CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204447Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW -- ADDENDUM Office of New Drug Quality Assessment			
Application No.:	NDA 204-447 (000)	**Reviewer:** Houda Mahayni, Ph.D.	
Division:	DPP		
Applicant:	Takeda Global Research & Development Center, Inc.	**Acting Team Leader:** Sandra Suarez, Ph.D.	
Trade Name:	Brintellix Tablets	**Acting Supervisor:** Richard T. Lostritto, Ph.D.	
Generic Name:	Vortioxetine (Lu AA21004)	**Date Assigned:**	June 20, 2013
Indication:	Treatment of major depressive disorder	**Date of Review:**	June 28, 2013
Formulation/strength	Immediate Release Film-Coated Tablet/5 mg, 10 mg, 15 mg, and 20 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT		
Submission Dates: June 20, 2013	**Dates of Consult**	**PDUFA DATE**
	June 20, 2013	October 2, 2013
Type of Submission:	Response to FDA Discipline Review Letter	
Key review points	Acceptability of the dissolution documentation in support of the comparability protocol for proposed additional manufacturing site (Oranienburg)	

I) SUMMARY OF BIOPHARMACEUTICS FINDINGS

Lu AA21004 (vortioxetine) is a new chemical class of psychotropics, the bis-aryl-sulfanyl amines. The proposed indication is for the treatment of major depressive disorder. LuAA21004 is a film-coated tablet. The proposed strengths are: 5 mg, 10 mg, 15 mg, and 20 mg. The recommended starting dose in adults is 10 mg taken once daily without regard to meals.

The following documents are referred to in this review:

- The Biopharmaceutics review of the Original submission in DARRTS by this reviewer (see Houda Mahayni's review dated April 8, 2013).
- The Applicant's submission dated April 8, 2013 and June 20, 2013 (Comparability Protocol for the proposed additional manufacturing site, Oranienburg).
- FDA Discipline Review Letter dated June 7, 2013.
- The Applicant Response to FDA Discipline Review Letter submission dated June 20, 2013.

This review focuses on the evaluation of the acceptability of the dissolution documentation in support of the comparability protocol for the proposed additional manufacturing site (Oranienburg).

The Acceptability of the Dissolution Documentation Included in the Comparability Protocol in Support of the Alternate Manufacturing Site:

In the original application submission dated October 2, 2012, the Applicant provided a comparability protocol describing the requirements to qualify Takeda GmbH (a Takeda Company), Oranienburg plant (Germany), as an alternate manufacturing site for the production of LuAA21004 immediate release tablets. The Applicant stated that no changes are proposed for the formulation composition and the manufacturing process at the new facility. Also, the same unit operations and the same manufacturing equipments of the same design and operating principles will be used as those used to manufacture the NDA primary batches. In support of the alternate manufacturing site, the Applicant planned to perform analytical testing, stability testing and final product release testing according to the approved product specification, analytical procedures, and dissolution. The Applicant planned to compare these results against the registration primary batches data to demonstrate similarity between sites.

Although the proposed alternate manufacturing site (different campus) is considered a Level 3 manufacturing site change as per SUPAC-IR requiring dissolution documentation using Case B testing, during the evaluation of the comparability protocol it was noted that the proposed change also affected the equipment used (considered moderate change Level 2 by the CMC reviewer), and possibly the process itself. Therefore, FDA requested the Applicant to apply SUPAC-IR Level 2 change in equipment which requires dissolution documentation using Case C. This request was communicated in the Discipline Review letter dated June 7, 2013 as follows:

Submit multi-point dissolution profiles comparisons (with f2 statistical testing) in water, 0.1 N HCl, and USP buffer media at pH 4.5, 6.5 and 7.5 (five separate profiles) for the proposed and current manufacturing sites. Adequate sampling should be performed (e.g. at 5, 15, 20, 30, 45, 60, and 120 minutes) until either (b) (4) *of drug from the drug product is dissolved or an asymptote is reached. A surfactant may be used with appropriate justification.*

In the submission dated June 20, 2013, Response to FDA Discipline Review Letter, the Applicant provided justification for FDA to reconsider the request for submitting multi-point dissolution profile comparisons from (Case C) to (Case B). The Applicant stated that in accordance with SUPAC-IR Guidance (November 1995), Section IV, C.2.b, the proposed addition of the Oranienburg manufacturing site (Level 3 Change) requires the dissolution documentation of a multi-point dissolution profile in the application/ compendia medium at 15, 30, 45, 60, and 120 minutes or until an asymptote is reached (Case B). The Applicant provided the following justification for providing the dissolution documentation according to Case B requirement in support of adding the Oranienburg manufacturing site based on the proposed changes as outlined below.

a) Components and Composition:
No changes are being proposed in either components or composition.
b) Site Changes:
The addition of the alternate site is defined as a Level 3 change requiring Case B dissolution documentation.
c) Changes in Batch Size:
The batch size will remain within a factor of 10 times the pilot/biobatch size or a Level 1 change requiring no dissolution documentation beyond application/compendial release requirements.
d) Manufacturing/Equipment:
The equipment to be used at the new site is of the same design and operating principles or a Level 1 change requiring no dissolution documentation beyond application/ compendial release requirements.
e) Manufacturing/Process:
There is no change to the manufacturing process, where the process parameter ranges may fall outside the application/validation ranges at the new manufacturing site due to slight differences in equipment. This is categorized as a Level 2 change requiring Case B dissolution documentation.

Based on the information presented in the submission dated June 20, 2013 and upon consultation with the CMC review team, it was found acceptable to consider the proposed equipment/process changes as Level 1/Level 2, respectively. Therefore, the Applicant's justification for providing the dissolution documentation according to Case B requirement in accordance with SUPAC-IR in support of adding the Oranienburg manufacturing site based on the proposed changes in the comparability protocol is adequate.

II) RECOMMENDATION

The ONDQA-Biopharmaceutics team reviewed submission dated: June 20, 2013 for NDA 204-447 for Vortioxetine (Lu AA21004) IR tablets, 5 mg, 10 mg, 15 mg, and 20 mg and

found the proposed dissolution documentation according to Case B acceptable in support of adding the Oranienburg manufacturing site as described in the comparability protocol.

The comparability protocol for additional manufacturing site is acceptable provided that the Applicant submits dissolution profile comparisons (with f2 statistical testing) in the application medium (0.1 N HCl) at 5, 15, 30, 45 and 60 minutes or until an asymptote is reached for the current and proposed manufacturing sites.

From the Biopharmaceutics perspective, NDA 204-447 for Vortioxetine (Lu AA21004) Tablets is recommended for approval.

Houda Mahayni, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Sandra Suarez, Ph.D.
Acting Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

III) BIOPHARMACEUTICS ASSESSMENT

Acceptability of the proposed dissolution documentation in support of the comparability protocol for additional manufacturing site (Oranienburg):
The Biopharmaceutics team requested the Applicant to perform muti-point dissolution profiles comparisons in five media to support the comparability protocol proposing alternative manufacturing site. FDA sent the following request in the Discipline Review Letter dated June 7, 2013:

Submit multi-point dissolution profiles comparisons (with f2 statistical testing) in water, 0.1 N HCl, and USP buffer media at pH 4.5, 6.5 and 7.5 (five separate profiles) for the proposed and current manufacturing sites. Adequate sampling should be performed (eg, at 5, 15, 30, 45, 60, and 120 minutes) until either (b) (4) *of drug from the drug product is dissolved or an asymptote is reached. A surfactant may be used with appropriate justification.*

The above request during the initial review of the comparability protocol was based on the Applicant's statement that "Due to equipment make and model differences between manufacturing sites, there is a potential that the processing ranges at the new facility may fall outside the registered ranges." Before sending the above request, this reviewer communicated with the CMC reviewer, Dr. Wendy Wilson, via e-mail dated May 7, 2013 to inquire about the SUPAC-IR Level to be assigned for the proposed changes in manufacturing equipments. Dr. Wilson stated that she considered the proposed change to be moderate (the differences in equipment represent differences in scale). Although this is a Level 3 manufacturing site change which requires dissolution documentation using Case B testing, the proposed change also affected the equipment used in the manufacturing process (considered moderate, change Level 2). Hence, the Applicant was requested to apply SUPAC-IR Level 2 change in equipment which requires dissolution documentation using Case C.

In the Response to FDA Discipline Review Letter submission dated June 20, 2013, the Applicant provided justification for FDA to consider accepting Case B instead for Case C, as dissolution documentation in support of the proposed manufacturing site change. The Applicant stated that in accordance with SUPAC-IR Guidance (November 1995), Section IV, C.2.b, the proposed addition of the Oranienburg manufacturing site (Level 3 Change) requires the dissolution documentation of a multi-point dissolution profile in the application/compendia medium at 15, 30, 45, 60, and 120 minutes or until an asymptote is reached (Case B). The Applicant provided the following justification for providing the dissolution documentation according to Case B (the dissolution profile comparison for the current and proposed site in application medium at 5, 15, 30, 45 and 60 minutes or until an asymptote is reached) requirement instead of Case C (multi-point dissolution profiles comparisons in water, 0.1 N HCl, and USP buffer media at pH 4.5, 6.5 and 7.5 media at 5, 15, 30, 45 and 60 minutes or until an asymptote is reached) in support of adding the Oranienburg manufacturing site based on the proposed changes as outlined below.

a) Components and Composition:
No changes are being proposed in either components or composition.
b) Site Changes:
The addition of the alternate site is defined as a Level 3 change requiring Case B dissolution documentation.
c) Changes in Batch Size:
The batch size will remain [redacted] (b) (4) the pilot/biobatch size or a Level 1 change requiring no dissolution documentation beyond application/compendial release requirements.
d) Manufacturing/Equipment:
The equipment to be used at the new site is of the same design and operating principles or a Level 1 change requiring no dissolution documentation beyond application/ compendial release requirements.
e) Manufacturing/Process:
There is no change to the manufacturing process, where the process parameter ranges may fall outside the application/validation ranges at the new manufacturing site due to slight differences in equipment. This is categorized as a Level 2 change requiring Case B dissolution documentation.

Reviewer's Note: The Applicant replaced the comparability protocol submitted on April 8, 2013 with an updated comparability protocol submitted on June 20, 2013. The comparability protocol was updated per FDA's request. The following revisions are made to the updated comparability protocol: changed the reporting category to Changes Being Effected in 30 days, updated the description of analytical procedures and acceptance criteria for process validation, updated the stability testing to include packaging configurations of blister and 7ct HDPE bottle, and included a commitment to not distribute any drug product that is deemed nonequivalent. These revisions do not affect the Biopharmaceutics' assessment of the comparability protocol.

Reviewer's Assessment:
Although the equipment described in the previously submitted comparability protocol of April 8, 2013 and the updated comparability protocol of June 20, 2013 comparing the equipment used for registration stability site and proposed new manufacturing site did not change, the Applicant labeled the equipment change as a Level 1 change (requiring no dissolution documentation beyond application/compendial release requirements), and the process change as Level 2 change (requiring Case B dissolution documentation). This reviewer communicated again on June 26, 2013 with the CMC reviewer, Dr. Wilson, about the assignment of the level of change per SUPAC-IR for the proposed change in equipment and for the proposed change in process. Dr. Wilson classified the equipment change as Level 1 and the process change as Level 2 which is in agreement with the Applicant assignments for the proposed change in equipments and process. Therefore, the Applicant's justification to apply Case B instead of Case C as previously requested for dissolution documentation per SUPAC-IR is acceptable. Hence, to support the proposed addition of the Oranienburg manufacturing site (Level 3 manufacturing site change, Level 1 equipment change, and Level 2 process change) the Applicant is requested per SUPAC-IR to submit comparative dissolution profiles for the current and proposed sites

using the application medium of 0.1 N HCl and sampling at 5, 15, 30, 45 and 60 minutes or until an asymptote is reached.

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

/s/

HOUDA MAHAYNI
07/01/2013

SANDRA SUAREZ
07/01/2013

BIOPHARMACEUTICS REVIEW -- ADDENDUM

Office of New Drug Quality Assessment

Application No.:	NDA 204-447 (000)	**Reviewer:** Houda Mahayni, Ph.D.	
Division:	DPP		
Applicant:	Takeda Global Research & Development Center, Inc.	**Acting Team Leader:** Sandra Suarez, Ph.D.	
Trade Name:	Brintellix Tablets	**Acting Supervisor:** Richard T. Lostritto, Ph.D.	
Generic Name:	Vortioxetine (Lu AA21004)	**Date Assigned:**	October 10, 2012
Indication:	Treatment of major depressive disorder	**Date of Review:**	June 11, 2013
Formulation/strength	Immediate Release Film-Coated Tablet/5 mg, 10 mg, 15 mg, and 20 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Dates:	**Dates of Consult**	**PDUFA DATE**
March 7, 2013 April 8, 2013 April 25, 2013 May 31, 2013	May 1, 2013 May 6, 2013 May 9, 2013 May 31, 2013	October 2, 2013

Type of Submission:	Original New Drug Application
Key review points	1. Acceptability of the dissolution acceptance criterion 2. Acceptability of the comparability protocol for additional manufacturing site (Oranienburg)

I) SUMMARY OF BIOPHARMACEUTICS FINDINGS

Lu AA21004 (vortioxetine) is a new chemical class of psychotropics, the bis-aryl-sulfanyl amines. The proposed indication is for the treatment of major depressive disorder. LuAA21004 is a film-coated tablet. The proposed strengths are: 5 mg, 10 mg, 15 mg, and 20 mg. The recommended starting dose in adults is 10 mg taken once daily without regard to meals.

The following documents are referred to in this review:

- The Biopharmaceutics review of the Original submission in DARRTS by this reviewer (see Houda Mahayni's review dated April 8, 2013).
- The Information Request (IR) sent by Hiren Patel via e-mail on February 28, 2013.
- The Applicant response dated March 6, 2013 to IR dated February 28, 2013.
- The Pre-Mid-Cycle teleconference communication dated March 26, 2012 in DARRTS based on the discussion during the Pre-Mid-Cylce teleconference on March 12, 2012.
- The Applicant submission dated April 8, 2013 (Comparability Protocol for proposed additional manufacturing site, Oranienburg)
- The Applicant submission dated April 25, 2013 (justification to address Biopharmaceutics Item 5 under section 3.0 in the mid-cycle review correspondence dated March 26, 2013).
- The Applicant submission dated May 31, 2013 (Response to IR communicated during May 22, 2013 teleconference.

This review focuses on the evaluation of: **1)** The acceptability of the dissolution acceptance criterion; **2)** the acceptability of the comparability protocol for additional manufacturing site.

1) The Acceptability of the dissolution acceptance criterion:
Based on the information presented in the submission dated May 31, 2013, it is acceptable to keep the proposed dissolution acceptance criterion of Q = (b) (4) at 30 minutes. The Applicant commitment to review and evaluate the dissolution acceptance criterion for the ongoing stability studies and commercial batches for one year after the approval of the NDA is not necessary. The provided BE data support a wider acceptance criterion.

2) Acceptability of the comparability protocol for additional manufacturing site:
The Applicant was requested to include the following information/data in the Discipline Review letter dated June 7, 2013: *Submit multi-point dissolution profiles comparisons (with f2 statistical testing) in water, 0.1 N HCl, and USP buffer media at pH 4.5, 6.5 and 7.5 (five separate profiles) for the proposed and current manufacturing sites. Adequate sampling should be performed (e.g. at 5, 15, 20, 30, 45, 60, and 120 minutes) until either* (b) (4) *of drug from the drug product is dissolved or an asymptote is reached. A surfactant may be used with appropriate justification.*

II) RECOMMENDATION

The ONDQA-Biopharmaceutics team reviewed submissions dated: March 7, 2013
April 8, 2013, April 25, 2013, and May 31, 2013 for NDA 204-447 for Vortioxetine (Lu AA21004) IR tablets, 5 mg, 10 mg, 15 mg, and 20 mg and found the proposed dissolution acceptance criterion of Q = (b) (4) at 30 minutes acceptable. The Applicant's commitment to review and evaluate the dissolution acceptance criterion for the ongoing stability studies and commercial batches for one year after the approval of the NDA is not necessary given that the provided BE data support a wider dissolution acceptance criterion.

The comparability protocol for an additional manufacturing site is acceptable provided that the Applicant submits the information communicated in the Discipline Review Letter dated June 7, 2013 which requests the submission of multi-point comparative dissolution profiles in 5 media for the proposed and current manufacturing sites

From the Biopharmaceutics perspective, NDA 204-447 for Vortioxetine (Lu AA21004) Tablets is recommended for approval.

Comments to be Conveyed to the Applicant

1. The proposed acceptance criterion of Q= (b) (4) at 30 min is acceptable. Your commitment to review and evaluate the dissolution acceptance criterion for the ongoing stability studies and commercial batches for one year after the approval of the NDA is not necessary. Your proposed acceptance criterion of Q (b) (4) at 30 min is supported by the bioequivalence data submitted on May 31, 2013.

2. The comparability protocol for an additional manufacturing site is acceptable provided that you submit the information communicated in the Discipline Review Letter dated June 7, 2013 which requests the submission of multi-point comparative dissolution profiles in 5 media for the proposed and current manufacturing sites.

Houda Mahayni, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Sandra Suarez, Ph.D.
Acting Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

III) BIOPHARMACEUTICS ASSESSMENT

1. Dissolution Acceptance Criterion

During review of the Original submission (See Houda Mahayni's review in DARRTS dated April 8, 2013), the proposed dissolution acceptance criterion of Q (b) (4) at 30 minutes was found not supported by the data, as the drug dissolved more than (b) (4) in 15 minutes. The Applicant was informed of FDA's finding and the information presented below is a chronological order of communications that occurred between FDA and the Applicant about the proposed dissolution acceptance criterion.

February 28, 2013 Information Request

FDA sent Information Request (IR) by email on February 28, 2013 regarding the proposed dissolution acceptance criterion among other Biopharmaceutics deficiencies requesting the following:

To support the proposed dissolution acceptance criterion of Q = (b) (4) in 30 minutes for your product, provide dissolution profile data at 15, 20, 30 minutes or until an asymptote is reached (n=12) for all the strengths of the clinical and stability (registration and validation) batches using the proposed dissolution method.

March 7, 2013 Applicant's Response

The Applicant responded on March 7, 2013 and provided the dissolution profiles of Registration and Process Validation batches. The Registration batches (manufactured at Lundbeck in Valby, Denmark) were also used in clinical studies. Therefore, these batches are both clinical and stability batches. Table 1 below list the batch numbers used to generate the representative dissolution profiles in Figure 1, Figure 2, and Figure 3. The raw dissolution data for all lots listed in Table 1 below are provided in the Appendix (Table 1, Table 2, and Table 3).

Table 1: Batch numbers for Vortioxetine tablets

	Registration Batch # (Clinical and Stability)	PV Batch # (Osaka, Japan)	PV Batch # (Valby, Denmark)
	PD 1858 (5mg)	G001 (5 mg)	2315829 (5 mg)
	PD 1859 (5mg)	G002 (5 mg)	
	PD 1881 (5mg)	G003 (5 mg)	
	PD 1863 (10 mg)	J001 (10 mg)	2315832 (10 mg)
	PD 1864 (10 mg)	J002 (10 mg)	
	PD 1865 (10 mg)	J003 (10 mg)	
	PD 1860 (15 mg)	K001 (15 mg)	2315835 (15 mg)
	PD 1861 (15 mg)	K002 (15 mg)	
	PD 1862 (15 mg)	K003 (15 mg)	
	PD 1855 (20 mg)	L001 (20 mg)	2315838 (20 mg)
	PD 1856 (20 mg)	L002 (20 mg)	
	PD 1869 (20 mg)	L003 (20 mg)	
Dissolution Data Points (minutes)	5, 10, 15, 20, 30 and 45	5, 10, 15, 20, 30 and 45	5, 10, 15, 30, 45 and 60*

(*) During last 15 minutes of dissolution paddle speed was increased to 250 rpm.

Figure 1: Dissolution Profiles of Registration Batches, 5, 10, 15, and 20 mg (n = 12)

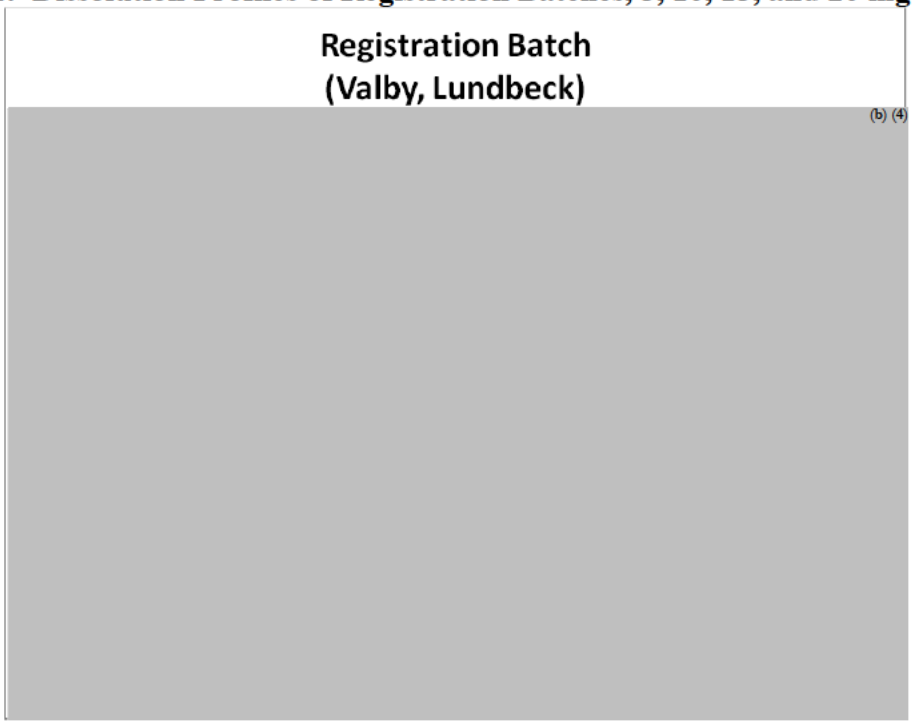


Figure 2: Dissolution Profile of PV Batches (Osaka, Japan), 5, 10, 15, and 20 mg (n=12)

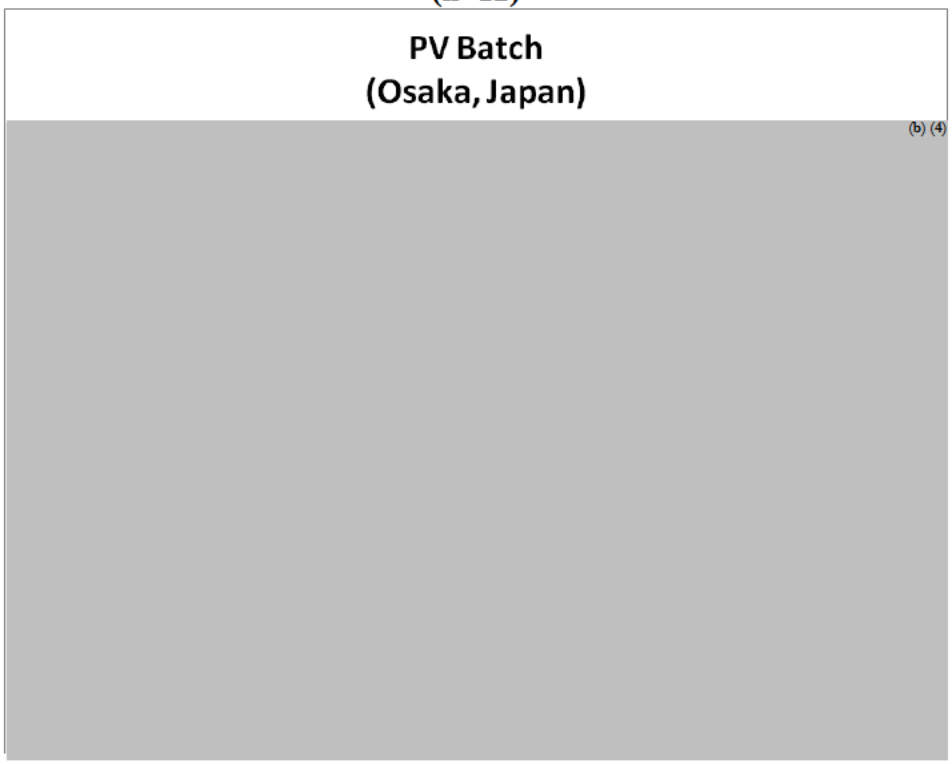
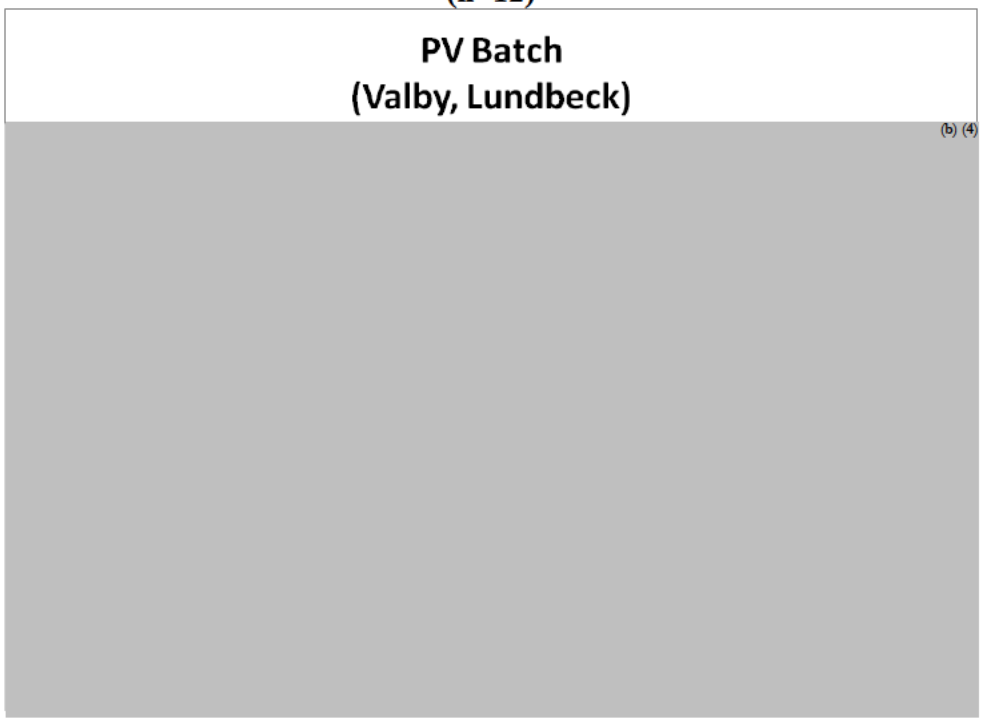


Figure 3: Dissolution Profile of PV Batches (Valby, Denmark), 5, 10, 15, and 20 mg (n=12)



March 12, 2013 Post-Mid-Cycle Meeting, Information Request

Based on the above information, FDA determined that the dissolution data provided support an acceptance criterion of Q = (b) (4) at 20 minutes, as the mean dissolution data for all dosage strengths is (b) (4) at 30 minutes for clinical batches placed on stability in all configurations and under all different test conditions. Also, the clinical and stability batches released greater than (b) (4) at 20 minutes. Therefore, during the Post-Mid-Cycle teleconference held on March 12, 2013, FDA stated that the dissolution data provided do not support your proposed acceptance criteria of NLT (b) (4) (Q) dissolved in 30 minutes. Therefore, implement an acceptance criterion of **Q =** (b) (4) **at 20 minutes** for the dissolution test and provide the updated specifications table for your drug product. Also, FDA requested the Applicant to update the specification table and all relevant sections of the NDA to reflect the acceptance criterion of Q = (b) (4) at 20 minutes and the Applicant agreed.

