5/1539 (0.3)	1/971 (0.1)	1/673 (0.1)	1/418 (0.2)	1/424 (0.2)	4/2907 (0.1)	1/703 (0.1)
≥5.5	32/1539 (2.1)	28/971 (2.9)	10/673 (1.5)	6/418 (1.4)	12/424 (2.8)	63/2907 (2.2)	19/703 (2.7)
Sodium (mmol/L)							
≤125	0/1540	0/971	0/673	0/418	1/425 (0.2)	1/2908 (<0.1)	2/703 (0.3)
≥155	0/1540	2/971 (0.2)	1/673 (0.1)	0/418	0/425	3/2908 (0.1)	2/703 (0.3)

Source: ISS Table 3.m, page 315/410, Calcium 1.75mmol/L = 7 mg/dL, Calcium 3 mmol/L = 12 mg/dL

Table 135: Post-baseline PCS Values for Electrolyte Variables in the MDD/GAD Short-Term Pool

Variable (units) Criteria	Number of Subjects (%)						
	Placebo N=2230	Lu AA21004 (mg)					Duloxetine N=907
		5 N=1466	10 N=1007	15 N=449	20 N=455	Total (a) N=4128	
Calcium (mg/dL)							
≤7	4/2106 (0.2)	1/1390 (<0.1)	0/957	1/418 (0.2)	0/424	2/3886 (<0.1)	0/842
≥12	1/2106 (<0.1)	1/1390 (<0.1)	1/957 (0.1)	0/418	0/424	2/3886 (<0.1)	0/842
Potassium (mmol/L)							
≤3.0	6/2106 (0.3)	2/1390 (0.1)	3/957 (0.3)	1/418 (0.2)	1/424 (0.2)	9/3887 (0.2)	1/842 (0.1)
≥5.5	45/2106 (2.1)	36/1390 (2.6)	12/957 (1.3)	6/418 (1.4)	12/424 (2.8)	77/3887 (2.0)	21/842 (2.5)
Sodium (mmol/L)							
≤125	0/2107	1/1390 (<0.1)	0/957	0/418	1/425 (0.2)	2/3888 (<0.1)	2/842 (0.2)
≥155	0/2107	2/1390 (0.1)	1/957 (0.1)	0/418	0/425	3/3888 (<0.1)	2/842 (0.2)

Source: ISS Table 3.n, page 316/410
Calcium 1.75mmol/L = 7 mg/dL
Calcium 3 mmol/L = 12 mg/dL

7.5.2.5 Fasting Glucose

Summary

There were no significant findings in fasting glucose.

7.5.2.5.1 Mean Changes from Baseline for Fasting Glucose

At each visit, the mean fasting glucose changes from Baseline generally were small and were not considered clinically meaningful.

7.5.2.5.1 PCS for Fasting Glucose

The PCS for fasting glucose (≥126 mg/dL) in Lu AA21004 treatment group were comparable to placebo in the MDD and MDD/GAD Short-Term Pools, and MDD/GAD relapse-prevention studies.

Table 136: Post-baseline PCS Values for Fasting Glucose in the MDD Short-Term Pool

Variable (units) Criteria	Number of Subjects (%)						
	Placebo N=1621	Lu AA21004 (mg)					Duloxetine N=753
		5 N=1013	10 N=699	15 N=449	20 N=455	Total (a) N=3060	
Glucose (mg/dL)							
≥126	149/1539 (9.7)	125/971 (12.9)	70/673 (10.4)	26/418 (6.2)	30/424 (7.1)	298/2906 (10.3)	71/703 (10.1)

Source: Table 3.1.1.3.2 in Appendix F: page 2642/26956 to 2643/26956
Total (a) included 1mg and 2.5mg Lu AA21004 doses

Table 137: Post-baseline PCS Values for Fasting Glucose in the MDD/GAD Short-Term Pool

Variable (units) Criteria	Number of Subjects (%)						
	Placebo N=2230	Lu AA21004 (mg)					Duloxetine N=907
		5 N=1466	10 N=1007	15 N=449	20 N=455	Total (a) N=4128	
Glucose (mg/dL)							
≥126	198/2106 (9.4)	155/1390 (11.2)	92/957 (9.6)	26/418 (6.2)	30/424 (7.1)	375/3886 (9.7)	83/842 (9.9)

Source: Table 3.3.1.3.2 in Appendix F: page 3389/26956 to 3390/26956

Table 138: Post-baseline PCS Values for Fasting Glucose in MDD Relapse-Prevention Study 11985A

Laboratory Test (Units)/ Criteria	Number of Subjects (%)		
	Open-Label	Double-Blind	
	LuAA21004 Total (N=639)	Placebo (N=192)	LuAA21004 Total (N= 204)
Glucose (mg/dL) ≥126	96/615 (15.6)	23/180 (12.8)	21/189 (11.1)

Source: Table 1.1.2 in 2013-03-05Resp-to-FDA-Req-for-Info-PCS-RP-studies (3).pdf

Table 139: Post-baseline PCS Values for Fasting Glucose in GAD Relapse-Prevention Study 12473A

Laboratory Test (Units)/ Criteria	Number of Subjects (%)		
	Open-Label	Double-Blind	
	LuAA21004 Total (N=687)	Placebo (N=230)	LuAA21004 Total (N= 229)
Glucose (mg/dL) >=126	52/675 (7.7)	14/211 (6.6)	14/216 (6.5)

Source: Table 1.2.2 in 2013-03-05Resp-to-FDA-Req-for-Info-PCS-RP-studies (3).pdf

7.5.2.6 Lipid profile

Summary
The proportions of subjects with at least 1 post-baseline total cholesterol ≥240 mg/dL and LDL ≥160 mg/dL were slightly higher in Lu AA21004 group than placebo but less than Duloxetine in both MDD and MDD/GAD short-term pool.

7.5.2.6.1 Mean Changes from Baseline for Lipid Variables
The mean changes from Baseline for the lipid variables (HDL, LDL, total cholesterol, and triglycerides) generally were small and were not considered clinically meaningful.

7.5.2.6.2 PCS for Lipid Variables

PCS for Lipid Variables in the MDD Short-Term Pool

Post-baseline PCS values for the lipid variables (total cholesterol, triglycerides, HDL, and LDL) in the MDD Short-Term Pool are presented in the following table. The proportions of subjects with at least 1 post-baseline total cholesterol ≥240 mg/dL and LDL ≥160 mg/dL were slightly higher in Lu AA21004 group than placebo but less than Duloxetine.

Table 140: Post-baseline PCS Values for Lipid Variables in the MDD Short-Term Pool (Lu AA21004 5 to 20 mg Doses)

Variable (units) Criteria	Number of Subjects (%)						
		Lu AA21004 (mg)					
	Placebo N=1621	5 N=1013	10 N=699	15 N=449	20 N=455	Total (a) N=3060	Duloxetine N=753
Total Cholesterol (mg/dL)							
≥240	300/1521 (19.7)	191/946 (20.2)	167/670 (24.9)	96/ 417 (23.0)	98/ 423 (23.2)	655/2859 (22.9)	191/ 693 (27.6)
Triglycerides (mg/dL)							
≥200	348/1521 (22.9)	213/ 946 (22.5)	157/ 670 (23.4)	83/ 417 (19.9)	91/ 423 (21.5)	628/2859 (22.0)	124/ 693 (17.9)
HDL Cholesterol (mg/dL)							
<40	253/1521 (16.6)	154/ 946 (16.3)	100/670 (14.9)	49/ 417 (11.8)	45/ 423 (10.6)	414/2859 (14.5)	104/ 693 (15.0)
LDL Cholesterol (mg/dL)							
≥160	222/1521 (14.6)	140/ 946 (14.8)	121/ 670 (18.1)	78/ 417 (18.7)	79/ 423 (18.7)	497/2859 (17.4)	143/ 693 (20.6)

Source: ISS Appendix F: Table 3.1.1.3.2
Studies included: 303, 304, 305, 315, 316, 317, 11492A, 11984A, 12541A, and 13267A.
(a) Lu AA21004 Total also includes 1 and 2.5 mg doses

PCS for Lipid Variables in the MDD/GAD Short-Term Pool

Similar to the MDD Short-Term Pool, the proportions of subjects with at least 1 post-baseline total cholesterol ≥240 mg/dL and LDL ≥160 mg/dL were slightly higher in Lu AA21004 group than placebo but less than Duloxetine and appeared to be dose-related.

Table 141: Post-baseline PCS Values for Lipid Variables in the MDD/GAD Short-Term Pool (Lu AA21004 5 to 20 mg Doses)

Variable (units) Criteria	Number of Subjects (%)						
		Lu AA21004 (mg)					
	Placebo N=2230	5 N=1466	10 N=1007	15 N=449	20 N=455	Total (a) N=4128	Duloxetine N=907
Total Cholesterol (mg/dL)							
≥240	365/2042 (17.9)	268/1347 (19.9)	207/ 928 (22.3)	96/ 417 (23.0)	98/ 423 (23.2)	794/3771 (21.1)	210/ 827 (25.4)
Triglycerides (mg/dL)							
≥200	427/2042 (20.9)	284/1347 (21.1)	199/ 928 (21.4)	83/ 417 (19.9)	91/ 423 (21.5)	776/3771 (20.6)	149/ 827 (18.0)

Variable (units) Criteria	Number of Subjects (%)						
	Placebo N=2230	Lu AA21004 (mg)					Duloxetine N=907
		5 N=1466	10 N=1007	15 N=449	20 N=455	Total (a) N=4128	
HDL Cholesterol (mg/dL)							
<40	341/2042 (16.7)	216/1347 (16.0)	142/ 928 (15.3)	49/ 417 (11.8)	45/ 423 (10.6)	570/3771 (15.1)	124/ 827 (15.0)
LDL Cholesterol (mg/dL)							
≥160	278/2042 (13.6)	203/1347 (15.1)	158/ 928 (17.0)	78/ 417 (18.7)	79/ 423 (18.7)	615/3771 (16.3)	156/ 827 (18.9)

Source: ISS Appendix F: Table 3.3.1.3.2
(a) Lu AA21004 Total also includes 1 and 2.5 mg doses

PCS for Lipid Variables in the MDD Long Term Relapse Prevention Study 11985A
The proportions of subjects with at least 1 post-baseline PCS for lipid variables were in similar between Lu AA21004 Total group and placebo in Double-Blind period.

Table 142: Post-baseline PCS Values for Lipid Variables in the MDD Long Term Relapse Prevention Study 11985A

Laboratory Test (Units)/Criteria	Number of Subjects (%)		
	Open-Label	Double-Blind	
	LuAA21004 Total (N=639)	Placebo (N=192)	LuAA21004 Total (N=204)
Total Cholesterol (mg/dL)			
≥240	149/ 615 (24.2)	42/ 182 (23.1)	43/ 189 (22.8)
Triglycerides (mg/dL)			
≥200	182/ 615 (29.6)	53/ 182 (29.1)	53/ 189 (28.0)
HDL Cholesterol (mg/dL)			
<40	140/ 615 (22.8)	39/ 182 (21.4)	44/ 189 (23.3)
LDL Cholesterol (mg/dL)			
≥160	106/ 615 (17.2)	28/ 182 (15.4)	30/ 189 (15.9)

Source: Table 1.1.2 in 2013-03-05 response to FDA request, page 9/120

PCS for Lipid Variables in the GAD Long Term Relapse Prevention Study 12473A
The proportions of subjects with at least 1 post-baseline PCS for lipid variables were in similar between Lu AA21004 Total group and placebo in Double-Blind period.

