CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200603

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	200603
Related IND	61,292
Generic Name:	Lurasidone
Trade Name:	Latuda®
Strength and Dosage Form:	40 mg, 80 mg, 120 mg Immediate Release Tablets
Sponsor:	Sunovion
Indication:	Treatment Of Schizophrenia
Submission Type:	Original NDA (NME),
Priority Classification:	Standard
Submission Dates:	12/30/09, 3/4/10, 3/29/10, 4/13/10, 4/20/10, 4/22/10, 4/26/10, 4/29/10, 5/11/10, 5/24/10, 5/26/10, 6/11/10, 6/14/10, 6/16/10, 6/29/10, 9/16/10
OCP Division:	DCP1 (HFD-860)
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CP Reviewer:	Bei Yu, Ph.D.
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1. Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology has determined that there is enough clinical pharmacology and biopharmaceutics information provided in the NDA to support a recommendation of approval of Lurasidone provided a satisfactory agreement is reached between the applicant and the Agency regarding language in the label

1.2 Comments to Medical Division

At the OCP briefing, the clinical division mentioned that they would be requesting the sponsor to study lower doses (i.e. 20 mg). This would necessitate the sponsor develops a 20 mg strength or score the 40 mg tablet. OCP supports this request since the availability of a 20 mg strength or a scored 40 mg tablet would be useful in providing flexibility in dosing in moderate and severe renal and hepatic impaired patients.

1.3 Comments to Sponsor

1) The sponsor should improve their in process analytical technique at the (b) (4) analytical site.

2) The sponsor should fulfill their commitment as stated by them in their response to FDA Form 483

3) It is suggested that the sponsor develop and market Lurasidone 20 mg strength or score the 40 mg tablet. The availability of a 20 mg strength would enable physicians to prescribe lower doses if needed for renal and hepatic impaired patients and during concomitant administration with moderate CYP3A inhibitors.

1.4 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Background: Lurasidone is an atypical antipsychotic which has been developed for the treatment of patients with schizophrenia. The effectiveness of lurasidone in the treatment of schizophrenia was reported by the sponsor to be established in four, well-controlled, randomized, double-blind, placebo-controlled, 6-week, multicenter studies.

Therapeutic Indication and Dosing Regimen: Lurasidone is indicated for the treatment of acute symptoms of schizophrenia .The sponsor proposed a recommended starting and target Lurasidone dose of 40 mg or 80 mg once daily. Initial dose titration is not required. The highest dose that has been demonstrated to be effective is 120 mg/day. Dose adjustments should occur in approximately 3-5-days. According to the medical reviewers there does not appear to be an advantage in effectiveness of the 120 mg over the 80 mg but there was an increase in certain adverse reactions with higher doses. Lurasidone is recommended to be administered orally with

food because in the safety and efficacy trials, doses were administered with food and higher exposure (AUC and Cmax) are observed when administered with food.
The doses were selected initially because Phase 2 studies indicated that 40 mg was efficacious.

Exposure-Response

Efficacy

There was no clear dose response relationship with respect to efficacy in the clinical studies

The relationship between AUC and changes in total Positive and Negative Syndrome Scale (PANSS) score could not be established.

The effects of Lurasidone on total PANSS scores were different in geographic regions (US vs. Non-US). The effect (efficacy) of Lurasidone in Non-US regions were higher than observed in US region. Overall, patients in US region have about 32- 44% lower median AUC in comparison to patients in Non-US region. These differences in AUC are unlikely to explain the differences observed in total PANSS score in US and Non-US regions observed in the pivotal safety and efficacy studies.

The sponsor evaluated the effects of placebo, 40, 80 and 120 mg Lurasidone dose on efficacy endpoints Brief Psychiatric Rating Scale derived (BPRSd) and PANSS in 4 primary clinical safety and efficacy trials (D1050006, D1050196, D1050229, D1050231). Lurasidone 40 and 80 were significantly better than placebo in either study D1050006 or D1050196. But in two other safety and efficacy studies that included patients from non-US sites, D1050229 and D1050231, the three dose groups were not consistently better than placebo. And there was differences in effectiveness between US and non-US sites.

Safety

Safety events such as akathisia, somnolence, sedation and increases in prolactin concentrations are dose related.

Thorough QT study (D1050249) was reported by the sponsor to be negative and lurasidone is not associated with clinically relevant QTc prolongation at either the intended maximum dose or the supratherapeutic dose (600 mg).

Intrinsic Factors

Renal Impairment

Cmax increased by 40%, 92%, and 54% in mild, moderate, and severe renal impairments, respectively compared to matched normal renal patients

AUC increased by 53%, 91%, and 103% in mild, moderate, and severe renal impairments, respectively compared to matched normal renal patients

At this time, it is recommended that doses in moderate and severe renal impaired patients should not exceed 40 mg as lower strengths are not currently available. No dose adjustment is recommended for mild renal impaired patients

Lurasidone 20 mg dosage strength should be developed and marketed by the sponsor and/or the 40 mg strength should be scored. A 20 mg strength would provide flexibility in dosing if needed for patients with moderate and severe renal impairment.

Hepatic Impairment

Cmax increased by 26%, 20%, and 25% for mild, moderate, and severe hepatic impairment groups, respectively compared to normal hepatic patients

The AUC increased by 35 - 49%, 66- 75%, and 3-fold for mild, moderate, and severe hepatic impairment groups, respectively compared to normal hepatic patients

At this time, it is recommended that doses in moderate and severe hepatic impaired patients should not exceed 40 mg as lower strengths are not currently available. No dose adjustment is recommended for mild hepatic impaired patients

Lurasidone 20 mg dosage strength should be developed and marketed by the sponsor and/or the 40 mg strength should be scored. A 20 mg strength would provide flexibility in dosing if needed for patients with moderate and severe hepatic impairment.

Age

The effect of age on the pharmacokinetics of lurasidone was not formally evaluated. But, in across study comparisons there was a trend towards higher AUC (about 21% higher) when the elderly was compared to the young in the across study comparison.
Dose adjustment is not recommended in the elderly.

Effect of Gender and Race

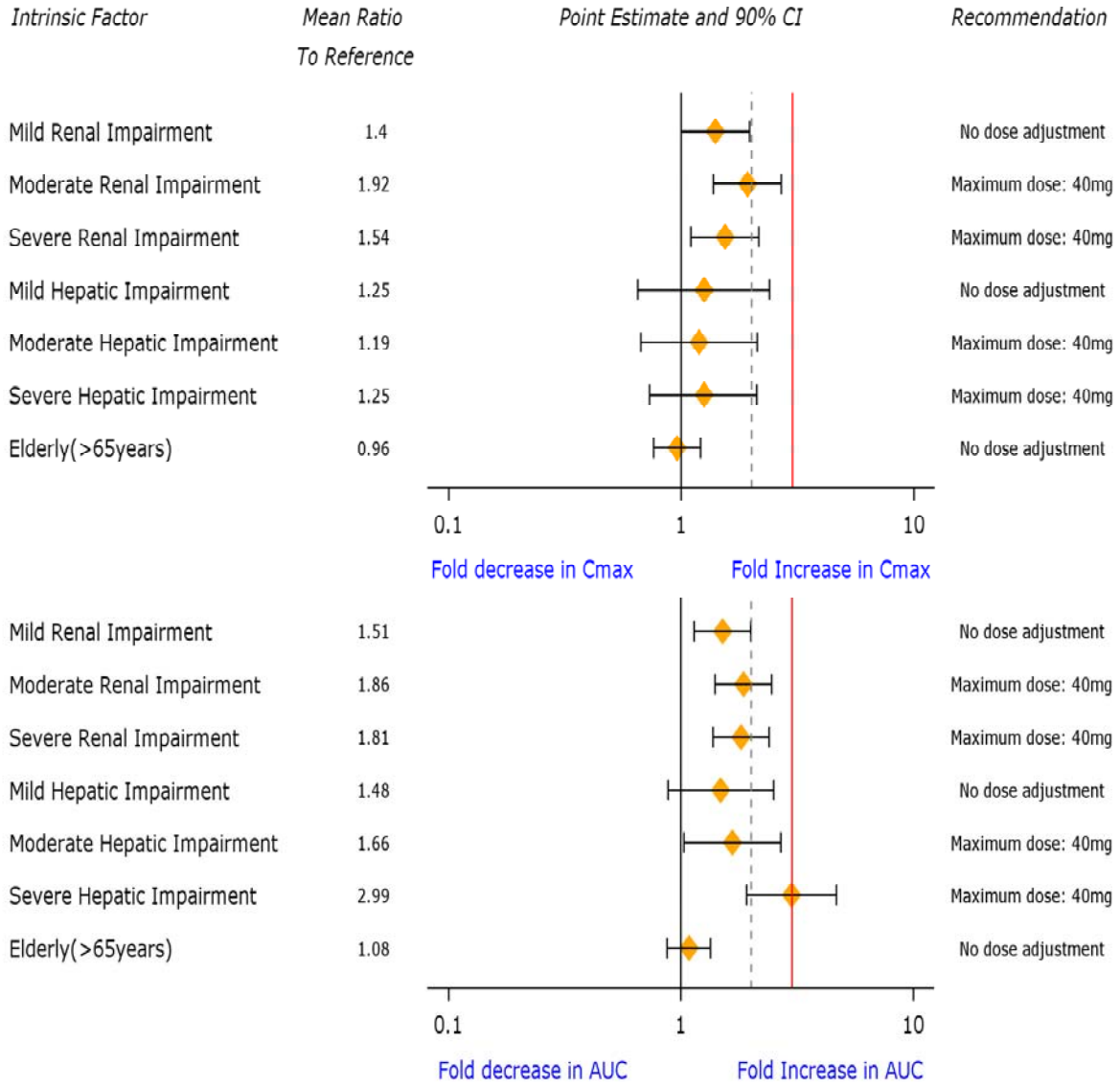
No significant difference in exposure between genders or ethnicity. Dose adjustment is not recommended based on ethnicity or gender.

Pediatric and Adolescents

Safety and effectiveness in pediatric and adolescent patients have not been evaluated.

The following is a plot of intrinsic factors on the pharmacokinetics of Lurasidone.

Intrinsic Factors



The red line at 3 fold change in AUC indicates the maximum change evaluated in clinical studies relative to starting dose. For example, in the current submission, the highest dose evaluated was 120 mg.

Extrinsic Factors

Lurasidone is metabolized primarily by CYP3A4. Lurasidone and its active metabolite, ID-14283, are not PgP substrates.

Effect of Lurasidone on other Drugs

Lurasidone did not significantly affect the concentrations of digoxin, midazolam and oral contraceptive (containing ethinyl estradiol and norelgestromin).
Dose adjustments is not recommended when Lurasidone is administered with digoxin, midazolam or oral contraceptive containing ethinyl estradiol and norelgestromin.

Effect of other drugs on Lurasidone

Ketoconazole increased lurasidone AUC and Cmax by 9-fold and 7-fold, respectively when they are coadministered together. *Lurasidone should not be administered with ketoconazole or other strong CYP3A inhibitors*

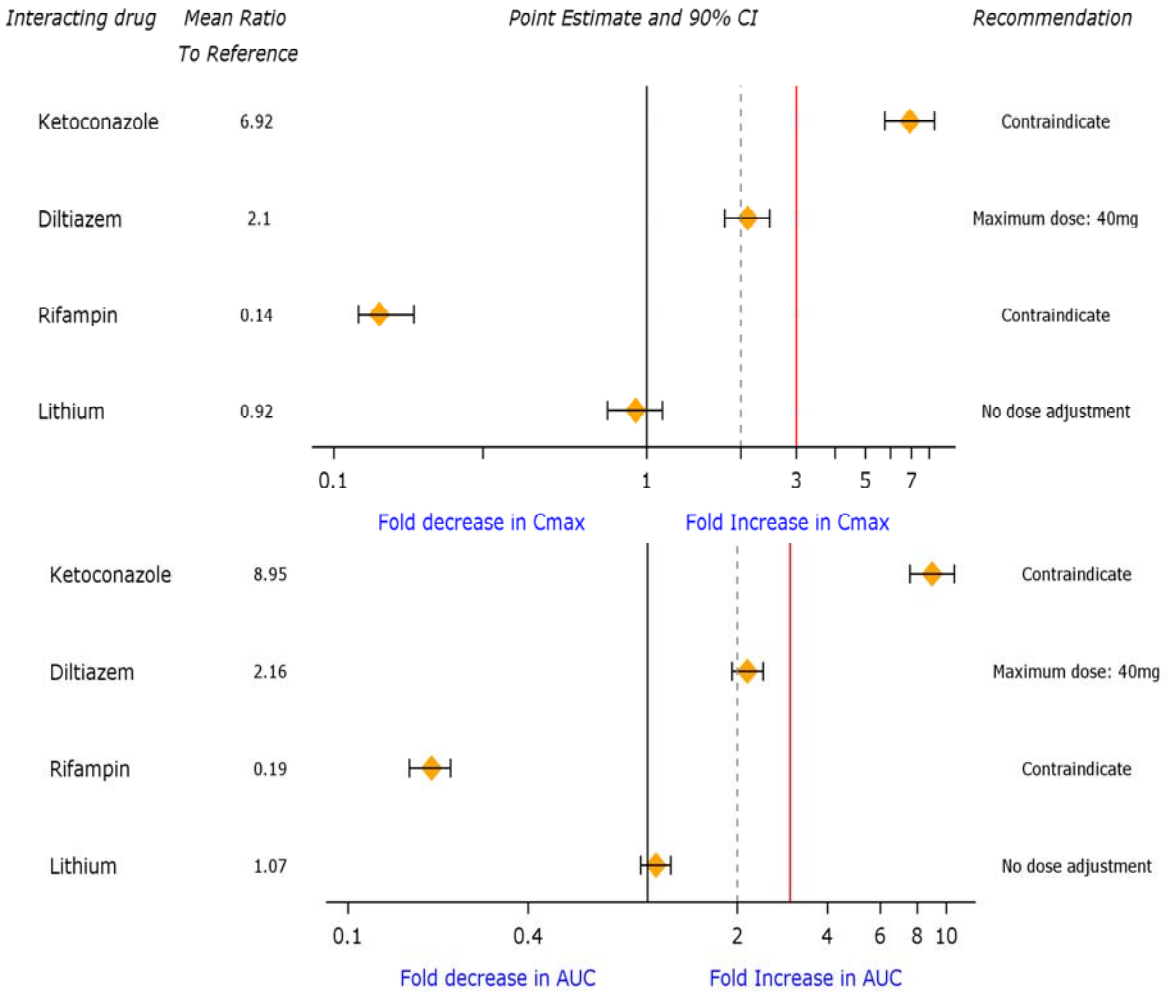
Diltiazem increased lurasidone AUC and Cmax by 116% and 110%, respectively when lurasidone is coadministered with diltiazem. *Lurasidone dose should not exceed 40 mg when administered with diltiazem. Lurasidone 20 mg strength should be developed to allow flexibility in dosing for patients who need diltiazem (or moderate CYP3A inhibitors) and lurasidone.*

Rifampin decreased lurasidone AUC and Cmax by 83% and 85%, respectively. *Rifampin or other strong inducers of CYP3A should not be administered with lurasidone.*

No significant interaction was observed when lithium was administered with lurasidone. *Dose adjustment of lurasidone is not recommended when lurasidone is coadministered with lithium.*

The following figure is a plot of extrinsic factors on the pharmacokinetics of Lurasidone

Extrinsic Factors (DDI)



The red line at 3 fold change in AUC indicates the maximum change evaluated in clinical studies relative to starting dose. For example, in the current submission, the highest dose evaluated was 120 mg.

Pharmacokinetics and Bioavailability

Absorption

Based on amount excreted in urine unchanged in radiolabeled studies, systemic bioavailability is estimated to be 9 to 19%. Tmax is about 1.5 and 3 hours after single and multiple dose administration, respectively.

Lurasidone exposure (AUC and Cmax) is proportional to dose in the range of 20 to 160 mg.