April 25, 2013 Applicant's Response

The Applicant provided a submission dated April 25, 2013 to address several CMC related IRs, communicated in the mid-cycle review correspondence dated March 26, 2013. Included in that submission, the Applicant raised the dissolution acceptance criterion again although in the Pre-Mid-Cycle teleconference of March 12, 2013 the Applicant agreed to implement FDA's recommended dissolution acceptance criterion of Q = (b) (4) at 20 minutes.

The Applicant provided a justification for Item 5 under section 3.0 in the mid-cycle review correspondence dated March 26, 2013. Table 2 was provided to show the frequency of Stage 2 testing based on Registration batch stability data for 24 months and PV batch stability data available through 3 months when using a dissolution acceptance criterion of Q= (b) (4) in 20 minutes vs. using a dissolution acceptance criterion of Q= (b) (4) in 30 minutes.

Table 2: Evaluation of Amount of Dissolution Stage 2 Testing

	Registration Batches		Osaka PV Batches	
Dose (mg)	% of Stage 2 Testing at 20 minutes	% of Stage 2 Testing at 30 minutes	% of Stage 2 Testing at 20 minutes	% of Stage 2 Testing at 30 minutes
5	(b) (4)			
10				
15				
20				

The Applicant considered the initial proposed dissolution acceptance criterion of Q (b) (4) at 30 minutes justified. According to the Applicant, FDA's recommended acceptance criterion of Q (b) (4) in 20 minutes is overly sensitive to normal lot to lot production variation and would impose a significant increase to the occurrence of Stage 2 testing. Also, the Applicant stated that the amount of Stage 2 testing required for the proposed acceptance criterion of Q= (b) (4) in 30 minutes demonstrates discriminating power towards normal lot to lot production variation.

Reviewer's Note:

The Applicant's proposed acceptance criterion of Q= (b) (4) at 30 minutes is not justified. The reviewer re-examined the long-term stability data in all configurations up to 24 months from all the batches (Registration, Osaka PV, and Denmark PV) submitted (submissions dated April 8, 2013 and April 25, 2013) and prepared a table listing all the dissolution data collected on Registration and Process Validation Batches (at the two manufacturing sites: Osaka and Denmark). The table includes dissolution data at release and on stability for all dosage strengths and all configurations up to 24 months on long-term stability. All the long-term stability data in all configurations up to 24 months met the agency's specification of Q = (b) (4) in 20 minutes except in two cases: the 15 mg strength (Lot PD1861) and the 20 mg strength (Lot PD 1856) (See attached spreadsheet in the Appendix).

May 22, 2013 Teleconference

FDA held a teleconference on May 22, 2013 to inform the Applicant that their proposed acceptance criterion of Q (b) (4) at 30 minutes is not supported by the long-term stability data provided in all configurations up to 24 months for Registration and PV batches of all dosage strengths because all batches met the dissolution acceptance criterion of Q = (b) (4) at 20 minutes at release and on stability. The minimum mean was below (b) (4) at 20 minutes for the 15 and 20 mg strengths in three cases: *the 15 mg dosage strength (Registration Batch PD1861) had a minimum mean of* (b) (4) *dissolved at 20 minutes on stability, and the 20 mg dosage strength (Registration Batch PD 1856) had a minimum mean of* (b) (4) *dissolved in 20 minutes at release, and the same batch (PD 1856) had a minimum mean of* (b) (4) *dissolved in 20 minutes on stability*. Therefore, FDA requested the Applicant to implement the dissolution acceptance criterion of Q = (b) (4) at 20 minutes as was requested during the Pre-Mid-Cycle meeting.

The Applicant asked how FDA came to the determination of batches meeting the Q of (b) (4) at 20 minutes. FDA informed the Applicant that setting dissolution acceptance criterion is based on long-term stability data not accelerated conditions. The Applicant planned to re-examine the stability data based on long-term stability conditions. However, the Applicant considered that the limited amount of data available for commercial scale drug product justifies keeping the proposed dissolution acceptance criterion of Q= (b) (4) in 30 minutes. The Applicant proposed a post-approval commitment to re-examine stability data in one year.

FDA recommended that if the Applicant has bioequivalence data to justify the proposed dissolution acceptance criteria to submit it for review. The Applicant referred to the bioequivalence data of tablet formulations used throughout drug product development and the overall bioavailability of Lu AA21004, as data for consideration to justify the proposed dissolution acceptance criterion.

FDA indicated that a new justification should be submitted for review based upon the clinical BE data, and the re-examination of the stability data using only long-term stability conditions.

May 31, 2013 Submission

The Applicant provided an amendment dated May 31, 2013 with the following information:

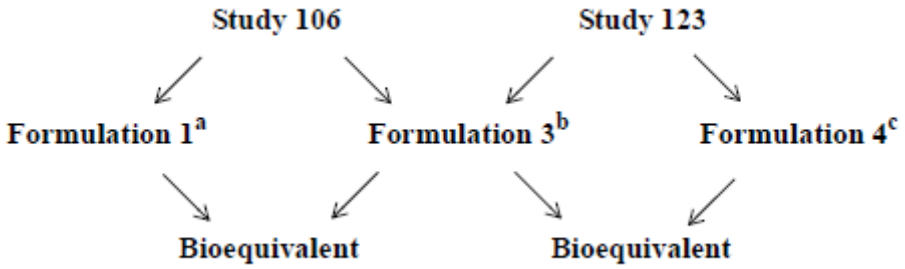
- A justification to support the Applicant's proposed dissolution acceptance criterion of Q (b) (4) in 30 minutes.
- Re-evaluation of available commercial scale stability data from Osaka site process validation batches using data from the long-term storage condition only (rather than long-term and accelerated conditions provided in the earlier response).
- A proposal for a post-approval commitment with respect to the dissolution acceptance criterion.

Below is a review of each of the information submitted in submission dated May 31, 2013 in response to FDA teleconference held on May 22, 2013.

- **Justification of Proposed Dissolution Criterion of Q (b) (4) in 30 minutes using BE data**

The Applicant provided PK data to demonstrate that the in vivo dissolution of LuAA21004 is not rate-limited by oral absorption. The Applicant provided a schematic (Figure 4) of the relative bioavailability studies performed to evaluate the IR tablet formulations of LuAA21004.

Figure 4: Relative Bioavailability Studies Comparing the IR Tablet Formulations of Lu AA21004



(a) Used in clinical studies initiated before June 2007.
(b) Used in clinical studies initiated between June 2007 and March 2010.
(c) Commercial formulation used in clinical studies initiated after March 2010.

The Applicant stated that Formulation III (10 mg) was bioequivalent to Formulation I (10 mg) and Formulation IV (commercial formulation, 20 mg) was bioequivalent to Formulation III (2x10 mg). The Applicant provided the 90% CIs for both AUC and Cmax (Table 3 and Table 4) from the two BE studies (Study 106 and Study 123).

Table 3: Statistical Analysis of the Pharmacokinetic Parameters of Lu AA21004 Following a Single Oral Dose (10 mg) of Formulation 3 or Formulation 1—Study 106

	Formulation 3 (Test)		Formulation 1 (Reference)		LS Mean Ratio (Test/Reference)	90% CI for
Parameter	N	LS Mean	N	LS Mean	(%)	Ratio
AUC(0-t) (ng·hr/mL)	23	209	23	213	98.26	(94.59, 102.07)
AUC(0-inf) (ng·hr/mL)	22	232	22	233	99.77	(95.77, 103.94)
Cmax (ng/mL)	23	4.11	23	4.05	101.58	(94.98, 108.64)
Tmax (hr)	23	6.0 (5.0, 16.0)	23	6.0 (5.0, 16.0)	NA	NA

NA=not applicable.
Note: Median (minimum, maximum) are presented for Tmax. Wilcoxon signed rank test was used for the analysis of Tmax (p=0.989).

Table 4: Statistical Analysis of the Pharmacokinetic Parameters of Lu AA21004 Following a Single Oral Dose (20 mg) of Formulation 4 or Formulation 3—Study 123

	Formulation 4 (Test)		Formulation 3 (Reference)		LS Mean Ratio (Test/Reference)	90% CI
Parameter	N	LS Mean	N	LS Mean	(%)	for Ratio
AUC(0-t) (ng·hr/mL)	19	612	19	607	100.90	(96.92, 105.05)
AUC(0-inf) (ng·hr/mL)	19	685	19	665	103.10	(98.64, 107.76)
Cmax (ng/mL)	19	7.98	19	8.02	99.44	(95.36, 103.70)
Tmax (hr)	19	10.0 (6.0, 12.0)	19	10.0 (8.0, 12.0)	NA	NA

AUC(0-t)= area under the plasma concentration-time curve from time 0 to time of last quantifiable concentration, NA=not applicable, Tmax=time to reach Cmax.
Note: Median (minimum, maximum) are presented for Tmax. Wilcoxon signed rank test was used for the analysis of Tmax (p=0.857).

Also, the Applicant provided the qualitative composition of LuAA21004 formulations (I, III, and IV) (Table 5) used in the BE studies and provided comparative dissolution profiles of these formulations (Figure 5). The raw data used to generate the comparative dissolution profiles and f2 values are provided in the Appendix (Table 4 and Table 5).

Table 5: Qualitative Composition of Lu AA21004 Film Coated Tablets

Formulation	I	III	IV
Ingredient	10 mg	10 mg	5/10/15/20 mg
Tablet core			
Lu AA21004 hydrobromide	x	x	x
(b) (4)	x	-	-
Mannitol	-	-	x
(b) (4)	-	x	-
	x	x	-
	x	x	-
Microcrystalline cellulose	x	x	x
(b) (4)	x	-	-
Hydroxypropyl cellulose	-	-	x
Sodium starch glycolate *	-	x	x
(b) (4)	-	x	-
Magnesium stearate	x	x	x
Film coating			
(b) (4)	x	-	-
	-	x	-
	-	-	x
	-	-	x(5mg)
	-	-	x(10mg)
	-	x	x(15mg)
	-	-	x(20mg)

(b) (4)

The Applicant stated that the results from the BE studies (106 and 123) indicate that the pharmacokinetics across the IR tablet formulations of LuAA21004 are similar, despite their different dissolution profiles in vitro (Figure 5). Furthermore, the Applicant stated that the observed median Tmax is 6.5 hr following a single dose of 50 mg ^{14}C-LuAA21004 aqueous solution formulation and cited Study 10477, an open-label, single-dose study investigating the absorption, metabolism, and excretion of LuAA21004. Also, the Applicant emphasized that there is no correlation between in vivo performance and in vitro dissolution profile of LuAA21004 based on the late Tmax of the tablet and aqueous solution formulations (6 to 10 hr) versus the rapid dissolution of the tablet in vitro because in vivo dissolution of LuAA21004 is not rate-limiting to oral absorption. The Applicant summarized that the data from the BE studies showing that the three formulations (I, III, and IV) of LuAA21004 are equivalent and the fact that there is no difference in Tmax comparing administration of IR tablet formulations to that of an oral solution confirms that tablet composition, disintegration and dissolution are not critical factors for oral bioavailability. Therefore, the Applicant concluded the proposed dissolution acceptance criterion of Q = (b) (4) in 30 minutes does not dictate the oral absorption/bioavailability of LuAA21004.

Figure 5: Comparative dissolution profiles of LuAA21004 Tablets, Formulation I, III and IV used in the bioequivalence studies 106 and 123

Table 6 below provides the mean dissolution data with f2 factor of the three formulations using the regulatory method.

Table 6: Mean Dissolution Values of Lu AA21004 film-coated tablets, Formulations I, III and IV in 0.1 M HCl, n=12

Clinical Study	Batch	Mean % Dissolved (time in minutes)						f2
		5	10	15	30	45	60*	
106	PD 1616 (10 mg) Formulation I	(b) (4)						
	2129772 (10 mg) Formulation III							
123	2139469 (10 mg) Formulation III							
	PD 1855 (20 mg) Formulaiton IV							

*Rotation speed changed from 50 rpm to 250 rpm during last 15 minutes.

Table 7 below provides an overview of clinical and dissolution test results. The Applicant stated that the proposed dissolution criterion of Q (b) (4) in 30 minutes is supported by the mean dissolution range (b) (4) at 30 minutes for the bioequivalent formulations which clearly indicates that dissolution rate is not a critical factor to oral bioavailability.

Table 7: Overview of Clinical and Dissolution Test Results

Study Number	Formulation	LS Mean Ratio (Test/reference) AUC(0-t) (ng·hr/mL)	AUC(0-inf) (ng·hr/mL)	Cmax (ng/mL)	Mean % Dissolved in 30 minutes (n=12)	f2
106	III (test) I (reference)	98.26	99.77	101.58	(b) (4)	
123	IV (test) III (reference)	100.9	103.1	99.4		

Reviewer's Note: ***Satisfactory.***
This reviewer agrees with the Applicant's statement above. The results from the BE studies (106 and 123) indicate that the pharmacokinetics across the IR tablet formulations of LuAA21004 are similar, despite their different dissolution profiles in vitro. This indicates that the dissolution method is over discriminating given that f2 failed despite the formulation being BE. Therefore, the BE data support a wider dissolution acceptance criterion.

- **Justification of Proposed Dissolution Criterion by Evaluation of Stability Data**

The Applicant evaluated the available long-term stability data (3 month at 25ºC/60% RH), (Table 8) for commercial scale drug product to determine the rate of Stage 2 testing when using the dissolution acceptance criterion Q= (b) (4) in 20 minutes v. Q (b) (4) in 30 minutes, as the analysis provided in submission dated April 25, 2013 (Table 2 above) included both accelerated and long-term conditions.

The Applicant reported that a total of 128 analyses (32 per strength) were performed through 3 months of stability testing for Osaka site Process Validation (PV) batches. The Applicant provided the mean percent dissolved and individual vessel values at 20 minutes and 30 minutes (See Table 6, Table 7, Table 8, and Table 9 in the Appendix). The Applicant stated that the amount of Stage 2 testing increased significantly (30%) when the Q time point is changed from 30 minutes to 20 minutes and is more pronounced with the higher strength tablets. Therefore, the Applicant concluded that the proposed dissolution acceptance criterion of Q= (b) (4) in 30 minutes is justified at this time given the limited amount of stability data available for drug product at commercial scale. Furthermore, the clinical BE data and comparative dissolution data presented above supports a specification of Q = (b) (4) in 30 minutes.

Table 8: Evaluation of Amount of Dissolution Stage 2 Testing (Long-term storage condition)

	Osaka PV Batches	
Dose (mg)	% of Stage 2 Testing at 20 minutes	% of Stage 2 Testing at 30 minutes
5	(b) (4)	
10		
15		
20		

Therefore, the Applicant requests to keep the acceptance of the proposed dissolution acceptance criterion of Q = (b) (4) in 30 minutes upon NDA approval.

Reviewer's Note:

Examining the raw dissolution data provided up to 3 months on stability under long-term condition, these data do not support the Applicant's proposed dissolution acceptance criterion of Q = (b) (4) at 30 minutes because of the following observations:

- The data is based on limited stability for only three months from one site (Osaka).
- For the 5 mg dosage strength, the Stage 2 testing rate is the same at the 20 and 30 minutes time points. It is not clear how the percentages in Table 8 are determined, as the % of Stage 2 Testing at 20 minutes is not (b) (4) for the 5 mg dosage strength, it is (b) (4) similar for testing at 30 minutes.

- For the 10 mg dosage strengths, same lots required S2 testing for the 20 and 30 minutes time points at 3 months (J002 90 ct bottle, J001 blister, J002 500 ct bottle and 7 ct bottle). Even at initial release some lots needing S2 testing at either 20 minutes or 30 minutes time points (J002, 500 ct bottle).
- For the 15 mg dosage strengths, there was one lot K002 90 ct bottle that required S2 at 20 minutes and the same lot and configuration needed S2 testing at 30 minutes.
- For the 20 mg dosage strengths, the same lots required S2 testing at the 20 and 30 minutes time point (L001 500 ct 170 cc bottle at initial release, L002 90 ct bottle at 3 month stability, and L003 7ct bottle at 3 month stability).

However, given the argument presented above supported by the clinical BE data and comparative dissolution data which supports a dissolution acceptance criterion of Q = (b) (4) in 30 minutes, it is acceptable to keep the proposed acceptance criterion of Q = (b) (4) at 30 minutes.

- **A proposal for a post-approval commitment with respect to the dissolution acceptance criterion.**

The Applicant stated that if FDA still requires further evaluation of the proposed dissolution acceptance criterion, the Applicant commits to review and evaluate the dissolution acceptance criterion for the ongoing stability studies and commercial batches for one year after the approval of the NDA. The results of the evaluation will be submitted in the Annual report with justification to continue using the proposed acceptance criterion (Q = (b) (4) at 30 minutes) or to change to Q = (b) (4) at 20 minutes.

Reviewer's Note: ***Satisfactory***

The proposed dissolution acceptance criterion of Q = (b) (4) at 30 minutes is found acceptable. Therefore, the Applicant's commitment to review and evaluate the dissolution acceptance criterion for the ongoing stability studies and commercial batches for one year after the approval of the NDA is not necessary given that the provided BE data support a wider dissolution acceptance criterion.

2. Acceptability of the comparability protocol for additional manufacturing site (Oranienburg)

The Applicant submitted a protocol describing the requirements to qualify Takeda GmbH (a Takeda Company), Oranienburg plant (Germany), as an alternate manufacturing site for the production of LuAA21004 immediate release tablets. The Applicant stated that no changes are proposed for the formulation composition and the manufacturing process at the new facility. The same unit operations and the same manufacturing equipments of the same design and operating principles to be used as those used to manufacture the NDA primary batches.

The Applicant plans to perform analytical testing, stability testing and final product release testing according to the approved product specification, analytical procedures, and dissolution. These results will be compared against the registration primary batches to demonstrate similarity between sites.

Reviewer's Note:
The proposed manufacturing site change is a change in the manufacturing site to a different campus. Per SUPAC-IR, it considered a Level 3 manufacturing site change. Therefore, the Applicant is requested to submit multi-point dissolution profiles comparisons (with *f2* statistical testing) in water, 0.1 N HCl, and USP buffer media at pH 4.5, 6.5 and 7.5 (five separate profiles) for the proposed and current manufacturing sites. Adequate sampling should be performed (e.g. at 5, 15, 20, 30, 45, 60, and 120 minutes) until either (b) (4) of drug from the drug product is dissolved or an asymptote is reached. A surfactant may be used with appropriate justification. This request was communicated in the Discipline Review letter dated June 7, 2013.

APPENDIX

Table 1 through 3 were provided in March 7, 2013 submission.

Table 1: Dissolution Data of Registration Batches, 5, 10, 15 and 20mg (n=12)

Unit: %

Time point (min)		5	10	15	20	30	45
PD 1858 (5mg)	Mean						(b) (4)
	max						
	min						
	RSD						
PD 1859 (5mg)	Mean						
	max						
	min						
	RSD						
PD 1881 (5mg)	Mean						
	max						
	min						
	RSD						
PD 1863 (10 mg)	Mean						
	max						
	min						
	RSD						
PD 1864 (10 mg)	Mean						
	max						
	min						
	RSD						
PD 1865 (10 mg)	Mean						
	max						
	min						
	RSD						
PD 1860 (15 mg)	Mean						
	max						
	min						
	RSD						
PD 1861 (15 mg)	Mean						
	max						
	min						
	RSD						
PD 1862 (15 mg)	Mean						
	max						
	min						
	RSD						

Table 1: Dissolution Data of Registration Batches, 5, 10, 15 and 20mg (n=12) (continued)

Unit: %

Time point (min)		5	10	15	20	30	45
PD 1855 (20 mg)	Mean						(b) (4)
	max						
	min						
	RSD						
PD 1856 (20 mg)	Mean						
	max						
	min						
	RSD						
PD 1869 (20 mg)	Mean						
	max						
	min						
	RSD						

Table 2: Dissolution Data of PV Batches (Osaka, Japan), 5, 10, 15 and 20mg (n=12)

Unit: %

Time point (min)		5	10	15	20	30	45
G001 (5 mg)	Mean						(b) (4)
	max						
	min						
	RSD						
G002 (5 mg)	Mean						
	max						
	min						
	RSD						
G003 (5 mg)	Mean						
	max						
	min						
	RSD						
J001 (10 mg)	Mean						
	max						
	min						
	RSD						
J002 (10 mg)	Mean						
	max						
	min						
	RSD						
J003 (10 mg)	Mean						
	max						
	min						
	RSD						
K001 (15 mg)	Mean						
	max						
	min						
	RSD						
K002 (15 mg)	Mean						
	max						
	min						
	RSD						
K003 (15 mg)	Mean						
	max						
	min						
	RSD						

Table 2: Dissolution Data of PV Batches (Osaka, Japan), 5, 10, 15 and 20mg (n=12) (Continued)

Unit: %

Time point (min)		5	10	15	20	30	45
L001 (20 mg)	Mean						(b) (4)
	max						
	min						
	RSD						
L002 (20 mg)	Mean						
	max						
	min						
	RSD						
L003 (20 mg)	Mean						
	max						
	min						
	RSD						

Table 3: Dissolution Data of PV Batches (Valby, Denmark), 5, 10, 15 and 20mg (n=12)

Unit: %

Time point (min)		5	10	15	30	45	60*
2315829 (5 mg)	Mean						(b) (4)
	max						
	min						
	RSD						
2315832 (10 mg)	Mean						
	max						
	min						
	RSD						
2315835 (15 mg)	Mean						
	max						
	min						
	RSD						
2315838 (20 mg)	Mean						
	max						
	min						
	RSD						

(*) During last 15 minutes of dissolution paddle speed was increased to 250 rpm.

Dissolution at 20 minutes of Registration and PV batches (Spreadsheet prepared by this reviewer using Stability data submitted in Submission of April 4 and April 25)

Dissolution at 20 minutes of Registration and PV batches (Spreadsheet prepared by this reviewer using Stability data submitted in Submission of April 4 and April 25) (Continued)

Table 4 though Table 9 were provided in May 31, 2013 Submission

Comparative Dissolution of BE Studies Batches

Table 4: Dissolution of Lu AA21004 film-coated tablets 10 mg (Formulation I) and of Lu AA21004 film-coated tablets 10 mg (Formulation III) in 0.1 M HCl

Time Point (min)	% Dissolved											
	PD 1616 (10 mg) Form. I						2129772 (10 mg) Form. III					
	5	10	15	30	45	60*	5	10	15	30	45	60*
	(b) (4)											
Mean												
%RSD												
Minimum												
f2**												

*Timepoint is after 15 min at 250 rpm.

** Similarity factor

Table 5: Dissolution of Lu AA21004 film-coated tablets 10 mg (Formulation III) and of Lu AA21004 film-coated tablets 20 mg (Formulation IV) in 0.1 M HCl

Time Point (min)	% Dissolved											
	2139469 (10 mg) Form. III						PD 1855 (20 mg) Form. IV					
	5	10	15	30	45	60*	5	10	15	30	45	60*
	(b) (4)											
Mean												
%RSD												
Minimum												
f2**												

*Timepoint is after 15 min at 250 rpm.