Table 143: Post-baseline PCS Values for Lipid Variables in the GAD Long Term Relapse Prevention Study 12473A

Laboratory Test (Units)/Criteria	Number of Subjects (%)		
	Open-Label	Double-Blind	
	LuAA21004 Total (N=687)	Placebo (N=230)	LuAA21004 Total (N=229)
Total Cholesterol (mg/dL)			
≥240	177/ 675 (26.2)	43/ 211 (20.4)	52/ 216 (24.1)

Laboratory Test (Units)/Criteria	Number of Subjects (%)		
	Open-Label	Double-Blind	
	LuAA21004 Total (N=687)	Placebo (N=230)	LuAA21004 Total (N=229)
Triglycerides (mg/dL)			
≥200	174/ 675 (25.8)	53/ 211 (25.1)	50/ 216 (23.1)
HDL Cholesterol (mg/dL)			
<40	176/ 675 (26.1)	52/ 211 (24.6)	43/ 216 (19.9)
LDL Cholesterol (mg/dL)			
≥160	136/ 675 (20.1)	32/ 211 (15.2)	38/ 216 (17.6)

Source: Table 1.1.2 in 2013-03-05 response to FDA request, page 26/120

PCS for Lipid Variables in the MDD Open-label Studies

Table 144: Post-baseline PCS Values for Lipid Variables in the MDD Open-label Studies

Variable (units) Criteria	Number of Subjects (%)		
	Studies	Studies	
	11492C/11984B/301	314/13267B	LuAA21004 Total
	(N=1443)	(N=1122)	(N=2565)
Total Cholesterol (mg/dL)			
≥240	521/1405 (37.1)	281/1016 (27.7)	802/2421 (33.1)
Triglycerides (mg/dL)			
≥200	559/1405 (39.8)	281/1016 (27.7)	840/2421 (34.7)
HDL Cholesterol (mg/dL)			
<40	357/1405 (25.4)	162/1016 (15.9)	519/2421 (21.4)
LDL Cholesterol (mg/dL)			
≥160	428/1405 (30.5)	194/1016 (19.1)	622/2421 (25.7)

Source: ISS Appendix F: Table 3.2.1.3.2

7.5.2.7 Urinalysis

In terms of outliers, one subject (026-0011) had protein 1+, which occurred at an unscheduled post-treatment visit. Presence of urine protein 1+ can also be clinically insignificant. There were no other meaningful differences between the treatment groups regarding the urinalysis results.

7.5.2.8 Dropouts due to Abnormal Laboratory Findings

Please refer to LFT section for dropouts due to abnormal LFTs. All other dropouts due to other abnormal laboratory findings are listed in the following table.

Table 145: Dropouts Due to Other Abnormal Laboratory Findings

Lu AA21004 Doses (mg)	Study No.	Subject No.	AEs
Hematology			
MDD Short-Term Pool			
2.5	11984A	UA002/S3867	White blood cell count decreased
MDD Open-Label Long-Term Pool			
5	11984B	LT002/S3171	Monocyte count increased Neutrophil count decreased White blood cell count decreased
5	301	0196/110	White blood cell count decreased
Chemistry			
MDD Short-Term Pool			
5	303	0343/314	Blood creatine phosphokinase increased
5	304	0455/415	Blood creatine phosphokinase increased
10	317	7068/707	Blood creatine phosphokinase increased
GAD Short-Term Pool			
10	308	9058/818	Blood creatine phosphokinase increased Neutrophil count decreased
MDD Relapse-Prevention Study Pool			
10	11985A-OL	DE004/S1257	Laboratory test abnormal (alpha-GST increased)
MDD Open-Label Long-Term Pool			
2.5	301	0175/104	Blood creatine phosphokinase increased
10	314	4067/405	Blood triglycerides increased
15		4023/408	Blood creatinine increased
20		4052/404(b)	Blood creatine phosphokinase increased
GAD Relapse-Prevention Study Pool			
5	12473A-OL	HU005/S3326	Hypoglycaemia
Urinalysis			
GAD Short-Term Pool			
5	311	0070/209	Blood urine present
MDD Relapse-Prevention Study Pool			
5	11985A-OL	KR002-S1699	Urine abnormality

a) Treatment at time of the adverse event; however, dose may have been adjusted during the relapse-prevention or open-label extensions studies before study discontinuation.
b) Data from 120-day safety update
Source: 2013-02-14-Response-to-FDA-Req-for-Info-Discon-Abnormal-Labs (2).pdf and ISS, Appendix B: page 10/52 to 52/52

We reviewed these cases listed in the above table and did not find any concerns regarding these discontinuations. The following described some cases with potentially clinically significant abnormal lab values.

UA002/S3867
69-year old Caucasian female subject on Lu AA21004 2.5 mg had white blood cell (WBC) count decreased (2.1×10^9/L) on study day 7 but was normal on Day 11 (4.5×10^9/L). She was withdrawn from the study due to this AE.

LT002/S3171
55-year old Caucasian female subject had monocyte count increased 17.0% (reference 3.1-12.5%); neutrophil count decreased 18.2% (reference range 40.9-77.0%) and white blood cell count decreased 2.4 $x10^9$/L (reference range 4.1-12.3 $x10^9$/L) on Study Day 135 and was withdrawn from the study the same day. She was on LuAA21004 5 mg at the time of the events. The events resolved 5 days following the drug discontinuation.

0196/110
55-year old Caucasian female subject on LuAA21004 5mg in an open-label extension study had decreased WBC ($1.99x10^9$/L) on Study Day 252 and was withdrawn from the study on Day 254. Her WBCs were 4.82 $x10^9$/L at Baseline and $4.26x10^9$/L on Day 260.

9058/818
45-year old African American male subject on Lu AA21004 10 mg/day had increased CK and lowered absolute neutrophils ($1.32x10^9$/L, reference: LLN $1.8x10^9$/L) on Study Day 26 and was withdrawn from the study on Study Day 40. The event of lowered neutrophil count was considered possibly related to study medication. His increased CK was not considered related to study medication because he had elevated CK at Baseline.

DE004/S1257
67-year-old Caucasian female subject with medical history including jaundice and alcohol dependency was on Lu AA21004 10mg and a statin for hypercholesterolemia and omeprazole for gastritis had elevated Alpha-glutathione s-transferase (alpha-GST) on Day 81 and withdrew from the study. Her alpha-GST returned to Baseline at Day 135.

4023/408
35-year old African American male subject had elevated creatinine (1.39 mg/dL, reference range 0.67 – 1.17 mg/dL) on Study Day 55 and discontinued on Study Day 62 with creatinine back to Baseline value (1.2 mg/dL).

HU005/S3326
62-year old Caucasian male subject on LuAA21004 5 mg open label treatment with medical history including type 1 diabetes mellitus on insulin and obesity had hypoglycaemia on Day 3. He was withdrawn from the study on Day also due to diarrhea and hypotension.

0070/209
49-year-old Caucasian male subject on LuAA21004 5 mg with medical history including nephrolithiasis had positive urine occult blood on Day 32, which was considered related

to his nephrolithiasis. The primary reason for early termination was withdrawal of consent.

KR002-S1699
66-year-old Asian male subject on LuAA21004 5 mg had “urine abnormality”, described as “cloudy” on Study Day 1 and he discontinued Study Day 6. “Cloudy” urine could be due to dehydration and not clinically significant.

7.5.3 Vital Sign Data

7.5.3.1. Vital Sign Assessments

Mean changes from Baseline to final visit in the MDD Short-Term Pool and the MDD/GAD Short-Term Pool; and the proportions of subjects with at least 1 post-baseline PCS value for vital sign variables in the MDD Short-Term Pool, the MDD/GAD Short-Term Pool, the MDD Long-Term Relapse-Prevention Study 11985A, the GAD Long-Term Relapse-Prevention Study 12473A, and the MDD Open-Label Long-Term Pool are presented in this section.

7.5.3.2. Mean Change from Baseline in Vital Sign Measures

Summary

Lu AA21004 20mg group was associated with mean increases of 0.8 mm Hg in standing systolic blood pressure (SBP) and 0.5 mm Hg in supine SBP compared to a mean decrease of 0.8 mm Hg in standing SBP and a mean decrease of 1.0 mm Hg in supine SBP in placebo in MDD short-term pool. Similar findings were also seen in MDD/GAD short-term pool.

<u>Mean Changes from Baseline at Final Visit for Vital Sign Variables in the MDD Short-Term Pool</u>

In the MDD Short-Term Pool, from baseline to endpoint, the mean change of standing systolic BP in Lu AA21004 5mg, 10mg, 15mg, and 20mg group was 0, 0, -0.3 and +0.8 mm Hg, respectively compared to mean change of -0.8 mm Hg in placebo group and -0.7 mm Hg in Duloxetine.

The mean change of supine systolic BP in Lu AA21004 5mg, 10mg, 15mg, and 20mg group was -0.7, -0.2, -0.5 and +0.5 mm Hg, respectively, compared to the mean change of -1.0 mm Hg in placebo group and +0.2 mm Hg in Duloxetine.

The mean change of supine diastolic blood pressure (DBP) in Lu AA21004 5mg, 10mg, 15mg, and 20mg group was -0.5, 0, -0.2, and +0.4 mm Hg, respectively, compared to the mean change of -0.6 mm Hg in placebo group and +1.0 mm Hg in Duloxetine.

The mean changes of standing DBP, pulse, and orthostatic SBP were small and there were no significant differences across the treatment groups.

Table 146: Mean Changes from Baseline at Final Visit for Vital Sign Variables in the MDD Short-Term Pool

	PBO N=1621 (a)		Lu AA21004										Duloxetine N=753	
			5 mg N=1013		10 mg N=699		15 mg N=449		20 mg N=455		Total (b) N=3060			
	N (c)	Mean Change (SD)	N	Mean Change (SD)	N	Mean Change (SD)	N	Mean Change (SD)	N	Mean Change (SD)	N	Mean Change (SD)	N	Mean Change (SD)
SBP standing (mmHg)	1594	-0.8 (11.92)	1001	-0.0 (11.60)	695	0.0 (11.66)	443	-0.3 (11.66)	446	0.8 (10.64)	3023	0.0 (11.37)	740	-0.7 (12.18)
DBP standing (mmHg)	1594	-0.1 (8.06)	1001	-0.2 (8.55)	695	-0.3 (8.21)	443	0.1 (8.14)	446	0.1 (8.12)	3023	-0.2 (8.20)	740	0.1 (8.10)
Pulse standing (bpm)	1594	-0.3 (9.92)	1001	-0.4 (10.66)	695	-0.6 (10.51)	443	-0.9 (10.36)	446	0.8 (10.68)	3023	-0.4 (10.61)	740	1.5 (10.53)
SBP supine (mmHg)	1594	-1.0 (11.83)	1002	-0.7 (11.26)	695	-0.2 (11.45)	443	-0.5 (10.86)	446	0.5 (10.95)	3025	-0.4 (11.21)	740	0.2 (11.64)
DBP supine (mmHg)	1594	-0.6 (8.04)	1002	-0.5 (8.26)	695	-0.0 (8.28)	443	-0.2 (8.47)	446	0.4 (7.67)	3025	-0.1 (8.13)	740	1.0 (8.54)
Pulse supine (bpm)	1594	-0.1 (9.29)	1002	-0.9 (9.58)	695	-0.6 (9.75)	443	-1.3 (9.21)	446	-0.1 (9.04)	3025	-0.8 (9.47)	740	0.7 (9.32)
SBP ortho-static (mmH)	1594	0.2 (9.76)	1001	0.7 (9.60)	695	0.2 (9.96)	443	0.2 (9.72)	446	0.3 (10.17)	3023	0.4 (9.57)	740	-1.0 (9.43)

Source: 2013-03-11-Resp-to-FDA-Req-for-Info-Mean-Change-Vitals.pdf, Table 1.
DBP=diastolic blood pressure, SBP=systolic blood pressure, SD=standard deviation.
(a) N in this row is the number in the safety set.
(b) Total also includes 1 and 2.5 mg doses.
(c) N in this row is the number at Final Visit.