Distribution

Lurasidone is highly bound (≥ 99 %) to HSA and α1-AGP. The mean fraction of lurasidone distributed in RBCs is approximately 12% in vivo, in humans.

Metabolism

Lurasidone is metabolized primarily by CYP3A4. The major biotransformation pathways of lurasidone are oxidative N-dealkylation, hydroxylation of the norbane ring, S-oxidation, reductive cleavage of the isothiazole ring followed by S-methylation.

In vitro studies, Lurasidone was a moderate inhibitor of CYP2C19, CYP3A4, CYP2C8, CYP2C9 and CYP2B6.

In vitro studies indicated Lurasidone is not a substrate of human P-gp

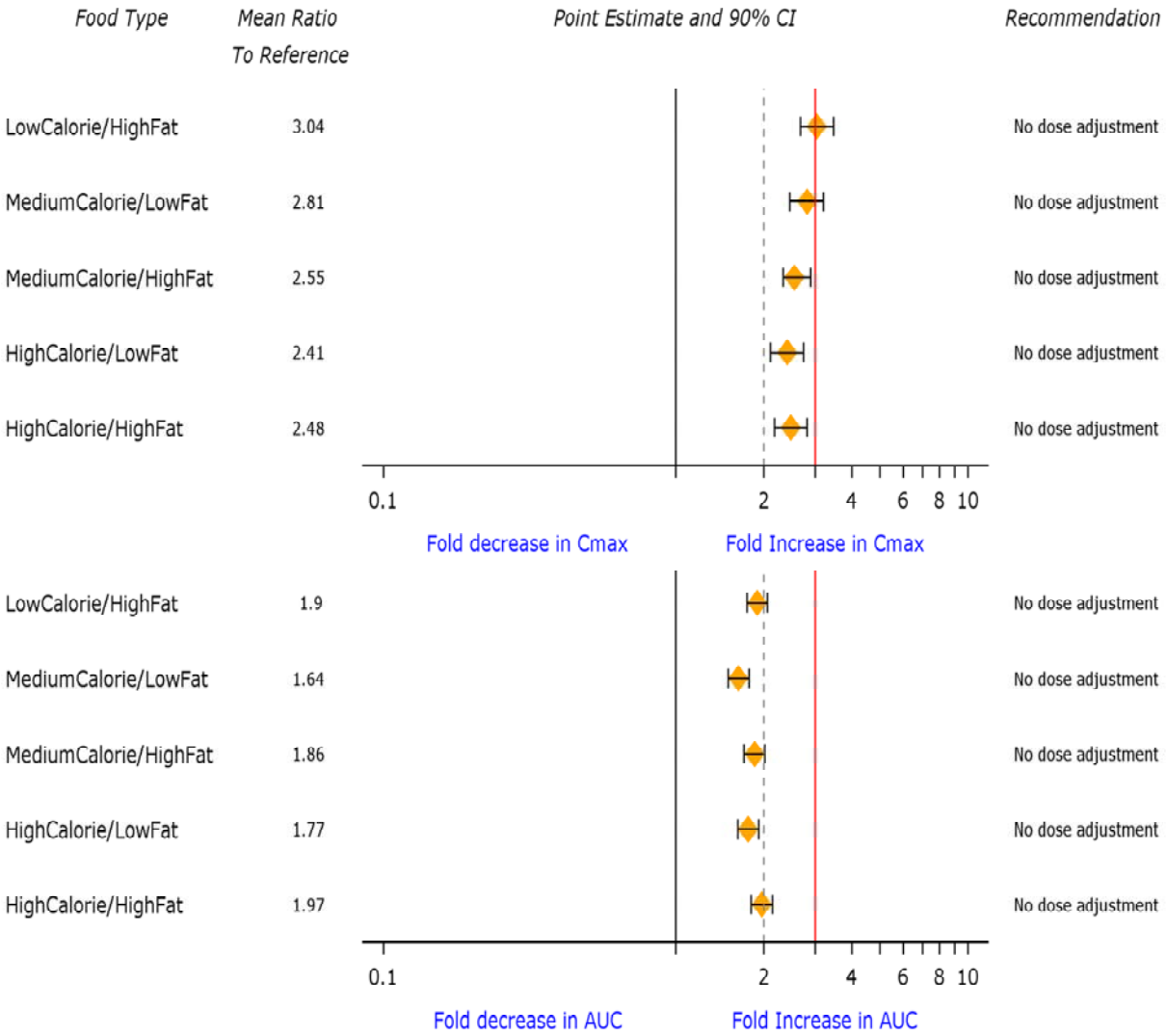
Excretion

Total excretion of the dose recovered in urine and feces combined was 89.3%, with 80.1% recovered in feces and 9.2% in urine

Food Effect

Food has significant effect on lurasidone exposure (about 2-fold increase in AUC) when Lurasidone is given with food compared to when administered under fasting conditions. But there was no significant difference in exposure based on the caloric/fat content of the meal. All clinical studies were conducted under fed conditions. Lurasidone should be administered with food because the clinical studies were conducted under fed conditions. But since concentration-response with respect to efficacy was not established and with elimination half-life of about 18 hours, incidental administration under fasting conditions may not be detrimental.

Extrinsic Factors (Food)



The red line at 3 fold change in AUC indicates the maximum change evaluated in clinical studies relative to starting dose. For example, in the current submission, the highest dose evaluated was 120 mg.

Bioequivalence

Lurasidone 120 (3 x 40) mg Clinical Trial Material (CTM) was bioequivalent to 120 mg To be Marketed (TBM) formulation under fed conditions after multiple dose administration.

Lurasidone 40 mg (2 x 20 mg) Clinical Trial Material (CTM) was demonstrated to be bioequivalent to Lurasidone 40 mg (1 x 40 mg) To Be Marketed (TBM) formulation under fed conditions after single dose administration.

It must be noted that both bioequivalence studies were conducted under fed conditions which is not ideal and not recommended unless for safety reasons.

DSI inspected the single dose study and recommended that it should not be accepted due primarily to analytical deficiencies noted at the analytical site (b) (4) *during analysis of the samples. Refer to OCP comments to the sponsor regarding the DSI inspection report*

The Division of Scientific Investigations (DSI) report states that the analytical site's responses to the deficiencies listed in Form 483 are inadequate. Therefore, DSI states that the integrity of the data for the single dose study 1053 cannot be assured. Therefore the study cannot be considered pivotal. (Refer to Appendix for DSI reports and OCP comments). The deficiencies identified by DSI were for in process analytical validation errors and in the recovery of samples (>150%). The analytical site was (b) (4) (b) (4). Study D1001053 was originally intended for (b) (4). OCP concurs with DSI that the integrity of the data for the single dose study cannot be assured. Therefore the determination of bioequivalence between the To be Marketed (TBM) formulation and the Clinical Trial Material (CTM) cannot be based solely on the single dose study (Protocol D1001053).

Bioequivalence was demonstrated after multiple dose administration of the TBM and CTM under fed conditions. Multiple dose bioequivalence studies are generally not the most sensitive to determine formulation differences. This multiple dose study (Protocol D1050263) was not inspected by DSI. The analytical report submitted by the analytical lab (b) (4) for study D1050263 included acceptable information on key in process analytical validation (e.g. Incurred Sample Reproducibility (ISR), Matrix effect, Recovery). Therefore, even though this study was not inspected, OCP has confidence in the integrity of the data. Based on the multiple dose data, we are confident that the TBM is bioequivalent to the CTM. There is an added degree of comfort to conclude that the TBM is bioequivalent to the CTM because the results from the multiple dose bioequivalence study is consistent with the information from single dose bioequivalent study even though the integrity of the data from bioequivalence single dose study cannot be fully assured. The geometric mean ratio (%) and 90% confidence interval (CI) for Cmax were 91.6% and 81.5 -102.9, respectively and for $AUC_{(0-\infty)}$ were 101.1% and 94.8-107.7, respectively for the single dose study. For the multiple dose study (D1050263), the

geometric mean ratio and 90% CI for Cmax were 101.1% and 94.37-108.39, respectively and for $AUC_{(0-\infty)}$ the geometric mean ratio and 90% CI were 99.3% and 95.40 – 103.27, respectively. The accumulation ratio was estimated to be at least 1.2. The pharmacokinetic parameters (Cmax and $AUC_{(0-\infty)}$ values obtained in the primary single dose study (D1050001) were similar to that observed after the single dose bioequivalence study (D1001053). The geometric mean (%CV) Cmax and $AUC_{(0-\infty)}$ after administration of Lurasidone 40 mg in study D1005001 were 52.9 (21.3) ng/mL and 171 (18) ng*h/mL, respectively. The geometric mean (%CV) Cmax and $AUC_{(0-\infty)}$ after administration of 40 mg Lurasidone in study D1001053 were 45.5 (40.4) ng/mL and 193.8 (31.8) ng*h/mL, respectively.

/s/: Kofi A. Kumi, Ph.D. (CP Primary Reviewer)

/s/: Atul Bhattaram, Ph.D. (PM Reviewer)

RD/FT Initialed by Yaning Wang, Ph.D. (PM TL)

RD/FT Initialed by Raman Baweja, Ph.D. (TL CP)

2. Question Based Review (QBR)

The QBR section of the review has used a deductive approach (i.e. starts with conclusions followed with supportive details) as instructed by CDER CPB Review Template MaPP 4000.4.

2.1 General Attributes

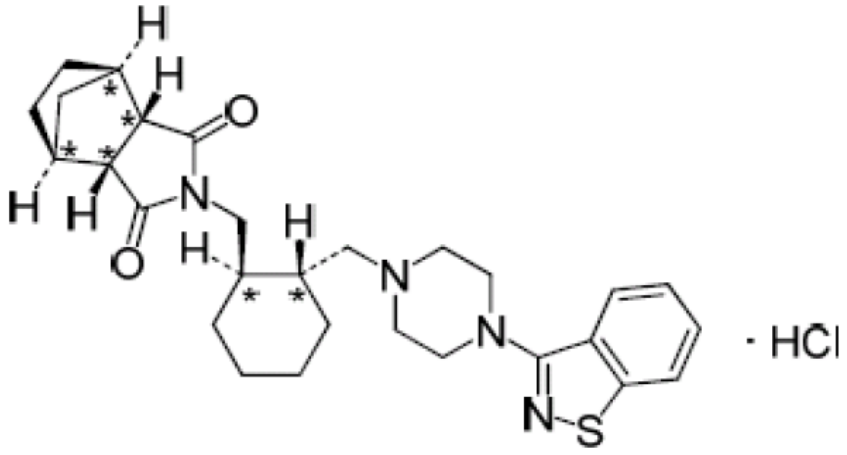
2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

A pre-NDA meeting to discuss the Clinical and Non-Clinical topics was held on May 22, 2009. The sponsor indicated the pharmacokinetic/ pharmacodynamic data set consisted of a total of 27 clinical pharmacology studies including 7 drug-drug interaction studies and a thorough QTc study.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics?

Lurasidone is an atypical antipsychotic belonging to the benzisothiazole derivative class. Lurasidone hydrochloride is described chemically as (3a*R*,4*S*,7*R*,7a*S*)-2-{(1*R*,2*R*)-2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-ylmethyl]cyclohexylmethyl}hexahydro-4,7-methano-2*H*-isoindole-1,3-dione hydrochloride. The chemical structure of Lurasidone is provided in the figure below

Lurasidone HCl



Asterisks (*) indicate chiral carbons

General Properties of Lurasidone HCl

Description	White to off-white powder
Molecular Formula	C28H36N4O2S·HCl
Molecular Weight	529.14.
Chirality /Stereochemistry	Lurasidone HCl has (b) (4).
Polymorphism	Lurasidone HCl is a (b) (4).
Aqueous Solubility at 20°C	Water: 0.224 mg/mL (pH of the saturated solution: 3.6) 0.1 mol/L HCl: 5.24×10^{-2} mg/mL pH 1.2 HCl/NaCl buffer: 4.11×10^{-2} mg/mL pH 3.5 McIlvaine buffer: 0.349 mg/mL pH 3.8 McIlvaine buffer: 0.236 mg/mL pH 4.0 McIlvaine buffer: 0.105 mg/mL pH 6.8 phosphate buffer: < 3.00 × 10-5 mg/mL
Solubility in Various Organic Solvents at 20°C	Ethanol 99.5%: 1.95 mg/mL Methanol: 15.6 mg/mL Toluene: 1.78×10^{-2} mg/mL Acetone: 0.244 mg/mL *N*-methyl-2-pyrrolidinone: 10.1 mg/mL
pKa	7.6
log P	5.6 (pH 9)

Lurasidone is formulated as film-coated tablets for oral administration containing either 40 mg, 80 mg or 120 mg of lurasidone. The core tablets of the three strengths for lurasidone are (b) (4). But the 80 mg tablet differs in overall

composition by (b) (4) The qualitative and quantitative composition is provided in the table below

Composition of Lurasidone 40 mg, 80 mg, and 120 mg Tablets

Component	% w/w	Quantity (mg)			Function
		40 mg	80 mg	120 mg	
Core Tablet					
Lurasidone HCl	25	40	80	120	API
Mannitol, USP	(b) (4)				
Pregelatinized Starch, NF					
Croscarmellose Sodium, NF					
Hypromellose (b) (4) USP					
Magnesium Stearate, NF					
(b) (4)					
Total					
(b) (4)					
OPADRY® (b) (4)					
Yellow Ferric Oxide, NF	(b) (4)				
FD&C Blue No.2 Aluminum Lake					
Carnauba Wax, NF					
(b) (4)					
Total Tablet Weight	-	162.61	324.328	(b) (4)	

(b) (4)

The following table contains the formulations used clinical in trials. Formulation B was used in the clinical trials and Formulation C is the proposed commercial formulation.

Lurasidone Tablets Formulations Used in Development Studies (Group A, B and C Formulations)

Group Formulations		A	B	C[a]			
		(b) (4)					
Strength (mg)				20	40	80	120
Purpose				Development	Primary stability study	Primary stability study	Clinical, Primary stability study
Component Name				(mg)			
Core Tablet	Lurasidone HCl			20	40	80	120
	Mannitol						(b) (4)
	Pregelatinized Starch						
	(b) (4)						
	Croscarmellose Sodium						
	(b) (4)						
	Hypromellose (b)						
	(b) (4)						
	Magnesium Stearate						
	(b) (4)						
Film-Coat	Hypromellose (b)						
	(b) (4)						
	OPADRY (b) (4)						
	Yellow Ferric Oxide						
	FD&C Blue No.2 Aluminum Lake						
	Carnauba Wax						
	(b) (4)						
Total							(b) (4)

(b) (4)

2.2 What are the proposed mechanism (s) of action and therapeutic indication(s)?

Lurasidone is an atypical antipsychotic agent for the treatment of acute symptoms of schizophrenia. It is reported that the efficacy of lurasidone in schizophrenia is mediated through a combination of central dopamine Type 2 (D2) and serotonin Type 2 (5-HT2A) receptor antagonism. The sponsor stated that Lurasidone exhibits little or no affinity for H1 (histamine) or M1 (muscarinic) receptors. Extrapyramidal symptoms (EPS), a common side effect of psychotropic agents, are reduced by administration with 5-HT2 receptor antagonists or 5-HT1A receptor agonists. Lurasidone showed relatively potent 5-HT2A receptor blocking actions and significantly enhanced the 5-HT1A receptor-mediated behavior.

In vitro receptor binding studies demonstrate that lurasidone is an antagonist with high affinity at dopamine D2 receptors (Ki = 0.994 nM) and the 5-hydroxytryptamine (5-HT, serotonin) receptors, 5-HT2A (Ki = 0.47 nM) and 5-HT7 (Ki = 0.495 nM). It is reported that Lurasidone exhibits little or no affinity for histamine H1 and muscarinic M1 receptors (IC50 ≥ 1,000 nM and > 1,000 nM, respectively).