** Similarity factor

Stability Data for Commercial Scale Lots up to 3 Months under Long-Term Conditions from the Osaka site

Table 6: Dissolution Data for Commercial Scale LuAA21004 Tablets, 5 mg

			20 minutes time point		30 minutes time point	
Batch Number	Package Configuration	Time Point	Mean % Dissolved	% Dissolved (Individual Vessel Values)*	Mean % Dissolved	% Dissolved (Individual Vessel Values)*
OBG001	30 ct bottle	Initial				
		3 month				
	90 ct bottle	Initial				
		3 month				
	500ct bottle (150 cc)	Initial				
		3 month				
	500ct bottle (170 cc)	Initial				
		3 month				
	7ct bottle	Initial				
		3 month				
	Blister	Initial				
		3 month				
OBG002	30 ct bottle	Initial				
		3 month				
	90 ct bottle	Initial				
		3 month				
	500ct bottle (170 cc)	Initial				
		3 month				
	7ct bottle	Initial				
		3 month				
	Blister	Initial				
		3 month				
OBG003	30 ct bottle	Initial				
		3 month				
	90 ct bottle	Initial				
		3 month				
	500ct bottle (170 cc)	Initial				
		3 month				
	7ct bottle	Initial				
		3 month				
	Blister	Initial				
		3 month				

(b) (4)

*Values in ***bold-italicized*** indicate stage 2 testing required.

Table 7: Dissolution Data for Commercial Scale Lu AA21004 Tablets, 10 mg

			20 minutes time point		30 minutes time point	
Batch Number	**Package Configuration**	**Time Point**	**Mean % Dissolved**	**% Dissolved (Individual Vessel Values)***	**Mean % Dissolved**	**% Dissolved (Individual Vessel Values)***
OBJ001	30 ct bottle	Initial				(b) (4)
		3 month				
	90 ct bottle	Initial				
		3 month				
	500ct bottle (150 cc)	Initial				
		3 month				
	500ct bottle (170 cc)	Initial				
		3 month				
	7ct bottle	Initial				
		3 month				
	Blister	Initial				
		3 month				
OBJ002	30 ct bottle	Initial				
		3 month				
	90 ct bottle	Initial				
		3 month				
	500ct bottle (170 cc)	Initial				
		3 month				
	7ct bottle	Initial				
		3 month				
	Blister	Initial				
		3 month				
OBJ003	30 ct bottle	Initial				
		3 month				
	90 ct bottle	Initial				
		3 month				
	500ct bottle (170 cc)	Initial				
		3 month				
	7ct bottle	Initial				
		3 month				
	Blister	Initial				
		3 month				

*Values in bold-italicized indicate stage 2 testing required.
(S2) = indicates stage 2 testing completed.

Table 8: Dissolution Data for Commercial Scale LuAA21004 Tablets, 15 mg

Batch Number	Package Configuration	Time Point	20 minutes time point Mean % Dissolved	20 minutes time point % Dissolved (Individual Vessel Values)*	30 minutes time point Mean % Dissolved	30 minutes time point % Dissolved (Individual Vessel Values)*
OBK001	30 ct bottle	Initial				(b) (4)
		3 month				
	90 ct bottle	Initial				
		3 month				
	500ct bottle (150 cc)	Initial				
		3 month				
	500ct bottle (170 cc)	Initial				
		3 month				
	7ct bottle	Initial				
		3 month				
	Blister	Initial				
		3 month				
OBK002	30 ct bottle	Initial				
		3 month				
	90 ct bottle	Initial				
		3 month				
	500ct bottle (170 cc)	Initial				
		3 month				
	7ct bottle	Initial				
		3 month				
	Blister	Initial				
		3 month				
OBK003	30 ct bottle	Initial				
		3 month				
	90 ct bottle	Initial				
		3 month				
	500ct bottle (170 cc)	Initial				
		3 month				
	7ct bottle	Initial				
		3 month				
	Blister	Initial				
		3 month				

*Values in ***bold-italicized*** indicate stage 2 testing required.
(S2) = indicates stage 2 testing completed.

Table 9: Dissolution Data for Commercial Scale LuAA21004 Tablets, 20 mg

			20 minutes time point		30 minutes time point	
Batch Number	**Package Configuration**	**Time Point**	**Mean % Dissolved**	**% Dissolved (Individual Vessel Values)***	**Mean % Dissolved**	**% Dissolved (Individual Vessel Values)***
OBL001	30 ct bottle	Initial				
		3 month				
	90 ct bottle	Initial				
		3 month				
	500ct bottle (150 cc)	Initial				
		3 month				
	500ct bottle (170 cc)	Initial				
		3 month				
	7ct bottle	Initial				
		3 month				
	Blister	Initial				
		3 month				
OBL002	30 ct bottle	Initial				
		3 month				
	90 ct bottle	Initial				
		3 month				
	500ct bottle (170 cc)	Initial				
		3 month				
	7ct bottle	Initial				
		3 month				
	Blister	Initial				
		3 month				
OBL003	30 ct bottle	Initial				
		3 month				
	90 ct bottle	Initial				
		3 month				
	500ct bottle (170 cc)	Initial				
		3 month				
	7ct bottle	Initial				
		3 month				
	Blister	Initial				
		3 month				

(b) (4)

*Values in ***bold-italicized*** indicate stage 2 testing required.
(S2) = indicates stage 2 testing completed.

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/s/

HOUDA MAHAYNI
06/12/2013

SANDRA SUAREZ
06/12/2013

CLINICAL PHARMACOLOGY REVIEW

NDA:	**204447**
IND:	**76307**
Submission Dates:	**10-29-2012**
Brand Name:	**NA**
Generic Name:	
Dosage & Strength:	**Tablets of 5, 10, 15, 20mg strength**
Indication:	**Treatment for MDD**
Applicant:	**Takeda**
Submission:	**Original NDA**
Division:	**DCP1**
Primary Clinical Pharmacology Reviewer:	**Andre Jackson, Ph.D.**
Pharmacometrics Reviewer:	**Li Zhang, Ph.D.**
Clinical Pharmacology Team Leader:	**Hao Zhu, Ph.D.**
Pharmacometrics Team Leader:	**Atul Bhattaram, Ph.D.**

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1.0 EXECUTIVE SUMMARY

The sponsor is seeking approval of vortioxetine (Lu AA21004) as oral tablets at dosage strengths of 5mg, 10mg, 15mg, and 20mg, for the treatment of major depressive disorder (MDD) via a 505 b(1) route. Vortioxetine is a new molecular entity. The mechanism of the antidepressant effect of vortioxetine is thought to be related to its enhancement of serotonergic activity in the central nervous system through selective inhibition of serotonin reuptake. The clinical development program consisted of 28 clinical pharmacology studies, 10 short-term placebo-controlled efficacy and safety studies, 1 long-term placebo-controlled, relapse prevention study, and 3 long-term open-label safety extension studies.

Vortioxetine exhibits dose-proportional pharmacokinetics with an absolute bioavailability of 75%. No food effect is identified. Plasma protein binding is about 98%.Vortioxetine is extensively metabolized through oxidation via multiple cytochrome P450 enzymes, primarily by CYP2D6, and followed by subsequent glucuronic acid conjugation. Only negligible amount of unchanged vortioxetine is eliminated. The half life of vortioxetine is 66 hours. A 5-fold accumulation at steady state is expected following a once daily dosing. The presence of hepatic impairment (mild to moderate) and renal impairment (mild to end stage) does not appear to affect the apparent clearance of vortioxetine.

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

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the Clinical Pharmacology and Biopharmaceutic information submitted in NDA 204447 and finds the submitted information acceptable, provided an agreement on the label can be obtained from the sponsor. The acceptability of specific drug information is provided below.

Decision	Acceptable to OCP	Recommendations and Comments
Overall	☒ Yes ☐ No ☐ NA	Pending labeling and PMC/PMR agreements with the sponsor.
Evidence of Effectiveness	☒ Yes ☐ No ☐ NA	Pivotal trials and supportive trials

Proposed dose for general population	☒ Yes ☐ No ☐ NA	The proposed starting dose is 10 mg. Maintenance dose can be adjusted between 5 to 20 mg.
Proposed dose adjustment in specific patients or patients with comedications	☐ Yes ☒ No ☐ NA	Recommendations: 1. No dose adjustment of vortioxetine is needed based on race, gender, age, and in patients with mild to moderate hepatic impairment or patients with mild to end stage renal impairment. 2. Vortioxetine dose should be increased by 3 fold in patients receiving a strong CYP inducer and vortioxetine dose should be reduced by half in patients receiving a strong CYP2D6 inhibitor. 3. No dose adjustment of vortioxetine is needed when voritoxetine is coadministered with ethanol or aspirin. PMC studies: 1. In vivo study in severe hepatic impairment patients (PMC) 2. In vitro assessment of potential inhibitor of major transporters
Pivotal bioequivalence studies	☒ Yes ☐ No ☐ NA	The to-be-marketing and clinical trial formulations are bioequivalent. Four tablets of 5 mg strength and one tablet of 20 mg strength of the to-be-marketed formulation are bioequivalent.
Labeling	☐ Yes ☒ No ☐ NA	Pending satisfactory agreement with the sponsor.

1.2 Post-Marketing Studies

PMC or PMR	Key drug development questions	Rationale	Design Summary

☒ PMC ☐ PMR	Should vortioxetine dose be reduced in severe hepatic impairment patients? If so, by how much?	Vortioxetine is extensively metabolized and depression appears to be associated with severe liver diseases.	Study population: Severe hepatic impaired patients and healthy subjects Study design: Parallel Sample size: Target 20% SE of Mean AUC Dose(s): 5 mg Study length: 4 half-lives after single-dose Endpoints: Mean AUC, Cmax Submit protocol by: Jul-14 Start study by: Oct-14
☒ PMC ☐ PMR	Is vortioxetine the inhibitor of the major transporters?	The objective is to determine whether vortioxetine increases exposure of other drugs which are substrates of the major transporters.	Study design: Refer to the agency's drug-drug interaction guidance Submit protocol by: Jul-14 Start study: Oct-14

1.3 Clinical Pharmacology Summary

The current submission consisted of 28 in vivo clinical pharmacology studies and 10 in vitro studies.

Pharmacokinetic Features of Vortioxetine:

Pharmacokinetic properties of vortioxetine are summarized in **Error! Reference source not found.** with the pharmacokinetic profiles demonstrated in **Error! Reference source not found.**. Food has no effect on vortioxetine absorption. Vortioxetine is extensively metabolized and then mainly eliminated through urine. CYP2D6 is the primary metabolic enzyme.

Figure 1: Mean Lu AA21004 Plasma Concentrations Over Time: Dose 20 mg

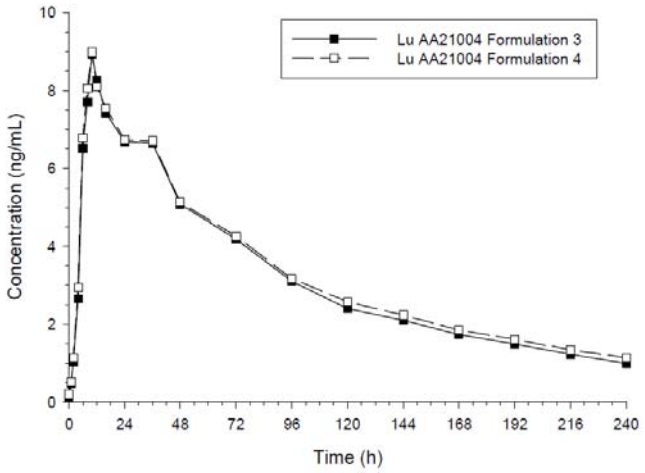


Table 1: Important PK properties of VortioxetineLu AA21004

PK Property	PK Parameter	
Dose-proportionality	PK dose-proportional for doses 2.5-60 mg	
Absorption	Tmax	7-11 hrs
	T 1/2	66 hrs
	Absolute Bioavailability	75%
	Food Effect	No food effect
Distribution	Protein Binding	98%
Metabolism	Pathways	Oxidation through P450 isozymes: CYP2D6 (primary enzyme), CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8 and CYP2B6 Followed by glucuronic acid conjugation
Elimination	Routes	Metabolites -60% urine -20% feces

Pharmacodynamic Features of Vortioxetine:

Some pharmacodynamic properties of vortioxetine are summarized in Table 2: Pharmacodynamic Features of Vortioxetine.

Table 2: Pharmacodynamic Features of Vortioxetine

Vortioxetine Dose	**Comedication and Dose**	**Study and Pharmacodynamic Variable**	**Conclusion**
10 mg	None	A on-road-driving test using standard deviation of lateral position (SDLP) as the pharmacodynamic variable	Driving performance was not meaningfully affected.

10 mg and 40 mg	None	A thorough QT study evaluating placebo-adjusted, baseline-correcte QTcNi.	Vortioxetine does not prolong QTc interval.
10 mg	Stable dose of Warfarin (1-10 mg)	A study compared INR and prothrombin time.	Vortioxetine, at the dose of 10 mg and when added to stable doses of warfarin (1-10mg), does not meaningfully change INR and prothrombin time.
10 mg	150 mg of aspirin	A study compared arachidonic acid (AA), adenosine diphasphate (AD), and collagen induced platelet aggregation.	Vortioxetine, at the dose of 10 mg and when added to 150 mg dose of aspirin, dose not change AA, AD, or collagen induced platelet aggregation.

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

2.0 QUESTION BASED REVIEW

2.1 What were the in vitro and in vivo Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA?

The clinical pharmacology package for votioxetine consists of ten *in vitro* and twenty eight *in vivo* studies in which pharmacokinetics and/or pharamcodynamics of votioxetine were evaluated.

Table 3 summarizes the *in vitro* studies included in the package. Seven *in vitro* studies were conducted to assess metabolism, metabolite

profiling, and CYP enzyme inhibition and induction potential. One study was conducted to assess the potential for vortioxetine as a P-gp substrate and a P-gp inhibitor. Two studies were conducted to evaluate plasma protein binding.

Table 3: Overview of *In Vitro* Studies

Study	Study Description
12287	In vitro plasma protein binding of ^{14}C-Lu AA21004
14179	In vitro plasma protein binding of Lu AA34443
124 (a)	Ex vivo plasma protein binding of ^{14}C-Lu AA21004 in healthy subjects
114 (a)	Ex vivo plasma protein binding of ^{14}C-Lu AA21004 in subjects with or without hepatic impairment
112 (a)	Ex vivo plasma protein binding of ^{14}C-Lu AA21004 in subjects with or without renal impairment
10477 (a)	Distribution of radioactivity into red blood cells in samples from the clinical mass balance study with ^{14}C-Lu AA21004
12814 and Amendment 1	In vitro evaluation of the Pgp substrate and inhibitor potential of Lu AA21004
10291	In vitro metabolism of Lu AA21004 by cDNA-expressed human CYP isoenzymes and in phenotyped human liver microsomes
12424	Supplementary investigations of the in vitro metabolism of Lu AA21004 by cDNA-expressed human CYP isoenzymes and in phenotyped human liver microsomes
10431	In vitro ^{14}C-Lu AA21004 metabolite profiling in human isolated cryopreserved hepatocytes
10882	Radioprofiling of ^{14}C-Lu AA21004 and metabolites in plasma, urine, and feces samples from the clinical mass balance study (Study 10477)
552-823	In vitro evaluation of the inhibitory effect of Lu AA21004 and its metabolites on human hepatic CYP enzyme activity
12742	In vitro evaluation of the inhibitory effect of Lu AA21004 and Lu AA34443 on human hepatic CYP2C8
12089	In vitro evaluation of Lu AA21004 and Lu AA34443 as inducers of CYP enzymes in fresh cultured human hepatocytes

cDNA=complementary DNA.
(a) Clinical pharmacology study (human biomaterial data are included in the Clinical Study Report).

(Note: Results of Study 10477, 112, 124, and 114 were included in clinical study reports.)

The firm submitted twenty eight *in vivo* studies to evaluate human pharamcokinetics and/or pharmacodynamics (Table 4). Of these studies, one study gave the results for mass balance and drug characterization. Four studies investigated dose proportionality and pharmacokinetic features of vortioxetine following single or multiple doses. Three studies assessed intrinsic factors. Eleven studies investigated drug-drug interactions and there were four biopharmceutics studies. The firm also submitted five pharmacodynamics studies.

Table 4: Overview of *In Vivo* Studies

Study	Type of Study	Dose (a)
Single- and Multiple-dose PK Studies		
10272	PK in male subjects and exploratory food effect	10, 20, 30, 50, or 75 mg
10467	PK in young female subjects (single- and multiple-dose), young male subjects (multiple dose), and elderly male and female subjects (single- and multiple-dose)	20 or 60 mg 2.5, 5, 10, 20, 40, or 60 mg QD
13921A (b)	Relative bioavailability, oral drops	20 mg (tablet and oral drops)
13138A (b)	Relative bioavailability, enteric-coated formulation	20 and 30 mg
13119A (b)	Food effect and relative bioavailability, enteric-coated formulation	Part A: 20 or 30 mg Part B: 20 mg
Japanese Single- and Multiple-dose PK Studies		
CPH-001	PK in Japanese male subjects (single- and multiple-dose) and female subjects (multiple-dose) and exploratory food effect	2.5, 5, 10, 20, or 40 mg 5, 10, or 20 mg QD (male subjects); 5 or 10 mg QD (female subjects)
CPH-002 (b)	Relative bioavailability, enteric-coated formulation	10 and 20 mg or 20 and 30 mg
CPH-003	PK in Japanese elderly subjects	10 mg
Mass Balance Study		
10477	Mass balance in healthy male subjects	^{14}C-Lu AA21004 50 mg oral solution
Absolute and Relative Bioavailability Studies		
10982	Absolute bioavailability and absorption profile	5 mg IV (pilot); 9 mg IV and 20 mg oral
123	Food effect and relative bioavailability	20 mg
106	Food effect and relative bioavailability	10 mg
Intrinsic Factor Studies		
111	Effect of age, gender, and race	10 mg
114	Effect of hepatic impairment	10 mg
112	Effect of renal impairment	10 mg
Extrinsic Factor Studies – Cytochrome P450 Interaction Studies		
117	DDI (bupropion)	10 mg
115	DDI (rifampicin)	20 mg
103	DDI (ketoconazole and fluconazole)	10 mg
11826A	DDI (omeprazole)	10 mg
101	DDI (drug cocktail)	10 mg
102	DDI (oral contraceptives)	10 mg
109	DDI (warfarin)	10 mg
113	DDI (diazepam)	10 mg
Extrinsic Factor Studies – Other Interaction Studies		
110	DDI (ethanol)	20 or 40 mg
116	DDI (aspirin)	10 mg
118	DDI (lithium)	10 mg
Pharmacodynamic Studies		
104	Effect on QTc interval (thorough QT)	10 or 40 mg
12689A	Effect on driving performance	10 mg
10985	PET occupancy (5-HTT and 5-HT1A) in White subjects	2.5, 10, 30, or 60 mg
12260A	PET occupancy (5-HTT) in White and Japanese subjects	2.5, 5, or 20 mg
124	Effect on neurotransmitter concentrations in the CSF	20 mg

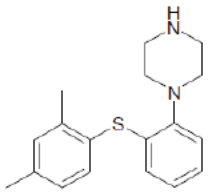
DDI=drug-drug interaction, QTc=corrected QT interval.
(a) Oral tablet dose of Lu AA21004, unless otherwise indicated.
(b) The pharmacokinetic data for the enteric-coated formulations (Studies 13119A and 13138A) and the oral drops formulation (Study 13921A) are not presented in this NDA because the sponsor is not seeking approval for these formulations; however, the pharmacokinetic data for the IR tablet formulation that were collected in these studies are presented in Appendix 2.

(Note: In addition to the studies listed in Table 4, Study 14520A, a BE study using the 5 mg strength, was submitted on March 21, 2012 per the agency's request through post mid-cycle meeting.)

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Vortioxetine (Figure 2) is a basic compound which has a solubility of 0.57 mg/ml in 50mM Tris buffer at 37ºC.The octanol/aqueous distribution coefficient (logD) for vortioxetine ranges from 2.2 (pH 3) to 4.7 (pH 11) at 25ºC.



Source: Report 18416 and 18303.
Molecular weight=298.45 g/mol.
Molecular formula=$C_{18}H_{22}N_2S$.
Chemical name=1-[2-(2,4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine.
Log $D_{7.4}$=3.1.
pKa=9.1 (±0.1) and 3.0 (±0.2).

Figure 2: Chemical Structure of Vortioxetine Drug Substance

The proposed commercial formulation is a film-coated, immediate-release, oral tablet containing either 5, 10, 15, and 20 mg of vortioxetine (Table 5). The β-form of vortioxetine is (b) (4) used in the to-be-marketed, clinical and nonclinical formulations. The proposed commercial tablet strengths from 20 mg to 10 mg are proportionally similar in composition, whereas the 5 mg strength is not compositionally proportional in its active and inactive ingredients to the corresponding highest strength product.

Table 5: Composition of 5, 10, 15 and 20 mg Vortioxetine Tablets

Ingredient	Quantity per Tablet (mg)				Function	Reference to Quality Standards
	5 mg	10 mg	15 mg	20 mg		
Lu AA21004 hydrobromide	6.355	12.71	19.065	25.42	Active ingredient	In-house standard
(Lu AA21004)	5	10	15	20		
Mannitol	(b) (4)					USP
Microcrystalline cellulose						NF
Hydroxypropyl cellulose						NF
Sodium starch glycolate (a)						NF
Magnesium stearate						NF
(b) (4)						USP
						NA
						In-house standard
						In-house standard
						In-house standard
						In-house standard
						USP
Total tablet weight (c)						NA
Magnesium stearate (d)						NF

Table 6 contains the formulations used in clinical trials. Formulation 1 was used in the early clinical trials. Formulation 3 was used in clinical pharmacology and efficacy and safety studies prior to March 2010. After

March 2010, Formulation 4, the proposed commercial formulation, was used.

Table 6: Composition of Vortioextine Tablet Formulation 1, 3, and 4.

	Formulation 1				Formulation 3 (a)		Formulation 4 (Commercial Formulation)			
Strength (mg)	2.5	5	10	25	1	10	5	10	15	20
Ingredient	Quantity per Tablet (mg)									
Drug Substance										
Lu AA21004 HBr	3.178	6.355	12.71	31.775	1.271	12.71	6.355	12.71	19.065	25.42
Corresponding to Lu AA21004	2.5	5	10	25	1	10	5	10	15	20
Excipients—Tablet Core										
(b) (4)	(b) (4)									
Mannitol										
(b) (4)										
Hydroxypropylcellulose										
Cellulose, microcrystalline										
(b) (4)										
Sodium starch glycolate										
(b) (4)										
Magnesium stearate										
(b) (4)										
Tablet core weight										
(b) (4)										
Tablet weight, film-coated										
(b) (4)										

2.2.2 What are the proposed mechanism of action and therapeutic indications?

The mechanism of the antidepressant effect of vortioxetine is not fully understood but is thought to be related to its enhancement of serotonergic activity in the CNS through selective inhibition of serotonin reuptake. Vortioxetine is also an antagonist at serotonergic 5-HT3, 5-HT7, and 5-HT1D receptors, a partial agonist at serotonergic 5-HT1B receptors, and an agonist at serotonergic 5-HT1A receptors; however, the net result of this action on serotonergic transmission and its role in vortioxetine's antidepressant effect are unknown.

2.2.3 What are the proposed dosages and routes of administration?

Vortioxetine tablets should be given orally without regard to food. The recommended starting dose is 10 mg once daily. Dose can be

administered at 5 to 20 mg once daily in maintenance treatment. The doses were selected based on the safety and efficacy trials conducted in support of the application.

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

Other selective serotonin reuptake inhibitors (SSRIs) indicated for the treatment of major depressive disorder include Celexa (citalopram), Lexapro (escitalopram oxalate), Luvox (fluvoxamine maleate), Paxil (paroxetine HCl), Pexeva (paroxetine mesylate), Prozac (fluoxetine HCl), and Zoloft (sertraline HCl).

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

The firm conducted a single-dose tolerability study investigating doses between 10 to 150 mg and showed the maximum tolerated dose was 75 mg. In addition, the firm conducted an absolute bioavailability study (Study #10982) and several food effect studies (studies #123 and 10272). The results indicated the absolute bioavailability of vortioxetine is 75% and no food effect on vorioxetine absorption was identified.

The firm further investigated potential therapeutic doses in two ligand-based 5-HTT PET studies. The results indicated that the mean 5-HTT occupancy in the raphe nuclei was approximately 50% at 5 mg QD, 65% at 10 mg QD, and increased to above 80% at 20 mg QD. The doses (i.e., 5 mg QD to 20 mg QD) were further tested in the clinical efficacy and safety trials.

2.3.2 What was the design of the short term efficacy studies and what were the clinical endpoints?

The 10 short-term studies were randomized, double-blind, placebo-controlled, fixed-dose studies of 6 or 8 weeks' duration; in 6 of the studies, an active reference was included for internal validation. Eligible subjects were randomized equally to each treatment groups with placebo, a fixed dose of Lu AA21004 (1, 2.5, 5, 10, 15, or 20 mg QD; the doses varied across studies), and, in some studies, a fixed dose of active reference. In Studies 315, 316, and 317, subject randomization was stratified by baseline sexual dysfunction status (normal or abnormal). In the studies where an active reference was included to validate the study, either venlafaxine (Study 11492A) or duloxetine (Studies 11984A, 13267A, 315, 304, and 12541A) was chosen. The

overall design is listed in Figure 3 with the results of the 10 short term studies listed in Table 6.