Mean Changes from Baseline at Final Visit for Vital Sign Variables in the MDD/GAD Short-Term Pool

In the MDD/GAD Short-Term Pool, from baseline to endpoint, the mean change of standing systolic BP in Lu AA21004 5mg, 10mg, 15mg, and 20mg group was -0.1, +0.3, -0.3 and +0.8 mm Hg, respectively compared to mean change of -0.4 mm Hg in placebo group and -0.2 mm Hg in Duloxetine.

The mean change of supine systolic BP in Lu AA21004 5mg, 10mg, 15mg, and 20mg group was -0.6, 0, -0.5 and +0.5 mm Hg, respectively, compared to the mean change of -0.7 mm Hg in placebo group and 0.6 mm Hg in Duloxetine.

The mean change of supine DBP in Lu AA21004 5mg, 10mg, 15mg, and 20mg group was -0.3, +0.5, -0.2, and +0.4 mm Hg, respectively, compared to mean change of -0.4 mm Hg in placebo group and +1.2 mm Hg in Duloxetine.

Table 147: Mean Changes from Baseline at Final Visit for Vital Sign Variables in the MDD/GAD Short-Term Pool

	PBO N=2230 (a)		Lu AA21004										Duloxetine N=907	
			5 mg N=1466		10 mg N=1007		15 mg N=449		20 mg N=455		Total (b) N=4128			
	N (c)	Mean Change (SD)	N	Mean Change (SD)	N	Mean Change (SD)	N	Mean Change (SD)	N	Mean Change (SD)	N	Mean Change (SD)	N	Mean Change (SD)
SBP standing (mmHg)	2188	-0.4 (11.46)	1443	-0.1 (11.45)	995	0.3 (11.64)	443	-0.3 (11.66)	446	0.8 (10.64)	4064	0.1 (11.33)	890	-0.2 (12.16)
DBP standing (mmHg)	2188	-0.1 (8.01)	1443	-0.1 (8.33)	995	0.2 (8.24)	443	0.1 (8.14)	446	0.1 (8.12)	4064	0.0 (8.17)	890	0.4 (8.34)
Pulse standing (bpm)	2188	-0.1 (9.97)	1443	-0.2 (10.78)	995	-0.5 (10.43)	443	-0.9 (10.36)	446	0.8 (10.68)	4064	-0.3 (10.65)	890	1.4 (10.55)
SBP supine (mmHg)	2188	-0.7 (11.43)	1444	-0.6 (10.84)	995	0.0 (11.37)	443	-0.5 (10.86)	446	0.5 (10.95)	4066	-0.3 (11.01)	890	0.6 (11.68)
DBP supine (mmHg)	2188	-0.4 (8.00)	1444	-0.3 (8.19)	995	0.5 (8.20)	443	-0.2 (8.47)	446	0.4 (7.67)	4066	0.1 (8.13)	890	1.2 (8.64)
Pulse supine (bpm)	2188	0.0 (9.20)	1444	-0.7 (9.60)	995	-0.6 (9.60)	443	-1.3 (9.21)	446	-0.1 (9.04)	4066	-0.7 (9.54)	890	0.9 (9.54)
SBP ortho- static (mmHg)	2188	0.3 (9.31)	1443	0.5 (9.45)	995	0.3 (9.88)	443	0.2 (9.72)	446	0.3 (10.17)	4064	0.4 (9.41)	890	-0.9 (9.25)

Source: 2013-03-11-Resp-to-FDA-Req-for-Info-Mean-Change-Vitals.pdf, Table 2.
DBP=diastolic blood pressure, SBP=systolic blood pressure, SD=standard deviation.
(a) N in this row is the number in the safety set.
(b) Total also includes 1 and 2.5 mg doses.
(c) N in this row is the number at Final Visit

7.5.3.3. Potentially Clinically Significant Vital Sign Changes

Summary

The proportions of subjects with at least 1 post-baseline PCS value of ≥180 mm Hg or increase ≥ 20 mm Hg for standing and supine SBP and ≥105 mm Hg or increase ≥ 15 mm Hg for standing and supine DBP in Lu AA21004 20mg group were slightly higher than placebo and Duloxetine.

PCS for Vital Sign Variables in the MDD Short-Term Pool

The proportion of subjects with at least 1 post-baseline PCS value of ≥180 mm Hg or increase ≥ 20 mm Hg for supine SBP in Lu AA21004 5mg, 10mg, 15mg, and 20mg group was 10.6%, 12.1%, 10.4% and 13.5% compared to 10.2% in placebo and 12.6% in Duloxetine.

The proportion of subjects with at least 1 post-baseline PCS value of ≥105 mm Hg or increase ≥ 15 mm Hg for supine DBP in Lu AA21004 5mg, 10mg, 15mg, and 20mg group was 11.8%, 10.4%, 10.4% and 12.3.% compared to 8.7% in placebo and 11.9% in Duloxetine.

The proportion of subjects with at least 1 post-baseline PCS value for other vital sign variables did not show significant differences across treatment groups.

Table 148: Post-baseline PCS Values for Vital Sign Variables in the MDD Short-Term Pool (Lu AA21004 5 to 20 mg Doses)

Variable (units)	Number of Subjects (%)						
		Lu AA21004 (mg)					
	Placebo N=1621	5 N=1013	10 N=699	15 N=449	20 N=455	Total (a) N=3060	Duloxetine N=753
Standing Systolic Blood Pressure (mmHg)							
≤90 or decrease ≥20	260/1594 (16.3)	126/1001 (12.6)	85/695 (12.2)	50/ 443 (11.3)	45/446 (10.1)	351/3025 (11.6)	116/740 (15.7)
≥180 or increase ≥20	193/1594 (12.1)	130/1001 (13.0)	89/695 (12.8)	55/443 (12.4)	63/446 (14.1)	388/3025 (12.8)	85/740 (11.5)
Standing Diastolic Blood Pressure (mmHg)							
≤50 or decrease ≥15	163/1594 (10.2)	102/1001 (10.2)	84/695 (12.1)	32/443 (7.2)	48/446 (10.8)	305/3025 (10.1)	85/740 (11.5)
≥105 or increase≥15	153/1594 (9.6)	126/1001 (12.6)	84/695 (12.1)	45/443 (10.2)	53/446 (11.9)	349/3025 (11.5)	75/740 (10.1)
Standing Pulse (bpm)							
≤50 or decrease ≥15	229/1594 (14.4)	169/1001 (16.9)	127/ 695 (18.3)	87/443 (19.6)	66/446 (14.8)	525/3025 (17.4)	83/740 (11.2)
≥120 or increase ≥15	331/1594 (20.8)	176/1001 (17.6)	149/695 (21.4)	81/443 (18.3)	100/446 (22.4)	576/3025 (19.0)	160/740 (21.6)
Supine Systolic Blood Pressure (mmHg)							
≤90 or decrease ≥20	231/1594 (14.5)	139/1002 (13.9)	84/695 (12.1)	48/443 (10.8)	51/446 (11.4)	377/3026 (12.5)	90/740 (12.2)
≥180 or increase≥20	163/1594 (10.2)	106/1002 (10.6)	84/695 (12.1)	46/443 (10.4)	60/446 (13.5)	350/3026 (11.6)	93/740 (12.6)
Supine Diastolic Blood Pressure (mmHg)							
≤50 or decrease ≥15	188/1594 (11.8)	113/1002 (11.3)	76/695 (10.9)	53/443 (12.0)	42/446 (9.4)	324/3026 (10.7)	71/740 (9.6)
≥105 or increase≥15	138/1594 (8.7)	118/1002 (11.8)	72/695 (10.4)	46/443 (10.4)	55/446 (12.3)	332/3026 (11.0)	88/740 (11.9)
Supine Pulse (bpm)							
≤50 or decrease ≥15	214/1594 (13.4)	171/1002 (17.1)	109/695 (15.7)	70/443 (15.8)	65/446 (14.6)	487/3026 (16.1)	87/740 (11.8)
≥120 or increase ≥15	265/1594 (16.6)	140/1002 (14.0)	109/695 (15.7)	67/443 (15.1)	67/446 (15.0)	447/3026 (14.8)	119/740 (16.1)
Orthostatic Systolic Blood Pressure (mmHg)							
Calculated decrease (Standing-Supine) ≥20	97/1594 (6.1)	50/1001 (5.0)	48/695 (6.9)	29/443 (6.5)	29/446 (6.5)	174/3025 (5.8)	76/740 (10.3)

Source: ISS Appendix F: Table 4.1.1.1.3, page 3736/26956 to 3737/26956
(a) Lu AA21004 Total also includes 1 and 2.5 mg doses.

The findings in MDD/GAD short-term pool were similar to those in MDD short-term pool.

PCS for Vital Sign Variables in the MDD Relapse-Prevention Study 11985A

The proportion of subjects with at least 1 post-baseline PCS value in Lu AA21004 Total group were slightly higher than those in placebo in most vital variables including orthostatic systolic blood pressure during the Double-Blind period.

Table 149: PCS for Vital Sign Variables in the MDD Relapse-Prevention Study 11985A

Parameter (Units)/ Criteria	Number of Subjects (%)		
	Open-Label	Double-Blind	
	LuAA21004 Total (N=639)	Placebo (N=192)	LuAA21004 Total (N=204)
Standing Systolic Blood Pressure (mmHg)			
≤90 or decrease ≥20	114/ 620 (18.4)	31/ 183 (16.9)	21/ 190 (11.1)
≥180 or increase ≥20	124/ 620 (20.0)	18/ 183 (9.8)	19/ 190 (10.0)
Standing Diastolic Blood Pressure (mmHg)			
≤50 or decrease ≥15	87/ 620 (14.0)	15/ 183 (8.2)	23/ 190 (12.1)
≥105 or increase≥15	88/ 620 (14.2)	15/ 183 (8.2)	22/ 190 (11.6)
Standing Pulse (bpm)			
≤50 or decrease ≥15	139/ 620 (22.4)	15/ 183 (8.2)	23/ 190 (12.1)
≥120 or increase ≥15	106/ 620 (17.1)	21/ 183 (11.5)	27/ 190 (14.2)
Supine Systolic Blood Pressure (mmHg)			
≤90 or decrease ≥20	117/ 620 (18.9)	23/ 183 (12.6)	18/ 190 (9.5)
≥180 or increase≥20	108/ 620 (17.4)	19/ 183 (10.4)	22/ 190 (11.6)
Supine Diastolic Blood Pressure (mmHg)			
≤50 or decrease ≥15	89/ 620 (14.4)	18/ 183 (9.8)	18/ 190 (9.5)
≥105 or increase≥15	78/ 620 (12.6)	14/ 183 (7.7)	23/ 190 (12.1)
Supine Pulse (bpm)			
≤50 or decrease ≥15	123/ 620 (19.8)	10/ 183 (5.5)	18/ 190 (9.5)
≥120 or increase ≥15	74/ 620 (11.9)	23/ 183 (12.6)	25/ 190 (13.2)
Orthostatic Systolic Blood Pressure (mmHg)			
Calculated decrease (Standing-Supine) ≥20	70/ 620 (11.3)	7/ 183 (3.8)	13/ 190 (6.8)

Source: Table 2.1.1 in 2013-03-05 response to FDA request, page 42/120

PCS for Vital Sign Variables in the GAD Relapse-Prevention Study 12473A

The findings were similar to those in MDD Relapse-Prevention Study.