2.3 What are the proposed dosage and route of administration?

The recommended starting and target dose of Lurasidone is 40 mg or 80 mg once daily. Initial dose titration is not required. The highest dose that has been tested in clinical trials was 120 mg. (b) (4) Lurasidone is recommended to be administered orally with food. The doses were selected based on the safety and efficacy trials conducted in support of the application. A proof of concept Phase 2 study showed that Lurasidone 40 mg was efficacious therefore Phase 3 studies were conducted with Lurasidone 40 mg or higher.

2.4 General Clinical Pharmacology

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

The effectiveness of lurasidone in the treatment of schizophrenia was reported established in four, well-controlled, randomized, double-blind, placebo-controlled, 6-week, multicenter studies: Studies D1050006, D1050196, D1050229, and D1050231. These studies evaluated subjects with a primary diagnosis of schizophrenia who had an acute exacerbation of psychotic symptoms and duration of illness ≥1 year. The studies were 6-week, multicenter, double-blind, randomized, fixed-dose, placebo-controlled trials. During the double-blind treatment phase, subjects were treated with lurasidone or placebo for 6 weeks. All four studies had fixed-dose administration of lurasidone at the target therapeutic doses (40, 80, and 120 mg) over a period of 6 weeks. Study D1050231 also included an active control arm (olanzapine) in order to assess study assay sensitivity. Lurasidone was assessed at once daily doses of 40 mg and 120 mg in Studies D1050006 and D1050231, 80 mg in Study D1050196, and 40, 80 and 120 mg in Study D1050229.

Subjects randomized to receive olanzapine were given a 10 mg dose for the initial 7 days and then received a fixed dose of 15 mg beginning on Day 8, consistent with the manufacturer's labeling and dosing recommendations. Studies were conducted in the US, Europe, and Asia.

2.4.2 What is the basis for selecting the response endpoints (i.e. clinical or surrogate endpoints) or biomarkers and how are they measured in clinical pharmacology and clinical studies

The Positive and Negative Syndrome Scale (PANSS) and the Brief Psychiatric Rating Scale Derived (BPRSd), which was derived from the PANSS, were used to assess schizophrenia symptoms. All four placebo-controlled studies also assessed global severity using the Clinical Global Impression of Severity (CGI-S). The PANSS, a 30-item scale, is designed to assess various symptoms of schizophrenia including delusions, grandiosity, blunted affect, poor attention, and poor impulse control. The PANSS was designed to capture several domains of psychopathology, including the Positive Syndrome Subscale (assesses florid symptoms that are superimposed on a normal mental status), Negative Syndrome Subscale (assesses symptoms representing a deficit in functioning or features that are absent from a normal mental status), and General Psychopathology Subscale (measures the overall severity of schizophrenic illness).
The CGI-S measures the global severity of illness at a given point in time. The CGI-S rates the severity of the subject's illness on a 7-point scale ranging from 1 (no symptoms) to 7 (very severe). The following table contains the method used in assessing efficacy in placebo controlled trials.

Efficacy Assessments in Placebo-Controlled Studies

Efficacy Endpoint, Method, Population, Handling of Missing Data	Study, Type of Analysis			
	D1050006	D1050196	D1050229	D1050231
BPRSd[a] change from Baseline at endpoint (Day 42/LOCF), ANCOVA, ITT, LOCF	Primary	Primary		
PANSS total score change from Baseline at Week 6, MMRM, ITT			Primary	Primary
PANSS total score change from Baseline at Week 6, ANCOVA, ITT, LOCF	Secondary	Secondary	Secondary	Secondary
CGI-S change from Baseline to Week 6, MMRM, ITT			Key Secondary	Key Secondary
CGI-S change from Baseline to Week 6, ANCOVA, ITT, LOCF	Secondary	Secondary	Secondary	Secondary
PANSS total score change from Baseline at Day 4, MMRM, ITT			Key Secondary	Secondary
PANSS total score change from Baseline at Day 4, ANCOVA, ITT, LOCF	Secondary	Secondary	Secondary	Secondary
PANSS change from Baseline at Week 6 in positive syndrome, negative syndrome and general psychopathology subscale scores, ANCOVA, ITT, LOCF	Secondary	Secondary	Tertiary	Tertiary
BPRSd[a] score change from Baseline at each visit, ANCOVA, ITT	Secondary	Secondary		
PANSS total score change from Baseline at each visit, MMRM, ITT			Other	Other
MADRS change from Baseline to Week 6, ANCOVA, ITT, LOCF		Secondary	Other	Other
Proportion of responders (≥ 20% decrease from Baseline in BPRSd[a] score) CMH, ITT, LOCF	Secondary	Secondary		
Proportion of responders (≥ 20% decrease from Baseline in PANSS Total Score), Logistic regression, ITT, LOCF			Tertiary	Tertiary
PANSS change from Baseline at Week 6 in positive syndrome, negative syndrome and general psychopathology subscale scores, MMRM, ITT			Other	Other
MADRS change from Baseline to Week 6, MMRM, ITT			Other	Other

[a] Derived from PANSS.

Abbreviations: ANCOVA = analysis of covariance; BPRSd = Brief Psychiatric Rating Scale derived; CGI-S = Clinical Global Impression of Severity; CMH = Cochran-Mantel-Haenszel test; ITT = intent-to-treat; LOCF = last observation carried forward; MADRS = Montgomery-Asberg Depression Rating Scale; MMRM = mixed model repeated measures; PANSS = Positive and Negative Syndrome Scale.

2.4.3 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The proposed dosage regimen for lurasidone in the treatment of patients in schizophrenia is based on the efficacy, safety, and pharmacokinetic data. Based on the accumulated starting dose experience and efficacy results of the pivotal studies presented, the sponsor is proposing lurasidone daily start dose of either 40 or 80 mg. (b) (4) (b) (4). The dose is to be administered with food because the exposure (AUC and Cmax) is significantly increased when lurasidone is administered with food. The sponsor therefore conducted the clinical studies under fed conditions in order to take advantage of the increase in exposure to improve the chances of lurasidone being effective. However, concentration-response relationship could not be demonstrated. Therefore it is not known whether administration with food is necessary for effectiveness.

2.4.5 What are the evidences of efficacy provided by the sponsor in support of the application?

The sponsor reported that for Studies D1050006 and D1050196, the least square (LS) mean change in the BPRSd score from Baseline to LOCF endpoint using an ANCOVA model was greater for subjects in the 40 mg, 80 mg and 120 mg lurasidone groups compared with the placebo groups, indicating greater improvement in BPRSd scores. The Agency medical review indicated that the drop out rate in study D1050006 was high (68% for 40 mg, 59.2% for 120 mg and 70% for placebo). The drop out rate for D1050196 was 42% for Lurasidone 80 mg and 48% for placebo. The high drop out rates complicates the interpretation of the results of the studies.

Change from Baseline to Day 42/LOCF Endpoints in BPRSd, ANCOVA Analysis (ITT Population): Studies D105006 and D1050196

Study		Lurasidone		
Statistic	**Placebo**	**40 mg**	**80 mg**	**120 mg**
Study D1050006[a]	N = 49	N = 49		N = 47
LS mean (SE)	−3.8 (1.57)	−9.4 (1.58)		−11 (1.58)
Treatment Difference				
LS Mean (SE)		−5.6 (2.13)		−6.7 (2.16)
95% CI		−9.8, −1.4		−11, −2.5
p-value		0.018*		0.004**
Study D1050196	N = 90		N = 90	
LS mean (SE)	−4.2 (1.36)		−8.9 (1.32)	
Treatment Difference[b]				
LS Mean			−4.7	
95% CI			−8.3, −1.1	
p-value			0.012*	

* $p \leq 0.05$; ** $p \leq 0.01$

[a] Analyses of Day 42 LOCF-3 (data on or after Day 3) using an ANCOVA model with treatment, center, and the Baseline efficacy score as covariates. Each dose group of lurasidone was compared to placebo with a 2-sided Dunnett's t-test. The p-value presented is the Dunnett's adjusted p-value.

[b] Least squares (LS) mean estimates and p-values are from an ANCOVA model with treatment group and study center as main effects, and Baseline efficacy score as a covariate.

In study D1050229, the comparison between 80 mg and placebo at Week 6 was statistically significant. In Study D1050229, although the lurasidone 40 mg and 120 mg groups had numerically greater estimated changes in PANSS total score from Baseline to Week 6 compared with placebo, the comparisons at Week 6 between these groups and placebo were not statistically significant. For Study D1050231, the estimated change in the PANSS total score from Baseline to Week 6 in the MMRM analysis was greater for subjects in the olanzapine 15 mg group compared with the placebo group. The comparison at Week 6 with the placebo group was statistically significant for the olanzapine 15 mg group (−12.6, $p < 0.001$). Direct comparisons between the lurasidone dose groups and olanzapine were not pre-specified or intended, per protocol and Statistical Analysis Plan. The comparison at week 6 with placebo was statistically significant for the 40 mg Lurasidone group. It must be noted that patients in the olanzapine 15 mg group had better efficacy outcome than those in lurasidone group.

Change from Baseline to Day 42/LOCF Endpoint PANSS Total Score: ANCOVA Analysis

Study		Lurasidone			Olanzapine
Statistic	Placebo	40 mg	80 mg	120 mg	15 mg
Study D1050006[a]	N = 49	N = 49		N = 47	
LS mean (SE)	-6.2 (2.74)	-14 (2.74)		-17 (2.73)	
Treatment Difference					
LS Mean (SE)		-7.6 (3.67)		-11 (3.74)	
95% CI		(-15, -0.3)		(-18, -3.3)	
p-value		0.076		0.009**	
Study D1050196[b]	N = 90		N = 90		
LS mean (SE)	–5.5 (2.17)		–14.1 (2.12)		
Treatment Difference					
LS Mean			–8.57		
95% CI			(–14.4, –2.8)		
p-value			0.004**		
Study D1050229[c]	N = 124	N = 121	N = 118	N = 123	
LS mean (SE)	−14.7 (1.6)	−17.4 (1.6)	−20.8 (1.6)	−18.5 (1.6)	
Treatment Difference					
LS Mean (SE)		−2.7 (2.2)	−6.1 (2.3)	−3.8 (2.2)	
95% CI		(-7.1, 1.7)	(-10.5, -1.6)	(-8.2, 0.5)	
p-value		0.236	0.007**	0.086	
Study D1050231[c]	N = 114	N = 118		N = 118	N = 121
LS mean (SE)	-15.2 (1.7)	-23.1 (1.7)		-20.0 (1.7)	-26.7 (1.7)
Treatment Difference					
LS Mean (SE)		-7.9 (2.4)		-4.8 (2.4)	-11.4 (2.4)
95% CI		(-12.7, -3.1)		(-9.6, -0.0)	(-16.2, -6.7)
p-value		0.001**		0.049*	<0.001**

* $p \leq 0.05$; ** $p \leq 0.01$

[a] Analyses of Day 42 LOCF-3 (data on or after Day 3) using an ANCOVA model with treatment, center, and the Baseline efficacy score as covariates. Each dose group of lurasidone was compared to placebo with a 2-sided Dunnett's t-test. The p-value presented is the Dunnett's adjusted p-value.

[b] Least squares (LS) mean estimates and p-values are from an ANCOVA model with treatment group and study center as main effects, and Baseline efficacy score as a covariate.

[c] P-values versus placebo, LS means, and CIs are from an ANCOVA with treatment and pooled center as fixed factors and Baseline value as a covariate.

2.4.6 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationship?

Yes, the active moieties in the plasma and other biological fluids were appropriately measured. The active moieties are the parent compound, lurasidone, the metabolites ID-14283, which is about 24% of the parent and ID-14326 which is about 2% of the parent. LC/MS/MS was developed for the determination lurasidone and its metabolites in human plasma, urine, and feces. The lower limit of quantitation for lurasidone and its two active metabolites (ID-14283 and ID-14326) was 0.02 ng/mL and linear range was 0.02 to 10 ng/mL. The inter-assay precision and accuracy values were determined. The assay was adequately validated and is acceptable (Refer to analytical section for details of analytical methods and validation).

Analytical methods were also validated in support of the analysis of midazolam, digoxin, ketoconazole, ethinyl estradiol, norelgestromin, rifampin, diltiazem, lithium in support of clinical studies with lurasidone and these therapeutic agents.

The analytical methods were adequately validated and are acceptable. However, DSI inspection of the (b) (4) *revealed that quality control during analysis of the samples for Protocol D1001053 was deficient. Please refer to the DSI report and OCP comments in the Appendix*

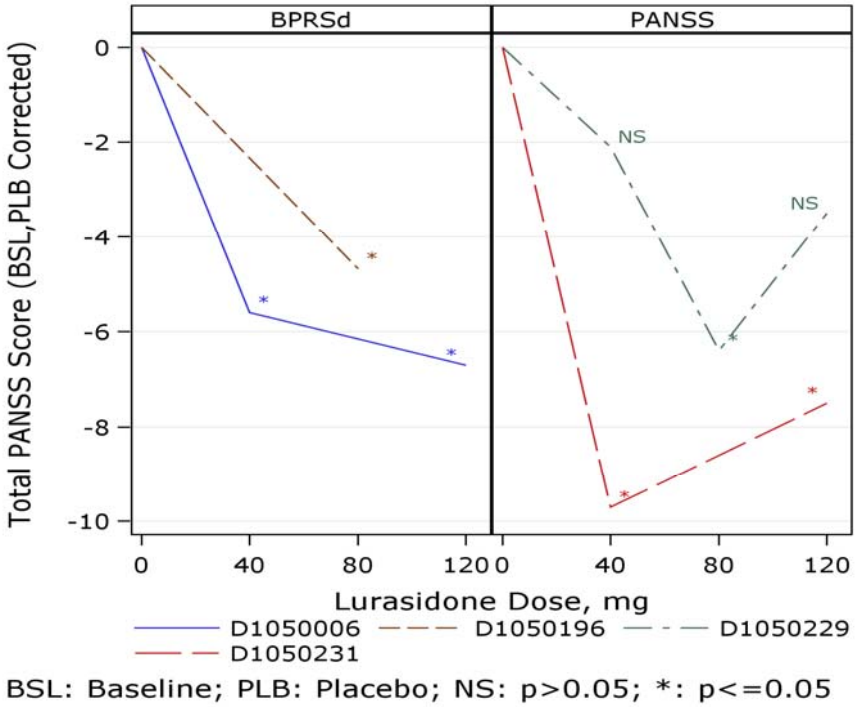
2.5 Exposure-response

2.5.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) with regards to efficacy?

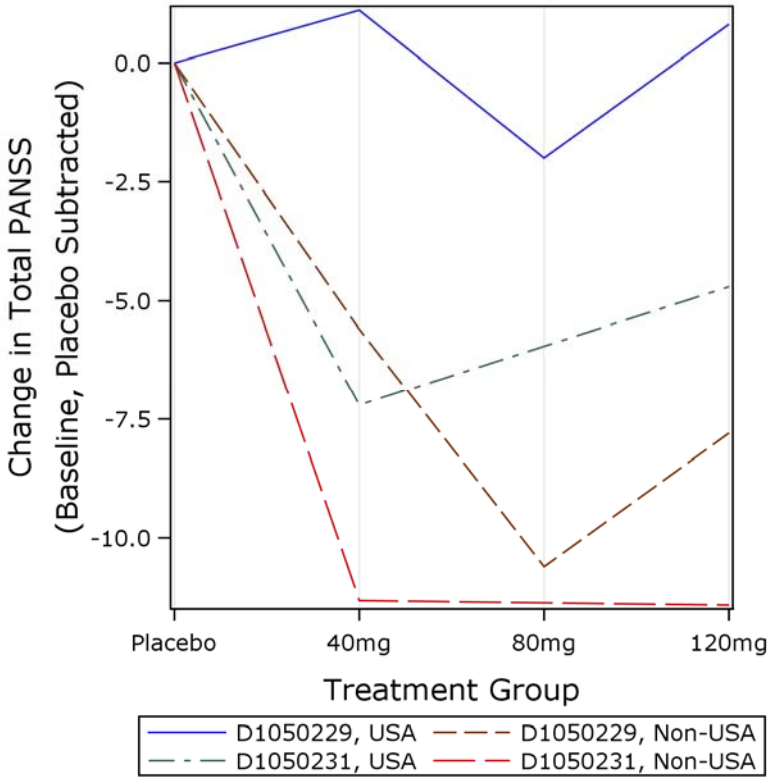
Sponsor evaluated the effects of placebo, 40, 80 and 120 mg Lurasidone dose on efficacy endpoints Brief Psychiatric Rating Scale derived (BPRSd) and the Positive and Negative Syndrome Scale (PANSS) in 4 clinical trials (D1050006, D1050196, D1050229, D1050231). The following figure shows the dose-response relationship observed in 4 clinical trials. All three dose groups (40, 80 and 120 mg) were significantly better than placebo for BPRSd in D1050006, D1050196. In D1050229 and D1050231, the three dose groups were not consistently better than placebo for PANSS. The effects of Lurasidone on total PANSS scores were different in geographic regions (US vs. Non-US). The effects of Lurasidone in Non-US regions were higher than observed in US region

Figure : (A) Relationship between baseline, placebo corrected change in primary endpoint and dose in four clinical trials (B) Relationship between baseline, placebo corrected change in primary endpoint and dose in four clinical trials by US and Non-US clinical study centers.