Figure 3: Overall Study Design – Short-Term Studies

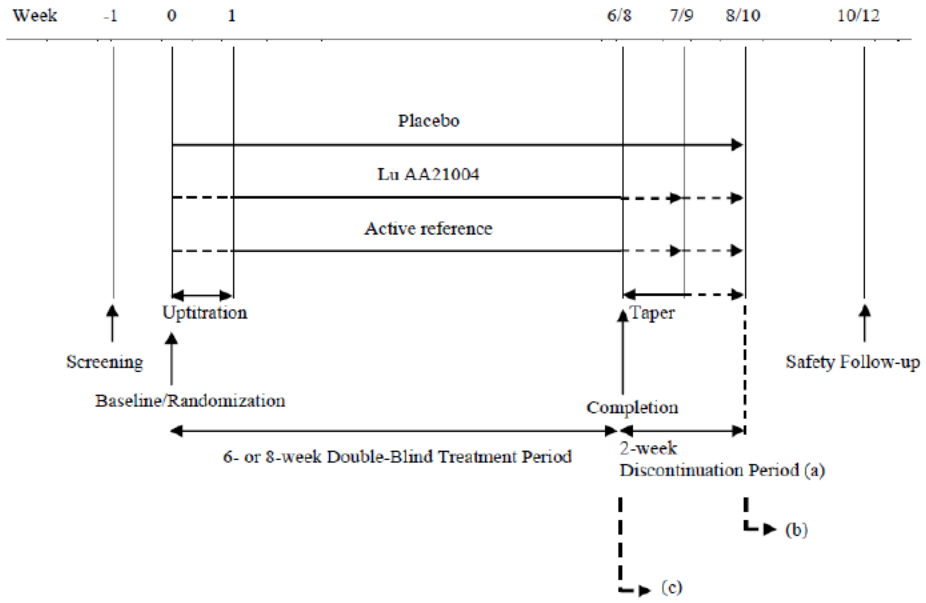


Table 7. Results of 10 MDD short term studies

Study No./ Region	Main Inclusion Criteria	Results of Study Drug Doses (mg) vs. PBO	Overall Study Results
11492A/Europe, Australia, Canada Asia	18-65 years MADRS ≥30	Lu AA21004 5 mg vs. PBO - p<0.001 Lu AA21004 10 mg vs. PBO - p<0.001 Venlafaxine 225 mg vs. PBO - p<0.001	Positive
305/Europe, Asia, Australia, South Africa	18-75 years, MADRS ≥26	Lu AA21004 5 mg vs. PBO - NS Lu AA21004 10 mg vs. PBO - p<0.001	Positive
13267A/Europe, South Africa	18-75 years, MADRS ≥26 and CGI-S ≥4	Lu AA21004 15 mg vs. PBO - p<0.0001 Lu AA21004 20 mg vs. PBO - p<0.0001 duloxetine 60 mg vs. PBO - p<0.0001	Positive
315/US	18-75 years, MADRS ≥26 and CGI-S≥4	Lu AA21004 15 mg vs. PBO - p=0.224 Lu AA21004 20 mg vs. PBO - p=0.023 duloxetine 60 mg vs. PBO - p<0.001	Positive
316/US	18-75 years, MADRS ≥26 and CGI-S ≥4	Lu AA21004 10 mg vs. PBO - p=0.058 Lu AA21004 20 mg vs. PBO - p=0.002	Positive
12541A (Elderly) /Europe, Canada, US	≥65 years, MADRS ≥26	Lu AA21004 5 mg vs. PBO - p=0.0011 duloxetine 60 mg vs. PBO - p<0.001	Positive
11984A/Europe, Canada, Asia, Australia	18-75 years, MADRS ≥26	Lu AA21004 5 mg vs. PBO - NS Lu AA21004 10 mg vs. PBO - NS duloxetine 60 mg vs. PBO - NS	Failed
317/US	18-75 years,	Lu AA21004 10 mg vs. PBO - NS	Negative

	MADRS ≥26	Lu AA21004 15 mg vs. PBO -	NS	
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 - duloxetine 60 mg vs. PBO -	NS p<0.05	Negative

Were there any long-term studies?

The completed long-term extension studies (11492C, 11984B, and 301) were 52-week,open-label, flexible-dose studies at doses of 5 or 10 mg (11492C) or 2.5, 5, or 10 mg (11984Band 301). The ongoing, extension studies (13267B and 314) are 52-week, open label flexible-dose studies at doses of 15 or 20 mg. In all 5 studies, the subjects were seen at Weeks 1, 2, and 4, then every 4 weeks to Week 28 and thereafter every 8 weeks until Week 52, with a safety follow-up after 4 weeks.

The long-term studies included subjects who had completed the lead-in studies, were willing to continue, and were judged by the investigator to benefit from a 52-week continuation treatment with vortioxetine.MADRS or HAM-D24 was assessed at every visit in Studies 11492C, 11984B, 301, 13267B, and 314. CGI-S was assessed at Baseline, Weeks 4 and 24 and at the Completion Visit in Studies 11984B, 301, 13267B, and 314. CGI-S was not assessed in 11492C. An overview of these studies is presented in Table 8.

Table 8. Overview of the Long-Term Open-Label Extension Studies in MDD

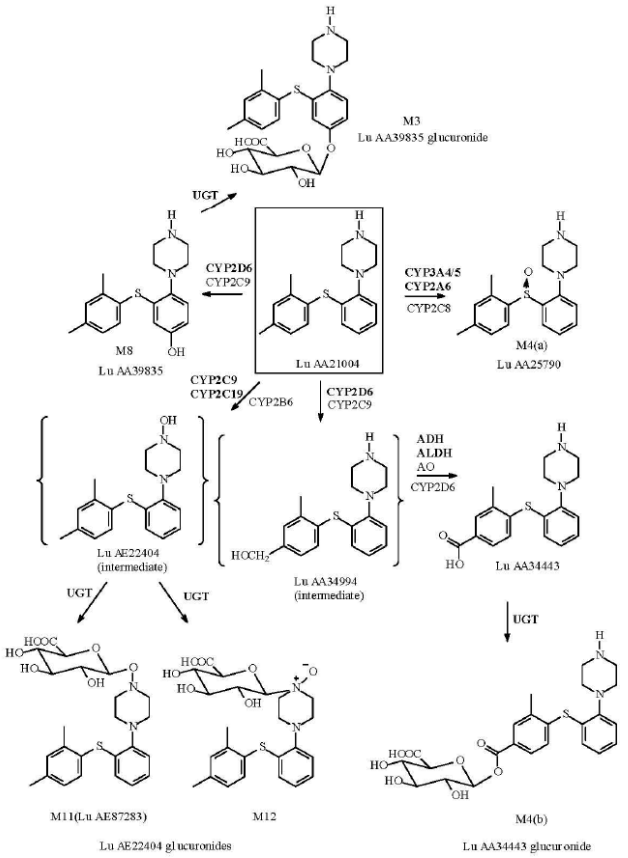
		Number of Subjects (Safety Set)
Study	**Study Design**	**Lu AA21004**
11492C	Lu AA21004 (5 or 10 mg), extension for Study 11492A	74
11984B	Lu AA21004 (2.5, 5, or 10 mg), extension for Study 11984A	535
301	Lu AA21004 (2.5, 5, or 10 mg), extension for Studies 304 and 305	834
13267B	Lu AA21004 (15 or 20 mg), extension for Study 13267A (ongoing)	71
314	Lu AA21004 (15 or 20 mg), extension for Studies 315, 316, and 317 (ongoing)	1059
Total		**2573**

Source: Studies 11492C Table 1, 11984B Table 1, 301 Table 15.1.2, 13267B Table 1, 314 Table 15.1.1.
All were designed as flexible-dose studies with a duration of 52 weeks.

2.3.3 What is the proposed metabolic scheme and enzymes involved in the metabolism of vortioxetine?

Vortioxetine is extensively metabolized through oxidation via CYP2D6, CYP3A4/5, CYP2C9, CYP2C19, CYP2A6, CYP2C8 and CYP2B6 and subsequent glucuronic acid conjugation. CYP2D6 appears to be the major enzyme. The proposed metabolic scheme is shown in Figure 4.

Figure 4.Biotransformation Scheme Showing the Enzymes Involved in the Metabolism of Vortioxetine in Humans



2.3.3.1 Does the mass balance indicate renal or hepatic as the major route of elimination?

The major route of elimination is metabolism. A mass balance study, showed that 80% of the radioactivity was recovered in the urine plus feces (Figure 5), ; however, only negligible amounts of unchanged vortioxetine was excreted. No detectable unchanged vortioxetine was identified (Table 9) in the 59% of the radioactivity recovered in the urine samples collected up to 48 hours.

Figure 5. A Study Conducted with 14C-Vortioxetine in Which Urine and Feces was Collected from 6 Subjects. Poor or Ultrafast Metabolizers for CYP2D6 were Excluded in Order to Obtain Metabolism Results that will Apply to the Vast Majority of Patients.

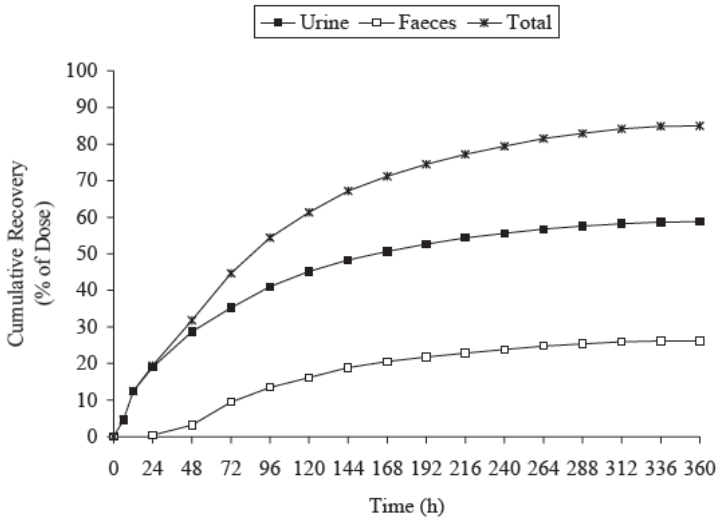


Table 9 Percent of Dose in Urine (0-48h) and Feces (0-120h) from Healthy Male Subjects Following a Single Oral Administration of 50 mg Free Base (1.85 MBq) of [14C]-Vortioxetine.

Metabolite[a]	% of administered dose ± standard deviation, n=6		
	Urine (0-48 h)[b] (28.7±4.9)[c]	Faeces (0-120 h)[b] (16.1±2.7)[c]	Urine + Faeces (44.8±5.3)[c]
M4(a)	-	0.6±0.6	0.6±0.6
M4(b)[d]	4.2±3.2	-	4.2±3.2
Lu AA34443	9.4±8.2	10.9±3.0	20.2±8.1
Lu AA21004	-	0.4±0.4	0.4±0.4
Total[e]	13.6±10.4	11.8±3.1	25.4±10.6

[a] Metabolites are shown in order of elution using LC-MS/MS method 1 and id.s were assigned in accordance with study No. 11304, where M1-M11 were identified. M4(a) and M4(b) corresponds to the two metabolites that co-elutes in the chromatographic peak assigned M4 in study No. 11304.
[b] The concentration of total radioactivity in samples from later timepoints was to low for metabolite profiling using liquid scintillation counting.
[c] Total amount (% of dose) of [^{14}C]-Lu AA21004 and its radiolabelled metabolites in urine (0-48 h) and faeces (0-120 h), determined by liquid scintillation counting under study No. 10477.
[d] Results were obtained by LC-MS/MS method 1
[e] More significant figures were used for the calculation.

(Note: LuAA21004 is vortioxetine)

2.3.3.2 Are there any active metabolites?

Based upon in vitro receptor binding and pharmacokinetic studies, the parent compound is thought to be responsible for in vivo activity.

Lu AA34443 is a major circulating metabolite. However, in vitro studies suggest that it does not bind to the main receptors related to effectiveness. The metabolite, Lu AA39835 (also referred to as C-448), is equipotent to vortioxetine as an inhibitor of the h5-HTT (Ki=15.5 nmol/L). However, affinity for the 5HTT is not expected to translate into central nervous system activity in vivo since this metabolite does not penetrate the blood brain barrier appreciably.

2.3.3.3 Does the drug exhibit linear Pharmacokinetics?

Yes. The pharmacokinetics of vortioxetine is linear and dose proportional over the doses ranging from 2.5 to 60 mg when vortioxetine is administered once daily.

The firm conducted a single ascending dose study with the doses administered between 2.5 to 75 mg. The results (Table 10) indicate that the pharmacokinetics of vortioxetine is linear. The 95% confidence interval of the slope estimate of AUC0-inf contains 1, which indicates that the AUC proportionally increases with dose between the dose range of 2.5 to 75 mg. Likewise, Cmax is considered approximately linear increase with dose based upon the value of 1.02 for the lower 95% confidence interval of the slope estimate.

Table 10.Dose Proportionality for Lu AA21004 Pharmacokinetics after Single Oral Dose (PKS)

Parameter	Dose Range	Slope (95% CI)	p-value for Testing Slope=1
Cmax	2.5 to 75 mg	1.09 (1.02, 1.16)	0.018
AUC(0-inf)	2.5 to 75 mg	1.03 (0.89, 1.18)	0.651

A multiple ascending dose study was conducted in subjects receiving vortioxetine 2.5 to 75 mg once daily. The results (Table 11) also indicate that the pharmacokientics of vortioxetine are linear, because the confidence intervals for the slope estimates of both AUC and Cmax contain 1. Due to accumulation, this study covers a wider vortioxetine exposure range than the single ascending dose study.

Table 11. Dose Proportionality of Lu AA21004 Following Multiple-Dose Administration: Pooled Data From Studies 104, 10467, 10985, and 12260A

Parameter	Dose Range	Slope (95% CI)	P-Value for Testing Slope=1
Cmax	2.5 - 60 mg QD	1.000 (0.946, 1.053)	0.987
AUC(0-24)		0.993 (0.938; 1.048)	0.806

2.3.3.4 What is the level of intra and inter-subject variability exhibited by vortioxetine?

In a bioequivalence study conducted in healthy subjects, a single dose of 50 mg Lu AA21004 was given on two separate occasions. The estimated intra and inter-subject variability are presented in Table 12. Compared to AUC 0-t and AUC 0-inf, the intrasubject variability, with the value of 14%, is the highest for Cmax. Therefore, vortioxetine would not be considered to be highly variable.

Table 12.Intra-subject and Inter-subject Variability of Pharmacokinetic Parameters of Vortioxetine Following Single Dosing of 50 mg Lu AA21004Vortioxetine on Two Separate Occasions

	Parameter			
CV	C_{max}	AUC_{0-t}	AUC_{0-inf}	$t_{½}$
Intra-subject	14.28	9.45	10.81	12.00
Inter-subject	10.46	31.79	49.94	36.49
Degrees of freedom	4	4	4	4

2.3.4 What are the in vitro characteristics of Vortioxetine

Vortioxetine in concentrations up to 20 µM (5969 ng/mL) was shown to be a poor P-glycoprotein (Pgp) substrate as the in vitro net efflux ratio was low (approximately 3) when compared with the Pgp substrate digoxin (efflux ratio >100).

Vortioxetine is metabolized extensively, primarily by oxidation and subsequent glucuronic acid conjugation. The 2 intermediary metabolites, Lu AE22404 and Lu AA34994, were only detected in vitro (Study 10431) and the metabolite Lu AA25790 was quantified in vivo in feces only (Study 10882). Six metabolites of Vortioxetine were quantified in plasma: Lu AA34443 (major inactive metabolite) and its glucuronide (M4(b)), Lu AA39835 (minor active metabolite) and its glucuronide (M3), and 2 Lu AE22404 glucuronides (Lu AE87283 [M11] and M12).

Binding of [14C]-vortioxetine to human serum albumin (mean range 85.1%-95.7%) was moderate to high.

The results in Table 13indicate that most of Lu AA21004 is located in plasma not in red cells.

Table 13. Individual and Mean AUC Ratios Between Total Radioactivity in Plasma and Whole Blood Following Single Oral Administration of 50 mg 14C-Vortioxetine : Study 10477

Subject	Common Time Points (hr)	Whole Blood AUC(0-ct) (ng equiv hr/g)	Plasma AUC(0-ct) (ng equiv hr/g)	Whole Blood Radioactivity: Plasma Radioactivity (a)
101	12	1089	1943	0.560
102	NC	NC	NC	NC
103	24	2563	3894	0.658
104	9	527	1091	0.483
105	12	342	994	0.344
106	15	1060	2348	0.452
n	NC	5	5	5
Mean	NC	1116	2054	0.500
SD	NC	872	1176	0.118
CV (%)	NC	78.1	57.3	23.6

2.3.5 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, the active moiety in plasma and clinically relevant tissues were appropriately identified and measured. The active moiety is thought to be the parent compound, vortioxetine. The assay was developed in plasma and urine where the species were measured. The concentrations in the clinical trials were covered by the validated concentration range for the assays. All assays developed by the firm had acceptable accuracy and precision to analyze for vortioxetine and its metabolites.

2.3.6. Were there any pharmacodynamic studies conducted to assess whether driving performance is affected in patients receiving vortioxetine?

Yes, there was a driving study conducted to compare the effects of 10 mg vortioxetine and placebo on actual driving performance in healthy subjects, following the first dose and at steady-state, as measured using the SDLP ((i.e. standard deviation of lateral position) during an on-the-road driving test. The study included mirtazapine 30 mg as the positive control. The results in Table 14 shows that the treatment is non-inferior to placebo on days 2 and 16 since the upper confidence interval does not contain the margin of 2 cm using the one-sided non-inferiority test of vortioxetine compared to placebo, tested at the 5% level of significance.

Table 14. Primary Analysis of Treatment Differences for SDLP (cm)

Day	Treatment	N	Least squares mean	Comparison	Difference	Upper 95% CI
2	10 mg Lu AA21004	20	20.41	Lu AA21004 - Placebo	-1.03	0.05
	Placebo	23	21.44			
16	10 mg Lu AA21004	21	20.18	Lu AA21004 - Placebo	-0.23	0.80
	Placebo	22	20.41			

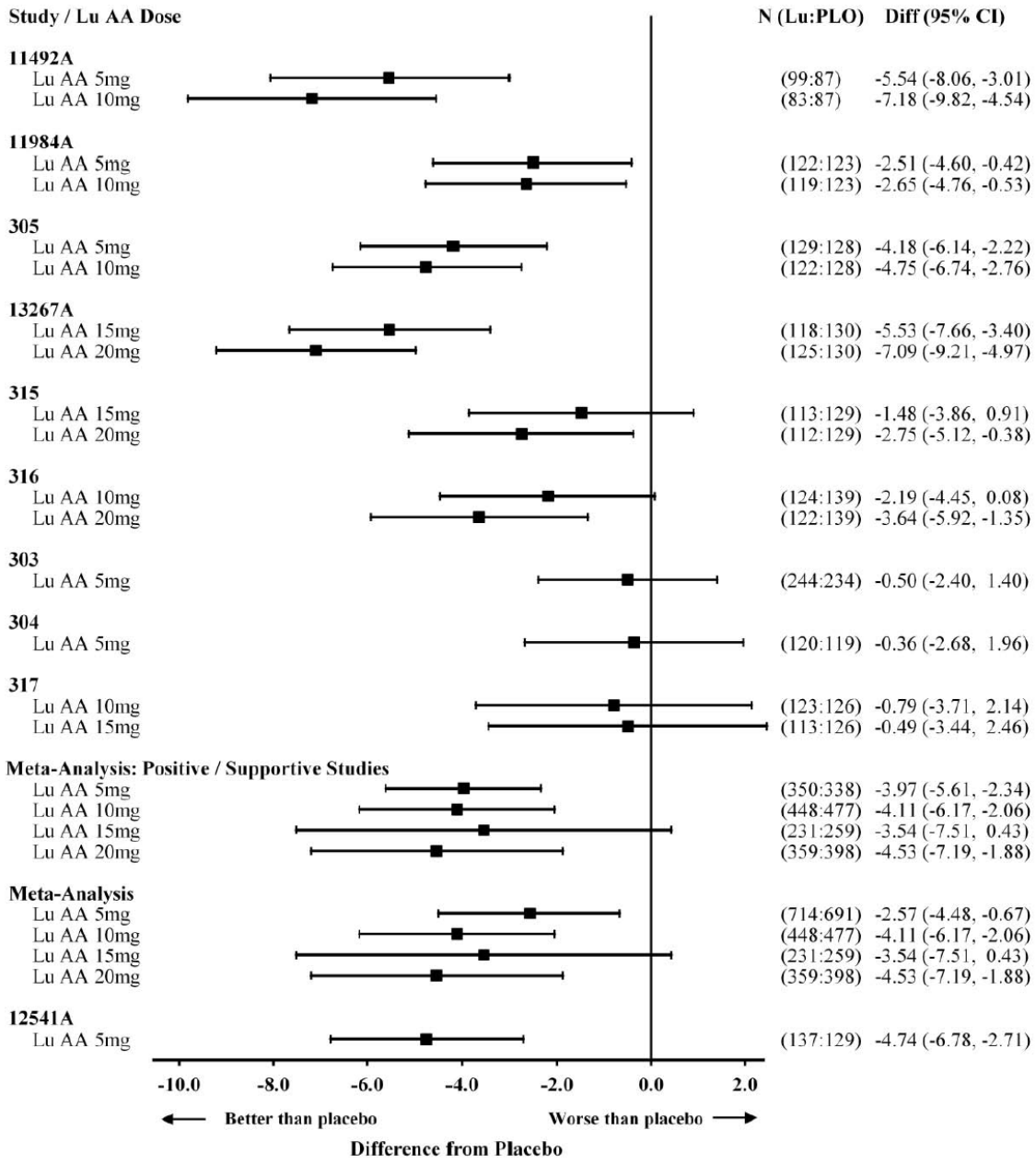
2.4 Exposure-Response

2.4.1 What are the characteristics of the exposure-response relationship for effectiveness?

There is no consistent relationship between vortioxetine dose from 5mg to 20mg and changes in primary efficacy endpoint (change from baseline in MADRS total score at week 6/8).

The sponsor conducted individual study and meta-analyses by a mixed-effect model repeated measures (MMRM) for placebo adjusted change from baseline in MADRS total score at Week 6/8 and the results are shown in Figure 6.

Figure 6: Treatment Effect on Change from Baseline in MADRS Total Score at Week 6/8 (MMRM)



Source: Sponsor's summary-of-clinical-efficacy.pdf, Pg 105

The 5 mg dose was statistically significantly better than placebo ($p < 0.001$) by the multiplicity controlled testing strategy in Study 11492A and separated from placebo ($p < 0.05$) in 2 studies (11984A and 305). In 2 studies (303 and 304), there was no separation from placebo.

The 10 mg dose was statistically significantly better ($p < 0.001$) than placebo by the multiplicity controlled testing strategy in 2 studies (11492A

and 305) and separated from placebo (p<0.05) in Study 11984A. In 2 studies (316 and 317), there was no separation from placebo and Week 8. In addition, the difference from placebo in Study 316 was -2.2 points and not statistically significant (p=0.058).

The 15 mg dose was statistically significantly better (p <0.001) than placebo by the multiplicity controlled testing strategy in 1 study (13267A). In 2 studies (315 and 317), there was no separation from placebo.

The 20 mg dose was statistically significantly better than placebo by the multiplicity controlled testing strategy in 3 studies (13267A, 315, and 316).

The results of the meta-analysis (MMRM) of the mean change from Baseline in MADRS total score at Week 6/8 in the 6 positive and supportive studies (11492A, 11984A, 305, 13267A, 315, 316) in adults were similar to the treatment effects observed in the individual studies. The overall mean difference from placebo across the studies was statistically significant for the 5, 10, and 20 mg doses, respectively. The 15 mg dose did not separate from placebo (p=0.08).

In conclusion, there is no consistent relationship between vortioxetine dose from 5mg to 20mg and changes in primary efficacy endpoint (change from baseline in MADRS total score at week 6/8).

2.4.2 What are the characteristics of the exposure-response relationships for safety?

The incidence of nausea appears to be dose-related.

The most frequently reported treatment-emergent adverse event (TEAE, incidence ≥5% in any treatment group) was nausea. In Table 15, among the individual vortioxetine treatment groups, a dose-related trend was observed for the incidence of nausea. At the dose range between 5-20 mg, the observed incidence is about 2 times higher than that observed in the placebo group. The incidence of nausea leading to discontinuation was higher in the voritoxetine treatment groups (2.2%) than in the placebo group (0.3%) and increased with increasing vortioxetine dose (range: 0.7% [1 mg] to 4.4% [20 mg]).