Table 150: PCS for Vital Sign Variables in the GAD Relapse-Prevention Study 12473A

Parameter (Units)/ Criteria	Number of Subjects (%)		
	Open-Label	Double-Blind	
	LuAA21004 Total (N=687)	Placebo (N=230)	LuAA21004 Total (N=229)
Standing Systolic Blood Pressure (mmHg)			
≤90 or decrease ≥20	103/ 677 (15.2)	24/ 218 (11.0)	20/ 216 (9.3)
≥180 or increase ≥20	69/ 677 (10.2)	27/ 218 (12.4)	28/ 216 (13.0)
Standing Diastolic Blood Pressure (mmHg)			
≤50 or decrease ≥15	72/ 677 (10.6)	19/ 218 (8.7)	15/ 216 (6.9)

Parameter (Units)/ Criteria	Number of Subjects (%)		
	Open-Label	Double-Blind	
	LuAA21004 Total (N=687)	Placebo (N=230)	LuAA21004 Total (N=229)
≥105 or increase≥15	81/ 677 (12.0)	20/ 218 (9.2)	19/ 216 (8.8)
Standing Pulse (bpm)			
≤50 or decrease ≥15	118/ 677 (17.4)	22/ 218 (10.1)	30/ 216 (13.9)
≥120 or increase ≥15	96/ 677 (14.2)	29/ 218 (13.3)	24/ 216 (11.1)
Supine Systolic Blood Pressure (mmHg)			
≤90 or decrease ≥20	106/ 677 (15.7)	30/ 218 (13.8)	19/ 216 (8.8)
≥180 or increase≥20	80/ 677 (11.8)	19/ 218 (8.7)	25/ 216 (11.6)
Supine Diastolic Blood Pressure (mmHg)			
≤50 or decrease ≥15	75/ 677 (11.1)	14/ 218 (6.4)	20/ 216 (9.3)
≥105 or increase≥15	65/ 677 (9.6)	18/ 218 (8.3)	25/ 216 (11.6)
Supine Pulse (bpm)			
≤50 or decrease ≥15	116/ 677 (17.1)	16/ 218 (7.3)	22/ 216 (10.2)
≥120 or increase ≥15	80/ 677 (11.8)	28/ 218 (12.8)	28/ 216 (13.0)
Orthostatic Systolic Blood Pressure (mmHg)			
Calculated decrease (Standing-Supine) ≥20	45/ 677 (6.6)	10/ 218 (4.6)	12/ 216 (5.6)

Source: Table 2.2.1 in 2013-03-05 response to FDA request, page 73/120

7.5.3.4. Dropouts due to Vital Sign Abnormalities

This reviewer examined the submission ISS Appendix B which included all dropouts/ discontinuations due to TEAEs. Table 151 lists all dropouts/discontinuations caused by TEAEs related to vital sign abnormalities.

Table 151: Dropouts due to Vital Sign Abnormalities

Lu AA21004 Doses (mg)	Study No.	Subject No.	AEs
MDD Short-Term Pool			
2.5	11984A	TW001/S3094	Bradycardia
		KR001/S3241	Heart rate decreased
	T21004-317	7039/718	Blood pressure increased
	T21004-316	6058/601	Hypertension
MDD Relapse-Prevention Study			
5	11985A-OL	DE006/S1636	Sinus bradycardia
		DE006/S1779	Tachycardia
GAD Relapse-Prevention Study			
5	12473A-OL	ZA010/S3234	Blood pressure increased
		HU005/S3326	Hypotension
MDD Open-Label Long-Term Pool			
10	T21004-301	0148/105	Hypertension
		0154/106	Blood pressure increased
Phase 1 Study Pool			
10	T21004-104	0001/432	Blood pressure increased
	T21004-111	0001/073	Blood pressure increased
		0001/111	Blood pressure increased
10 + Lithium 450 mg BID	T21004-118	0001/005	Syncope (blood pressure decreased)
40	T21004-104	0001/032	Sinus tachycardia

Compiled from ISS, Appendix B: page 10/52 to 52/52

7.5.4 Weight

7.5.4.1. Mean Weight Changes from Baseline

Summary:

The mean weight changes from Baseline to final/early termination (ET) visit were small and did not show significant differences across treatment groups.

Mean Body Weight Changes from Baseline in MDD Short-Term Pool and MDD/GAD Short-Term Pool

There were no clinically meaningful differences in mean weight changes from Baseline in both MDD Short-Term Pool and MDD/GAD Short-Term Pool.

Table 152: Mean Changes from Baseline for Body Weight in MDD Short-Term Pool and MDD/GAD Short-Term Pool

Study Pool	N	Mean (SD) (kg)	N	Mean (SD) (kg)
MDD Short-Term Pool	Baseline		Change from Baseline to Final/ET Visit	
Placebo	1621	82.51 (21.642)	1536	0.07 (1.888)
Lu AA21004 5 mg	1013	80.09 (21.728)	967	-0.05 (1.909)
Lu AA21004 10 mg	699	79.47 (20.983)	665	0.16 (1.922)
Lu AA21004 15 mg	449	82.14 (20.849)	420	-0.11 (1.880)
Lu AA21004 20 mg	455	83.09 (22.036)	425	-0.02 (1.999)
Lu AA21004 Total (a)	3060	80.18 (21.376)	2893	0.03 (1.926)
Duloxetine	753	79.29 (20.439)	703	-0.54 (2.154)
MDD/GAD Short-Term Pool	Baseline		Change from Baseline to Final/ET Visit	
Placebo	2230	82.27 (21.547)	2098	0.15 (1.866)
Lu AA21004 5 mg	1466	79.55 (20.952)	1388	-0.03 (1.832)
Lu AA21004 10 mg	1007	80.53 (21.487)	949	0.18 (1.908)
Lu AA21004 15 mg	449	82.14 (20.849)	420	-0.11 (1.880)
Lu AA21004 20 mg	455	83.09 (22.036)	425	-0.02 (1.999)
Lu AA21004 Total (a)	4128	80.33 (21.243)	3879	0.04 (1.881)
Duloxetine	906	79.32 (20.352)	842	-0.49 (2.186)

Sources: ISS Table 4.f, page 342/410, (a) Lu AA21004 Total also includes 1 and 2.5 mg doses.
ET=early termination

Mean Body Weight Changes from Baseline in MDD Long-Term Relapse-Prevention Study 11985A and GAD Long-Term Relapse-Prevention Study 12473A

There were no clinically significantly weight changes in the end of the open-label period and no meaningful weight change differences between Lu AA21004 and placebo at the end of double blind period in both studies.

Table 153: Mean Changes from Baseline for Body Weight in MDD Long-Term Relapse-Prevention Study 11985A and GAD Long-Term Relapse-Prevention Study 12473A

Study Pool	N	Mean (SD)	N	Mean (SD) (kg)
MDD Long-Term Relapse-Prevention Study 11985A	Baseline		Change from Baseline I to Week 12 (OL) or Baseline II to Final/ET Visit (DB)	
OL: Lu AA21004 5 to 10 mg	639	74.3 (18.8)	496	0.2 (2.5)
DB: Placebo	189	76.5 (20.5)	187	0.1 (3.6)
DB: Lu AA21004 5 or 10 mg	203	73.4 (18.1)	198	0.4 (3.0)
GAD Long-Term Relapse-Prevention Study 12473A	Baseline		Change from Baseline I to Week 20 (OL) or Baseline II to Final/ET Visit (DB)	
OL: Lu AA21004 5 to 10 mg	685	73.5 (16.4)	514	0.2 (2.9)
DB: Placebo	221	74.8 (17.4)	223	0.4 (3.0)
DB: Lu AA21004 5 or 10 mg	217	73.8 (16.3)	222	0.6 (2.8)

Sources: ISS Table 4.f, page 342/410. DB=double-blind, ET=early termination, OL=open-label
Baseline: Double-Blind Study Baseline. Baseline II: Open-Label Study Baseline

Mean Body Weight Changes from Baseline in MDD Open-Label Long-Term Pool

In the MDD Open-Label Long-Term Pool, the mean weight changes were small.

Table 154: Mean Changes from Baseline for Body Weight in MDD Open-Label Long-Term Pool

Study Pool or Individual Study	N	Mean (SD)	N	Mean (SD) (kg)
MDD Open-Label Long-Term Pool	**Baseline**		**Change from Baseline II**	
Completed Studies 11492C/11984B/301: Lu AA21004 2.5 to 10 mg	1443	77.45 (19.650)	1423	0.77 (4.029)
Ongoing Studies 314/13267B: Lu AA21004 10 to 20 mg	1122	88.10 (24.058)	1047	0.44 (3.991)
Lu AA21004 Total: Lu AA21004 2.5 to 20 mg	2565	82.11 (22.320)	2470	0.63 (4.015)

Sources: ISS Table 4.f, page 342/410
Baseline: Double-Blind Study Baseline. Baseline II: Open-Label Study Baseline

7.5.4.2. Potentially Clinically Significant Weight Changes

Post-baseline PCS Values for Body Weight in the MDD Short-Term Pool

Small proportions of subjects had at least 1 post-baseline weight decrease or increase ≥7% from baseline. The incidences of PCS in body weight changes were similar in Lu AA21004 and placebo.

Table 155: Post-baseline PCS Values for Body Weight in the MDD Short-Term Pool

Weight (kg)	Number of Subjects (%)						
	Placebo N=1621	Lu AA21004 (mg)					Duloxetine N=753
		5 N=1013	10 N=699	15 N=449	20 N=455	Total N=3060	
Decrease from Baseline ≥7%	10/1536 (0.7)	2/967 (0.2)	3/665 (0.5)	2/420 (0.5)	6/425 (1.4)	17/2893 (0.6)	15/703 (2.1)
Increase from Baseline ≥7%	9/1536 (0.6)	9/967 (0.9)	8/665 (1.2)	0/420 (0)	1/425 (0.2)	24/2893 (0.8)	6/703 (0.9)

Source: ISS Table 4.g, page 344/410

Post-baseline PCS Values for Body Weight in the MDD/GAD Short-Term Pool

The findings were similar to those of the MDD Short-Term Pool.