(A)



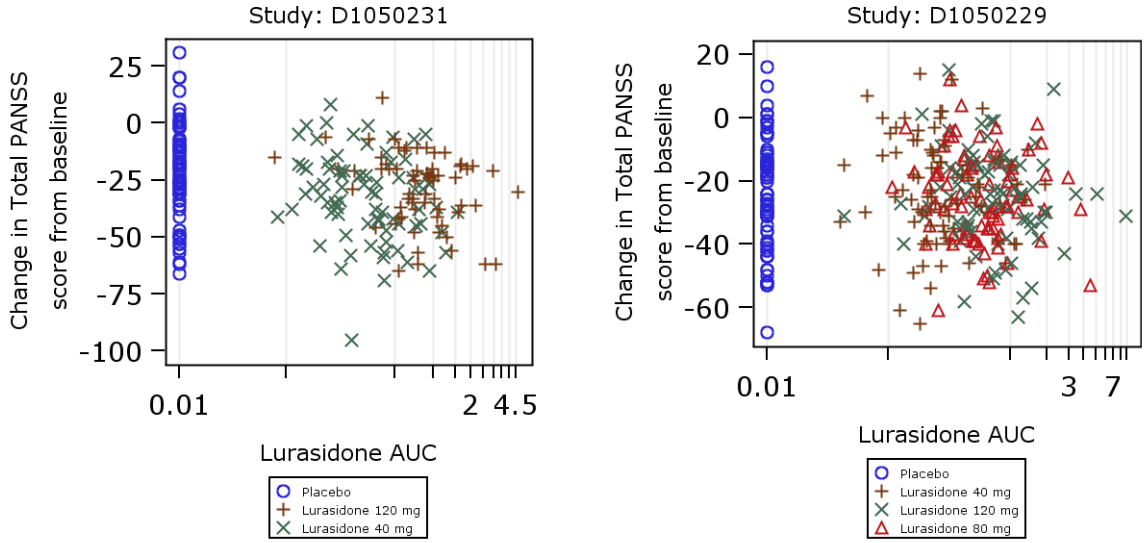
(B)



The relationship between Lurasidone AUC and changes in total PANSS score in D1050229 and D1050231 was explored by Agency due to lack of consistent dose-response relationship.

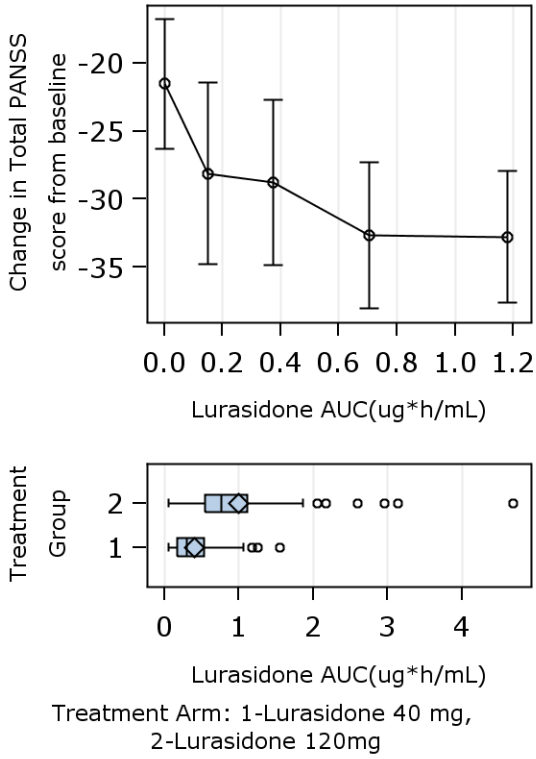
The following figure shows the relationship between change in Total PANSS Score from baseline and Lurasidone AUC (based on estimated clearance, dose) in patients who completed 6 weeks of Study D1050231 and D1050229.

Relationship between change in Total PANSS Score from baseline and Lurasidone AUC in patients who completed 6 weeks of Study D1050231 and D1050229.



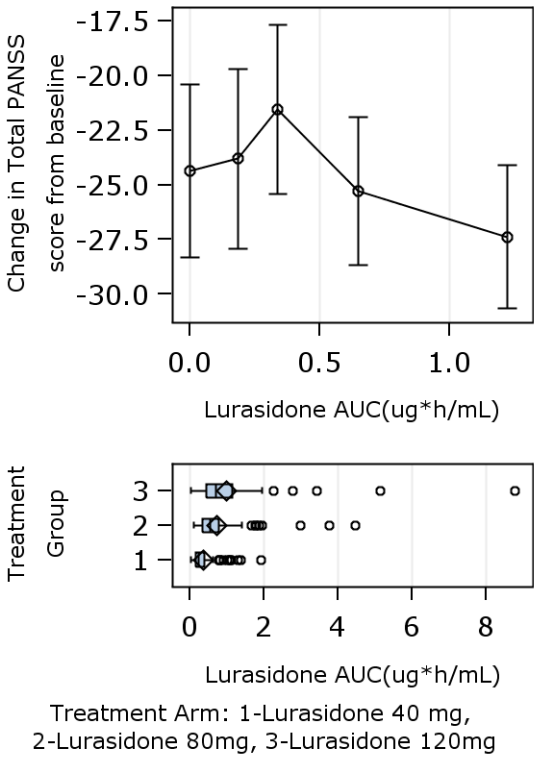
The following figure shows the mean change in total PANSS scores at midpoint of Lurasidone AUC quartiles by study. Also shown in the figure is the distribution of Lurasidone AUC by dose in the studies. In patients who completed the D1050231 study, the decrease in Total PANSS score is related to Lurasidone AUC. In patients who completed D1050229 study, there is no clear relationship between decrease in Total PANSS score and Lurasidone AUC.

Relationship between change in Total PANSS score from baseline and midpoints of Lurasidone AUC quartiles. Also shown are the box plots for Lurasidone AUC by treatment group.



Treatment Arm: 1-Lurasidone 40 mg, 2-Lurasidone 120mg

D1050231

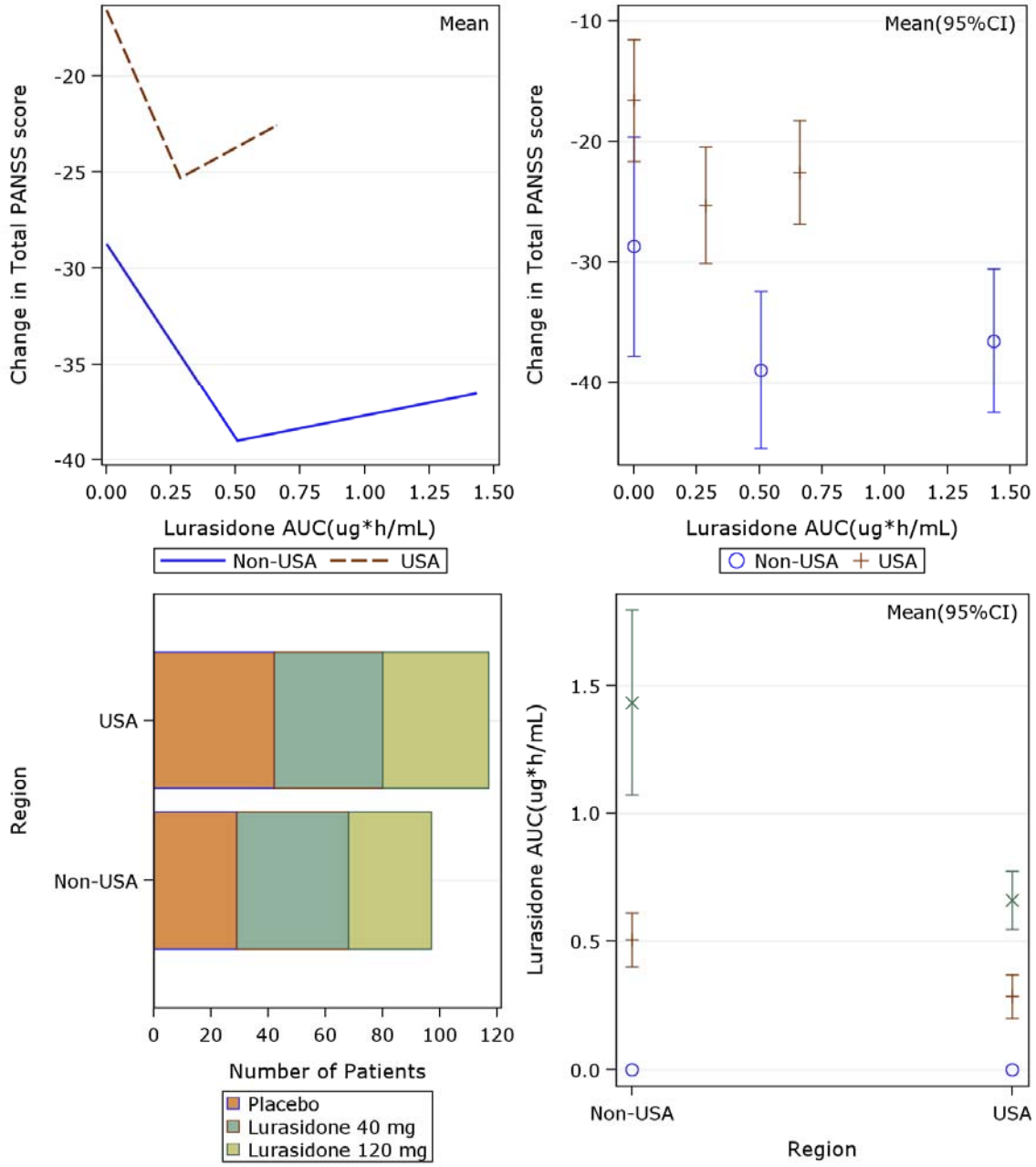


Treatment Arm: 1-Lurasidone 40 mg, 2-Lurasidone 80mg, 3-Lurasidone 120mg

D1050229

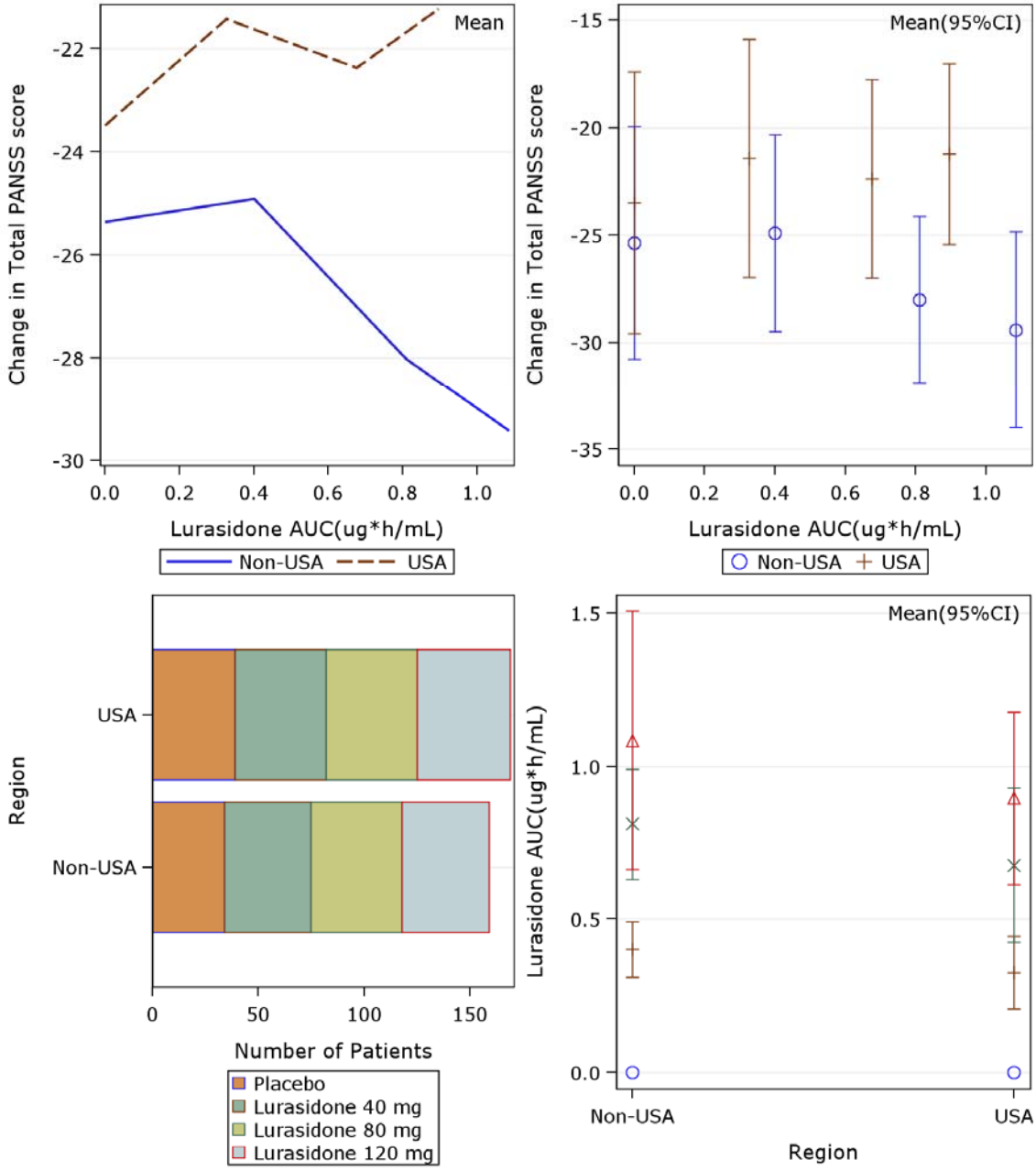
The following figure show that the patients in Non-USA region have higher Lurasidone AUC and higher change from baseline Total PANSS score in placebo and treatment groups.

(TOP) Relationship between mean and mean (95%CI) change in Total PANSS score from baseline and mean AUC by region. (BOTTOM) Number of patients and mean(95%CI) Lurasidone AUC by dose group in USA and Non-USA region in Study D1050231.