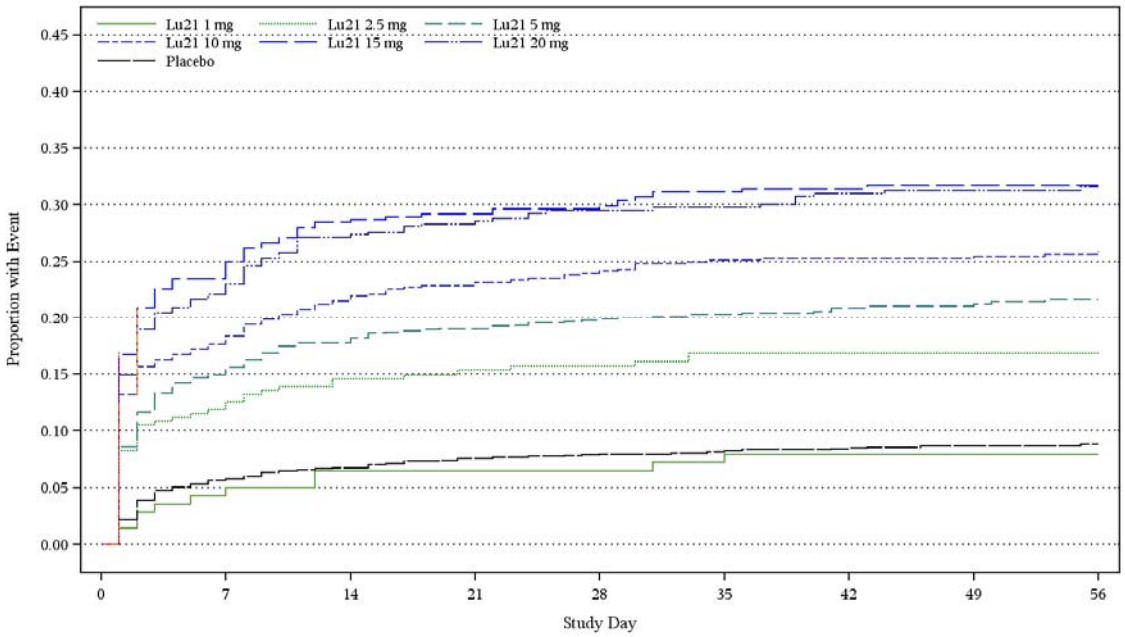
Table 15: Nausea Leading to Discontinuation in ≥1% Subjects in Any Lu AA21004 Group (study 303, 304, 305, 315, 316, 317, 11492A, 11984A, 12541A and 13267A).

	Placebo	1mg	2.5mg	5mg	10mg	15mg	20mg	Total
No. of patients	1621	140	304	1013	699	449	455	3060
No. of nausea	149 (9.2%)	11 (7.9%)	50 (16.4%)	216 (21.3%)	180 (25.8%)	144 (32.1%)	144 (31.6%)	745 (24.3%)
No. of discontinuation due to nausea	5 (0.3%)	1 (0.7%)	3 (1%)	13 (1.3%)	13 (1.9%)	17 (3.8%)	20 (4.4%)	67 (2.2%)

Source: \\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Vortioxetine_NDA 204447_LZ\ER Analyses\Final Model\Exposure-Safety.ssc

Additional analyses were performed by sponsor to evaluate the nausea AEs. The time to first nausea event during the treatment period in study 303, 304, 305, 315, 316, 317, 11492A, 11984A, 12541A and 13267A is provided in Figure 7. The majority of subjects in each treatment group who had nausea experienced their first event during the first week of dosing.

Figure 7: Time to First Event of Nausea



Source: Sponsor's summary-of-clinical-safety.pdf, Pg 129

The total duration, time to first event, and time to discontinuation due to nausea is presented in Table 16.

Table 16: Nausea Events During the Treatment Period

		Lu AA21004 (mg)						
	Placebo	1mg	2.5mg	5mg	10mg	15mg	20mg	Total
	N=1621	N=140	N=304	N=1013	N=699	N=449	N=455	N=3060
Total duration (days)								
Median	7	7	10.5	10	13	10.5	16	12
Min-Max	1-76	1-32	1-59	1-74	1-81	1-63	1-70	1-81
Time to First Event (days)								
Median	3	5	1.5	2	1	1	2	2
Min-Max	1-55	1-35	1-33	1-53	1-56	1-43	1-59	1-59
Time to discontinuation due to event (days)								
Median	2	3	1	1	5	1	2.5	1
Min-Max	1-18	3-3	1-13	1-15	1-44	1-17	1-14	1-44

Source: Sponsor's summary-of-clinical-safety.pdf, Pg 132

2.4.3 Does this drug prolong QT/QTc Interval?

No, vortioxetine does not prolong the QTc interval.

No significant QT prolongation effect of vortioxetine was detected in this thorough QT study. The largest upper bounds of the 2-sided 90% confidence interval for the mean differences between vortioxetine 10 mg q.d. and placebo, between vortioxetine 40 mg q.d. and placebo, were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% confidence interval for the placebo-adjusted, baseline-corrected QTc (ΔΔQTcNi (QT interval corrected by individual linear formula)) for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated indicating that assay sensitivity was established. The point estimates are presented in Table 17 .

Table 17. The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds of ΔΔQTcNi for Lu AA21004 (10 and 40 mg q.d.) 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.

2.5 What are the PK characteristics of the drug?

2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

Table 18 summarizes pharmacokinetic data for vortioxetine from 14 phase 1 studies in which single doses of vortioxetine 5, 10 and 20 were administered to healthy subjects were pooled. The single dose data shows that the parent drug, vortioxetine, has linear kinetics between the 5 mg and 20 mg dose range for Cmax and AUC and has a half-life of 69 h. The major metabolite Lu AA34443 is linear between the 5 m and 20 mg dosage levels with a half-life of 81 h. However, Lu AA39835 shows some nonlinearity in Cmax and AUC between the 5 mg and 10 mg dose only in single dose studies. The metabolite Lu AA39835 has a half-life of 32 h at 20 mg (i.e., may have been related to low levels) which increases to 85 h at the 10 mg and 20 mg doses.

Table 18. Noncompartmental Pharmacokinetic Parameters for Vortioxetine, and metabolites Lu AA34443, and Lu AA39835 following Single Oral Doses of 5 mg, 10 mg and 20 mg. Pooled Data From Studies 10272, 103, 10467, 106, 10982, 110, 111, 112, 114, 115, 123, 13138A, CPH-001,and CPH-003.

Lu AA21004 Dose/Analyte/ Statistic	Non-Compartmental PK Parameters							
	Tmax (hr)	Cmax (ng/mL)	AUC(0-t) (ng·hr/mL)	AUC(0-inf) (ng·hr/mL)	T1/2 (hr)	CL/F (L/hr)	Vz/F (L)	Metabolic Ratio
5 mg								
Lu AA21004								
N	6	6	6	6	6	6	6	NA
Mean	10.00	1.87	157.13	188.13	69.44	29.62	2737.53	NA
SD	2.280	0.090	48.096	68.323	20.832	10.329	415.474	NA
Minimum	7.0	1.7	103.3	118.2	44.6	18.0	2283.6	NA
Median	10.50	1.90	156.12	173.22	62.57	28.87	2676.59	NA
Maximum	12.0	2.0	211.5	278.2	103.7	42.3	3520.7	NA
%CV	22.80	4.79	30.61	36.32	30.00	34.87	15.18	NA
Lu AA34443								
N	6	6	6	6	6	NA	NA	6
Mean	6.00	4.72	151.47	190.34	81.23	NA	NA	1.06
SD	0.894	3.437	65.328	64.549	31.101	NA	NA	0.603
Minimum	5.0	2.0	73.9	114.9	44.5	NA	NA	0.4
Median	6.00	3.55	159.43	194.91	82.63	NA	NA	0.94
Maximum	7.0	11.2	255.1	278.1	121.9	NA	NA	2.1
%CV	14.91	72.85	43.13	33.91	38.29	NA	NA	56.89
Lu AA39835								
N	3	6	6	2	2	NA	NA	2
Mean	9.00	0.04	0.99	4.80	32.32	NA	NA	0.04
SD	2.646	0.047	2.061	4.624	18.590	NA	NA	0.035
Minimum	7.0	0.0	0.0	1.5	19.2	NA	NA	0.0
Median	8.00	0.02	0.17	4.80	32.32	NA	NA	0.04
Maximum	12.0	0.1	5.2	8.1	45.5	NA	NA	0.1
%CV	29.40	129.69	208.29	96.30	57.52	NA	NA	94.85

Footnotes are on last table page

Lu AA21004 Dose/Analyte/ Statistic	Non-Compartmental PK Parameters							
	Tmax (hr)	Cmax (ng/mL)	AUC(0-t) (ng·hr/mL)	AUC(0-inf) (ng·hr/mL)	T1/2 (hr)	CL/F (L/hr)	Vz/F (L)	Metabolic Ratio
10 mg								
Lu AA21004								
N	228	228	228	152	222	164	152	NA
Mean	9.15	4.60	254.72	273.42	60.62	40.52	2772.68	NA
SD	3.563	1.339	91.028	105.895	41.913	16.185	743.253	NA
Minimum	3.0	1.2	22.3	105.4	27.0	13.3	1185.3	NA
Median	8.00	4.47	241.10	258.79	53.07	37.53	2714.71	NA
Maximum	36.0	11.0	711.1	723.3	522.6	94.9	5810.0	NA
%CV	38.92	29.09	35.74	38.73	69.14	39.94	26.81	NA
Lu AA34443								
N	231	231	231	141	226	NA	NA	80
Mean	5.91	8.80	252.49	312.90	70.16	NA	NA	1.14
SD	4.525	4.835	96.216	109.847	37.317	NA	NA	0.551
Minimum	4.0	0.8	1.7	124.9	17.3	NA	NA	0.3
Median	5.00	8.04	246.23	303.36	62.10	NA	NA	1.08
Maximum	72.0	36.1	585.0	782.0	298.7	NA	NA	3.5
%CV	76.56	54.96	38.11	35.11	53.19	NA	NA	48.16
Lu AA39835								
N	221	222	222	21	186	NA	NA	55
Mean	14.14	0.11	7.18	14.64	86.74	NA	NA	0.04
SD	11.591	0.043	3.362	4.010	39.139	NA	NA	0.014
Minimum	3.0	0.0	0.0	8.3	28.7	NA	NA	0.0
Median	10.00	0.10	6.84	14.37	77.95	NA	NA	0.04
Maximum	72.0	0.3	18.9	29.2	308.3	NA	NA	0.1
%CV	81.98	38.03	46.80	27.40	45.12	NA	NA	32.04
20 mg								
Lu AA21004								
N	165	165	165	142	164	142	142	NA
Mean	9.89	8.11	561.20	645.51	64.28	41.47	3287.56	NA
SD	3.211	2.215	208.606	264.835	22.513	24.944	1142.586	NA
Minimum	4.0	3.9	171.4	193.5	27.9	12.0	1705.8	NA
Median	9.98	8.01	534.17	594.58	61.66	35.62	3016.86	NA
Maximum	24.0	14.5	1295	1670	139.5	166.9	8617.0	NA
%CV	32.46	27.31	37.17	41.03	35.03	60.14	34.75	NA

Lu AA21004	Non-Compartmental PK Parameters							
Dose/Analyte/ Statistic	Tmax (hr)	Cmax (ng/mL)	AUC(0-t) (ng·hr/mL)	AUC(0-inf) (ng·hr/mL)	T1/2 (hr)	CL/F (L/hr)	Vz/F (L)	Metabolic Ratio
20 mg (continued)								
Lu AA34443								
N	172	172	172	145	170	NA	NA	122
Mean	5.90	13.20	426.00	505.97	65.93	NA	NA	0.92
SD	1.450	8.456	195.204	202.942	22.237	NA	NA	0.737
Minimum	3.0	2.8	74.0	193.7	23.4	NA	NA	0.2
Median	5.98	11.15	384.21	461.74	63.34	NA	NA	0.70
Maximum	10.1	62.6	1405	1452	159.7	NA	NA	5.4
%CV	24.59	64.05	45.82	40.11	33.73	NA	NA	80.52
Lu AA39835								
N	159	167	159	96	136	NA	NA	91
Mean	18.95	0.20	15.97	23.79	84.64	NA	NA	0.03
SD	16.094	0.116	7.070	6.681	29.312	NA	NA	0.010
Minimum	1.0	0.1	0.1	13.1	37.6	NA	NA	0.0
Median	12.00	0.17	15.26	22.48	79.44	NA	NA	0.03
Maximum	96.0	1.0	59.3	39.8	191.6	NA	NA	0.1
%CV	84.94	58.05	44.27	28.08	34.63	NA	NA	30.10

Pharmacokinetic data for vortioxetine from 12 phase 1 studies in which once daily dosing of vortioxetine 5, 10 and 20 mg were administered to healthy subjects are summarized in Table 19. Noncompartmental Pharmacokinetic Parameters of Vortioxetine and metabolites Lu AA34443 and Lu AA39835 following Multiple Oral Doses of 5mg, 10 mg and 20 mg. Pooled Data From 104, 10467, 10985, 111, 113, 116, 117, 11826A, 12260A, 13119A, CPH-001, and CPH-002

. Steady state for vortioxetine is attained within 2 weeks of dosing (i.e., 10-11 days of dosing). At steady state, LuAA39835 follows linear PK over the dose range of 5 mg to 20 mg QD with a half life of 65 h.

Table 19. Noncompartmental Pharmacokinetic Parameters of Vortioxetine and metabolites Lu AA34443 and Lu AA39835 following Multiple Oral Doses of 5mg, 10 mg and 20 mg. Pooled Data From 104, 10467, 10985, 111, 113, 116, 117, 11826A, 12260A, 13119A, CPH-001, and CPH-002

Lu AA21004	Non-Compartmental PK Parameters										
Dose/Analyte/ Statistic	Tmax,ss (hr)	Cmax,ss (ng/mL)	Cmin,ss (ng/mL)	Cmax,ss/ Cmin,ss	AUC(0-24) (ng·hr/mL)	Fluctuation (a)	Accumulation (b)	T1/2 (hr)	CL/F,ss (L/hr)	Vz/F,ss (L)	Metabolic Ratio
5 mg											
Lu AA21004											
N	30	30	N/A	N/A	29	N/A	18	26	29	26	NA
Mean	7.30	8.69	N/A	N/A	175.15	N/A	5.17	60.05	32.96	2497.47	NA
SD	1.999	3.673	N/A	N/A	79.212	N/A	1.386	23.740	10.977	520.616	NA
Minimum	1.0	4.9	N/A	N/A	97.9	N/A	3.1	28.9	13.0	1600.7	NA
Median	7.00	7.40	N/A	N/A	149.52	N/A	5.35	52.77	33.41	2470.56	NA
Maximum	12.0	17.7	N/A	N/A	384.5	N/A	8.9	124.6	51.0	3645.0	NA
%CV	27.39	42.24	N/A	N/A	45.22	N/A	26.78	39.53	33.31	20.85	NA
Lu AA34443											
N	30	30	N/A	N/A	28	N/A	17	25	NA	NA	28
Mean	6.34	9.18	N/A	N/A	157.66	N/A	5.28	60.60	NA	NA	0.97
SD	2.224	2.940	N/A	N/A	44.974	N/A	10.532	22.814	NA	NA	0.400
Minimum	4.0	4.0	N/A	N/A	52.5	N/A	1.5	7.4	NA	NA	0.2
Median	6.00	9.33	N/A	N/A	156.42	N/A	2.50	58.00	NA	NA	0.91
Maximum	12.0	16.9	N/A	N/A	253.2	N/A	45.9	101.7	NA	NA	1.7
%CV	35.08	32.03	N/A	N/A	28.53	N/A	199.38	37.65	NA	NA	41.21
Lu AA39835											
N	23	23	N/A	N/A	23	N/A	N/A	23	NA	NA	23
Mean	8.43	0.28	N/A	N/A	5.62	N/A	N/A	71.47	NA	NA	0.03
SD	5.426	0.068	N/A	N/A	1.547	N/A	N/A	21.437	NA	NA	0.008
Minimum	1.0	0.2	N/A	N/A	3.0	N/A	N/A	44.3	NA	NA	0.0
Median	7.00	0.27	N/A	N/A	5.34	N/A	N/A	68.60	NA	NA	0.03
Maximum	24.0	0.4	N/A	N/A	8.5	N/A	N/A	127.7	NA	NA	0.1
%CV	64.33	24.33	N/A	N/A	27.55	N/A	N/A	30.00	NA	NA	25.71

Lu AA21004	Non-Compartmental PK Parameters										
Dose/Analyte/ Statistic	Tmax,ss (hr)	Cmax,ss (ng/mL)	Cmin,ss (ng/mL)	Cmax,ss/ Cmin,ss	AUC(0-24) (ng·hr/mL)	Fluctuation (a)	Accumulation (b)	T1/2 (hr)	CL/F,ss (L/hr)	Vz/F,ss (L)	Metabolic Ratio
10 mg											
Lu AA21004											
N	242	242	199	199	242	199	3	92	168	15	NA
Mean	8.45	17.92	11.33	1.68	344.00	0.50	4.87	58.84	38.27	3293.22	NA
SD	2.483	7.922	5.900	0.477	161.041	0.253	1.638	26.593	23.034	1649.217	NA
Minimum	0.0	2.3	2.7	1.2	38.1	0.2	3.1	20.4	10.1	1532.4	NA
Median	8.00	16.50	10.30	1.57	315.31	0.45	5.13	51.65	33.83	2739.61	NA
Maximum	23.9	58.9	45.9	5.9	1226	3.0	6.4	182.5	262.6	7717.8	NA
%CV	29.41	44.22	52.09	28.32	46.81	50.51	33.64	45.19	60.18	50.08	NA
Lu AA34443											
N	243	243	N/A	N/A	243	N/A	3	94	NA	NA	161
Mean	5.52	17.30	N/A	N/A	286.66	N/A	2.21	61.92	NA	NA	0.99
SD	1.892	8.004	N/A	N/A	109.870	N/A	0.503	26.054	NA	NA	0.974
Minimum	2.0	4.5	N/A	N/A	84.7	N/A	1.7	18.6	NA	NA	0.2
Median	5.10	15.70	N/A	N/A	269.37	N/A	2.17	57.59	NA	NA	0.85
Maximum	16.1	60.3	N/A	N/A	668.5	N/A	2.7	193.2	NA	NA	11.3
%CV	34.26	46.27	N/A	N/A	38.33	N/A	22.76	42.07	NA	NA	98.03
Lu AA39835											
N	239	239	N/A	N/A	239	N/A	N/A	88	NA	NA	157
Mean	8.14	0.56	N/A	N/A	11.03	N/A	N/A	65.50	NA	NA	0.03
SD	3.669	0.202	N/A	N/A	3.790	N/A	N/A	26.058	NA	NA	0.010
Minimum	0.0	0.1	N/A	N/A	1.3	N/A	N/A	19.6	NA	NA	0.0
Median	8.00	0.52	N/A	N/A	10.34	N/A	N/A	62.03	NA	NA	0.03
Maximum	24.0	1.5	N/A	N/A	31.9	N/A	N/A	190.8	NA	NA	0.1
%CV	45.06	36.18	N/A	N/A	34.35	N/A	N/A	39.79	NA	NA	28.55

Lu AA21004	Non-Compartmental PK Parameters										
Dose/Analyte/ Statistic	Tmax,ss (hr)	Cmax,ss (ng/mL)	Cmin,ss (ng/mL)	Cmax,ss/ Cmin,ss	AUC(0-24) (ng·hr/mL)	Fluctuation (a)	Accumulation (b)	T1/2 (hr)	CL/F,ss (L/hr)	Vz/F,ss (L)	Metabolic Ratio
20 mg											
Lu AA21004											
N	56	56	N/A	N/A	56	N/A	26	39	39	39	NA
Mean	8.11	33.03	N/A	N/A	645.78	N/A	5.68	64.23	40.11	3372.39	NA
SD	2.213	12.541	N/A	N/A	254.067	N/A	2.165	19.870	18.896	1048.017	NA
Minimum	3.0	12.1	N/A	N/A	222.6	N/A	3.1	36.2	17.9	1767.0	NA
Median	8.00	32.25	N/A	N/A	639.77	N/A	4.97	59.70	36.40	3319.86	NA
Maximum	14.0	60.8	N/A	N/A	1180	N/A	12.8	106.4	89.9	5769.1	NA
%CV	27.29	37.97	N/A	N/A	39.34	N/A	38.12	30.94	47.11	31.08	NA
Lu AA34443											
N	56	56	N/A	N/A	56	N/A	26	38	NA	NA	56
Mean	5.81	32.93	N/A	N/A	563.46	N/A	3.00	65.75	NA	NA	1.00
SD	1.965	15.422	N/A	N/A	218.897	N/A	1.274	28.604	NA	NA	0.624
Minimum	3.0	10.7	N/A	N/A	221.2	N/A	1.5	35.4	NA	NA	0.2
Median	6.00	30.50	N/A	N/A	538.31	N/A	2.75	58.09	NA	NA	0.84
Maximum	12.0	81.7	N/A	N/A	1164	N/A	6.1	181.6	NA	NA	3.0
%CV	33.84	46.83	N/A	N/A	38.85	N/A	42.48	43.50	NA	NA	62.56
Lu AA39835											
N	42	42	N/A	N/A	42	N/A	N/A	25	NA	NA	42
Mean	9.55	1.19	N/A	N/A	23.78	N/A	N/A	64.96	NA	NA	0.04
SD	7.313	0.406	N/A	N/A	7.945	N/A	N/A	17.336	NA	NA	0.012
Minimum	3.0	0.6	N/A	N/A	11.9	N/A	N/A	42.0	NA	NA	0.0
Median	8.00	1.13	N/A	N/A	22.68	N/A	N/A	62.70	NA	NA	0.03
Maximum	48.0	2.4	N/A	N/A	49.8	N/A	N/A	96.8	NA	NA	0.1
%CV	76.59	33.98	N/A	N/A	33.41	N/A	N/A	26.69	NA	NA	33.24

Source: Appendix I Table 11.3.2.
Cmin=minimum observed plasma concentration, NA=not applicable, N/A=not available, ss=steady state.
(a) Fluctuation=(Cmax,ss – Cmin,ss)/Cavg,ss where Cavg,ss=AUC(0-tau)/tau.
(b) Accumulation=AUC(0-tau) at steady state/AUC(0-24) Day 1.

2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

The PK data for subjects in the target population were collected in phase 2 and phase 3 studies for population PK analyses. However, several of these studies had analytical deficiencies identified by the sponsor. OCP and OSI have agreed that the OSI inspection with (b) (4) the CRO that conducted bioassays in question, would focus only on key clinical pharmacology studies. Because the PK data collected in patients from the Phase 2/3 trials cannot be validated, it is difficult to compare PK features

of the drug and its relevant metabolites between healthy adults and patients with target disease.

2.5.3 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?

See response for 2.5.2

2.5.4 What are the characteristics of drug absorption?

The absolute bioavailability (F) is 78% determined after a single oral dose and a 6 h intravenous infusion of vortioxetine. The maximal plasma vortioxetine concentration is reached within 6 hours. Mean maximal concentration is 13 ng/ml at a 20 mg oral dose.

The effect of food intake (high-fat meal) on the oral absorption of vortioxetine was evaluated in Study 123. There was no effect of food on vortioxetine absorption as supported by the 90% confidence intervals of the ratios for the exposure variables (Cmax, AUC 0-t, and AUC 0-∞) of voritoxetine and major metabolites between fed and fasted conditions being within the BE limits of 80-125% for the study (Table 20).

Table 20: Statistical Analysis of Plasma Pharmacokinetic Parameters Following Administration of Vortioxetine 20 mg Formulation 4 (To-Be-Marketed) in the Fed vs Fasted State-Study 123.

			Relative Bioavailability	
Analyte Parameter (units)	LS Mean Reg B (a)	LS Mean Reg C (a)	Point Estimate of Ratio (Regimen C/Regimen B) ×100 (b)	90% CI×100 (c)
Lu AA21004				
AUC(0-tlqc) (ng·hr/mL)	612.04	643.73	105.18	(101.02, 109.50)
AUC(0-inf) (ng·hr/mL)	685.17	705.54	102.97	(98.52, 107.63)
Cmax (ng/mL)	7.98	8.12	101.8	(97.63, 106.16)
Lu AA34443				
AUC(0-tlqc) (ng·hr/mL)	353.49	371.01	104.95	(100.31, 109.81)
AUC(0-inf) (ng·hr/mL)	386.75	402.96	104.19	(99.65, 108.94)
Cmax (ng/mL)	8.65	8.55	98.85	(92.12, 106.08)
Lu AA39835				
AUC(0-tlqc) (ng·hr/mL)	15.59	17.18	110.17	(103.03, 117.80)
AUC(0-inf) (ng·hr/mL)	20.80	21.86	105.09	(99.54, 110.94)
Cmax (ng/mL)	0.16	0.17	106.8	(100.00, 114.07)

2.5.4 What are the characteristics of drug distribution?

The mean apparent volume of distribution of vortioxetine (Vz/F) is 2500 to 3400 L. Using equilibrium dialysis at concentrations ranging from 10 to 12000 ng/mL, the human *in vitro* plasma protein binding was 98.8% for vortioxetine. *In vivo* studies showed that the fraction of unbound vortioxetine is 1 %, consistent across healthy subjects, subjects with mild to moderate hepatic impairment, and subjects with mild to end stage renal

impairment (Table 21). The data from Table 22 shows that the drug in plasma has a concentration twice that in whole blood.