Table 156: Post-baseline PCS Values for Body Weight in MDD/GAD Short-Term Pool

Weight (kg)	Number of Subjects (%)						
	Placebo N=2230	Lu AA21004 (mg)					Duloxetine N=907
		5 N=1466	10 N=1007	15 N=449	20 N=455	Total N=4128	
Decrease from Baseline ≥7%	12/2098 (0.6)	7/1388 (0.5)	4/949 (0.4)	2/420 (0.5)	6/425 (1.4)	24/3879 (0.6)	19/842 (2.3)
Increase from Baseline ≥7%	15/2098 (0.7)	10/1388 (0.7)	9/949 (0.9)	0/420 (0)	1/425 (0.2)	26/3879 (0.7)	8/842 (1.0)

Source: ISS Table 4.h, page 344/410

Post-baseline PCS Values for Body Weight in the MDD Open-Label Long-Term Pool

The proportions of body weight changes in the MDD Open-Label Long-Term Pool were greater than those in the short-term pools. The incidence of subjects with a PCS weight change was higher in the completed studies than the ongoing studies.

Table 157: Post-baseline PCS Values for Body Weight in the MDD Open-Label Long-Term Pool

Body Weight (kg)	Number of Subjects (%)		
	Completed Studies 11492C/11984B/301 N=1443	Ongoing Studies 314/13267B N=1122	Lu AA21004 Total N=2565
Decrease from Baseline ≥7%	88/1423 (6.2)	46/1047 (4.4)	134/2470 (5.4)
Increase from Baseline ≥7%	189/1423 (13.3)	70/1047 (6.7)	259/2470 (10.5)

Source: ISS Table 4.i, page 344/410

7.5.4.3. Dropouts due to Weight Changes

This reviewer examined the Appendix B: 3.0 ADVERSE EVENTS LEADING TO DISCONTINUATION and compiled Table 158 which lists all discontinuations due to weight increased/decreased as PT.

All subjects discontinued the study due to weight changes were females. All were due to weight increased except 2 subjects with weight decreased – one caused by diarrhea and the other caused by nausea.

Table 158: Discontinuations Due to Weight Changes

Treatment LuAA21004	Study No.	Subject No.	Sex	Age	Preferred Term	Onset (a)
MDD Phase 2/3 Controlled Studies						
5 mg	T21004-303	0323/320	F	52	Weight increased	15
MDD Phase 2/3 Open-Label Extension Studies						
10 mg	11492C	FI008/4407	F	42	Weight increased	-1/55
	T21004-301	0123/102	F	50	Diarrhea Weight decreased	29/87 29/87
		0149/103	F	37	Weight increased	31/87
	T21004-314	4037/405	F	46	Weight increased	7/78
15 mg	T21004-314	4081/401	F	39	Weight increased	29/99
		4003/405	F	51	Weight increased	56/134
20 mg	T21004-314	4031/403	F	39	Weight increased	168/238
GAD Relapse-Prevention Study						
5 mg	12473A-OL	FI010/S3050	F	35	Weight increased	11
		AR013/S3619	F	41	Weight increased	86
		ZA004/S3276	F	52	Weight increased	112
		CL008/S3485	F	49	Nausea Weight decreased	41 46

Source: compiled from Appendix B: Tabular Listing of Subject Narratives for LuAA21004 Studies page 10 to 52: 3.0 ADVERSE EVENTS LEADING TO DISCONTINUATION

(a) Study day of adverse event onset followed by cumulative study day of adverse event where applicable.
OL: open-label period

7.5.5 Electrocardiograms (EKGs)

Summary
There were no significant findings. The thorough QT study was negative.

7.5.5.1 Mean Changes from Baseline for ECG Variables

Overall, the mean changes for the ECG variables (heart rate and RR, PR, QRS, QT, QTcB, and QTcF intervals) from Baseline were small and were not considered clinically meaningful.

7.5.5.2 PCS Values for ECG Variables

PCS Values for ECG Variables in MDD Short-Term Pool
The incidences of Post-baseline PCS values for selected ECG variables (heart rate and RR, PR, and QRS intervals) were small and similar among Lu AA21004 Total and placebo groups the MDD Short-Term Pool.

A categorical analysis of the QTcB and QTcF intervals in MDD Short-Term Pool is shown in the following table. The incidences of each QTcB and QTcF category analyzed were small and similar among Lu AA21004 Total and placebo groups.

Table 159: Categorical Analysis of QTcB and QTcF Intervals in the MDD Short-Term Pool (Lu AA21004 5 to 20 mg Doses)

Variable (units) Criteria	Number of Subjects (%)						
	Placebo N=1621	Lu AA21004 (mg)					Duloxetine N=753
		5 N=1013	10 N=699	15 N=449	20 N=455	Total N=3060	
QTcB interval (msec)							
>450	144/1527 (9.4)	105/963 (10.9)	65/671 (9.7)	28/416 (6.7)	24/424 (5.7)	273/2891 (9.4)	72/694 (10.4)
>480	8/1527 (0.5)	7/963 (0.7)	4/671 (0.6)	2/416 (0.5)	1/424 (0.2)	18/2891 (0.6)	3/694 (0.4)
>500	2/1527 (0.1)	2/963 (0.2)	1/671 (0.1)	1/416 (0.2)	0/424 (0)	4/2891 (0.1)	0/694 (0)
Increase from Baseline >30	125/1521 (8.2)	84/959 (8.8)	65/671 (9.7)	28/414 (6.8)	26/423 (6.1)	234/2882 (8.1)	56/691 (8.1)
Increase from Baseline >60	6/1521 (0.4)	5/959 (0.5)	7/671 (1.0)	1/414 (0.2)	2/423 (0.5)	16/2882 (0.6)	5/691 (0.7)
QTcF interval (msec)							
>450	40/1527 (2.6)	39/963 (4.0)	20/671 (3.0)	11/416 (2.6)	13/424 (3.1)	102/2891 (3.5)	13/694 (1.9)
>480	4/1527 (0.3)	2/963 (0.2)	0/671 (0)	1/416 (0.2)	0/424 (0)	3/2891 (0.1)	0/694 (0)
>500	0/1527 (0)	0/963 (0)	0/671 (0)	0/416 (0)	0/424 (0)	0/2891 (0)	0/694 (0)
Increase from Baseline >30	48/1521 (3.2)	33/959 (3.4)	33/671 (4.9)	12/414 (2.9)	12/423 (2.8)	105/2882 (3.6)	27/691 (3.9)
Increase from Baseline >60	2/1521 (0.1)	1/959 (0.1)	5/671 (0.7)	0/414 (0)	1/423 (0.2)	7/2882 (0.2)	3/691 (0.4)

Source: ISS Table 4.I, page 350/410
Lu AA21004 Total included 1mg and 2.5mg

PCS Values for ECG Variables in MDD/GAD Short-Term Pool

The findings of the proportions of subjects with at least 1 post-baseline PCS value for the ECG variables were similar to the MDD Short-Term Pool. The incidences were low and similar in the Lu AA21004 Total and placebo groups in the MDD/GAD Short-Term Pool.

A categorical analysis of the QTcB and QTcF intervals in MDD/GAD Short-Term Pool is shown in the following table. The incidences of each QTcB and QTcF category analyzed were small and similar among Lu AA21004 Total and placebo groups.

Table 160: Categorical Analysis of QTcB and QTcF Intervals in the MDD/GAD Short-Term Pool (Lu AA21004 5 to 20 mg Doses)

Variable (units) Criteria	Number of Subjects (%)						
	Placebo N=2230	Lu AA21004 (mg)					Duloxetine N=907
		5 N=1466	10 N=1007	15 N=449	20 N=455	Total N=4128	
QTcB interval (msec)							
>450	183/2089 (8.8)	129/1381 (9.3)	87/954 (9.1)	28/416 (6.7)	24/424 (5.7)	342/3872 (8.8)	86/834 (10.3)
>480	10/2089 (0.5)	7/1381 (0.5)	9/954 (0.9)	2/416 (0.5)	1/424 (0.2)	24/3872 (0.6)	5/834 (0.6)
>500	3/2089 (0.1)	2/1381 (0.1)	2/954 (0.2)	1/416 (0.2)	0/424 (0)	5/3872 (0.1)	0/834 (0)
Increase from Baseline >30	167/2083 (8.0)	112/1377 (8.1)	93/954 (9.7)	28/414 (6.8)	26/423 (6.1)	317/3863 (8.2)	67/831 (8.1)
Increase from Baseline >60	7/2083 (0.3)	7/1377 (0.5)	8/954 (0.8)	1/414 (0.2)	2/423 (0.5)	20/3863 (0.5)	5/831 (0.6)
QTcF interval (msec)							
>450	50/2089 (2.4)	44/1381 (3.2)	29/954 (3.0)	11/416 (2.6)	13/424 (3.1)	121/3872 (3.1)	18/834 (2.2)
>480	6/2089 (0.3)	2/1381 (0.1)	2/954 (0.2)	1/416 (0.2)	0/424 (0)	5/3872 (0.1)	0/834 (0)
>500	1/2089 (<0.1)	0/1381 (0)	0/954	0/416	0/424 (0)	0/3872 (0)	0/834 (0)
Increase from Baseline >30	58/2083 (2.8)	41/1377 (3.0)	42/954 (4.4)	12/414 (2.9)	12/423 (2.8)	130/3863 (3.4)	30/831 (3.6)
Increase from Baseline >60	3/2083 (0.1)	1/1377 (<0.1)	6/954 (0.6)	0/414 (0)	1/423 (0.2)	8/3863 (0.2)	3/831 (0.4)

Source: compiled from ISS Table 4.n, page 354/410

7.5.5.3 Dropouts/Discontinuations due to EKG changes

This reviewer examined the Appendix B which lists all the AEs that caused dropouts/discontinuations and identified the following abnormal EKG changes that caused dropouts/discontinuations.

Table 161: Dropouts/Discontinuations Due to AEs of EKG changes

Lu AA21004 Doses (mg)	Study No.	Subject No.	AEs
MDD Short-Term Pool			
5	11492A	SK002/3243	Electrocardiogram ST segment
	T21004-304	0441/433	Atrial fibrillation
MDD Relapse-Prevention Study			
5	11985A-OL	IN005/S1546	Electrocardiogram QT prolonged
		DE006/S1636	Sinus bradycardia
		DE006/S1779	Tachycardia
GAD Relapse-Prevention Study			
5	12473A-OL	FI010/S3043	Ventricular tachycardia
		FI006/S3339	Electrocardiogram QT prolonged
MDD Open-Label Long-Term Pool			
5	11984B	BG004/S3397	Electrocardiogram QT prolonged
10	T21004-301	0245/134	Electrocardiogram QT prolonged
		0118/122	Atrial fibrillation
15	T21004-314	4003/404	Atrial fibrillation
Phase 1 Study Pool			
9	LuAA21004_123	4001/082	Electrocardiogram PR prolongation

Source: Compiled from ISS, Appendix B: page 10/52 to 52/52, OL: open-label period

7.5.5.4 Thorough QT/QTc Study - Study 104

Study 104 was a randomized, double-blind, placebo- and moxifloxacin-controlled, parallel-group study evaluating the effect of Lu AA21004 on cardiac repolarization following 14 day q.d. dosing in healthy adult male subjects. The primary endpoint was the largest time-matched, baseline-adjusted LS mean difference in QTcNi (Linear) between Lu AA21004 and placebo on Day 14.