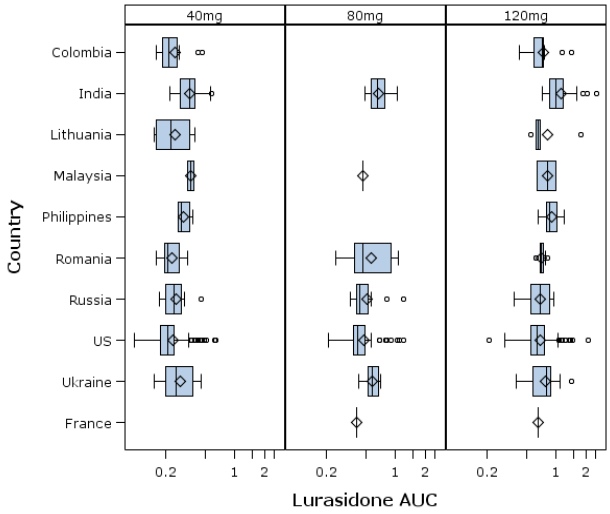


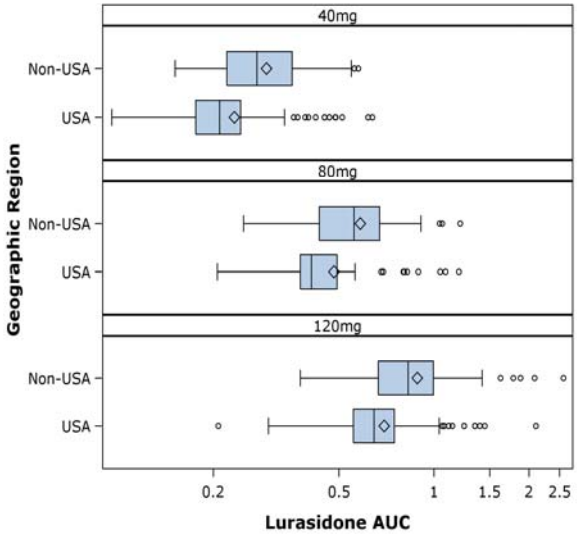
The following figure shows the distribution of Lurasidone AUC by dose, geographic region or country.

(TOP) Relationship between mean and mean (95%CI) change in Total PANSS score from baseline and mean AUC by region. (BOTTOM) Number of patients and mean(95%CI) Lurasidone AUC by dose group in USA and Non-USA region in Study D1050229.



Box plots showing Lurasidone AUC by Country and Geographic Region.





The following table shows the mean, standard deviation, median AUC of Lurasidone after 40, 80 and 120 mg by country and region. Overall, patients in US region have about 32-44% lower median AUC in comparison to patients in Non-US region. This is probably due to the lower body weight of patients in Non-USA region in comparison to those in USA

Summary statistics (Mean, Standard Deviation(Std), Median) of Lurasidone AUC by Country and Region.

Country	Treatment Group			Treatment Group								
				40mg			80mg			120mg		
	40mg	80mg	120mg	AUC			AUC			AUC		
	N	N	N	Mean	Std	Median	Mean	Std	Median	Mean	Std	Median
Colombia	12	.	12	0.37	0.22	0.30	.	.	.	0.94	0.57	0.82
France	.	1	1	.	.	.	0.21	.	0.21	0.38	.	0.38
India	35	15	32	0.61	0.32	0.54	0.92	0.38	0.79	1.68	1.55	1.22
Lithuania	7	.	6	0.30	0.25	0.19	.	.	.	1.10	0.92	0.74
Malaysia	2	1	2	0.26	0.03	0.26	0.44	.	0.44	0.54	0.27	0.54
Philippines	7	.	6	0.35	0.16	0.32	.	.	.	0.98	0.59	0.83
Romania	7	7	9	0.30	0.12	0.29	0.69	0.54	0.49	0.82	0.29	0.74
Russia	14	15	12	0.31	0.24	0.25	0.75	0.87	0.51	0.76	0.50	0.57
US	125	58	127	0.28	0.28	0.19	0.62	0.73	0.42	0.77	0.68	0.63
Ukraine	12	10	12	0.44	0.41	0.27	0.72	0.18	0.74	0.82	0.69	0.65
All	221	107	219	0.35	0.30	0.24	0.69	0.66	0.49	0.93	0.89	0.72

Geographic Region	Treatment Group			Treatment Group								
				40mg			80mg			120mg		
	40mg	80mg	120mg	AUC			AUC			AUC		
	N	N	N	Mean	Std	Median	Mean	Std	Median	Mean	Std	Median
Non-USA	96	49	92	0.45	0.31	0.34	0.77	0.57	0.67	1.15	1.09	0.93

Summary statistics of body weight (Weight, kg) and age (Age, Years) in patients by geographic region (USA vs Non-USA).

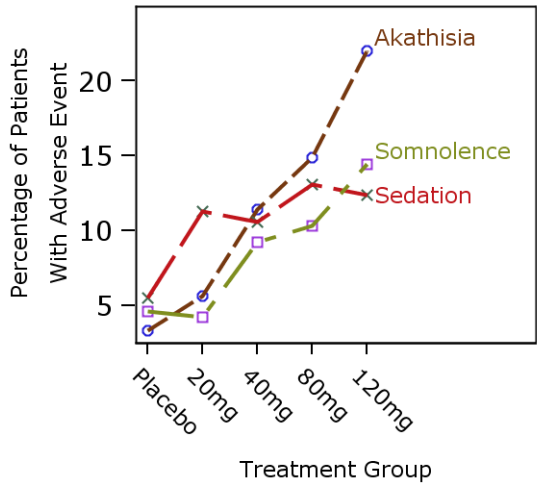
Country	Weight, kg				Age, Years			
	N	Mean	Std	Median	N	Mean	Std	Median
Non-USA	237	65.14	14.53	62.00	237	34.74	9.91	34.00
USA	310	86.20	17.97	84.19	310	41.13	10.80	43.00

2.5.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) with regards to safety?

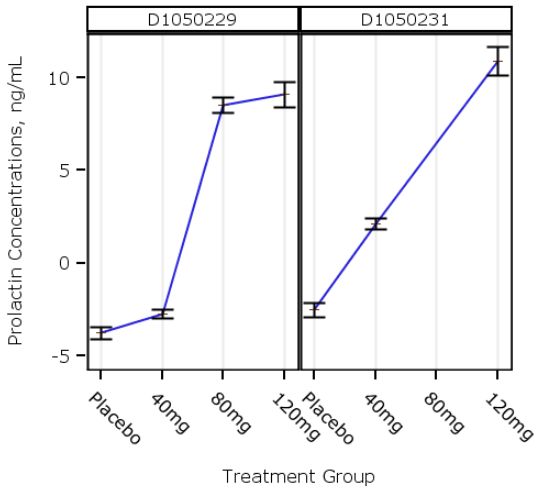
The sponsor reported that assessment of safety dose-response was performed based on pooled safety data from the five short-term, placebo controlled studies (P23STC). These five studies utilized fixed dose administration of lurasidone 40, 80, and 120 mg/day over a period of 6 weeks. A total of 1653 subjects received at least one dose of study medication: 1004 subjects received lurasidone (71 subjects received 20 mg QD, 360 subjects received lurasidone 40 mg QD, 282 subjects received lurasidone 80 mg QD, and 291 subjects received lurasidone 120 mg QD), 455 subjects received placebo QD, 72 subjects received haloperidol 10 mg QD, and 122 subjects received olanzapine 15 mg QD. The sponsor reported that Lurasidone was demonstrated to be generally safe and well-tolerated across the lurasidone daily dose range studied (20-120 mg), in patients with schizophrenia or schizoaffective disorder. The sponsor reported that Lurasidone has been shown to have no clinically relevant effects on vital signs or ECG assessments including the QTc interval. In addition, no consistent adverse effects on measures of body weight or laboratory parameters including, lipids, and measures of glycemic control have been observed.

Safety events such as akathisia, somnolence, sedation, increases in prolactin concentrations are dose related as shown in the following figure. The Agency's medical review also showed dose dependent increase in extra pyramidal symptoms (EPS). A modest weight gain was observed in patients taking Lurasidone.

(LEFT) Percentage of patients with adverse event in Lurasidone (20mg, 40mg, 120 mg) treatment group in Phase 2, Phase 3 studies combined. Also shown in footnote are the percentage of patients with adverse event in active control groups (Haloperidol, Olanzapine). (RIGHT) Change from baseline prolactin concentrations by dose group in studies D1050229 and D1050231. Also shown in footnote is the change from baseline prolactin concentrations in active control group (Olanzapine).



% Patients with Akathisia in control groups:Haloperidol (19.4) Olanzapine (7.4)
% Patients with Sedation in control groups:Haloperidol (20.8) Olanzapine (14.8)
% Patients with Somnolence in control groups:Haloperidol (12.5) Olanzapine (9.0)



Mean Change in Olanzapine group is 5.02 ng/mL

2.5.3 Does this drug prolong the QT or QTc interval?

A QT study (Study D1050249) was conducted by the sponsor. This was a double-blind, positive-controlled, randomized, parallel-group study conducted in subjects with schizophrenia or schizoaffective disorder designed to evaluate the potential effects of lurasidone on the QT interval. Subjects were administered either lurasidone 120 mg/day (standard dose, n = 23) or 600 mg/day (supratherapeutic dose, n = 20) over 11 days. Subjects in the positive-control arm were administered ziprasidone 160 mg/day (n = 23) over the 11-day treatment period.

The sponsor reported that the lurasidone Total QT study (D1050249) was negative and lurasidone is not associated with clinically relevant QTc prolongation at either the intended maximum dose or the supratherapeutic dose. The CDER QT team was consulted and are reviewing this study. Refer to medical review for conclusions of the CDER QT review team.

2.6 What are the Pharmacokinetic Characteristics of the drug and its major metabolite?

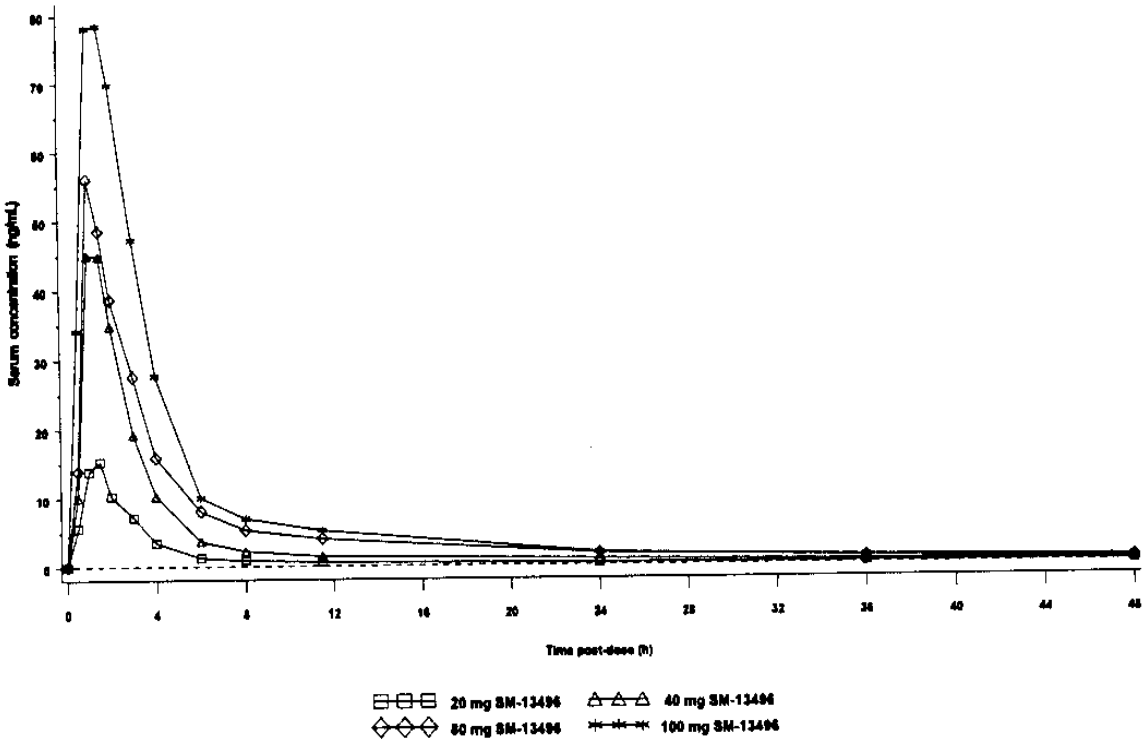
Single Dose (Healthy Subjects)

What are the single dose and multiple dose pharmacokinetic parameters?

The results of the single dose study (Study D1050001-P01) are summarized below in the following table. The study was conducted in 21 Caucasian subjects in UK where single dose of lurasidone 20 to 100 mg was assessed in a double-blind, single center, placebo controlled study. Lurasidone doses were administered under fed conditions. The inter-subject variability (%CV) was generally high, except for 40 mg dose, ranging from 38.5% to 51.1% for AUC and 47.9% to 67.7% for Cmax.

The geometric mean serum concentration-time profiles for lurasidone are presented in the following figure. The disposition kinetics were characterized by a bi-phasic decline.

Geometric Mean Serum Concentrations of Lurasidone



Pharmacokinetic Parameters of Single Dose of Lurasidone (SM-13496) in Healthy Subjects

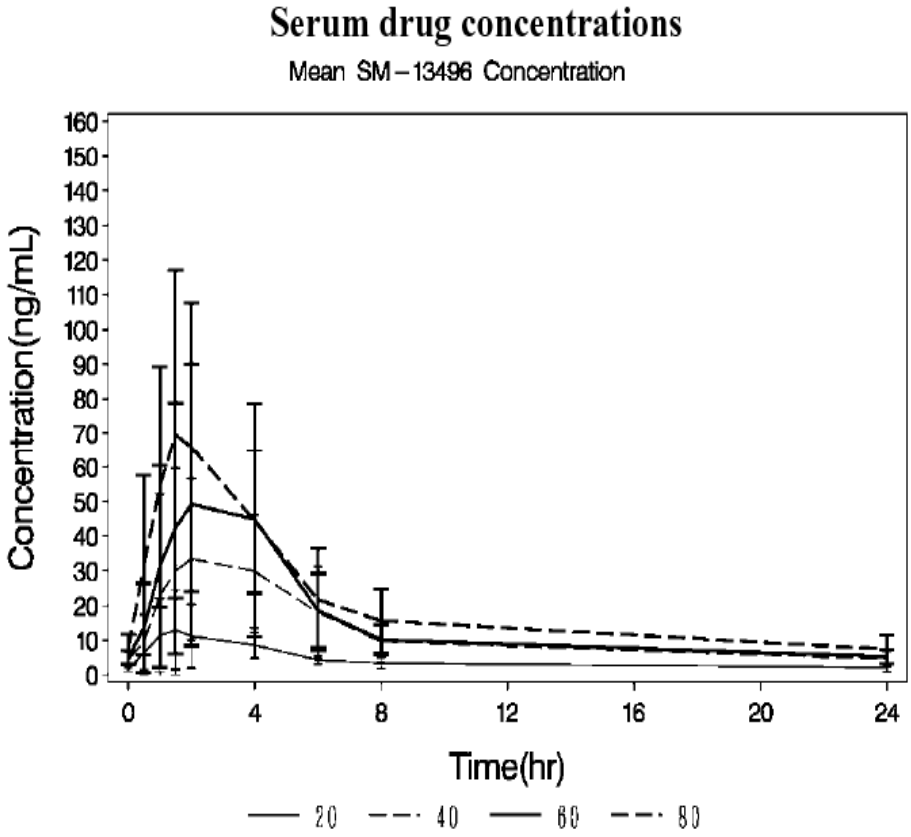
Parameter	Dose of SM-13496			
	20 mg (N=5)	40 mg (N=4)	80 mg (N=6)	100 mg (N=6)
AUC(0-t_z) (ng.h/mL)	57.8 (45.4)	160 (17.8)	248 (40.1)	374 (50.8)
AUC(0-∞) (ng.h/mL)	60.7 (44.6)	171 (18.0)	261 (38.5)	387 (51.1)
C_{max} (ng/mL)	18.4 (67.7)	52.9 (21.3)	58.5 (47.9)	97.1 (48.6)
t_{max}† (h)	1.5 (1.0-1.5)	1.3 (1.0-1.5)	1.0 (1.0-2.0)	1.3 (1.0-2.0)
AUC(0-t_z)(norm)	195 (50.3)	285 (26.8)	226 (41.8)	252 (43.8)
AUC(0-∞)(norm)	204 (49.4)	304 (27.0)	238 (40.9)	261 (43.8)
C_{max}(norm)	62.1 (74.4)	94.0 (21.5)	53.3 (50.7)	65.5 (42.6)
t½ (h)	16.3 (12.1)	18.3 (6.98)	13.7 (25.1)	12.1 (12.3)

Geometric mean (%CV) data presented
Median (min-max)
#Normalized for body weight
N= Number of subjects
Norm = Normalized for dose and body weight (mg/kg)

Multiple Dose Pharmacokinetics in schizophrenic patients

Lurasidone was administered to Japanese male and female patients with schizophrenia using the flexible dose method at doses ranging from 20 to 80 mg/day. Serum lurasidone concentrations were determined after administration for 6 consecutive days or longer when pharmacokinetics was at steady state. The plasma concentrations decline bi-exponentially. Steady-state concentrations of lurasidone were achieved within 7 days . The mean Cmax and AUC(0-24) of the active metabolite ID-14283 were approximately 23 to 26% and approximately 24 to 29% of lurasidone, respectively. The mean Cmax and AUC(0-24) of the metabolite ID-14326 were approximately 2 to 3% and approximately 2 to 4% of lurasidone, respectively. The following table contains the pharmacokinetic parameters after multiple dosing.