Table 21.Individual and Mean AUC Ratios Between Total Radioactivity in Plasma and Whole Blood Following Single Oral Administration of 50 mg 14C-Vortioxetine: Study 10477

Subject	Common Time Points (hr)	Whole Blood AUC(0-ct) (ng equiv hr/g)	Plasma AUC(0-ct) (ng equiv hr/g)	Whole Blood Radioactivity: Plasma Radioactivity (a)
101	12	1089	1943	0.560
102	NC	NC	NC	NC
103	24	2563	3894	0.658
104	9	527	1091	0.483
105	12	342	994	0.344
106	15	1060	2348	0.452

Table 22.Fraction of Unbound Vortioextine in Plasma From Healthy Subjects and Subjects With Hepatic or Renal Impairment: Studies 124, 114, and 112

Study	Group	N	Mean Fraction (%) of Unbound Lu AA21004 (%CV) (a)
124	Healthy subjects	12	1.68 (11.85)
114	Healthy control subjects	16	0.91 (19.23) and 1.06 (14.82) (b)
114	Mild hepatic impairment	8	1.00 (28.84)
114	Moderate hepatic impairment	8	0.90 (13.32)
112	Healthy control subjects	32	1.02 - 1.10 (13.02 - 22.09) (c)
112	Mild renal impairment	8	1.02 (27.81)
112	Moderate renal impairment	8	1.04 (15.07)
112	Severe renal impairment	8	0.99 (19.7)
112	End-stage renal disease	8	0.88 (19.31)

2.5.5 What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?

The percent of the total radioactivity found in the plasma as parent drug is between 8%-13% from 4 h to 72 h. The glucuronide metabolites comprise the largest component of the observed radioactivity with values of 16-19% for M4(b) glucuronide from 4-72 h and 22-36% from 4-72 h for the M12 glucuronide (Table 23).

Table 23. Percentage of Total Radioactivity for [14C]-Vortioxetine and Its Radiolabelled Metabolites in Plasma from Healthy Male Subjects Following A Single Oral Administration of 50 mg Free Base (1.85 MBq) of [14C]-Vortioxetine

	Metabolite % of total radioactivity			
Metabolite[a]	4 hours (n=6)	12 hours (n=6)	24 hours (n=6)[b]	72 hours (n=1)[c]
M3 (glucuronide)	10 ± 7	12 ± 5	11 ± 2	8
M4(b) (glucuronide)	16 ± 12	14 ± 10	11 ± 4	19
Lu AA34443	28 ± 22	20 ± 12	14 ± 6	14
Lu AA39835	4 ± 3	4 ± 2	4 ± 2	4
M12 (glucuronide)	22 ± 11	33 ± 34	20 ± 8	36
Lu AA21004	8 ± 5	7 ± 2	10 ± 9	13
M11 (glucuronide)	11 ± 5	8 ± 4	8 ± 3	8
Total	99 ± 58	99 ± 65	77 ± 30	102

Source: Study No. 10882, Table 8 and Study No. 10477 CSR amendment 1, Table 9
a: Refer to Figure 2.a in Module 2.7.2 for biotransformation scheme
b: No other metabolites were observed, thus the lower recovery at this time point was ascribed to experimental error.
c: Only one sample obtained from subject R0104 at 72 hours post-dose was analyzed in study No. 10882

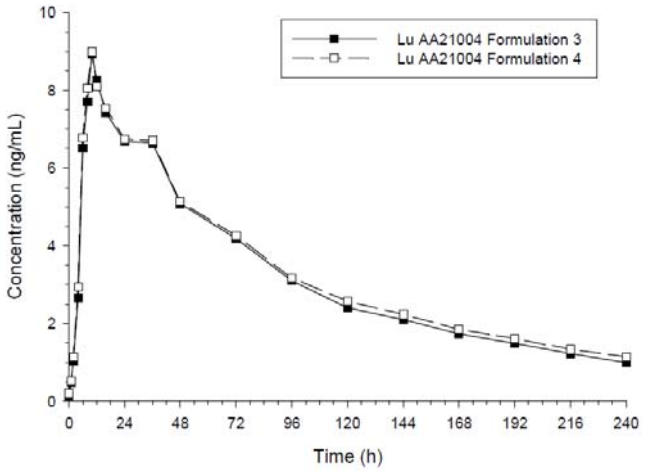
2.5.7 Is there evidence for excretion of parent drug and/or metabolites into bile?

Yes, there is evidence for the excretion of parent drug and metabolites into the bile. The mean recovery of total radioactivity in feces was 26% following a single dose of 50 mg 14C-vortioxetine to healthy male subjects [Study 10477]. The predominant component in the fecal samples was Lu AA34443, which constituted 92% of the 0-120 hour fecal radioactivity or 43% of total radioactivity recovered. Only negligible amounts of vortioxetine and metabolite Lu AA25790 were excreted in feces and accounted for 1.6% and 2.4% of the quantified material, respectively.

2.5.8 Is there evidence for enterohepatic recirculation for parent and/or metabolites?

Some of the studies, such as the second peak shown in Figure 8, suggest that there is the potential for enterohepatic recirculation for vortioxtine in humans.

Figure 8. Mean Vortioxetine Plasma Concentrations Over Time: Formulation 4 vs Formulation 3 (Fasted) for study 123.



2.5.10 What are the characteristics of drug excretion in urine?

Unchanged vortioxetine was not detected in urine. Lu AA34443 was excreted both in urine and in feces and accounted for 80% of the quantified material. M4(b) was excreted in urine only and accounted for 17% of the quantified material.

2.5.11 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

See section 2.3.3.4

2.5.12 How do the PK parameters change with time following chronic dosing?

The clearance (CL/F), volume of distribution (V), and time to maximal concentration (Tmax) are similar following single and multiple doses. Therefore the pharmacokinetic parameters do not change appreciably from single to multiple dosing (Table 24 and Table 25).

Table 24. Single-Dose Pharmacokinetic Parameters of Lu AA21004 in Young Male Subjects: Study 10272

	Dose of Lu AA21004				
	10 mg N=6	20 mg N=6	30 mg N=6	50 mg N=6	75 mg N=6
Parameter	Mean (%CV)				
AUC(0-t) (ng·hr/mL) (a)	157 (77)	282 (24)	324 (28)	805 (21)	1183 (38)
AUC(0-inf) (ng·hr/mL) (a)	282 (88) (b)	349 (30)	379 (37)	999 (30)	1743 (70)
Cmax (ng/mL) (a)	2.70 (37)	5.69 (18)	7.10 (15)	15.4 (11)	21.3 (23)
Tmax (hr) (c)	8.0 (8.0, 36.0)	8.0 (8.0, 8.0)	8.0 (6.0, 8.0)	8.0 (4.5, 12.0)	10.0 (8.0, 12.0)
T1/2 (hr) (d)	59.2 (44) (b)	45.9 (23)	37.1 (31)	46.0 (21)	57.1 (60)
CL/F (L/hr)	50.7 (45) (b)	62.4 (35)	86.7 (30)	53.6 (27)	57.6 (46)
Vz/F (L)	3697 (30)	3871 (12)	4325 (13)	3392 (9)	3772 (18)

Table 25. Multiple-Dose Pharmacokinetic Parameters of Lu AA21004 in Young and Elderly Male and Female Subjects Days 16-25: Study 10467

	Dose of Lu AA21004 (a)								
	2.5 mg Young Female N=8 (b)	5 mg Young Female N=8 (c,d,e)	20 mg Elderly Male N=2	20 mg Elderly Female N=6	20 mg Young Male N=6	10/20/40 mg Young Female N=8 (d)	40 mg Young Male N=6	40 mg Young Female N=6 (e)	60 mg Young Male N=6
Parameter	Mean (%CV)								
AUC(0-24) (ng·hr/mL) (f)	64.2 (48)	132 (20)	478 (NA)	707 (33)	361 (35)	928 (33)	922 (46)	1176 (16)	1543 (16)
Cmax (ng/mL) (f)	3.39 (42)	6.39 (16)	26.2 (NA)	37.3 (33)	19.2 (34)	48.7 (29)	47.2 (40)	63.9 (19)	84.4 (12)
Tmax (hr) (g)	7.0 (7.0, 10.0)	7.9 (5.0, 10.0)	8.0 (8.0)	7.0 (7.0, 10.0)	7.0 (5.0, 8.0)	5.0 (4.0, 8.0)	8.0 (6.0, 10.0)	6.0 (5.0, 7.0)	7.0 (4.0, 8.0)
T1/2 (hr)	41.0 (NA)	39.3 (40)	76.7 (NA)	87.4 (26)	51.2 (19)	56.9 (32)	67.6 (44)	52.2 (24)	69.3 (20)
CL/F (L/hr) (h)	47.9 (50)	39.2 (22)	44.4 (34)	32.7 (52)	61.8 (36)	47.4 (35)	50.7 (40)	34.7 (18)	39.7 (16)
Vz/F (L) (h)	3594 (77)	2147 (22)	4699 (8)	3706 (19)	4340 (21)	3618 (19)	4298 (15)	2555 (13)	3990 (27)
AI	5.46 (34)	5.35 (14)	5.25 (NC)	6.82 (29)	4.16 (18)	4.29 (13)	4.71 (30)	4.78 (23)	4.98 (10)

2.5.13 Is there evidence for a circadian rhythm of the PK?

The PK profile of Lu AA21004 was not evaluated by dosing at different times of the day.

2.6 Intrinsic Factors

2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, Cmax, Cmin) in subjects and how much of the variability is explained by the identified covariates?

The major intrinsic factors investigated for impact on the inter-subject variability in exposure (AUC, Cmax, Cmin) in subjects was age, gender, race, renal function. However, none of these factors had a significant influence on inter-subject variability (Figure 9 and Figure 10). The same is true for mild and moderate hepatic failure but since severe hepatic failure was not studied it could be an important covariate for inter-subject variability.

Figure 9. Impact of Age, Gender, and Race on the Multiple-dose Pharmacokinetics of Vortioxetine - Study 111

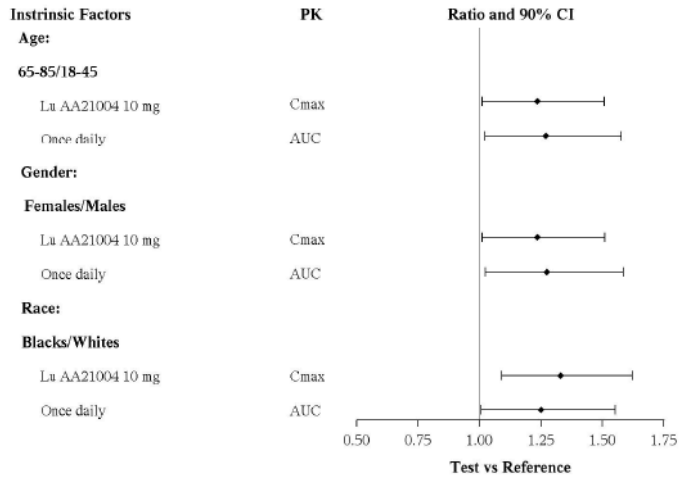
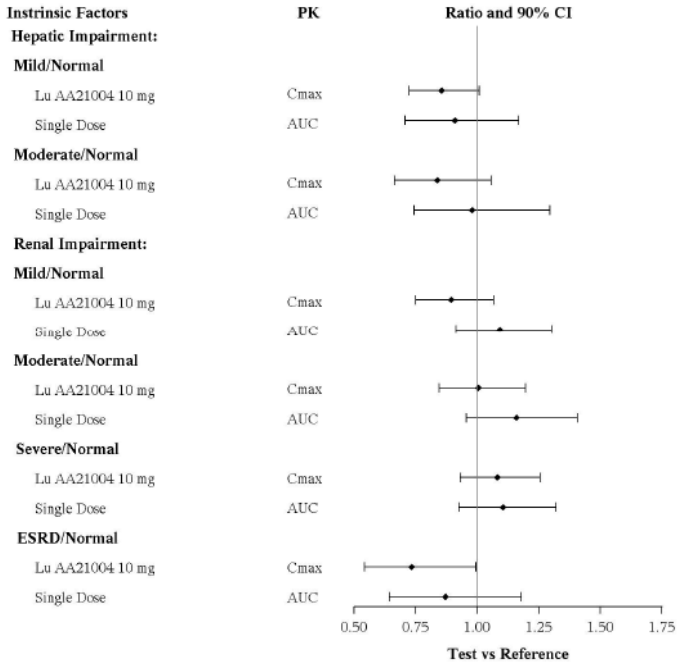


Figure 10 . Impact of Hepatic or Renal Impairment on the Single-dose Pharmacokinetics of Lu AA21004 - Studies 114 and 112



2.6.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

No dose adjustment is needed based on race, gender, and age of the patients. In addition, no additional dose adjustment in patients with mild to moderate hepatic impairment or in patients with mild to end stage renal impairment is necessary.

2.6.2.1 Severity of Disease State

No information was supplied by the firm in the NDA to address this issue.

2.6.2.2 Body Weight

See 2.5.2 for an explanation.

2.6.2.3 Elderly

See 2.6.2

2.6.2.4 Pediatric Patients

No pediatric studies were conducted by the firm.

2.6.2.5 Race/Ethnicity

See 2.6.2

2.6.2.6 Renal Impairment

See 2.6.2

2.6.2.7 Hepatic Impairment

See 2.6.2

2.6.2.8 What pregnancy and lactation use information is available?

No pregnancy and lactation information is available.

2.6.3 Does genetic variation impact exposure and/or response?

No definitive conclusion can be drawn on whether genetic variation impact vortioxetine exposure based on existing data. The firm collected genetic information for CYP2C9, CYP2C19 and CYP2D6 in amongst of the intrinsic factor studies. However in every case the number of poor metabolizers is small (e.g.N=2) which makes reaching any conclusion quite tenuous.

2.7 Extrinsic Factors

2.7.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

In Studies 10291 and 12424, the enzymes involved in the metabolism of vortioxetine and Lu AA34994 (hydroxy-intermediate for Lu AA34443) were investigated *in vitro* using recombinant CYP isozymes and flavin-containing monooxygenase 3, human liver microsomes, and human liver S9 fraction. The results suggested that several CYP isozymes were

involved in the metabolism of vortioxetine. CYP2D6 was responsible for the formation of Lu AA34994 and Lu AA39835 with some contribution from CYP2C9. The formation of Lu AA25790 was catalyzed by CYP3A4/5 and CYP2A6 with some contribution from CYP2C8. The formation of the intermediate Lu AE22404 was catalyzed by CYP2C9 and CYP2C19 with CYP2B6 contributing to a minor extent.

2.7.2 Is the drug a substrate of CYP enzymes?

See 2.7.1

2.7.3 Is the drug an inhibitor and/or an inducer of enzymes?

Vortioxetine does not appear to be an inhibitor or an inducer of CYP enzymes.

In Study 552-823, the inhibition of the human CYP isozymes CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 by vortioxetine or its metabolites (Lu AA34443, Lu AA25790, Lu AA34994, and Lu AA39835) were investigated using pooled human liver microsomes and CYP isoenzyme-specific probe substrates. All estimated [I]/Ki ratios were much smaller than 0.1, which indicates a very low potential for clinically relevant CYP inhibition by vortioxetine or any of the tested metabolites (Table 26).

Table 26 . Inhibitory Ki Constants and Estimated [I]/Ki Ratios for Vortioxetine and Metabolites for Different CYP Isozymes – Studies 552-823 and 12742

Study	CYP	Compound	Ki (μM)	Ki (ng/mL) (a)	[I]/Ki (b)
552-823	2C19	Lu AA39835	<1	<314	>0.004
	2C9	Lu AA21004	~15-30	~4477-8754	0.004-0.007
	2C9	Lu AA39835	~8	~2716	0.0004
12742	2C8	Lu AA21004	9.34	2788	0.012
	2C8	Lu AA34443	4.24	1393	0.024

In Study 12089, vortioxetine and the metabolite Lu AA34443 were tested as potential inducers of CYP expression in human hepatocytes. Vortioxetine (<2.54 μM, which corresponds to <7600 ng/mL) and Lu AA34443 (<20 μM, which corresponds to <6600 ng/mL) had little or no induction potential (defined as <2-fold effect on activity or messenger ribonucleic acid [mRNA] levels) of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4/5. The relative effectiveness of vortioxetine compared with the positive controls was negligible (<7%) at all concentrations examined.

2.7.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

Vortioxetine is considered as a poor Pgp substrate but not an inhibitor of PgP.

In Study 12814, bidirectional transport was investigated in vitro using multi-drug resistant protein-transfected Madin-Darby canine kidney (MDR1-MDCK) cells to determine whether vortioxetine in concentrations up to 20 µM (approximately 6000 ng/mL) is a Pgp substrate. The results indicated that Pgp may represent an efflux pathway for vortioxetine; however, vortioxetine is considered a poor Pgp substrate as the efflux ratio was low (approximately 3) compared with the Pgp substrate digoxin (efflux ratio above 100).

The ability of vortioxetine, in concentrations up to 10 uM, to inhibit Pgp transport was evaluated in human colonic adenocarcinoma (Caco-2) cell monolayers. The systemic efflux inhibition potential of Lu AA21004 is considered low ([I]1/IC50 <0.1).

2.7.5 Are there other metabolic/transporter pathways that may be important?

The firm has not conducted formal in vitro studies to investigate if other metabolic/transporter pathways may be important.

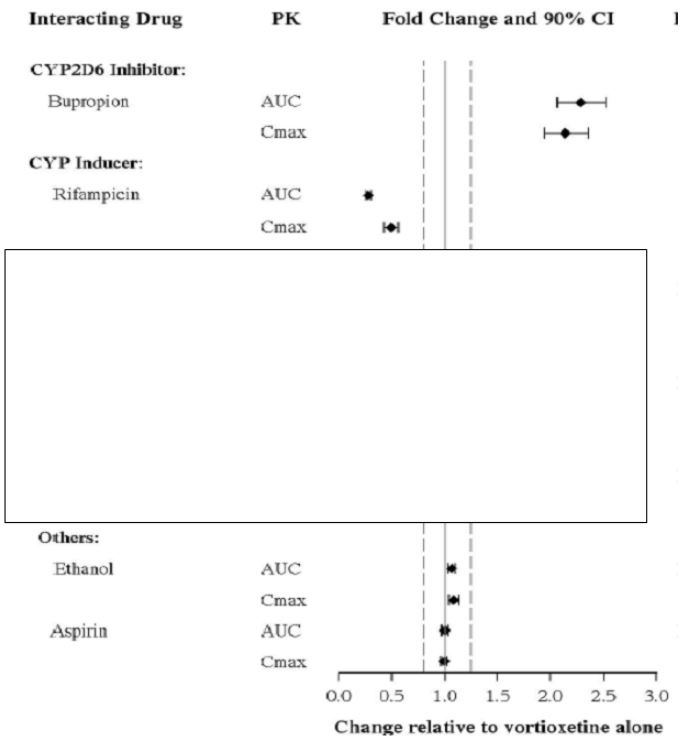
2.7.6 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

See section 2.7.1

2.7.7 What are the drug-drug interactions?

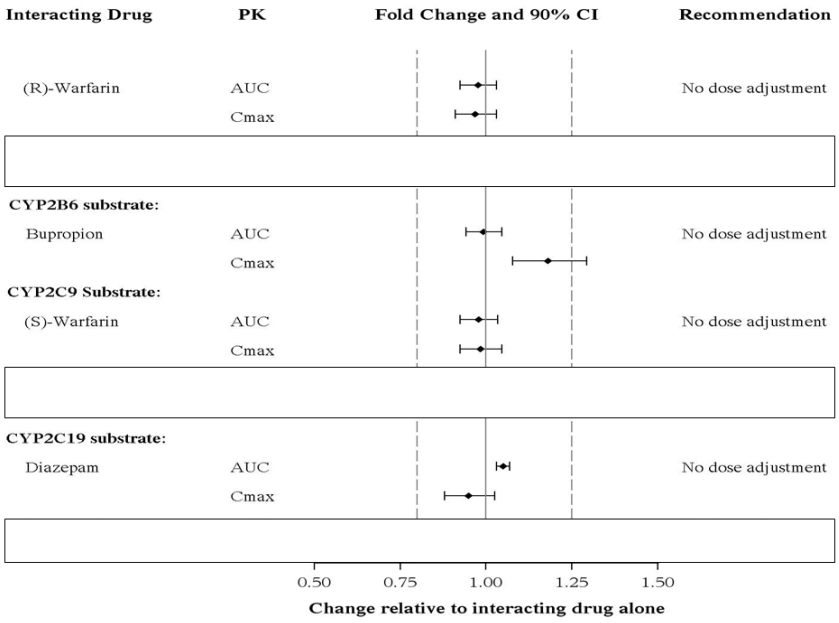
The impact of coadministered drugs on the pharmacokinetics of vortioxetine is summarized in Figure 11. Based on the observed results, a dose decrease may be needed whenever vortioxetine is taken with a potent CYP2D6 inhibitor, such as bupropion (i.e., take one-half the dose). On the other hand, vortioxetine dose should be increased by 3 fold when voritoxetine is administered with strong CYP inducers (e.g.Rifampacin).

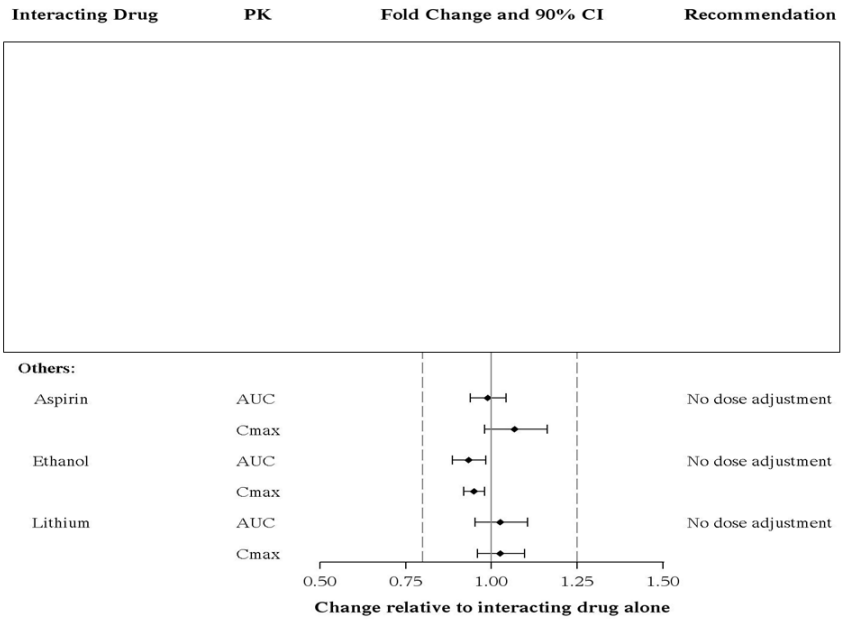
Figure 11. Impact of Co-administered Drugs on the Pharmacokinetics of Vortioxetine



The impact of vortioxetine on the pharmacokinetics of coadministered drugs is summarized in Figure 12. No dose adjustment on the coadministered drugs is needed when vortioxetine is coadministered with a CYP2B6 substrate (e.g, bupropion), a CYP2C9 substrate (e.g., S-warfarin), a CYP2C19 substrate (e.g., diazepam), a CYP3A substrate (e.g., midazolam), aspirin, ethanol, R-warfarin, or lithium.

Figure 12 . Impact of Vortioxetine on the Pharmacokinetics of co-administered Drugs





2.7.8 Does the label specify co-administration of another drug?

Coadministration of other drugs with Lu AA21004 are not specified in the proposed label.

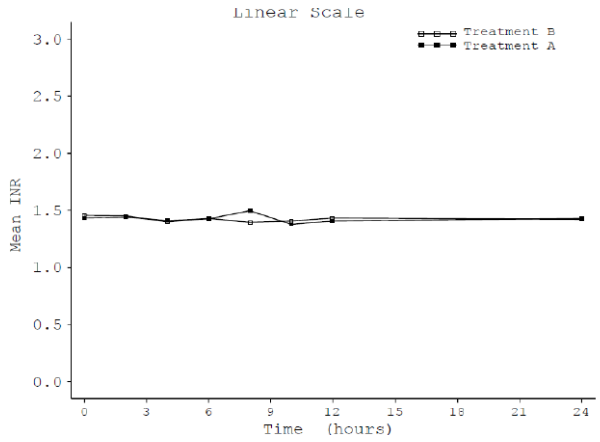
2.7.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

In vitro studies indicate that vortioxetine is a 5-HT3, 5-HT7, and 5-HT1D receptor antagonist, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist, and inhibitor of the serotonin (5-HT) transporter (5-HTT).Adverse reactions, some of which are serious or fatal, can develop in patients who use Monoamine Oxidase Inhibitor (MAOIs) or who have recently discontinued MAOI therapy and started treatment with a serotonergic antidepressant(s), or who have recently had Selective Serotonin Reuptake Inhibitor (SSRI) or Serotonin Norepinephrine Reuptake Inhibitor (SNRI) therapy discontinued prior to initiation of an MAOI.

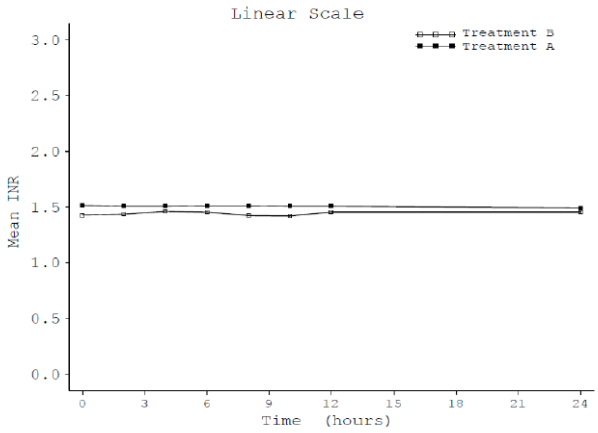
The firm studied the interaction between vortioxetine and warfarin, an oral anticoagulant. The study was designed to compare matching placebo of vortioxetine in combination with stable doses (1-10 mg) of warfarin versus vortioxetine (10 mg) coadministered with stable doses of warfarin (1- 10 mg) for 14 days. There were no meaningful differences in

International Normalized Ratio (INR) or prothrombin times between the groups on Day 14 (Figure 13).