The thorough QT team reviewed the Study 104 under IND 76307 and did not find significant QT prolongation effect of Lu AA21004. The final review was signed on 11/19/2010. The following table is from the QT team review.

Table 162: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds of ΔΔQTcNi for Lu AA21004 (10 and 40 mg, QD) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcNi (ms)	90% CI (ms)
Lu AA21004 10 mg q.d.	4	3.7	(1.2, 6.1)
Lu AA21004 40 mg q.d.	4	4.9	(2.5, 7.4)
Moxifloxacin 400 mg	3	10.8	(8.2, 13.3) *

*Multiple endpoint adjustment was applied. The largest lower bound after Bonferroni adjustment for 4 time points is 7.2 ms.

7.5.6 Special Safety Studies/Clinical Trials

Thorough QT study was conducted in this program. See **section 7.4.5.4.**

7.5.7 Immunogenicity

No immunogenicity study was conducted.

7.6 Other Safety Explorations

7.6.1 Dose Dependency for Adverse Events

Refer to respective adverse event sections.

7.6.2 Time Dependency for Adverse Events

Refer to nausea section for time dependency for AEs.

7.6.3 Drug-Demographic Interactions

The drug-demographic interactions were studied by age, gender, race and BMI.

Age
The sponsor analyzed the overall and most common TEAEs on Lu AA21004 dose by MedDRA preferred term and age (<65 and ≥65 years) in the MDD Short-Term Pool.

No consistent pattern was seen in the distribution of AEs across treatment groups between aged <65 and ≥65 years.

Gender
Table 163 shows the overall and most common TEAEs (nausea, constipation and vomiting) on Lu AA21004 dose by MedDRA preferred term and gender in the MDD Short-Term Pool.

Across Lu AA21004 5 - 20mg groups, any TEAEs, related TEAEs, TEAEs leading to discontinuations, nausea and constipation occurred more often in female than male subjects. SAEs did not demonstrate the same pattern across Lu AA21004 doses, probably because the number of SAEs was small. Of note, the incidence of SAEs only occurred in the female and not the male subjects for the 20 mg dose group (2 subjects, 0.6%). Vomiting was seen more in male subjects (3.1% vs. 2.7%) only in Lu AA21004 5mg group. It occurred more often in females in Lu AA21004 10 - 20mg.

In both Placebo and Duloxetine groups, any TEAEs, related TEAEs, nausea, constipation and vomiting occurred more often in female subjects. TEAEs leading to discontinuations and SAEs occurred more often in male subjects.

Table 163: Overall and Most Common TEAEs on Lu AA21004 Dose by MedDRA Preferred Term and Gender in the MDD Short-Term Pool

	Subjects (%) based on gender													
	Placebo		Lu AA21004 (mg) 5		10		15		20		Total (a)		Duloxetine	
	F	M	F	M	F	M	F	M	F	M	F	M	F	M
n (b)	1047	574	659	354	480	219	308	141	312	143	2058	1002	514	239
Any TEAEs	673 (64.3)	329 (57.3)	442 (67.1)	230 (65.0)	332 (69.2)	133 (60.7)	228 (74.0)	88 (62.4)	235 (75.3)	96 (67.1)	1407 (68.4)	622 (62.1)	403 (78.4)	180 (75.3)
Related	529 (50.5)	254 (44.3)	363 (55.1)	180 (50.8)	283 (59.0)	115 (52.5)	206 (66.9)	73 (51.8)	198 (63.5)	86 (60.1)	1188 (57.7)	509 (50.8)	378 (73.5)	161 (67.4)
Leading to D/C	39 (3.7)	23 (4.0)	36 (5.5)	17 (4.8)	32 (6.7)	10 (4.6)	27 (8.8)	9 (6.4)	29 (9.3)	9 (6.3)	141 (6.9)	50 (5.0)	44 (8.6)	24 (10.0)
SAEs	9 (0.9)	6 (1.0)	10 (1.5)	5 (1.4)	7 (1.5)	2 (0.9)	1 (0.3)	1 (0.7)	2 (0.6)	0	21 (1.0)	10 (1.0)	4 (0.8)	4 (1.7)
Most Common TEAEs														
Nausea	114 (10.9)	35 (6.1)	156 (23.7)	60 (16.9)	135 (28.1)	45 (20.5)	111 (36.0)	33 (23.4)	113 (36.2)	31 (21.7)	561 (27.3)	184 (18.4)	199 (38.7)	69 (28.9)
Constipation	41 (3.9)	12 (2.1)	25 (3.8)	10 (2.8)	28 (5.8)	7 (3.2)	22 (7.1)	4 (2.8)	25 (8.0)	3 (2.1)	109 (5.3)	26 (2.6)	60 (11.7)	14 (5.9)
Vomiting	19 (1.8)	3 (0.5)	18 (2.7)	11 (3.1)	27 (5.6)	6 (2.7)	22 (7.1)	7 (5.0)	19 (6.1)	7 (4.9)	92 (4.5)	32 (3.2)	22 (4.3)	9 (3.8)

Source: Compiled from ISS Table 5.c, page 364/410, F: female, M: male, D/C: discontinuation
(a) Lu AA21004 Total also includes 1 and 2.5 mg doses.
(b) n= number of subjects with non-missing factor

Race
The sponsor analyzed the overall and most common TEAEs on Lu AA21004 dose by MedDRA preferred term and race (Caucasian, Black and Asian) in the MDD Short-Term Pool.

No consistent pattern was seen in the distribution of AEs across treatment groups among the race (Caucasian, Black and Asian).

Body Mass Index
The sponsor analyzed the overall and most common TEAEs on Lu AA21004 dose by MedDRA preferred term and BMI (<25, 25-<30, and ≥30).

No consistent pattern was seen in the distribution of AEs across treatment groups and BMI.

7.6.4 Drug-Disease Interactions

The sponsor investigated the effect of hepatic impairment on the pharmacokinetics (PK) of Lu AA21004 and its metabolites Lu AA34443 and Lu AA39835 following administration of a single dose of Lu AA21004 10 mg. They concluded that no clinically meaningful differences in exposure of Lu AA21004 were observed in subjects with mild or moderate hepatic impairment compared to that in healthy matched control subjects.

The sponsor also investigated the effect of renal impairment on the pharmacokinetics (PK) of Lu AA21004 and its metabolites Lu AA34443 and Lu AA39835 following administration of a single dose of Lu AA21004 10 mg. Although exposure of Lu AA21004 and its metabolites Lu AA34443 and Lu AA39835 increased with decreasing renal function (mild, moderate, and severe renal impairment), the sponsor did not consider the increases clinically meaningful.

Please also refer to the comprehensive review by Clinical Pharmacology team.

7.6.5 Drug-Drug Interactions

Please refer to Clinical Pharmacology for the comprehensive review of this issue.

7.7 Additional Safety Evaluations

7.7.1 Human Carcinogenicity

No human carcinogenicity studies were conducted in this program.

The deaths, SAEs and discontinuations as of October 26, 2012 were reviewed to determine whether there may be a potential signal of human carcinogenicity in the Lu AA21004 development program.

There were 2 deaths due to cancer: a 74 year old female on Lu AA21004 5 mg group died of gallbladder cancer and a 46 year old male on Lu AA21004 10 mg group died of pancreatic cancer.

The following cancer/neoplasms were reported as SAEs as of May 04, 2012: breast cancer (3 cases), renal cell carcinoma, colon cancer, and sebaceous carcinoma, benign neoplasm of eye, benign salivary gland neoplasm, bone neoplasm malignant, malignant melanoma, and uterine leiomyoma. Two additional cases of breast cancer were reported in 120-Day (between May 05, 2012 and October 26, 2012, inclusive) Safety Update.

There were no discontinuations caused by cancer/neoplasms.

7.7.2 Human Reproduction and Pregnancy Data

A total of 52 pregnancies in enrolled subjects (34 pregnancies in Lu AA21004 group) were reported in the entire Lu AA21004 clinical program. The majority of 34 pregnancies in Lu AA21004 group were reported in the MDD/GAD Short-Term Pool (N=17). Similar numbers were reported in the 2 long-term relapse-prevention studies combined (N=6) and in the MDD Open-Label Pool (N=6), with the rest reported in the Phase 1 Pool or non-US phase 2 and 3 studies (N=5).

Table 164 shows the pregnancy outcomes (excluding partner pregnancies).

25% of the pregnancies (13/52) were terminated by elective abortions. Of these 13 subjects, 10 were exposed to Lu AA21004. Where information is available, these elective abortions occurred at gestational weeks 6 to 10.

There were 10 female subjects who were exposed to Lu AA21004 group had a known outcome of a live birth. According to the sponsor, no congenital anomalies or any other defects were reported.

Table 164: Pregnancy Outcomes (Excluding Partner Pregnancies)

Pregnancy Outcome	Treatment (a, b)				Total
	Placebo N=3095	Lu AA21004 N=7666	Duloxetine N=907	Blinded	
Abortion spontaneous (c)	4	9	0	0	13
Abortion induced	3	10	0	0	13
Ectopic pregnancy	1	0	0	0	1
Live birth (d)	3	10	0	0	13
Lost to follow-up	3 (e)	2	2	0	7
Pending	0	3	0	2	5
Total	14	34	2	2	52

Source: Table 5.h, ISS page 381/410
Note: All spontaneous abortions were reported as SAEs; narratives are provided in Appendices B and C
(a) Approximately two-thirds of subjects in phase 3 studies are female subjects.
(b) Sample sizes do not include the number of subjects in ongoing Studies CCT-002 and 14178A.
(c) Includes the following preferred terms: abortion incomplete, abortion missed, and fetal death.
(d) Includes one live birth that is double-counted in this table (mother received placebo) and Table of partner pregnancy outcomes (father received Lu AA21004 5 mg at time of conception).
(e) Per protocol, follow-up of pregnancy outcome in subjects randomized to placebo is not required.

Seven pregnancies were reported lost to follow-up and 5 pregnancies were reported pending ((outcome unknown). 25% of the pregnancies (13/52) resulted in spontaneous or missed abortions. 9 female subjects were exposed to Lu AA21004.

Table 165 shows the further analyses of the determinants of pregnancy outcome (increased maternal age [the risk increases after the mid-30s], previous history of miscarriages, and obesity) for the 9 female subjects who had spontaneous abortion while receiving Lu AA21004.

Table 165: Spontaneous Abortion Risk Factors in Subjects Exposed to Lu-AA21004

Study	Subject No.	Pregnancy Outcome	Age (years)	Any Prior Abortions	Other Known Risk Factors	BMI (kg/m^2)	Gestationa Age (weeks
309	0020-909 TPA2008A01976	Abortion spontaneous	25	None	Unk	34.2	6
310	1005-007 TPA2008A01582	Fetal death	23	2	Unk	35.2	6
CCT-002	3017-001 TPG2011A01079	Abortion spontaneous	44	None	Unk	28.5	7
314/315	4012-405 TPA2011A04152	Abortion missed	41	2	Unk	52.7	6
314/315	4047-404 TPA2012A00528	Abortion spontaneous	32	None	Unspecified infertility problem	34.9	6
317	7039-718 TPA2011A03373	Abortion spontaneous	37	2	Unk	27.5	6
11826A	S108 TPA2010A02509	Abortion spontaneous	40	None	Unk	27	12
11985A	S1630.R3289 THQ2009A02340	Abortion incomplete	28	None	Received an aborticide from her general practitioner	25.15	14
12473A	S3806 THQ2009A04439	Abortion spontaneous	32	Unk (a)	Unk	31.6	17

Source: Table 5.i, ISS page 382/410
(a) Subject had 3 prior pregnancies but only 2 live births; the outcome of the other pregnancy is unknown.
Unk=Unknown.