Lurasidone serum concentration time profile after repeated dose administration



Summary Pharmacokinetics of Lurasidone after Multiple Dose Administration

Dose (mg)		Cmax ng/mL	Tmax hr	Cmin ng/mL	AUC(0-24) ng*hr/mL
20 mg	N	6	6	6	6
	Mean	16.37	3.25	1.60	95.16
	SD	8.99	2.61	0.59	29.01
	CV (%)	54.9	80.4	36.7	30.5
40 mg	N	9	9	9	9
	Mean	48.33	3.40	4.34	285.56
	SD	25.35	1.72	2.15	113.37
	CV (%)	52.4	50.7	49.6	39.7
60 mg	N	8	8	8	8
	Mean	65.97	2.20	5.01	362.83
	SD	37.42	1.11	1.91	175.77
	CV (%)	56.7	50.6	38.1	48.4
80 mg	N	7	7	7	7
	Mean	79.39	2.13	7.32	487.39
	SD	41.39	1.25	4.33	211.90
	CV (%)	52.1	58.7	59.2	43.5

2.6.1 How does the PK of the drug and its major metabolites in healthy volunteers compare to that in patients?

Based on population pharmacokinetic analysis conducted using data from healthy subjects and schizophrenia and schizoaffective disorder patients , no difference was found in the pharmacokinetics of lurasidone in schizophrenia and those with schizoaffective disorder patients compared to healthy subjects.

2.6.2 What are the general ADME (Absorption, Distribution, Metabolism and Elimination) Characteristics of Lurasidone?

Absorption

Lurasidone bioavailability was not formally evaluated and is unknown. But based on amount excreted in urine unchanged in radiolabeled studies, it is estimated to be about 9 to 19%. The maximum concentration is reached in about 1.5 and3 hours after single dose and multiple administration, respectively.

Distribution

The mean apparent volume of distribution after single and multiple-dose administration ranges from 4182 L to 11236 L (D1050001, D1050160) and 3220 L and 4410 L, respectively. Lurasidone is highly bound (≥ 99 %) to HSA and α1-AGP. The mean fraction of lurasidone distributed in RBCs is approximately 9% in vitro, in human blood, and approximately 12% in vivo, in humans. Protein binding of lurasidone was not affected by concomitant drugs. Protein binding of concomitant drugs were not affected by lurasidone. The binding of the two active metabolites in human serum was ≥ 98.8%

Metabolism

Lurasidone is metabolized primarily by the cytochrome P450 (CYP) system. CYP3A4 is the major enzyme involved in the metabolism of lurasidone. The major biotransformation pathways are oxidative N-dealkylation, hydroxylation of the norbornane ring, S-oxidation, reductive cleavage of the isothiazole ring followed by S-methylation, and a combination of two or more of these pathways.

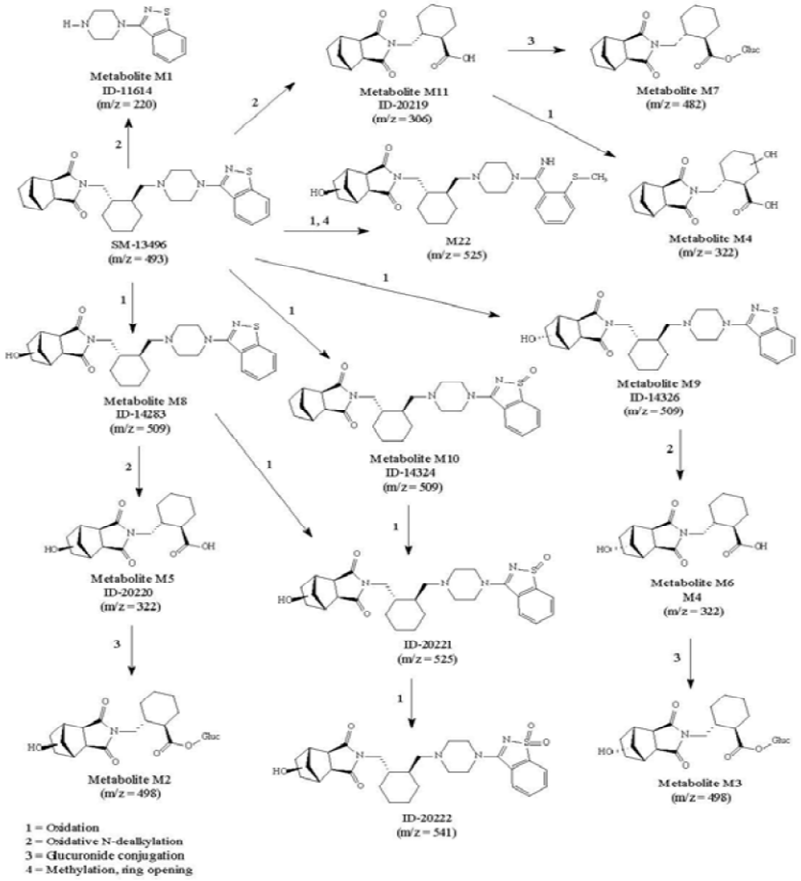
Lurasidone was a moderate inhibitor of CYP2C19 and CYP3A4. Lurasidone was a moderate inhibitor of CYP2C8, CYP2C9, CYP2C19, CYP3A4, and CYP2B6-mediated reactions. Lurasidone and ID-14283 were not substrates for human or mouse P-gp

Metabolite profiling as demonstrated by Liquid Chromatography-Mass Spectrometry (LC-MS) qualitative analysis and radioactivity monitoring indicated that lurasidone is metabolized to several metabolites. The parent compound, Lurasidone accounted for about 12% of the observed total radioactivity. Based on AUC(0-12) total radioactivity was 2.8%, 0.4% for active metabolites ID-14283 and ID-14326, respectively. The major metabolites, ID-20219 and ID-20220 accounted for approximately 24% and 11% of the total radioactivity AUC from time 0 to 8 hours , respectively using [carbonyl-14C] lurasidone). The metabolites ID-20219 and 20220 are not active.

The proposed metabolic pathway is provided in the following figure

Metabolism

Figure 1
Proposed metabolic pathway of [carbonyl-^{14}C]-SM-13496



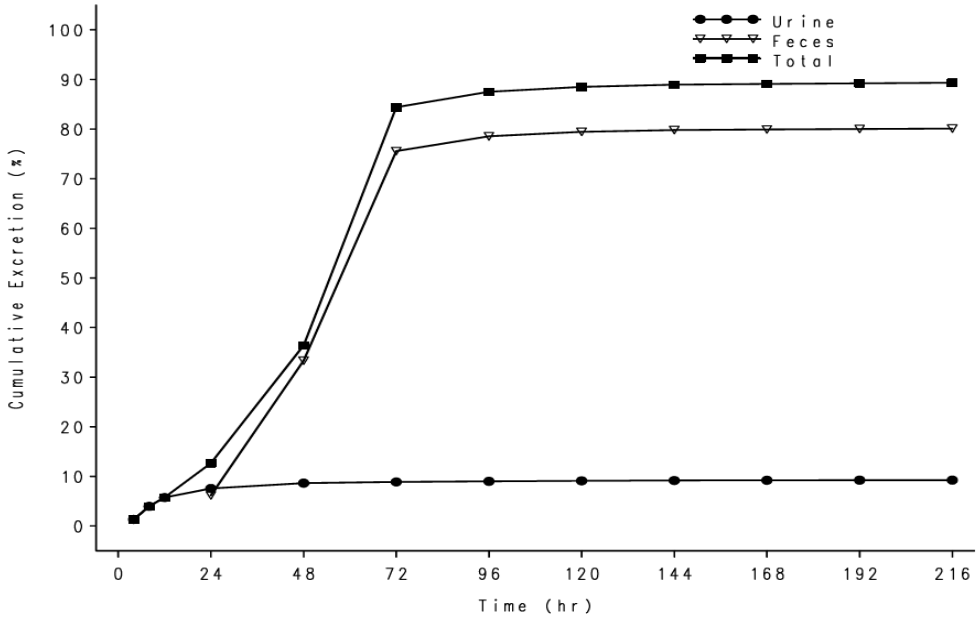
Excretion

Total excretion of the dose recovered in urine and feces combined was 89.3 %, with 80.1 % recovered in feces and 9.2% recovered in urine.

A single postprandial dose of approximately 40 mg (150 µCi [5.55 MBq]) [isothiazolyl-3-14C]-lurasidone was administered to six subjects. In this study, lurasidone accounted for 12% of the total radioactivity, and the remainder of the

radioactivity was from the metabolites, based on the mean AUC from time 0 through the dosing interval [AUC(0- t)]. The following figure and table contain the cumulative excretion of radioactivity

Mean Cumulative Excretion of Radioactivity-Time Profile



		Total Radioactivity Recovered (216 hr)	
		Total Ae[a]	Total % Excreted
Matrix	Statistics	(mg equivalents)	(%)
Urine	N	6	6
	Mean	3.51	9.19
	SD	0.844	2.39
	Min	1.85	4.69
	Median	3.82	9.79
	Max	4.17	11.6
	CV%	24	26
Feces	N	5	5
	Mean	30.2	80.1
	SD	2.39	6.21
	Min	27.6	73.3
	Median	29.5	78.6
	Max	33.9	87.6
	CV%	8	8
Total	N	33.71	89.29

[a]Aeu is presented for urine total radioactivity and Aef is presented for feces total radioactivity

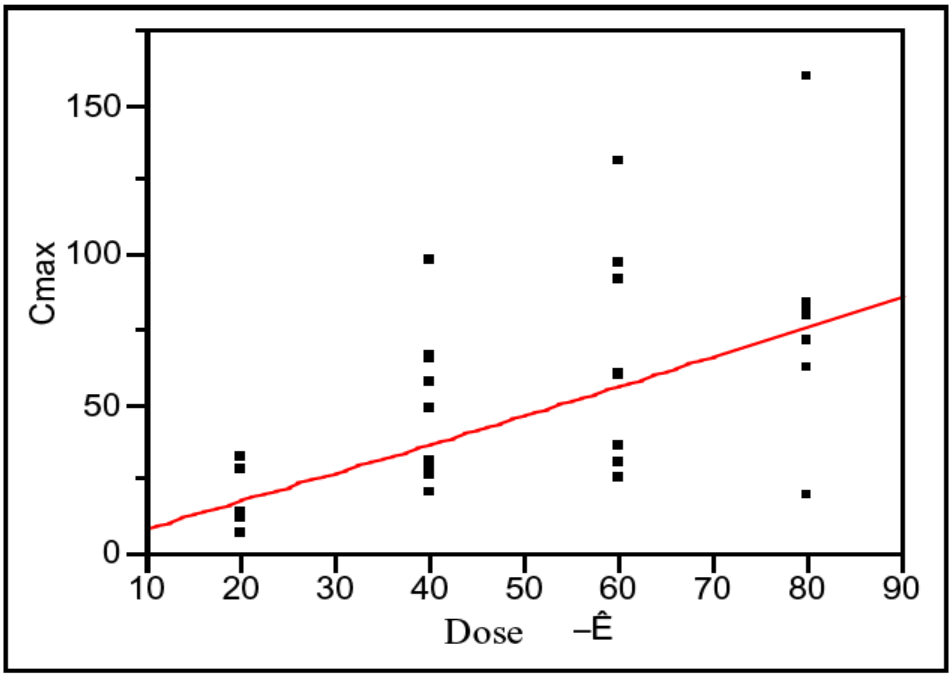
In another study of single postprandial dose of approximately 40 mg (150 µCi [5.55 MBq]) [isothiazolyl-3-14C]-lurasidone was administered to five subjects. In this study, the mean percent (%CV) excreted in feces and urine was 67.2% (6) and 19.1% (6), respectively. Total mean percent (%CV) excreted in urine and feces were 86.5% (5).

2.6.3 Based on PK parameters, what is the degree of linearity or nonlinearity?

Multiple-dose pharmacokinetics of lurasidone is dose proportional in the 20 mg to 160 mg dose range. However, there was large variability in the data.

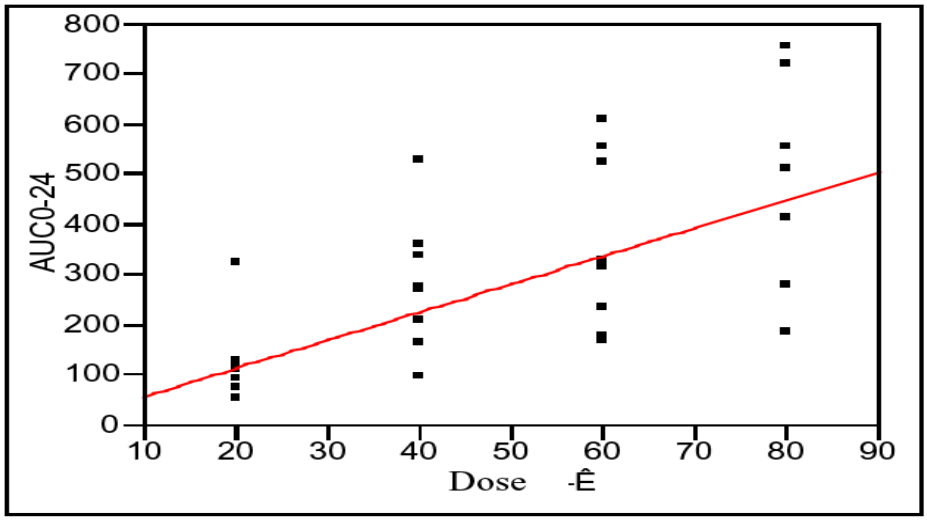
Assessment of linearity was conducted for Cmax , AUC(0-24) and Cmin of lurasidone using an exponential model (power model, not adjusted for weight). After administration of lurasidone at 20, 40, 60 and 80 mg, Cmax, AUC(0-24) and Cmin of lurasidone in serum all increasing linearly with dose. The following figures and equation suggest linearity between dose and Cmax, AUC and Cmin.