Figure 13. Mean INR Profile for Day -1 (A) versus Day 14 (B)



(A)



(B)

It has been reported that there was a potential increased risk of gastrointestinal bleeding associated with SSRIs, when an SSRI is taken concurrently with aspirin or another non-steroidal anti-inflammatory drug (NSAID). The study was designed to compare aspirin (150 mg QD) coadministered with vortioxetine (10 mg QD) versus with placebo over 6 days. Arachionic acid induced platelet aggression, adenosine diphasphate induced platelet aggregation, and collagen induced platelet aggregation were compared between the two treatment groups with no apparently meaningful differences identified.

2.8 General Biopharmaceutics

IR Product

2.8.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Solubility:

Solubility of vortioxetine is shown in Table 27.

Table 27 .Solubility of Vortioxetine-HBr at 37ºC

Buffer	pH	Solubility (Free Base; mg/mL)
0.1 N HCl	1	0.8
50 mM acetate	4.5	2.4
50 mM phosphate (a)	6.8	0.078
50 mM phosphate (a)	7.5	0.054
50 mM TRIS (a)	6.8	0.57

Dissolution:

The compound dissolved rapidly [redacted] (b) (4) in 15 minutes) in 0.1 N HCl.

Permeability:

In vitro permeability studies were not conducted due to the non-specific binding. However 59% of radioactivity was recovered in urine in a mass balance study in combination with an absolute bioavailability of 75% suggests that vortioxetine has medium permeability.

Based upon the available data, vortioxetine appears to be a BCS class 3 (i.e., High Solubility – Low Permeability) compound.

2.8.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

The proposed to-be-marketed formulation (Formulation 4) is the formulation used in the current phase 3 studies initiated after March 2010. Formulation 3 was used in clinical trials initiated between June 2007 and March 2010. Bioequivalence between Formulation 3 and 4 was demonstrated in Studies123 (Table 28).

Table 28. Statistical Analysis of Plasma Pharmacokinetic Parameters Following Administration of Lu AA21004 20 mg Formulation 4 vs Formulation 3 in the Fasted State

Analyte Parameter (units)	Relative Bioavailability LS Mean Reg A (a)	 LS Mean Reg B (a)	 Point Estimate of Ratio (Regimen B/Regimen A) ×100 (b)	 90% CI×100 (c)
Lu AA21004				
AUC(0-tlqc) (ng·hr/mL)	606.58	612.04	100.9	(96.92, 105.05)
AUC(0-inf) (ng·hr/mL)	664.56	685.17	103.1	(98.64, 107.76)
Cmax (ng/mL)	8.02	7.98	99.44	(95.36, 103.70)

2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

There is no effect of food on the bioavailability of vortioxetine. A food effect study was conducted when 20 mg to-be-marked formulation (Formulation 4) was administered with or without a high-fat and high-calorie breakfast. The results shown in Table 29, indicated no food effect on vortioxetine absorption.

Table 29. Statistical Analysis of Plasma Pharmacokinetic Parameters Following administration of vortioxetine 20 mg formulation 4 in the fed vs fasted state: Study 123

Analyte Parameter (units)	Relative Bioavailability LS Mean Reg B (a)	 LS Mean Reg C (a)	 Point Estimate of Ratio (Regimen C/Regimen B) ×100 (b)	 90% CI×100 (c)
Lu AA21004				
AUC(0-tlqc) (ng·hr/mL)	612.04	643.73	105.18	(101.02, 109.50)
AUC(0-inf) (ng·hr/mL)	685.17	705.54	102.97	(98.52, 107.63)
Cmax (ng/mL)	7.98	8.12	101.8	(97.63, 106.16)
Lu AA34443				
AUC(0-tlqc) (ng·hr/mL)	353.49	371.01	104.95	(100.31, 109.81)
AUC(0-inf) (ng·hr/mL)	386.75	402.96	104.19	(99.65, 108.94)
Cmax (ng/mL)	8.65	8.55	98.85	(92.12, 106.08)
Lu AA39835				
AUC(0-tlqc) (ng·hr/mL)	15.59	17.18	110.17	(103.03, 117.80)
AUC(0-inf) (ng·hr/mL)	20.80	21.86	105.09	(99.54, 110.94)
Cmax (ng/mL)	0.16	0.17	106.8	(100.00, 114.07)

2.8.4 Was the bioequivalence of the different strengths of the to-be-marketed formulation tested? If so, were they bioequivalent or not?

Yes, the 5 mg strength of the to-be-marketed formulation was tested in a bioequivalence study. The results showed that 4 tablets of 5 mg strength are bioequivalent to one 20 mg tablet. A biowaiver was granted between the 10 to 20 mg strengths.

2.8.5 If unapproved products or altered approved products were used as active controls, how is BE to the to-be-marketed product demonstrated? What is the link between the unapproved/altered and to be marketed products?

No unapproved products or altered approved products were used.

2.9 Analytical Section

2.9.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

A liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) method was used to analyze the plasma samples from the clinical studies. The method used for the clinical studies was solid phase extraction (SPE) followed by liquid chromatography (LC) based on cation exchange chromatography and tandem mass spectrometric detection (MS/MS), with the mass spectrometer operated in the Multiple Reaction Monitoring mode with positive ion electrospray.

2.9.2 Which metabolites have been selected for analysis and why?

Lu AA34443 and Lu AA39835 were selected for analysis. Lu AA34443 is a major, pharmacologically inactive metabolite, and Lu AA39835 is a minor, active metabolite that does not appear to cross the blood-brain barrier.

The other 4 metabolites(M3 ~8%), (M4(b)~19%), (M12 ~36%), (M11 ~ 8%) identified in human plasma are all glucuronide conjugates. Their precursors are not considered pharmacologically active in the central nervous system. In addition, glucuronidation increases water solubility and decreases brain penetration. Therefore the 4 metabolites are less likely to contribute to the pharmacological activity in vivo and hence were not selected for analysis.

2.9.3 For all moieties measured, is free, bound, or total measured?

Total drug was analyzed in the plasma for the parent drug. This is due to the fact that the drug is 98% protein bound.

The ex vivo protein binding of 14C-Lu vortioxetine in plasma was determined using equilibrium dialysis in subjects with hepatic or renal impairment and their healthy control subjects in Studies 114 and 112, respectively, and the unbound plasma concentrations of vortioxetine were calculated in these 2 studies.

2.9.4 What bioanalytical methods are used to assess concentrations of the measured moieties?

Table 30 contains all of the relevant bioanalytical assay and assay qualification information. Acceptance of assay results for clinical pharmacological studies with identified deficiencies will depend upon the final OSI report.

Table 30. Summary of Analytical Methods.

Parameter	Lu AA21004 ng base/mL	Lu AA34443 ng base/mL	Lu AA39835 ng base/mL
Method	LC\ Mass Spectrometric \ Mass Spectrometric Detection	LC\ Mass Spectrometric \ Mass Spectrometric Detection	LC\ Mass Spectrometric \ Mass Spectrometric Detection
Number of Freeze-thaw	3 Cycles-24 h QC's 0.2 and 60ng/ml	3 Cycles-24 h QC's 0.5 and 150 ng/mL	3 Cycles-24 h QC's 0.1 and 30 ng/mL
Benchtop Stability at RT	0.2 and 60ng/ml-24 hrs	0.5 and 150 ng/mL-24hrs	0.1 and 30 ng/mL-24 hrs
Long term at –20° C	19 months	19 months	19 months
Extract Stability	70 h	70 h	70 h
Extraction Recovery	97.9 - 104	96.9 - 102	95.5 - 97.5
Carryover single injection of control matrix after each ULOQ calibration standard.	8.71% 8.97%	12%	0%

Parameter	Lu AA21004 ng base/mL	Lu AA34443 ng base/mL	Lu AA39835 ng base/mL
Method	LC-MS/MS	LC-MS/MS	LC-MS/MS
Sensitivity/LOQ	0.08 ng/mL	0.2 ng/mL	0.04
Linearity (Standard curve samples)	0.08,0.2,0.8,4 16,40,60,80	0.2,0.5,2,10,40 100,150,200	0.04,0.1,0.4,2 8,20,30,40
Quality Control (QC) Samples	0.08, 80 ng/mL	0.2, 200 ng/mL	0.04, 40 ng/ml
Precision of Standards (%CV)	3.2 to 7.5%	3.3 to 7.1%	2.4-4.55%
Precision of QC Samples (%CV)	2-3.7%	1.4-4.28%	1.4-5.7%
Accuracy of Standards (%)	-1.0 to 2.6%	128%-105%	97-103%
Accuracy of QC Samples (%)	92-109%	94-109%	93-113%

2.9.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

The analytes measured, their concentration ranges, and their curve fitting techniques for each bioanalytical methods are presented in Table 31.

Table 31: Concentration Ranges and Curve-Fitting Techniques for Bioanalytical Assays

Method	Analyte	Concentration Range of Calibration Curve
10395	Lu AA21004	0.4 to 100 (1/x weighted linear regression)
	Lu AA34443	0.8 to 200 (1/x weighted linear regression)
10874	Lu AA21004	0.4 to 100 (1/x weighted linear regression)
	Lu AA34443	2.0 to 500 (1/x weighted linear regression)
11939 + Addendum 1	Lu AA21004	0.08 to 80 ($1/x^2$ weighted linear regression)
	Lu AA34443	0.2 to 200 ($1/x^2$ weighted linear regression)
	Lu AA39835	0.04 to 40 ($1/x^2$ weighted linear regression)
LCMSC525	Lu AA21004	0.08 to 80 (quadratic, 1/concentration squared weighted, least-squares regression)
	Lu AA34443	0.2 to 200 (quadratic, 1/concentration squared weighted, least-squares regression)
	Lu AA39835	0.04 to 40 (quadratic, 1/concentration squared weighted, least-squares regression)
LuAA21004/00009	Lu AA21004	0.08 to 80 ($1/y^2$ weighted least squares regression)
	Lu AA34443	0.2 to 200 ($1/y^2$ weighted least squares regression)
	Lu AA39835	0.04 to 40 ($1/y^2$ weighted least squares regression)

2.9.5.1 What are the lower and upper limits of quantitation?

Lower limit of quantitation, upper limit of quantitation, and upper limit of quantitation for dilution for bioanalytical methods are summarized in Table 32.

Table 32: Lower Limit of Quantitation, Upper Limit of Quantitation, and Upper Limit of Quantitation for Dilution for the Bioanalytical Methods

Method	Analyte	LLOQ (ng/mL)	ULOQ (ng/mL)	ULOQ for Dilution (ng/mL)
10395	Lu AA21004	0.4	100	1000
	Lu AA34443	0.8	200	2000
10874	Lu AA21004	0.4	100	1252
	Lu AA34443	2	500	6248
11939 + Addendum 1	Lu AA21004	0.08	80	800
	Lu AA34443	0.2	200	2000
	Lu AA39835	0.04	40	400
LCMSC525	Lu AA21004	0.08	80	160
	Lu AA34443	0.2	200	400
	Lu AA39835	0.04	40	80
LuAA21004/00009	Lu AA21004	0.08	80	200
	Lu AA34443	0.2	200	500
	Lu AA39835	0.04	40	100

2.9.5.2 What are the accuracy, precision, and selectivity at these limits?

Refer to 2.9.4

2.9.5.3 What is the sample stability under conditions used in the study?

Sample stability and storage conditions for sample clinical pharmacology studies are summarized in Table 33.

Table 33. Analytes, Temperatures, and Duration of Stability

Analyte	Temperature (°C)	Duration Studied	Report
Lu AA21004	-20	8 months	11879
Lu AA34443	-20	8 months	11879
Lu AA39835	-20	8 months	11879
Lu AA21004	-80	8 months	11879
Lu AA34443	-80	8 months	11879
Lu AA39835	-80	8 months	11879
Lu AA21004	-80	8 weeks	10396
Lu AA34443	-80	8 weeks	10396
Lu AA21004	-20	26 weeks	10848
Lu AA34443	-20	26 weeks	10848
Lu AA21004	-80	26 weeks	10848
Lu AA34443	-80	26 weeks	10848
Lu AA21004	-20	357 days	LCMSC 525 Validation Report Addendum I
Lu AA34443	-20	357 days	LCMSC 525 Validation Report Addendum I
Lu AA39835	-20	357 days	LCMSC 525 Validation Report Addendum I
Lu AA21004	-70	357 days	LCMSC 525 Validation Report Addendum I
Lu AA34443	-70	357 days	LCMSC 525 Validation Report Addendum I
Lu AA39835	-70	357 days	LCMSC 525 Validation Report Addendum I
Lu AA21004	-20	365 days	Lu AA21004/10663
Lu AA34443	-20	365 days	Lu AA21004/10663
Lu AA39835	-20	365 days	Lu AA21004/10663
Lu AA21004	-80	365 days	Lu AA21004/10663
Lu AA34443	-80	365 days	Lu AA21004/10663
Lu AA39835	-80	365 days	Lu AA21004/10663

2.9.5.4 Are there any analytical issues identified? If so, what is the status?

The firm informed the agency at the IND stage that pharmacokinetic samples from a total of 12 clinical studies analyzed by (b) (4) an analytic CRO, were identified with various misconducts and deficiencies. The affected studies include 1 relative BA and food effect study (Study 106), 4 extrinsic factor studies (Study 101, 102, 103, and 11826A), 2 PET scan studies (Study 10985 and 12260A), and 5 Phase 2/3 studies (Study 11492A, 11984A, 11985A, 11492C, 11984B). OCP, through DPP, requested an OSI analytical site inspection when the NDA was submitted. It has been agreed between OCP and OSI that the inspection should focus on the relative BA and food effect study and 4 extrinsic factor studies, which contain key clinical pharmacology information for vortioxetine and its metabolites. The pharmacokinetic information obtained from the 2 PET studies and 5 phase 2/3 studies should not be the focus of the inspection and hence would not be applied for major decisions.

With the identified deficiencies from the 5 clinical pharmacology studies, OCP evaluated the potential impact of carryover effect. OSI inspection will address other deficiencies, (b) (4)

(b) (4)

For the carryover effect, OCP found the potential impact of worst-case carryover effect (i.e., low concentration samples analyzed immediately after a high concentration standard) is about 3.42% (i.e., mistakenly increase the concentration readings by 3.42%) and therefore concluded

that the overall impact of the carryover effect is small and should not alter the results/conclusions of the clinical pharmacology studies being affected.

OSI performed inspection between May 5-16, 2013 and issued a 483 form on May 17, 2013 with additional issues identified with the 5 clinical pharmacology studies. At the current stage, the firm has not submitted their responses and remedial actions. Therefore, OCP decided to exclude the pharmacokinetic information from the 5 clinical pharmacology studies in the current review. Further actions related to the results/conclusions of the 5 clinical pharmacology studies would rely on OSI's assessment on the future actions from the sponsor.

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/s/

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06/04/2013

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BIOPHARMACEUTICS REVIEW

Office of New Drug Quality Assessment

Application No.:	NDA 204-447 (000)	**Reviewer:** Houda Mahayni, Ph.D.	
Division:	DPP		
Applicant:	Takeda Global Research & Development Center, Inc.	**Team Leader:** Angelica Dorantes, Ph.D.	
Trade Name:	Brintellix Tablets	**Acting Supervisor:** Richard Lostritto, Ph.D.	
Generic Name:	Vortioxetine (Lu AA21004)	**Date Assigned:**	October 10, 2012
Indication:	Treatment of major depressive disorder	**Date of Review:**	April 5, 2013
Formulation/strength	Immediate Release Film-Coated Tablet/5 mg, 10 mg, 15 mg, and 20 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Dates	Date of Consult	PDUFA DATE
	October 10, 2012	October 2, 2013

Type of Submission:	Original New Drug Application
Key review points	1. Dissolution method and acceptance criterion 2. Data supporting the acceptability of the 5 mg strength (Biowaiver) 3. Acceptability of data supporting the bridging of the proposed formulation throughout product development 4. Acceptability of data supporting the bridging of the proposed manufacturing sites

TABLE OF CONTENTS

I) SUMMARY OF BIOPHARMACEUTICS FINDINGS

Lu AA21004 (vortioxetine) is a new chemical class of psychotropics, the bis-aryl-sulfanyl amines. The proposed indication is for the treatment of major depressive disorder. Lu AA21004 was discovered and patented by H. Lundbeck and then was co-developed with Takeda. LuAA21004 is a film-coated tablet. The proposed strengths are: 5 mg, 10 mg, 15 mg, and 20 mg. The recommended starting dose in adults is 10 mg taken once daily without regard to meals.

This review focuses on the evaluation of: **1)** The acceptability of the dissolution method and acceptance criterion; **2)** Data supporting the acceptability of the 5 mg strength (biowaiver), **3)** The acceptability of data supporting the bridging throughout the LuAA21004 clinical development, and **4)** The acceptability of data supporting the bridging of the proposed manufacturing sites.

1) Dissolution Method and Acceptance Criterion:
The following dissolution method and acceptance criterion for LuAA21004 IR tablets, 5 mg, 10 mg, 15 mg, and 20 mg were proposed by the Applicant:

USP Apparatus	Paddle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
II	50 rpm	900mL	37°C	0.1 N Hydrochloric acid	Q= (b) (4) at 30 min

The proposed dissolution method is acceptable. However, the proposed acceptance criterion of Q = (b) (4) at 30 minutes is not acceptable. During the Post-Mid-Cycle meeting held on March 12, 2012, FDA requested the Applicant to tighten the acceptance criteria to Q = (b) (4) at 20 minutes. The Applicant agreed to tighten the acceptance criteria and to update the specification table and all relevant sections in the NDA. The dissolution acceptance criterion was based on the mean dissolution profiles of clinical and stability batches. The Applicant submitted sufficient information to support the discriminating ability of the dissolution method.

2) Data Supporting the Acceptability of the 5 mg strength (Biowaiver)
The Applicant developed for commercialization four immediate-release film-coated tablet strengths, 5 mg, 10 mg, 15 mg and 20 mg. Regardless of tablet strength, the tablets have the same size. The difference between tablet strengths is the amount of active drug substance (b) (4) (b) (4) to achieve final tablet weight.

During the conduct of the review, Biopharmaceutics assessed that the 5 mg strength does not qualify for a biovaiver because it is not compositionally proportional in its active and inactive ingredients to the corresponding highest strength product for which the BA/BE study was conducted, and Formulation IV (5 mg) strength was not used in clinical studies.

FDA sent information request to the Applicant on February 28, 2013, regarding the biowaiver. The Applicant responded on March 7, 2013 that a bioequivalence study (Study 14520) was conducted comparing dose strengths (5 mg and 20 mg) of Formulation IV. However, at the time of the NDA submission the study was ongoing. FDA requested the bioequivalence study report and is being reviewed by OCP. Therefore, a biowaiver assessment for the 5 mg strength is no longer needed because this strength's pharmacokinetics was characterized in vivo (Study 14520).

3) Acceptability of data supporting the bridging of the proposed formulation throughout the LuAA21004 development

Four different IR tablet formulations of Lu AA21004 were developed: Formulation I, II, III, and IV. PK studies including efficacy and safety of Lu AA21004 have been generated with Formulation I, III, and IV. Formulation II was not used in any clinical studies. The Applicant conducted two relative bioavailability studies (Study 106 and Study 123) to link formulation used throughout the different phases of drug development. Study 106 investigated the bioavailability of Formulation III (10 mg) relative to Formulation I (10 mg). Study 123 investigated the bioavailability of the commercial formulation (Formulation IV, Colored-Almond) (1x 20 mg) of LuAA21004 relative to Formulation III (2x 10 mg). These studies are being reviewed by OCP.

Although Formulation IV is identical to the intended commercial formulation, there are 3 presentations of the Formulation IV tablets. All presentations consisted of the same 150 mg core tablet with variations in the color and shape of the tablet. The commercial tablet formulation (Formulation IV, Colored-Almond) had minor modifications when compared to the Phase 3 tablet (Formulation IV, White-Round). The Phase 3 and commercial tablets are immediate release film coated tablets that differ only in the shape or tablet film coat color/composition. These changes are considered minor differences that will not affect tablet performance. Therefore, pivotal bioequivalence or dose strength equivalence studies were not needed to qualify the commercial formulation from the Phase 3 tablet, as it was established through dissolution testing in three different media that these changes are minor and do not affect the release of LuAA21004 from the drug product.

4) Acceptability of data supporting the bridging of the proposed manufacturing sites

The components and composition of Formulation IV differ between the two sites: (b) (4)

(b) (4)

In addition, there are debossing differences in Formulation IV between the registration stability batches (debossed "V20") and the commercial batches (debossed "TL" on one side of the tablet and the respective strength on the other side of the tablet).

Moreover, registration stability batches manufactured at Lundbeck, Denmark were included in clinical studies. However, process validation batches manufactured at Takeda, Japan were not included in clinical studies. The Applicant plans on using the two sites: Takeda (Osaka, Japan) and Lundbeck (Valby, Denmark) for commercial manufacturing.

The dissolution testing results in three different media established the bridge between the manufacturing sites, Lundbeck and Takeda, and confirmed that all the above changes in (b) (4) film-coat, and debossing between the two sites are minor and do not affect the release of LuAA21004 from the drug product. Therefore, it is acceptable to use Takeda, Japan site as an alternative site for commercial manufacturing.

II) RECOMMENDATION

The ONDQA-Biopharmaceutics team reviewed NDA 204-447 for Vortioxetine (Lu AA21004) IR tablets, 5 mg, 10 mg, 15 mg, and 20 mg.

The following dissolution method and dissolution acceptance criterion are acceptable.

USP Apparatus	Paddle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
II	50 rpm	900mL	37°C	0.1 N Hydrochloric acid	Q= (b) (4) at 20 min

The provided overall dissolution and other information/data supports the bridge of the proposed formulation throughout the LuAA21004 development.

The Applicant's request to use Takeda at Osaka, Japan, as an alternate site for commercial manufacturing of their product is supported by the provided information and is acceptable.

From the Biopharmaceutics perspective, NDA 204-447 for Vortioxetine (Lu AA21004) Tablets is recommended for approval.

Houda Mahayni, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

III) BIOPHARMACEUTICS ASSESSMENT-QUESTION BASED REVIEW APPROACH

A) GENERAL ATTRIBUTES

1. ***What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?***

Drug Substance

The drug substance is Lu AA21004 hydrobromide. (b) (4). The β-form is (b) (4) the one used in all the clinical studies. LuAA21004 is white and very slightly beige powder. The solubility in water was determined at ambient temperature (~ 22ºC) to be 1.7 mg LuAA21004 hydrobromide /mL giving pH =5.5 in the solution. The solubility at various pH in different buffer systems is listed in Table 1, and the corresponding solubility curve is shown in Figure 1.

Table 1: Solubility in Aqueous Solution at Ambient Temperature (~22ºC) versus pH

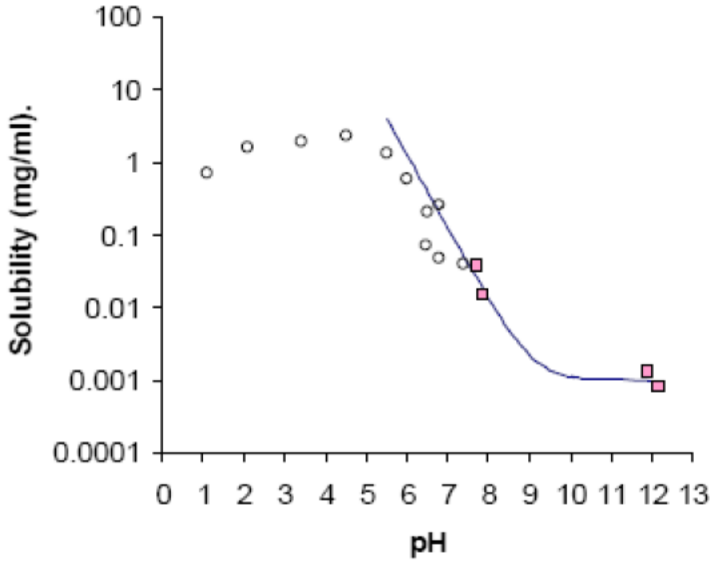
pH	Solution	Solubility (mg Lu AA21004/mL)
1.1	Lu AA21004 hydrobromide in 0.1M HCl	0.7
2.1	Lu AA21004 hydrobromide in 0.01M HCl	1.6
3.4	Lu AA21004 hydrobromide in 0.001M HCl	1.9
4.5	Lu AA21004 hydrobromide in 50mM Acetate buffer	2.3
5.5	Lu AA21004 hydrobromide in water	1.3
6.0	Lu AA21004 hydrobromide in TRIS-buffer, pH6.8	0.58
6.5	Lu AA21004 hydrobromide in ACES-buffer, pH6.8	0.2
6.8	Lu AA21004 hydrobromide in Hepes-buffer, pH6.8	0.26
6.45	Lu AA21004 hydrobromide in 50mM Phosphate buffer	0.07
6.8	Lu AA21004 hydrobromide in 100mM Phosphate buffer	0.047
7.4	Lu AA21004 hydrobromide in Phosphate buffer	0.039
7.7	Lu AA21004 free base in Phosphate buffer	0.037
7.9	Lu AA21004 free base in 0.9% NaCl	0.015
11.9	Lu AA21004 free base in 0.01M NaOH	0.0013
12.2	Lu AA21004 free base in 0.1M NaOH	0.0008

Figure 1: Solubility of LuAA21004 versus pH

-: Calculated from pKa and intrinsic solubility,

○: Measured using Lu AA21004 hydrobromide,

▭: Measured using Lu AA21004 free base



It was observed that a precipitate (a salt or complex) is formed between the phosphate buffer and LuAA21004.