Three cases had prior abortions. One had unspecified infertility problem and one received an aborticide from her general practitioner. Five women were obese. The casual relationship of spontaneous abortion and Lu AA21004 use is hard to determine due to many compounding factors.

In addition to the 52 pregnancies that occurred in female subjects in the Lu AA21004 studies, there were also 4 pregnancies reported for partners of male subjects receiving Lu AA21004 as shown in Table 166. No congenital anomalies or other fetal defects were reported for the 2 live birth.

Table 166: Partner Pregnancy Outcomes

Pregnancy Outcome	Treatment (a)		Total
	Placebo N=3095	Lu AA21004 N=7666	
Abortion spontaneous (b)	0	1	1
Live birth (c)	0	2	2
Lost to follow-up	1 (d)	1	2
Total	1	4	5

Source: Table 5.j, ISS page 383/410
Note: Spontaneous abortion was reported as SAE; the narrative is provided in Appendix B
(a) Sample sizes do not include the number of subjects in ongoing Studies CCT-002 and 14178A
(b) Includes the following preferred terms: abortion incomplete, abortion missed, and fetal death.
(c) Includes one live birth that is double-counted in this table (father received Lu AA21004 5 mg at time of conception) and (the mother received placebo).
(d) Per protocol, follow-up of pregnancy outcome in subjects randomized to placebo is not required.

7.7.3 Pediatrics and Assessment of Effects on Growth

Vortioxetine has not been tested in subjects aged < 18 years.

7.7.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose
This reviewer searched SAEs and discontinuations due to TEAEs using "overdose" as preferred term. Two cases were reported as SAEs due to overdose. Neither was overdose with Lu AA21004.

FR003/S3107: Intentional overdose with Zopiclone
TW001/S1376: Accidental overdose with hypnotics

The sponsor performed an LTMQ search and did not find subjects took overdose of Lu AA21004 with suicidal intent during Lu AA21004 clinical studies.

Drug Abuse Potential
At the End-of-Phase 2 Meeting, the Division determined that it was not required to have an abuse potential assessment for vortioxetine because vortioxetine was in a class of drugs that we were concerned about abuse potential; and there was no binding at targets that we were concerned about. In addition, there was no evidence in animal studies of abuse potential (for example, self-mutilation or hyperactivity, as per our Pharmacology/Toxicology reviewer Dr. Antonia Dow). Therefore, Lu AA21004 was systematically studied in humans for its potential for abuse. The sponsor asserted that they did not find any evidence of drug-seeking behavior in the clinical studies.

Drug Withdrawal and Rebound
Please refer to DESS in the safety section.

7.8 Additional Submissions / Safety Issues

The Sponsor submitted a 120-Day (between May 05, 2012 and October 26, 2012, inclusive) Safety Update report which included a summary of new safety data (deaths, SAEs and discontinuations due to AEs) on January 24, 2013. The following is a brief summary of the safety report.

Death
No deaths occurred during the reporting period for the 120-Day Safety Update.

SAEs
This reviewer did not identify serious safety concerns.

SAEs in the Open-Label Pool from May 05 to October 26, 2012
In the Open-Label Pool, 75 subjects (2.9%) had SAEs as of October 26, 2012 (the cutoff date for 120-Day Safety Update) while 70 subjects (2.7%) had SAEs as of May 04, 2012 (the cutoff date for the filing of the Integrated Summary of Safety, ISS). A total of 5 subjects had a total of 7 SAEs: suicide attempt, complicated migraine, latent syphilis, transient ischemic attack, subcutaneous abscess, esophageal rupture, and atrial fibrillation. None were considered to be related to Lu AA21004 treatment except suicide attempt was considered possibly related.

SAEs in the Ongoing Un-pooled Phase 1, 2, and 3 Studies
The sponsor performed a search of the safety database to identify any SAEs reported between May 05 to October 26, 2012, inclusive, in the 8 ongoing un-pooled phase 2 and 3 MDD studies (202, CCT-002, CCT-003, 14122A, 14178A, 318, 13926A, and OCT-001) and the 6 ongoing un-pooled phase 1 studies (14077A, 14029A, 14520A, CPH-004, 12708A, and 14137A).

A total of 15 subjects in the ongoing un-pooled studies had 16 new SAEs during the period from 05 May to 26 October 2012. The following table lists the SAEs. There are 2 SAEs are bleeding related: subdural hematoma and metrorrhagia. Subdural hematoma was probably caused by head trauma while metrorrhagia is hard to determine. It is less likely that the subject developed metrorrhagia after exposure of only 1 dose of IMP (do not even know whether the IMP was Lu AA21004).

Table 167: New SAEs Reported From May 05 to October 26, 2012 in the Ongoing Un-pooled Studies

Study Site-Subject No. (Dose)	Preferred Term	Causality	Additional Information
Study OCT-001 0002-012 (Lu AA21004 5 mg)	Subdural hematoma	Not related	A 40-year-old male subject with a history of hypertension received a diagnosis of chronic subdural hematoma after approximately a year of exposure to Lu AA21004. The condition required surgical intervention. Coagulation parameters were within normal limits. The attending physician considered the event had been due to head trauma although the patient had no memory of such event. The subject recovered from the event and discontinued from the study.
Study CCT-003			
0018-004 Blinded	Suicidal behavior	Possible	N/A
0034-008 Blinded	Breast cancer recurrent	Not related	N/A

Study Site-Subject No. (Dose)	Preferred Term	Causality	Additional Information
Study 14178A			
ES007-S1030 Blinded	Metrorrhagia	Possible	A 30-year-old female patient administered blinded IMP experienced metrorrhagia 14 weeks after the first dose of the study medication. The subject completed the study as planned.
SE002-S1481 Blinded	Anxiety Edema peripheral	Possible Probable	N/A
RO004-S1442 Blinded	Depression	Possible	N/A
GB001-S1617 Blinded	Liver function test abnormal	Possible	A 46-year-old subject had elevated ALT 166 (IU/L) 4 weeks after first dose of blinded IMP. The subject was discontinued from the study and the event resolved.
PL001-S1505 Blinded	Breast cancer	Not related	N/A
Study 14122A			
MX003-S1327 Blinded	Hiatus hernia	Probable	N/A
Study 318			
5063-803 Blinded	Nephrolithiasis	Possible	N/A
5037-810 Blinded	Angina pectoris	Possible	A 41-year-old female subject with history of smoking, obesity, elevated lipids, and elevated blood pressure experienced chest pain 6 days after the last dose of blinded IMP. The ischemic nature of the event was not confirmed
Study 13926A			
TW001-S1013 Blinded	Depression	Possible	N/A
KR001-S1058 Blinded	Ligament sprain	Not related	N/A
R5009-S1060 Blinded	Vertigo positional	Not related	N/A
KR007-S1030 Blinded	Varicocele	Not related	N/A

Source: Table 2.g in 120-Day-Safety Update dated January 24, 2013.

Discontinuations

The proportion of subjects treated with Lu AA21004 who had discontinuations due to TEAEs in the Open-Label Pool (8.3%) as of October 26, 2012 was similar to that reported on May 04, 2012 (7.6%). The leading causes of discontinuations were nausea and vomiting.

8 Post-market Experience

There are post-market experiences because vortioxetine is not marketed in any country.

9 Appendices

9.1 Literature Review/References

The submission included a list of literature references (about 180 articles). Due to time constraints, this reviewer did not review these references.

9.2 Labeling Recommendations

We have the following revisions for labeling. The red strikethrough shows deletion and the words in red show insertion:

2.1 [redacted] **General Instruction for Use**

The recommended starting dose [redacted] is 10 mg administered orally once daily without regard to meals. [redacted] Doses can be increased up to 20 mg per day based on tolerability and efficacy. Initial dose titration is recommended for dose above 10 mg per day. [redacted]

The efficacy and safety of doses above 20 mg per day was not [redacted] evaluated.

[redacted]

2.2 Maintenance/Continuation/Extended Treatment

[redacted]

2.3 Discontinuing Treatment

[redacted]

Patients who are on higher doses of BRINTELLIX (15 and 20mg) may experience headache, muscle tension/stiffness, mood swings, and sudden outburst of anger, dizziness/lightheadedness/vertigo and runny nose in the 1st week of discontinuation if they abruptly stop BRINTELLIX.

A dose decrease to 10 mg for 1 week before the complete discontinuation of Lu AA21004 15 and 20 mg whenever possible.

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4 CONTRAINDICATIONS

Hypersensitivity to vortioxetine and other ingredients in the BRINTELLIX formulation

5.1 Clinical Worsening and Suicide Risk

5.6 Hyponatremia

“Hyponatremia has occurred as a result of treatment with serotonergic drugs. In many cases, hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). One case with serum sodium lower than 110mmol/L was reported in a subject treated with BRINTELLIX in a pre-marketing clinical study. Elderly patients may be at greater risk of developing hyponatremia with a serotonergic antidepressant. Also, patients taking diuretics ~~or who are otherwise volume depleted~~ can be at greater risk. Discontinuation of BRINTELLIX in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls. More severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.”

6.1 Clinical Studies Experience

Adverse reactions reported as reasons for discontinuation of treatment

(b) (4)

(b) (4) The incidence of patients who received BRINTELLIX 5 mg, 10 mg, 15 mg and 20 mg discontinued treatment due to an adverse reaction was 5%, 6%, 8% and 8% respectively, compared with 4% of placebo-treated patients in these studies. Nausea was the most common adverse reaction reported as a reason for discontinuation and considered to be drug-related.

Common adverse reactions in placebo-controlled MDD studies

(b) (4)

Nausea

The incidence of nausea in Lu AA21004 was significantly higher than placebo and was dose-related. 15-20% patients experienced nausea in the first 1-2 days of BRINTELLIX treatment. Approximate 10% patients in BRINTELLIX 10mg - 20mg experienced nausea throughout the 8 week study period.

(b) (4)

(b) (4)

There were 3 discontinuations of BRINTELLIX treatment due to adverse reactions of sexual function compared to none in placebo.

In male patients, the incidence of adverse reaction of sexual function was 3.1%, 4.1%, 3.5% and 4.9% in BRINTELLIX 5mg, 10mg, 15mg and 20mg respectively, while it was 1.7% in placebo.

In female patients, the incidence of adverse reaction of sexual function was 0.9%, 1.3%, 0.6% and 1.6% in BRINTELLIX 5mg, 10mg, 15mg and 20mg respectively, while it was 0.7% in placebo.

Laboratory Tests

BRINTELLIX ~~has not been associated with any~~ did not cause clinically important changes in ~~laboratory test parameters in serum chemistry~~ (b) (4), hematology and urinalysis, as measured in placebo-controlled studies. For hyponatremia, see Warnings 5.6. Few subjects had elevated liver enzymes leading to discontinuations in the clinical program. (b) (4)

(b) (4)

[redacted]

Weight

[redacted].