Dose-relationship for serum Cmax of SM-13496 (not adjusted for weight)



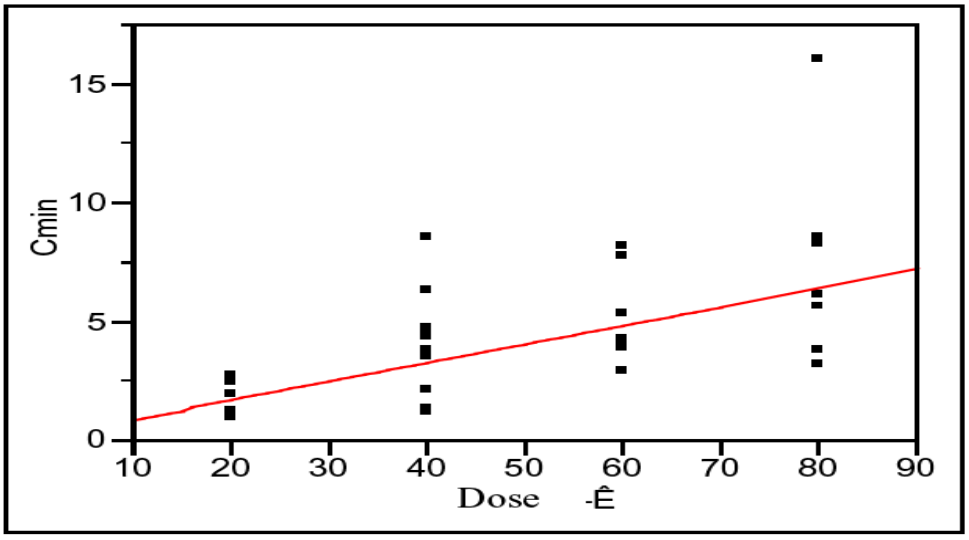
$$\log (C_{max}) = -0.54933 + 1.11856 \log (\text{dose})$$

Dose-relationship for serumAUC0-24 of SM-13496 (not adjusted for weight)



$$\log(AUC_{0\text{-}24}) = 1.34607 + 1.09832 \log(\text{dose})$$

Dose-relationship for serum Cmin of SM-13496 (not adjusted for weight)



$$\log(C_{min}) = -2.51726 + 1.00764 \log(\text{dose})$$

The following table contains the results of the power model analyses

Estimate of regression parameters for log (Cmax) and log (dose) for serum Lurasidone (not adjusted for weight)

Term	Estimate	S.E.	Lower 95% CI	Upper 95% CI
Intercept	–0.54933	0.83556	–2.26090	1.16225
Slope	1.11856	0.21699	0.67408	1.56305

Estimates of regression parameters for log (AUC0-24) and log (dose) for serum Lurasidone (not adjusted for weight)

Term	Estimate	S.E.	Lower 95% CI	Upper 95% CI
Intercept	1.34607	0.65166	0.01121	2.68093
Slope	1.09832	0.16923	0.75167	1.44498

Estimates of regression parameters for log (Cmin) and log (dose) f or serum Lurasidone (not adjusted for weight)

Term	Estimate	S.E.	Lower 95% CI	Upper 95% CI
Intercept	–2.51726	0.68551	–3.92146	–1.11306
Slope	1.00764	0.17802	0.64298	1.37230

Also, based on population pharmacokinetic modeling, dose proportional increase in Cmax and AUC [AUC(0-∞) and AUC(0-24)] were observed in subjects with schizophrenia after single and multiple-dose administration of lurasidone doses ranging from 20 mg to 160 mg.

2.6.4 What is the variability of PK parameters in volunteers and patients, and what are the major causes of variability?

In healthy subjects, inter-patient variability (%CV) was 30% to 46% and 32 to 35% for Cmax and AUC(0-τ), respectively. In subjects with schizophrenia it was 33% to 54% and 36% to 63% for Cmax and AUC(0-τ), respectively.

2.7 Intrinsic Factors

2.7.1 What intrinsic factors influence exposure and what is the impact of any differences in exposure on efficacy or safety? Based upon what is known about exposure-response relationships and their variability and the groups studied, what dosage regimen adjustments, if any, are recommended for each of these groups?

Race, age and gender do not alter the pharmacokinetics of lurasidone or its active metabolites. Renal and hepatic impairment change the exposure of lurasidone hence dose adjustments are needed.

2.7.2 Effect of Renal Impairment

The effect of varying degrees of renal impairment on the single-dose PK of orally administered lurasidone 40 mg tablet was evaluated. Mean exposures to lurasidone (Cmax and AUC) increased with increase in severity of renal impairment after oral administration of 40 mg lurasidone tablet.

- The Cmax increased by 40%, 92%, and 54% in mild, moderate, and severe renal impairments, respectively;
- The AUC∞ increased by 53%, 91%, and 103% in mild, moderate, and severe renal impairments, respectively;
- The t1/2 prolonged with increasing severity of renal impairment for lurasidone.

It is recommended that doses in moderate and severe renal impaired patients should not exceed 40 mg as lower strengths are not currently available. No dose adjustment is recommended for mild renal impaired patients

Lurasidone 20 mg dosage strength should be developed and marketed by the sponsor and/or the 40 mg strength should be scored. A 20 mg strength would allow flexibility in dosing if needed in moderate and severe renally impaired patients.

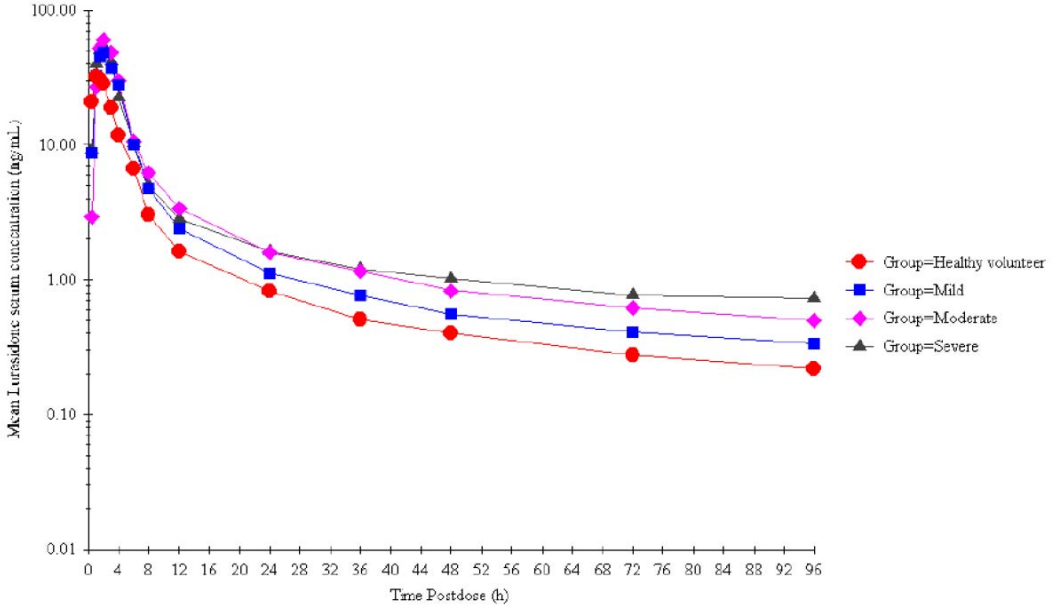
The study was an open-label, single dose, oral administration study of lurasidone 40 mg in subjects with mild, moderate and severe renal impairment including matched healthy controls under fed conditions. Healthy subjects were matched to renally impaired subject with respect to age, weight, BMI, and gender. The following is the demographics of subjects who participated in the study

Baseline Demographics of Subjects with Renal Impairment and Matched Healthy Controls

Creatinine Clearance (CLcr)[a]	Mean ClCr, mL/min	Renal function	N Male/Female
> 80 mL/min	90.0	Normal[b]	6/3
50 – 80 mL/min	70.6	Mild	6/3
≥ 30 and < 50 mL/min	42.2	Moderate	5/4
CrCl < 30 mL/min	24.1	Severe	7/2

[a] Calculated using Cockcroft and Gault formula
[b] Normal subjects matched with respect to age, weight (BMI), and gender

The following figure contains Lurasidone concentration time profile for renal impaired patients



PK parameters (mean ± SD, (CV%)) of lurasidone in patients with renal impairment and healthy subjects after a single oral dose of 40 mg lurasidone tablet are shown below:

Group	Cmax (ng/mL)	Tmax* (h)	AUC_{0-last} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	t1/2 (h)	CL/F (L/h)	Vz/F (L)
Healthy (N=9)	42.81 ± 24.68 (57.64)	1.5 (1-6)	166.74 ± 60.12 (36.06)	184.70 ± 71.84 (38.89)	52.25 ± 14.67 (28.07)	242.91 ± 79.83 (32.87)	17514.97 ± 5852.28 (33.41)
Mild (N=9)	59.23 ± 30.40 (51.33)	2 (1 - 4)	259.27 ± 105.46 (40.67)	291.88 ± 128.96 (44.18)	57.42 ± 28.05 (48.86)	165.79 ± 79.69 (48.07)	12101.97 ± 4310.41 (35.62)
Moderate (N=9)	76.31 ± 25.20 (33.02)	2 (1.5 - 3)	317.55 ± 144.38 (45.47)	362.59 ± 178.47 (49.22)	58.29 ± 12.51 (21.47)	129.11 ± 44.92 (34.79)	10336.37 ± 3079.61 (29.79)
Severe (N=9)	66.12 ± 38.32 (57.96)	2 (1 - 3)	302.70 ± 112.43 (37.14)	378.60 ± 157.85 (41.69)	67.18 ± 16.53 (24.61)	121.28 ± 43.81 (36.13)	11297.61 ± 3693.82 (32.70)

* Median (min-max)

The following table contains the statistical comparisons of Lurasidone PK parameters among subjects with varying degrees of Renal impairment and matched healthy controls.

Statistical Comparison of Lurasidone PK Parameters Among Subjects with Varying Degrees of Renal Impairment and Matched Healthy Controls (Ratio of Geometric Mean and 90% CI)

	Mild Renal Impairment versus Healthy	Moderate Renal Impairment versus Healthy	Severe Renal Impairment versus Healthy
Lurasidone			
Cmax	140.31 (100.39;196.11)	192.10 (137.45;268.49)	154.38 (110.46;215.77)
AUClast	151.32 (114.60;199.80)	186.13 (140.96;245.77)	181.05 (137.11;239.06)
AUC∞	153.06 (113.13;207.08)	191.01 (141.18;258.43)	202.60 (149.75;274.11)

2.7.3 Effect of Hepatic Impairment

Mean exposures to total lurasidone (Cmax and AUC) increased with increase in severity of hepatic impairment after oral administration of a 20 mg lurasidone tablet.

- The Cmax increased by 26%, 20%, and 25% for mild, moderate, and severe hepatic impairment groups, respectively;

- The AUClast increased by 49%, 66%, and 3-fold for mild, moderate, and severe hepatic impairment groups, respectively;
- The AUCinf increased by 35%, and 75% for mild and moderate hepatic impairment groups, respectively; there is no available data for severe hepatic impairment.
- The mean t1/2 for patients with mild hepatic impairment was similar to that for healthy subjects. However, the mean t1/2 for patients with moderate hepatic impairment was prolonged compared to that for healthy subjects (112 hours vs., 93 hours); there is no available data for severe hepatic impairment.
- Increases in AUC and t1/2 of metabolites ID-14283 and ID-14326 were also observed with increasing severity of hepatic impairment compared with the healthy matched control group. The Cmax values of metabolites ID-14283 and ID-14326 also increased for mild and moderate hepatic impairments.

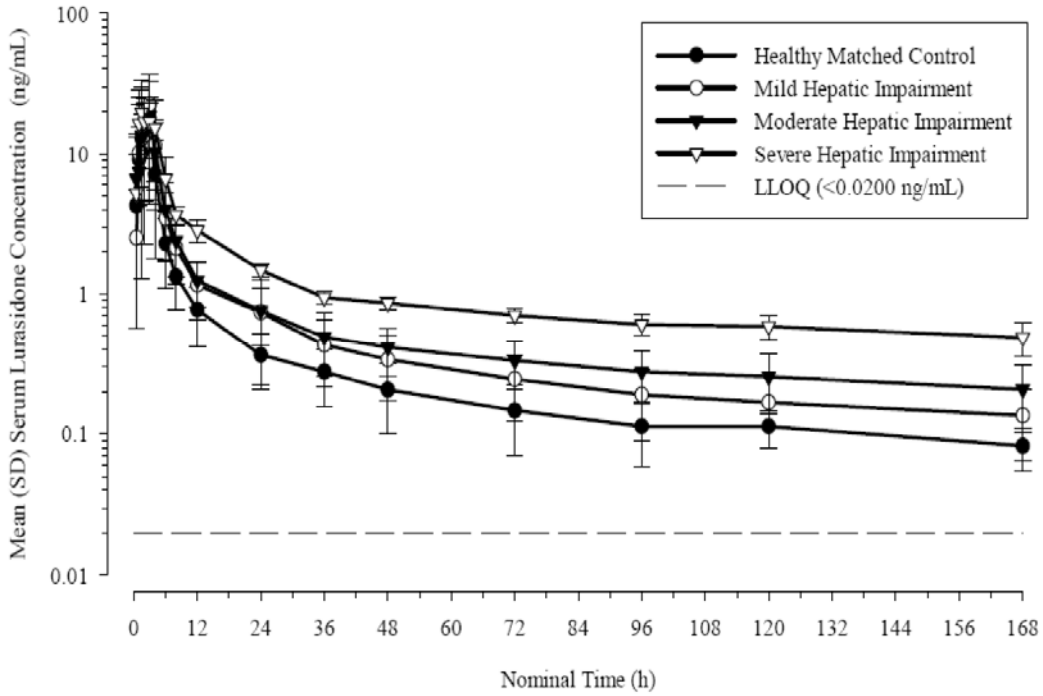
It is recommended that doses in moderate and severe hepatic impaired patients should not exceed 40 mg as lower strengths are not currently available. No dose adjustment is recommended for mild hepatic impaired patients

Lurasidone 20 mg dosage strength should be developed and marketed by the sponsor and/or the 40 mg strength should be scored. A 20 mg strength would allow flexibility in dosing if needed in moderate and severe hepatically impaired patients.

The effect of varying degrees of hepatic impairment on the single-dose PK of orally administered lurasidone 20 mg was investigated. This was an open label, single dose, multicenter and parallel group comparative study. A total of 21 subjects were dosed: 6 subjects with mild hepatic impairment (Child Pugh Class A); 6 subjects with moderate hepatic impairment (Child Pugh Class B); 3 subjects with severe hepatic impairment (Child Pugh Class C); and 6 healthy subjects matched for age, weight, and gender.

The following figure contains lurasidone concentration-time profile among subjects with varying degrees of hepatic impairment.

Lurasidone Concentration-Time Profile Among Subjects with Varying Degrees of Hepatic Impairment and Healthy Matched Controls



PK parameters (mean ± SD, CV%) of lurasidone in patients with hepatic impairment and healthy subjects after a single oral dose of 20 mg lurasidone tablet are shown below:

Group	Cmax (ng/mL)	Tmax** (h)	AUC_{0-last} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	t1/2 (h)	CL/F (L/h)	Vz/F (L)
Healthy (N=6)	22.9 ± 10.3 (44.8)	2 (1-3)	83.2 ± 34.9 (41.9)	94.0 ± 41.5 (44.1)	93.1 ± 31.3 (33.6)	279 ± 201 (71.9)	30980 ± 7776 (25.1)
Mild* (N=6)	29.3 ± 14.4 (49.2)	3 (1.5 - 3)	121 ± 50.8 (41.9)	123 ± 62.2 (50.5)	90.7 ± 17.0 (18.8)	192 ± 92.2 (48.0)	24115 ± 8673 (36.0)
Moderate* (N=6)	26.6 ± 11.5 (43.3)	1.5 (0.5 - 3)	131 ± 40.6 (31.1)	155 ± 61.9 (39.8)	112 ± 33.3 (29.8)	144 ± 59.7 (41.5)	21973 ± 6568 (29.9)
Severe* (N=3)	25.8 ± 6.13 (23.7)	1.5 (1 - 4)	225 ± 12.0 (5.3)	NC	NC	NC	NC

* $AUC_{0-\infty}$ extrapolation exceeded 20% for some subjects; N=3 for PK parameters of $AUC_{0-\infty}$, t1/2, CL/F and Vz/F.
** Median (min-max).
NC, not calculated.

The following table contains statistical comparisons of lurasidone pharmacokinetics parameters of subjects with varying degrees of hepatic impairment.