The drug substance particle size has an effect on dissolution rate if large particles are used. Consequently, the Applicant decided [redacted] (b) (4) to produce batches with particle size distribution as follows: [redacted] (b) (4). The Applicant reported that with the proposed particle size distribution, no effect were seen on the critical drug product parameters as a function of particle size within the proposed limits.

Drug Product

Lu AA21004 tablets are almond shaped, biconvex, film-coated tablets. The proposed strengths are: 5 mg, 10 mg, 15 mg, and 20 mg. The tablets are the same size regardless of tablet strengths. The difference between tablet strengths is the amount of active drug substance [redacted] (b) (4) to achieve final tablet weight. The four strengths are also differentiated by tablet color and debossment.

The components and composition of the proposed commercial formulation for Lu AA21004 tablets, 5 mg, 10 mg, 15 mg and 20 mg are provided in Table 2.

Table 2: Components and Composition of Lu AA21004 Tablets, 5 mg, 10 mg, 15 mg and 20 mg

Component	Reference to Quality Standards	Function	Amount (mg) 5 mg	10 mg	15 mg	20 mg
Tablet Core						
Lu AA21004 hydrobromide (b) (4)	In-house standard	Active ingredient	6.355 (a) (5)	12.71 (a) (10)	19.065 (a) (15)	25.42 (a) (20)
Mannitol	USP					(b) (4)
Microcrystalline cellulose	NF					
Hydroxypropyl cellulose	NF					
Sodium starch glycolate (d)	NF					
Magnesium stearate	NF					
(b) (4)	USP					
	In-house standard					
	(e) In-house standard					
	(c) In-house standard					
	In-house standard					
	USP					
	USP					
	NF					
	NF					
	NF					
	USP					
	NF					
						(b) (4)

The Applicant developed four different IR tablet formulations of Lu AA21004: Formulation I, II, III, and IV. Of the four IR formulations, Formulation IV is the one identical to the intended commercial formulation. However, the Applicant made three changes to Formulation IV over the course of product development. These changes are due to variations in color and shape, as follows:

- Formulation IV, White-Round tablets: used for initial phase 3 clinical studies.
- Formulation IV, Colored-Round tablet: used in Phase 2/3 clinical studies.
- Formulation IV, Colored-Almond shape tablet: used in Phase 2/3 clinical studies. Furthermore, Formulation IV was debossed with V20 for registration stability or debossed with TL and dose for commercial (TBM) formulation.

The Applicant performed two bioequivalence studies to demonstrate equivalence between formulations. These studies are:

- Study 106: Formulation I, 10 mg vs. Formulation III, 10 mg.
- Study 123: Formulation III, 2 x 10 mg, vs. Formulation IV (Colored-Almond shape), 20 mg.

These studies are being reviewed by OCP.

2. ***Is there any information on BCS classification? What claim did the applicant make based on BCS classification? What data are available to support this claim?***

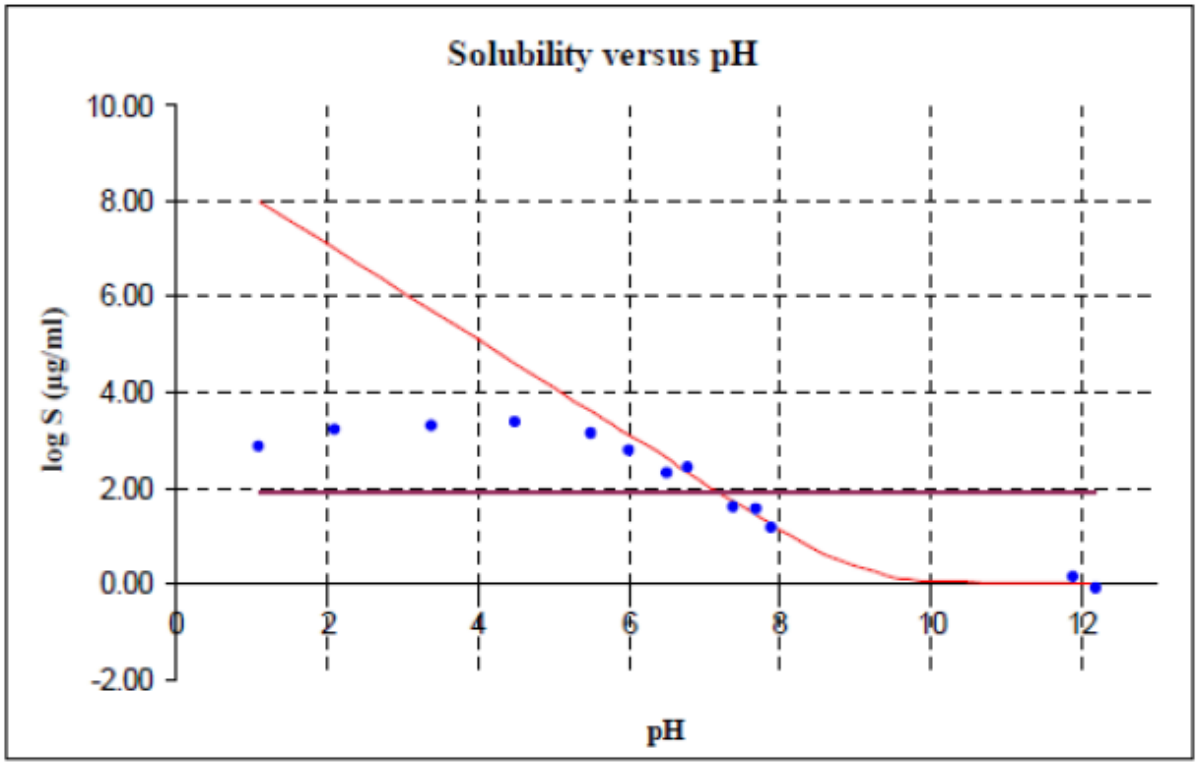
The Applicant did not provide a Biopharmaceutics Classification System (BCS) for LuAA21004 hydrobromide. However, the Applicant provided the solubility of LuAA21004 at 37ºC using different pH conditions (Table 3), and the pH solubility profile (Figure 2).

Table 3: Solubility of Lu AA21004-HBr at 37ºC

Buffer	pH	Solubility (Free Base; mg/mL)
0.1 N HCl	1	0.8
50 mM acetate	4.5	2.4
50 mM phosphate (a)	6.8	0.078
50 mM phosphate (a)	7.5	0.054
50 mM TRIS (a)	6.8	0.57

Source: Module 3.2.P.2.2.
HCl=hydrochloride, TRIS=tris(hydroxymethyl)aminomethane.
(a) Complex or salt formed with phosphate buffer; therefore, TRIS buffer was used. Refer to Module 3.2.P.2.2 for discussion of the phosphate buffer at pH 6.8 and above.
Note: Mean values are presented.

Figure 2: pH Solubility Profile of Lu AA21004 hydrobromide at 37 °C. Red (curved) line: Theoretical solubility of the compound. Straight horizontal line: Solubility needed for the highest strength (20 mg) to be soluble in 250 mL of water.



At all relevant physiologically relevant pHs (pH below 7.5), Lu AA21004 hydrobromide meet the definition of highly soluble according to the BCS definition (the solubility of the highest strength 20 mg in 250 mL of water), since the dose/solubility ratio is ≤ 250 mL (20 mg/0.08 mg/mL = 250 mL).

According to the Applicant, the in-vitro permeability of Lu AA21004 across epithelial cell monolayer was not evaluated due to large non-specific binding that prohibited achieving the required concentrations of Lu AA21004.

B) DISSOLUTION INFORMATION

B.1. DISSOLUTION METHOD

3. What is the proposed dissolution method?

The dissolution method conditions proposed as a quality control tool for LuAA21004 hydrobromide film-coated IR tablets, 5 mg, 10 mg, 15 mg, and 20 mg is summarized below:

Apparatus:	USP <711> Dissolution Apparatus 2 (paddle)
Rpm:	50 rpm
Temperature:	37°C ± 0.5°C
Dissolution medium:	0.1 N hydrochloric acid
Volume:	900 mL
Sample:	1 tablet / vessel
Sample volume(1):	10 ml, filtered through a filter (pore size 0.45 – 10 µm)
Sampling:	Profile: (5) – 10 – (15) – 20 – 30 minutes (only used for validation) Single time point: 30 minutes

(1) Note that method validation conducted with a sample volume of 1.5 mL. Routine testing of commercial product will be 10 mL.

4. What data are provided to support the adequacy of the proposed dissolution method (e.g medium, apparatus selection, etc.)?

Dissolution Method Development

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D) DISSOLUTION APPLICATIONS

D.1 BIOWAIVERS

15. Is there a request for waiver of in vivo BE data (Biowaiver)? What is/are the purpose/s of the biowaiver request/s? What data support the biowaiver request/s?

There was a biowaiver request included in the submission for the 5 mg dosage strength, but it is no longer needed because the Applicant conducted a bioequivalence study comparing the 5 mg to the 20 mg (see the answer to Question 13 above).

16. Is there any IVIVC information submitted? What is the regulatory application of the IVIVC in the submission? What data is provided to support the acceptability of the IVIVC?

There is no IVIVC data included in the submission.

D.2 SURROGATES IN LIEU OF DISSOLUTION

17. Are there any manufacturing parameters (e.g. disintegration, drug substance particle size, etc.) being proposed as surrogates in lieu of dissolution testing? What data is available to support this claim?

No, there are no manufacturing parameters being proposed as surrogates in lieu of dissolution testing.

D.3 DISSOLUTION AND QBD

18. If the application contains QbD elements, is dissolution identified as a CQA for defining design space?

No, dissolution is not identified as CQA for defining design space.

19. Was dissolution included in the DoE? What raw materials and process variables are identified as having an impact on dissolution? What is the risk assessment performed to evaluate the criticality of dissolution?

NA

20. What biopharmaceutics information is available to support the clinical relevance of the proposed design space?

NA

21. Is there any dissolution model information submitted as part of QbD implementation? What is the regulatory application of the dissolution model in the submission? What data are provided to support the acceptability of the dissolution model?

NA

Appendix

Table 1: Dissolution Data of Registration Batches 5, 10, 15, and 20 mg (n=12)

Unit: %

Time point (min)		5	10	15	20	30	45
PD 1858 (5mg)	Mean						(b) (4)
	max						
	min						
	RSD						
PD 1859 (5mg)	Mean						
	max						
	min						
	RSD						
PD 1881 (5mg)	Mean						
	max						
	min						
	RSD						
PD 1863 (10 mg)	Mean						
	max						
	min						
	RSD						
PD 1864 (10 mg)	Mean						
	max						
	min						
	RSD						
PD 1865 (10 mg)	Mean						
	max						
	min						
	RSD						
PD 1860 (15 mg)	Mean						
	max						
	min						
	RSD						
PD 1861 (15 mg)	Mean						
	max						
	min						
	RSD						
PD 1862 (15 mg)	Mean						
	max						
	min						
	RSD						

Table 1: Dissolution Data of Registration Batches, 5, 10, 15 and 20 mg (n = 12) (continued)

Unit: %

Time point (min)		5	10	15	20	30	45
PD 1855 (20 mg)	Mean						(b) (4)
	max						
	min						
	RSD						
PD 1856 (20 mg)	Mean						
	max						
	min						
	RSD						
PD 1869 (20 mg)	Mean						
	max						
	min						
	RSD						

Table 2: Dissolution Data of PV Batches (Osaka, Japan), 5, 10, 15 and 20 mg (n = 12)

Unit: %

Time point (min)		5	10	15	20	30	45
G001 (5 mg)	Mean	(b) (4)					
	max						
	min						
	RSD						
G002 (5 mg)	Mean						
	max						
	min						
	RSD						
G003 (5 mg)	Mean						
	max						
	min						
	RSD						
J001 (10 mg)	Mean						
	max						
	min						
	RSD						
J002 (10 mg)	Mean						
	max						
	min						
	RSD						
J003 (10 mg)	Mean						
	max						
	min						
	RSD						
K001 (15 mg)	Mean						
	max						
	min						
	RSD						
K002 (15 mg)	Mean						
	max						
	min						
	RSD						
K003 (15 mg)	Mean						
	max						
	min						
	RSD						

Table 2: Dissolution Data of PV Batches (Osaka, Japan) 5, 10, 15, and 20 mg (n=12) (continued)

Unit: %

Time point (min)		5	10	15	20	30	45
L001 (20 mg)	Mean	(b) (4)					
	max						
	min						
	RSD						
L002 (20 mg)	Mean						
	max						
	min						
	RSD						
L003 (20 mg)	Mean						
	max						
	min						
	RSD						

Table 3: Dissolution Data of PV Batches (Valby, Denmark), 5, 10, 15, and 20 mg (n=12)

Unit: %

Time point (min)		5	10	15	30	45	60*
2315829 (5 mg)	Mean	(b) (4)					
	max						
	min						
	RSD						
2315832 (10 mg)	Mean						
	max						
	min						
	RSD						
2315835 (15 mg)	Mean						
	max						
	min						
	RSD						
2315838 (20 mg)	Mean						
	max						
	min						
	RSD						

(*) During last 15 minutes of dissolution paddle speed was increased to 250 rpm.

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/s/

HOUDA MAHAYNI
04/05/2013

ANGELICA DORANTES
04/08/2013

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**204447**	**Brand Name**	**Brintellix**
OCP Division (I, II, III, IV, V)	**1**	**Generic Name**	**Vortioxetine**
Medical Division	Psychiatry	**Drug Class**	
OCP Reviewer	**Andre Jackson**	**Indication(s)**	**Depresssion**
OCP Team Leader	**Hao Zhu**	**Dosage Form**	**Tablet**
Pharmacometrics Reviewer	**Li Zhang**	**Dosing Regimen**	**5mg,10mg,15mg and 20 mg**
Date of Submission	**10/2/12**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**6/17/13**	**Sponsor**	**Takeda**
Medical Division Due Date	**7/17/13**	**Priority Classification**	**Normal**
PDUFA Due Date	**10/2/13**		

Summary

The purpose of this New Drug Application (NDA) is to obtain approval of Lu AA21004 5, 10, 15, and 20 mg film-coated tablets for the treatment of major depressive disorder (MDD). The efficacy and safety of Lu AA21004 in adults with MDD (including elderly subjects) have been established in short-term and long-term maintenance studies. The major claim for this product is that it is an effective treatment across doses with increased efficacy with increasing dose but with similar tolerability that gives the prescribing physician full flexibility in individualizing the dose to the patients' needs without needing to switching therapy and increasing rates of relapse.

Figure 1.a Overview of Lu AA21004 Clinical Development Program

Completed Clinical Pharmacology Studies	
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

Completed Clinical Studies in MDD	
Short-term, placebo-controlled, fixed-dose	11492A, 11984A, 305, 13267A, 315, 316, 303, 304, 317
Short-term, placebo-controlled, elderly	12541A
Long-term, placebo-controlled, relapse-prevention	11985A
Long-term, open-label, safety	11492C, 11984B, 301

Completed Clinical Studies in GAD	
Short-term, placebo-controlled, fixed-dose	308, 309, 310, 311
Long-term, placebo-controlled, relapse-prevention	12473A

Ongoing Clinical Pharmacology Studies (c)	
Japanese Food effect study	CPH-004
Polysomnographic study	14029A
Functional MRI	14137A
BE component	14520A
Pediatric PK tolerability	12708A
PK	14077A

Ongoing Clinical Studies in MDD (c)	
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

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.
(c) As of 04 May 2012.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE	**NDA**			
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			The analytical assays conducted (b) (4) for Takeda for several studies are in question due to reported assay problems(See Attached Appendix)
Tabular Listing of All Human Studies	**x**	**1**	**1**	
HPK Summary	**x**	**1**	**1**	
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**			
I. Clinical Pharmacology				
Mass balance:	**x**	**1**	**1**	
Isozyme characterization:	**x**	**1**	**1**	
Blood/plasma ratio:		**1**	**1**	
Plasma protein binding:	**x**	**1**		
Pharmacokinetics (e.g., Phase I) -	**x**			
Healthy Volunteers-				
single dose:	**x**	**1**	**1**	
multiple dose:	**x**	**1**	**1**	
Patients-				
single dose:				
multiple dose:	**x**	**1**	**1**	Relapse Study
Dose proportionality -				
fasting / non-fasting single dose:	**x**	**1**	**1**	
fasting / non-fasting multiple dose:	**x**	**1**	**1**	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**x**	**4**	**4**	
In-vivo effects of primary drug:	**x**	**7**	**7**	
In-vitro:		**2**	**2**	
Subpopulation studies -				
ethnicity:	**x**	**1**	**1**	
gender:	**x**	**1**	**1**	
pediatrics:				
geriatrics:	**x**	**1**	**1**	
renal impairment:	**x**	**1**	**1**	
hepatic impairment:	**x**	**1**	**1**	
PD -				
Phase 2:	**x**	**5**	**2**	Driving Study Warfarin Study
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**x**	**1**	**1**	
Phase 3 clinical trial:	**x**			
Population Analyses -				

Data rich:	**x**	**(26)**		Includes some phase 1 studies to be reviewed by OCP. The following studies submitted for PM analysis may have scientific integrity issues: 10985, 11826A, 12260A, and 103.
Data sparse:	**x**			
II. Biopharmaceutics				
Absolute bioavailability	**x**	**1**	**1**	
Relative bioavailability -				
solution as reference:	**x**	**1**	**1**	
alternate formulation as reference:	**x**			
Bioequivalence studies -				
traditional design; single / multi dose:		**1**	**1**	
replicate design; single / multi dose:				
Food-drug interaction studies	**x**	**1**	**1**	
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**41(OCP)**	**1**	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			The assay had compliance issues at the (b) (4) site and has to be inspected for cause

					The firm has a number of studies with compliance problems in which they have identified problematic batches. Two of these studies are LuAA21004-103 **(**The Effect of Multiple-Doses of Fluconazole, or Ketoconazole, on the Single-Dose Pharmacokinetic Profile of Lu AA21004 in Healthy Adult Subjects) and Lu AA21004_106 (A Phase 1, Open-Label, Randomized, Single-Dose, 3-Period Crossover Study to Evaluate the Effect of Food on the Pharmacokinetics of Formulation 3 of Lu AA21004 and to Determine the Relative Bioavailability of Formulation 3 to Formulation 1 of Lu AA21004 in Healthy Adult Subjects). For each study non-compliant analysis batches have been identified. For 103 they were SA001 and SA003 while for 106 they were SA027 and SA028. OCP would like the firm to repeat their analysis and delete all data from the problematic batches and prepare and submit new study results for review based only upon the other batches.
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				

9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?				x

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
___Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Clinical Pharmacologist Andre Jackson Date 10/26/12

Team Leader/Supervisor Hao Zhu, Ph.D. Date

APPENDIX

Appendix-Compliance issue studies

Extrinsic Factor Studies - Cytochrome P450 Interaction Studies

103 (5.3.3.4) DDI (ketoconazole and fluconazole) (Carryover from high standards).
11826A (5.3.3.1) DDI (omeprazole) (Carryover from high standards , Lu AA39835 only).
101 (5.3.3.4) DDI (drug cocktail) (Carryover from high standards, Lu AA34443 only).
102 (5.3.3.4) DDI (oral contraceptive) (Carryover from high standards).

Pharmacodynamic Studies

10985 (5.3.4.1) PET occupancy (5-HTT and 5-HT1A) in White subjects (Carryover from high standards and Poor or unacceptable integrations particularly for standards and QCSs., Lu AA39835 not measured in this study)

12260A (5.3.4.1) PET occupancy (5-HTT) in White and Japanese subjects (Carryover from high standards and unknown sample injections without bracketing by calibration standards). (Carryover from high standards , Lu AA34443 only)

Phase 2/3 Clinical Studies (for popPK)

11492A (5.3.5.1) 6-week, fixed-dose Lu AA21004 (5 or 10 mg), active reference (venlafaxine 225 mg) (Carryover from high standards , unknown samples were re-injected after the end of an analytical batch without having been bracketed by calibration standards or QCSs).

11984A (5.3.5.1) 8-week, fixed-dose Lu AA21004 (2.5, 5, or 10 mg), active reference (duloxetine 60 mg) (Carryover from high standards , Samples not bracketed by QCSs or calibration standards.).

11985A (5.3.5.1) 12-week, open-label, flexible-dose Lu AA21004 (5 or 10 mg), followed by 24- to 64-week, randomized, double-blind, placebo-controlled, fixed-dose Lu AA21004 (5 or 10 mg) (Carryover from high standards , re-injections without QC samples).

11492C (5.3.5.2) Lu AA2l 004 (5 or 10 mg), extension to Study 11492A

(Carryover from high standards, analysis stopped due to hardware or software failure).

11984B (5.3.5.2) Lu AA2I004 (2.5, 5, or 10 mg), extension to Study 11984A (Carryover from high standards).

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/s/

ANDRE J JACKSON
11/15/2012

HAO ZHU
11/15/2012

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	204-447
Submission Date	October 2, 2012
Product name, generic name of the active	Brintellix (Vortioxetine)
Dosage form and strength	Film-coated tablets, 5 mg, 10 mg, 15 mg, and 20 mg
Indication	Treatment of major depressive disorder
Applicant	Takeda Global Research & Development Center
Clinical Division	DPP
Type of Submission	Original New Drug Application
Biopharmaceutics Reviewer	Houda Mahayni, Ph.D.
Biopharmaceutics Team Leader (Acting)	Sandra Suarez, Ph.D.

The following parameters from the ONDQA Quality (CMC and Biopharmaceutics) joint filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS
A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING

	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?	x		The following dissolution method is proposed for routine testing: Apparatus 2 (Paddle), 900 mL of 0.1 N Hydrochloric acid, 50 rpm, 37° C, sampling times 10, 20, and 30 minutes.
2.	Is the dissolution test part of the DP specifications?	x		The Applicant listed two dissolution specifications: the first specification is for process validation (NLT (b) (4) (Q) of the labeled amount dissolved in 30 minutes), and the second specification is for registration stability batches (NLT (b) (4) (Q) dissolved in 30 minutes).
3.	Does the application contain the dissolution method development report?	x		
4.	Is there a validation package for the analytical method and dissolution methodology?	x		The validation of the HPLC method is included.
5.	Does the application include a biowaiver request?	x		The Applicant performed BE study to link the Phase 3 (Formulation III) and commercial formulation (Formulation IV) using the highest strength 20 mg and is requesting a biowaiver for the three lower strengths (5, 10, and 15 mg).
6.	Does the application include an IVIVC model?		x	

7.	Does the application include information/data on in vitro alcohol dose-dumping potential?		x	
8.	Is information such as BCS classification mentioned, and supportive data provided?		x	The Applicant submitted solubility and permeability information. However, there was no claim made that the compound is BCS Class I.
9.	Is information on mixing the product with foods or liquids included?		x	
10.	Is there any in *vivo* BA or BE information in the submission?	x		BE Study# 123 was performed to link (formulation III, Phase 3) and (formulation IV, commercial) and will be reviewed by OCP.

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
11.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		• The NDA is fileable from Biopharmaceutics Perspective. • The acceptability of the proposed dissolution method and acceptance criteria will be a review issue. • The adequacy of the data provided to support the bridging between (formulation III) and (formulation IV) formulations will be a review issue. • The acceptability of the biowaiver for the three lower strengths (5, 10, 15 mg) will be a review issue.
12.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not Applicable.
13.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not Applicable.

14.	Are there any **potential review** issues identified?	x		• The Applicant plans to use two commercial manufacturing sites (Lundbeck, Denmark, and Takeda, Japan). • Both sites plan to manufacture the commercial formulation (formulation IV). However, there are two differences in the components and composition between the two sites: Lundbeck uses [(b) (4)] (in only 5, 10, 15 mg), and unspecified amount (qs) of [(b) (4)] Whereas, Takeda uses [(b) (4)] • Also, there is debossing differences in formulation IV: debossed V20 for registration stability or debossed TL and dose for commercial. • Registration stability batches are manufactured at Lundbeck site and included in clinical studies. However, process validation batches are manufactured at Takeda and were not included in clinical studies. • Two dissolution acceptance criteria were included in the submission: for registration stability batches (NLT [(b) (4)] (Q) dissolved in 30 minutes) at Lundbeck; and for process validation batches (NLT [(b) (4)] dissolved in 30 minutes) at Takeda. The Applicant proposed using NLT [(b) (4)] dissolved at 30 minutes. • All strengths are not compositionally proportional. They have the same weight, but differ in active [(b) (4)]. The difference between the 5 mg and 20 mg [(b) (4)] is [(b) (4)] (above SUPAC-IR, Level II limit of [(b) (4)]). There is dose proportionality study (CPH-001) over dose range 2.5-75 mg that included the three strengths (2.5, 5, and 10 mg) using formulation III tablet.

15.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		X	

{See appended electronic signature page}
Houda Mahayni, Ph.D.
Biopharmaceutics Reviewer Date
Office of New Drug Quality Assessment

{See appended electronic signature page}
Sandra Suarez, Ph.D.
Acting Biopharmaceutics Team Leader Date
Office of New Drug Quality Assessment

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/s/

HOUDA MAHAYNI
11/14/2012

SANDRA SUAREZ
11/14/2012