Vital Signs

BRINTELLIX ~~has not been~~ [redacted] ~~associated with any~~ did not cause clinically significant effect on vital signs, including systolic and diastolic blood pressure and heart rate, as measured in placebo-controlled studies. [redacted]

[redacted]

17 PATIENT COUNSELING INFORMATION

Discontinuation of Treatment

Patients who are on higher doses of BRINTELLIX (15 and 20mg) may experience headache, muscle tension/stiffness, mood swings, and sudden outburst of anger, dizziness/lightheadedness/vertigo and runny nose in the 1st week of discontinuation if they abruptly stop their medicine.

[redacted] ~~-~~Advise patients not to stop taking BRINTELLIX without first talking with their healthcare provider.

Nausea

Advise patients that nausea is the most common adverse reaction, and [redacted] is dose related. [redacted] It occurs commonly [redacted] in the first two weeks of treatment and might persist throughout the treatment [redacted]

9.3 Advisory Committee Meeting

The Division decided not to take this NDA to the Psychopharmacological Drugs Advisory Committee.

9.4 Requests for Information to Sponsor

The following requests for information were sent to the Sponsor during the course of the review. The Sponsor has submitted data in response to these requests as amendments to the NDA and we have reviewed the responses from the sponsor:

FDA email dated January 15, 2013
We are reviewing the safety data and found some SAE number discrepancies. Please clarify and help us understand the SAE incidence data. For examples, according to Table 2.i in ISS, there were 15 SAEs in the placebo group in MDD short-Term Pool, but according to the Appendix B (Tabular Listing of Subject Narratives for LuAA21004 Studies), 2.0 SERIOUS ADVERSE EVENTS in MDD Phase 2/3 Controlled Studies, there were 17 SAEs experienced by 16 subjects. The SAE number discrepancies are also found in some other Lu AA21004 groups in MDD short-term pool between Table 2.i and Appendix B. The SAE number discrepancies in the MDD Relapse-Prevention Study and GAD Relapse-Prevention Study are also found between Table 2.j (SAEs in the Individual Relapse Prevention Studies, MDD Open-Label Pool, and Phase 1 Pool) and Appendix B.

FDA email dated January 30, 2013
1. Please provide tables of elevated post-baseline values for liver function test variables in the MDD Long-Term Relapse-Prevention Study 11985A and the GAD Long-Term Relapse-Prevention Study 12473A. You provided the narratives for subjects with ALT and/or AST ≥5×ULN, were there any other cases of elevated post-baseline LFT values meeting PCS criteria in these 2 studies?

2. Was INR tested during the trials? If yes, were there any cases of ALT or AST > 3 x ULN and INR >1.5?

FDA email dated February 5, 2013
We are reviewing the discontinuations/dropouts due to abnormal laboratory results. Specifically, we are reviewing the discontinuations/dropouts due to elevated LFTs. We compiled Table 1 from Appendix B 3.0 ADVERSE EVENTS LEADING TO DISCONTINUATION. Please verify Table 1 and let us know if any other dropouts due to abnormal LFTs were not included.

Please provide the narratives for these discontinuations including the outcomes of the discontinued subjects. Please submit all the discontinuations/dropouts due to all other abnormal laboratory results (hematology, renal function, chemistry, etc.) using the format of Table 1. Also provide the narratives including the outcomes of the discontinued subjects.

FDA email dated March 6, 2013 (Statistician team made the request, we agreed)
Please refer to the maintenance study 11985A in your original NDA 204447.
At the End of Phase II Meeting held on February 5, 2008, we expressed the rationale for requiring responders to be stabilized for at least 12 weeks before randomization. In this trial, patients were eligible for randomization as long as they stayed in remission state

for the last two visits (Weeks 10 and 12) of the open-label phase. To explore the actual stabilization durations, please provide the following information:
For each patient obtain the stabilization duration (ie, the number of consecutive weeks the patient remained in remission immediately prior to randomization). Submit the SAS program that generated this variable (stabilization duration) and a .xpt data set that contains this variable. Summarize the outcome of this variable.

FDA email dated March 21, 2013
This request is regarding the incidence of DESS Items by Visit in MDD Studies 315, 316, and 13267A. Please make a table listing the incidence of DESS Items in LuAA21004 15 mg and 20 mg groups by Visit in MDD Studies 315, 316, and 13267A using the format of Table 5.1.4.1 (Appendix F in ISS). Please only list the DESS Items which the incidences in either Lu AA21004 15mg or Lu AA21004 20mg are twice of placebo.

FDA email dated April 23, 2013
This request is regarding the potentially clinically significant abnormal labs which occurred only in Lu AA21004 groups but not in the placebo or duloxetine group. Please provide narratives and/or lab follow ups.

Hematology
In the MDD Short-Term Pool, 3 subjects in Lu AA21004 groups had platelets ≤75 ×109/L but none in placebo or Duloxetine group.

Liver Function Test (LFT)
The following cases with AST/ALT and Alkaline Phosphatase (ALP) elevation concurrently only occurred in Lu AA21004 treatment groups not in placebo or Duloxetine group.

MDD and MDD/GAD Short-Term Pool
Two subjects in Lu AA21004 5 mg group had AST ≥3×ULN and ALP >1.5×ULN concurrently.

MDD Relapse-Prevention Study 11985A
ALT ≥3×ULN and Alkaline Phosphatase (> 1.5xULN) concurrently:
Subject CA204-S1129
Subject IN001-S1765

AST ≥3×ULN and ALT ≥3×ULN and Alkaline Phosphatase (> 1.5xULN) concurrently:
Subject FR006-S1343
Subject FI001-S1151

GAD Relapse-Prevention Study 12473A
Subject ALT ≥3×ULN and ALP (> 1.5xULN) concurrently:
Subject FR005-S3304
Subject AR012-S3559

ALT ≥3×ULN and AST ≥3×ULN and ALP (> 3xULN) concurrently:
Subject FR005-S3347

FDA email dated May 13, 2013
Request 1:
For Study 11492A, we reviewed Table 34: Recent and Concomitant Medication Potentially Taken after Last Dose of IMP in the clinical study report of Study 11492A (page 212-232). The following table summarizes the disallowed concomitant antidepressants, antipsychotics and benzodiazepines which were started at or after Baseline according to Table 34.

We also reviewed Panel 11: Inclusion/Exclusion/Withdrawal Criteria Deviations. It appeared that the subject who took Olanzapine was withdrawn from the study and the subject who took Citalopram was excluded from the Per-protocol set (PPS). But the subjects who took Escitalopram and Benzodiazepine Derivatives/ Benzodiazepine Related Drugs were not excluded from PPS.

Please confirm our findings. If these subjects indeed were included in the analyses, please describe the dosage, treatment duration of each disallowed medication in the treatment group.

Request II:
Please list all disallowed concomitant antidepressants, antipsychotics, benzodiazepine derivatives and benzodiazepine related drugs that started at or after baseline or continued at baseline for other positive studies: 305, 13267A, 315, 316, 12541A and 11985A using the format of Table 1. Please describe the dosage, treatment duration of each disallowed medication in the treatment group if the subjects were included in the analyses.

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/s/

JENN W SELLERS
06/04/2013

JING ZHANG
06/05/2013

NDA #204447 filing meeting on November 13, 2012

NDA CLINICAL SUBMISSION CHECKLIST

NDA # 204447, Brintellix (Vortioxetine) in Adult MDD

Data	Location/Comments	Go	No Go	N/A
REGULATORY				
Draft Labeling	M1	x		
Foreign Regulatory Actions				N/A
Pediatric Plan	M1	x		
Debarment Certification	M1	x		
Financial Disclosure Info.	M1	x		
SOURCES OF DATA				
Table of Studies	M5.2	x		
Patient Enumeration by Study Type/Treatment Group	M5	x		
Demographics (Phase 1)	M5.3.3. & M5.3.4.	x		
Dose vs. Duration (Phase 1)	M5.3.3. & M5.3.4.			
Demographics (Phase 2/3)	M5	x		
Dose vs. Duration (Phase 2/3)	M5	x		
Person-Time PEY's (Phase 2/3)	M5	x		
Foreign PM Surveillance Reports				x
Literature Search (methodology and results)	M5	x		
SAFETY DATA				
Enumeration of All Deaths and Other SAE's	M2.7	x		
Enumeration of All Dropouts by Reason/Treatment Group	M2.7	x		
Enumeration of AE Dropouts by AE/Treatment Group	M2.7	x		
Other Special Searches (e.g., suicidality, serotonin syndrome)	M2.7	x		
Enumeration of Common AE's from PC Trials (1 or 2% Table)	ISS Table 2.1.1.4.1	x		
AE Dose-Relatedness	ISS	x		
Demographic Analysis for AE's	ISS	x		
Labs/Chem: Mean Δ from Baseline (BL)	Module 5.3.5.3 Integrated Summary of Safety (ISS) Section 3.1.1.	x		
Labs/Chem: Outlier Criteria	ISS Section 3.1.2.	x		
Labs/Chem: Outliers (%)	ISS	x		
Labs/Hem: Mean Δ from BL	ISS	x		
Labs/Hem: Outlier Criteria	ISS	x		
Labs/Hem: Outliers (%)	ISS	x		
Labs/U-A: Mean Δ from BL	ISS	x		

Labs/U-A: Outlier Criteria	ISS	x		
Labs/U-A: Outliers (%)	ISS	x		
Vital Signs: Mean Δ from BL	ISS	x		
Vital Signs: Outlier Criteria	ISS	x		
Vital Signs: Outliers (%)	ISS	x		
ECG: Mean Δ from BL	ISS	x		
ECG: Outlier Criteria	ISS	x		
ECG: Outliers (%)	ISS	x		
Withdrawal/Abuse Liability Data	Mod 2.7.4, Sect 5.5 Mod 2.6.6, Sect 3.4.2, 3.4.3, 3.6.2, and 3.6.3	x		
Human Reproduction Data	No human but has animal data: Mod 2.6.6, Sect 6.0 and 9.1.7	x		
Human Overdose Experience	Mod 2.7.4, Sect 5.4 Study 10272 (Sect 10)	x		
PATIENT LEVEL SAFETY DATA				
.XPT AE Listings (indicating all SAE's and AE Dropouts)	M5.3.5.3	x		
.XPT AE Coding	M5.3.5.3	x		
Index to CRF's	M5.3.5.3	x		
CRF's (Deaths, AE Dropouts)	M5.3.5.3	x		
Index to Narrative Summaries	M5.3.5.3	x		
Narrative Summaries	M5.3.5.3	x		
EFFICACY DATA				
Minimum Number Positive Trials	6	x		
Dosing Rationale	Mod 2.7.3, Sect 4.0 Mod 2.7.1, Sect 3.7	x		
Demographic Analysis for Efficacy	M5.3.5.3: Integrated Summary of Efficacy (ISE)	x		
FOR EACH KEY EFFICACY STUDY				
Study Protocol	M5.3.5.1	x		
List of Investigators	M5.3.5.1	x		
Study Design	M5.3.5.1	x		
Dosing Schedule	M5.3.5.1	x		
Protocol-Specified Analysis	M5.3.5.1	x		
Baseline Demographics	M5.3.5.1	x		
Baseline Severity of Illness	M5.3.5.1	x		
Mean Daily Doses by Visit	M5.3.5.1	x		
Concomitant Medications	M5.3.5.1	x		
Efficacy Results	M5.3.5.1	x		

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/s/

JENN W SELLERS
11/13/2012

JING ZHANG
11/13/2012