Statistical Comparison of Lurasidone PK Parameters Among Subjects with Varying Degrees of Hepatic Impairment and Matched Healthy Controls

Parameter (Units)	Group	Comparison	N	Geometric LS Means	Ratio (%)	90% CI
C_{max} (ng /mL)	Matched Healthy Control	--	6	20.3	--	--
	Mild[a]	Mild/Matched Healthy Control	6	25.5	125.53	65.82 – 239.40
	Moderate[b]	Moderate/Matched Healthy Control	6	24.3	119.70	67.55 – 212.11
	Severe[c]	Severe/Matched Healthy Control	3	25.4	125.06	73.95 – 211.50
$AUC_{0\text{-}last}$ (ng•h/mL)	Matched Healthy Control	--	6	75.2	--	--
	Mild[a]	Mild/Matched Healthy Control	6	112	148.64	88.29 – 250.24
	Moderate[b]	Moderate/Matched Healthy Control	6	125	166.15	103.00 – 268.02
	Severe[c]	Severe/Matched Healthy Control	3	225	299.08	191.64 – 466.77
$AUC_{0\text{-}\infty}$ (ng•h/mL)	Matched Healthy Control	--	6	84.0	--	--
	Mild[a]	Mild/Matched Healthy Control	3	113	134.59	62.32 – 290.66
	Moderate[b]	Moderate/Matched Healthy Control	3	147	175.04	90.60 – 338.18
	Severe[c]	Severe/Matched Healthy Control	0	NA	NA	NA

[a] Mild Impairment: Child Pugh Score (CPS) 5-6 points
[b] Moderate Impairment: CPS 7-9 points
[c] Severe Impairment: CPS 10-15 points

2.7.4 Effects of Age

Overall, in cross study comparison, there was trend towards differences in pharmacokinetics based on age. But the statistical analysis was based a small number of subjects therefore the results are inconclusive. Population PK analysis indicated no difference in pharmacokinetics based on age. No dose adjustment is required in elderly subjects.

The AUC and Cmax of lurasidone in elderly males and females from the present study and young males and females from the designated historical studies were natural log-transformed and evaluated using a fixed effects analysis of variance (ANOVA) model having factors for age group, gender, and age by gender interaction. A two-sided 90% confidence interval (CI) for the difference in mean log AUC (test - reference) was

calculated using the mean square error from the model and referencing a t-distribution for each comparison. These confidence limits were exponentiated to obtain the 90% CI for the AUC ratio of geometric means (test/reference).

Statistical analysis of lurasidone PK parameters to compare elderly subjects to young subjects is

Analyte	Parameter (Units)	Comparison	LS Means[a]				Test/Reference (%)[b]	90% Confidence Interval (%)[c]	P-value[d]
			N	Test	N	Reference			
Lurasidone	AUC_{0-t} (ng·hr/mL)	Elderly (T) vs. Young (R)	9	105	10	96.2	108.68	(87.87 , 134.41)	0.1055
	$AUC_{0-\infty}$ (ng·hr/mL)	Elderly (T) vs. Young (R)	7	128	10	106	121.04	(96.03 , 152.57)	0.0406
	C_{max} (ng/mL)	Elderly (T) vs. Young (R)	9	21.7	10	22.6	96.11	(76.03 , 121.48)	0.7897

[a] Least squares mean from ANOVA. Natural log parameter means calculated by transforming the ln means back to the linear scale (ie, geometric means). N was the number of subjects for the corresponding group.

[b] Ratio of parameter means for ln-transformed parameters (expressed as a percent), transformed back to linear scale.

[c] 90% CI for ratio of parameter means for ln-transformed parameters (expressed as a percent), transformed back to linear scale.

[d] P-value is testing for age by gender interaction. If the p-value is less than 0.10, applicable subgroup comparison as specified in the statistical methodology (ie, elderly males/young males, elderly females/young females, and young females/young males) were added to Table 14.2.3-2.

NOTE: T=test; R=reference. Data for young subjects are from prior study (D1050250 [MK-3756 Protocol 022]).

Reference: Table 14.2.3-1.

2.7.5 Effect of Gender and Race

AUC in females are about 20% higher than males. Asians have 40% less clearance than Caucasians. The changes in exposure are not expected to be clinically relevant.

No dose adjustment is recommended based on race or gender.

2.7.6 Pediatric and Adolescents

Safety and effectiveness in pediatric and adolescent patients have not been evaluated.

2.8 Extrinsic Factors

What Extrinsic Factors (Such as Herbal Products, Diet, Smoking and Alcohol) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

2.8.1 In Vitro

In vitro studies indicate that Lurasidone is primarily metabolized by CYP3A4. Lurasidone had inhibitory effects on CYP2C8, CYP2C9, CYP2C19, CYP3A4 and CYP2B6. Lurasidone and its active metabolite, ID-14283 are not P-gp substrates. Lurasidone inhibited P-gp mediated transport of digoxin.

2.8.2 In Vivo

2.8.1.1 Influence of Lurasidone on other drugs

Effect of lurasidone on other drugs

Drug Name	Dosing Regimen	Effect on Other Drug	Recommendation
Digoxin	Day 1: 0.25 mg digoxin Days 6 – 12: lur 120 mg daily Day 13: digoxin 0.25 mg plus lur 120 mg Doses with food	AUC ↑ 10 -13% Cmax ↑ 9%	No significant effect. No Digoxin dose adjustment
Midazolam	Day 1: 5 mg mdz Day 6: 120 mg lur + 5 mg mdz Days 7 -12: lur 120 mg daily Day 13: lur 120 mg + 5 mg lur Washout: 5 days	SD AUC ↑ 18- 20% Cmax ↑ 5% MD #AUC ↑ 37-43% #Cmax ↑ 21%	Dose adjustment for MDZ not recommended. Close observation
Oral Contraceptive	Periods 1 and 2: Ortho Tri-Cyclen (OC) 28 day lead in period Then, OC for 10 days. Then OC + either lur 40 mg or placebo for 10 days Then OC for 5 days Cross-over study	Ethinyl Estradiol AUC ↑ 3% Cmax ↓ 2% Norelgestromin AUC ↑ 12% Cmax ↑ 8%	No dose adjustment for OC

#90% CI not within 80% - 125%

Statistical Analysis of Effect of Lurasidone on the Pharmacokinetics of Coadministered Drugs

Study	PK Parameter (unit)		Ratio of LS Mean (%) (Lurasidone + Concomitant Medication)/ Concomitant Medication	90% CI (%)
Digoxin **[D1050279, Table 15]**	AUC_{0-last} (ng*hr/mL)		110.53	102.22 – 119.51
	C_{max} (ng/mL)		109.42	93.14 – 128.54
Oral Contraceptive **[D1050246, Table 14, 15]**	AUC_{0-24} (pg*hr/mL)	Ethinyl Estradiol	103	91.74 – 114.72
	C_{max} (pg/mL)	Ethinyl Estradiol	98.0	86.94 – 110.37
	AUC_{0-24} (pg*hr/mL)	Norelgest-romin	112	105.75 – 118.46
	C_{max} (pg/mL)	Norelgest-romin	108	96.65 – 120.57
Midazolam **[D1050269, Table 14]**	AUC_{0-24} (ng*hr/mL)	Single Dose	117.95	111.62 – 124.64
		Steady State	137.92	125.81 – 151.21
	$AUC_{0-\infty}$ (ng*hr/mL)	Single Dose	119.82	113.08 – 126.97
		Steady State	143.87	129.60 – 159.71
	C_{max} (ng/mL)	Single Dose	104.93	92.95 – 118.46
		Steady State	121.47	108.77 – 135.65

$AUC_{(0-\infty)}$ = area under serum concentration-time curve from time 0 extrapolated to infinity; $AUC_{(0-last)}$ = area under serum concentration-time 0 to last quantifiable collection; $AUC_{(0-24)}$ = area under serum concentration-time curve from time 0 to 24 hours; C_{max} = maximum observed serum concentration; LS = Least Squares; CI = Confidence Interval

Lurasidone does not significantly affect the exposure of digoxin, midazolam or oral contraceptives containing ethinyl estradiol and norelgestromin. Dose adjustment is not recommended when lurasidone is co-administered with digoxin, midazolam and oral contraceptives.

2.8.1.2 Influence of other drugs on Lurasidone

Statistical Analysis of Effect of Coadministered Drugs on the Pharmacokinetics of Lurasidone

Study	PK Parameter (unit)	Ratio of LS Mean (%) (Lurasidone + Concomitant Medication)/Lurasidone	90% CI (%)
Ketoconzole **[D1050183; Table 10.2.1-4]**	AUC_{0-last} (ng*hr/mL)	895	754 - 1062
	C_{max} (ng/mL)	692	576 - 830
Diltiazem **[D1050250; Table 12]**	$AUC_{0-\infty}$ (ng*hr/mL)	216	192 - 244
	C_{max} (ng/mL)	210	177 - 247
Rifampin **[D1050270, Table 13]**	$AUC_{0-\infty}$ (ng*hr/mL)	19.28	16.90 - 21.99
	C_{max} (ng/mL)	14.67	12.29 - 17.52
Lithium **[D1050247, Table 12]**	AUC_{tau} (ng*hr/mL)	107.26	95.54 – 120.43
	C_{max} (ng/mL)	92.03	75.52 – 112.15

$AUC_{(0-\infty)}$ = area under serum concentration-time curve from time 0 extrapolated to infinity; $AUC_{(0-last)}$ = area under serum concentration-time 0 to last quantifiable collection; AUC_{tau}= AUC over a dosing interval for steady-state; C_{max} = maximum observed serum concentration; LS = Least Squares; CI = Confidence Interval

The following table contains study design and dosing recommendations on the effect of other drugs on lurasidone.

Effect of other drugs on Lurasidone

Drug	Dosing Regimen	Effect on Lurasidone	Effect on active metabolite (ID-14283)
Ketoconazole (pilot study) Subtherapeutic doses of lur used Effect of lur on Keto not evaluated	Day 1: Lur 10 mg Days 7 -13: Keto 400 mg daily Day 11: Lur 10 mg + Keto 400 mg Days 12 – 13: Keto 400 mg daily Dose with food	#AUC ↑ 795% #Cmax ↑ 592% Recommendation: Contraindicate	Not evaluated
Diltiazem Low dose used Effect of lur on diltiazem not evaluated	Period 1: 20 mg of lurasidone or matching placebo Period 2 days 1 -7, 240 mg diltiazem daily Period 2 day 5: lur 20 mg Dose with food 5-day washout	#AUC ↑ 116% #Cmax ↑ 110% Recommendation: Max lur dose: 40 mg Close monitoring or use alternate therapy	#AUC ↑ 138% #Cmax ↑ 114%
Rifampin Effect of lur on rifampin not evaluated	Period 1 day 1: 40 mg lur Period 2 days 1-8: 600 mg rifampin daily Period 2 day 8: lur 40 mg. Lur dose with food	#AUC ↓ 81 – 83% #Cmax ↓ 85% Recommendation: Contraindicate	#AUC ↓ 90% #Cmax ↓ 93%
Lithium	Period 1 days 1 -8: lur 120 mg daily Period 2 days 1 – 8: lur 120 mg daily and lithium 600 mg BID	AUC ↑ 7% #Cmax ↓ 8% Recommendation: No change in dose	No effect

#90% CI not within 80% - 125%

Significant interactions are observed between lurasidone and ketoconazole and between lurasidone and rifampin when they are administered together. It is recommended lurasidone should not be administered with either ketoconazole or rifampin.

When lurasidone is administered with diltiazem, a CYP3A4 moderate inhibitor, the dose of lurasidone should not exceed 40 mg.

It is recommended that a lower 20 mg strength be developed by the sponsor and/or the Lurasidone 40 mg strength should be scored. This will allow flexibility in dosing if needed if Lurasidone is to be coadministered with diltiazem.

2.9 General Biopharmaceutics

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

BCS classification was not sought and determined. But lurasidone has very low aqueous solubility (water: 0.224 mg/mL) and the bioavailability is estimated to be about 9% to 19%, therefore Lurasidone is not expected to be BCS1.

2.9.2 Is the proposed to-be-marketed formulation of Lurasidone bioequivalent to the formulation used in the primary bioavailability and clinical trials?

The sponsor conducted an open-label, randomized, single-dose, 2-period crossover study to evaluate the bioequivalence between single oral doses of one lurasidone 40 mg tablet (test), which is a planned formulation for approval, and those of two lurasidone 20 mg tablets (reference), which is the clinical study formulation. The doses were administered under fed conditions. This study was conducted in Japan in Japanese subjects.

Bioequivalence was demonstrated between the test formulation (To-be marketed) and the reference (clinical trial) formulation under fed conditions. The following table contains the statistical results of the bioequivalence analysis.

Bioequivalence Assessment

Analysis set: Bioequivalence assessment population

Dependent variable	Least-square geometric mean of the test formulation	Least-square geometric mean of the reference formulation	Geometric mean ratio (%)	Lower limit of 90% confidence interval	Upper limit of 90% confidence interval	Lower limit of 95% confidence interval	Upper limit of 95% confidence interval
Ln ($AUC_{0\text{-}t}^{*}$)	179.373	177.353	101.14	94.65	108.07	93.39	109.53
Ln (C_{max})	45.461	49.534	91.78	81.76	103.03	79.86	105.47

Dependent variable	Least-square geometric mean of the test formulation	Least-square geometric mean of the reference formulation	Geometric mean ratio (%)	Lower limit of 90% confidence interval	Upper limit of 90% confidence interval	Lower limit of 95% confidence interval	Upper limit of 95% confidence interval
Ln ($AUC_{0\text{-}\infty}$)	194.194	191.483	101.42	95.17	108.08	93.95	109.48
Ln (CL/F)	205.979	208.896	98.60	92.53	105.08	91.34	106.44
Ln (λz^{**})	0.032	0.033	99.01	92.48	105.99	91.21	107.47
Ln (MRT)	12.691	12.069	105.15	98.51	112.24	97.22	113.74
Ln (Vz/F)	6371.701	6397.871	99.59	90.58	109.50	88.85	111.63

Dependent variable	Test formulation Median (hr)	Reference formulation Median (hr)	Median of difference (hr)	Lower limit of 90% confidence interval (hr)	Upper limit of 90% confidence interval (hr)	Lower limit of 95% confidence interval (hr)	Upper limit of 95% confidence interval (hr)
t_{max}	2	1.5	0.25	0.25	0.5	0.25	0.5

Test formulation = SM-13496 40 mg tablets, Reference formulation = SM-13496 20 mg tablets

*: In this study, t=48h. **: Synonymous with k_{el}

It must be noted that Lurasidone 20 mg tablets is not going to be marketed in the US but has been used in clinical studies. The study was conducted under fed conditions. Bioequivalence study conducted under fasting conditions was not submitted. Patients in the pivotal clinical trials were administered their doses under fed conditions.

After Division of Scientific Investigation (DSI) inspected the analytical site, DSI noted that wrong calibration curve was used in the analysis of samples from patients who received on particular batch (Batch No. 090804a). The sponsor was asked to re-calculate the concentrations for patients who received this batch and bioequivalence between the To be Marketed material (TBM) and Clinical Trial Material (CTM) was determined again using the correct concentrations from these patients. The re-calculated data also indicate that the TBM is bioequivalent to the CTM. The following table contains the results of the re-calculated bioequivalence assessment.

Results of Bioequivalence Assessment (Re-calculated data)

Dependent variable	Least-square geometric mean of the test formulation	Least-square geometric mean of the reference formulation	Geometric mean ratio (%)	Lower limit of 90% confidence interval	Upper limit of 90% confidence interval
Ln (AUC_{0-t}*)	179.955	178.491	100.82	94.28	107.82
Ln (C_{max})	45.602	49.794	91.58	81.51	102.90

Test formulation = SM-13496 40 mg tablets, Reference formulation = SM-13496 20 mg tablets
*: In this study, t=48h.

Table 3B Results of the bioequivalence assessment

Dependent variable	Least-square geometric mean of the test formulation	Least-square geometric mean of the reference formulation	Geometric mean ratio (%)	Lower limit of 90% confidence interval	Upper limit of 90% confidence interval
Ln ($AUC_{0-\infty}$)	194.814	192.735	101.08	94.78	107.79
Ln (CL/F)	205.324	207.539	98.93	92.77	105.50
Ln (λz**)	0.032	0.033	99.12	92.62	106.09
Ln (MRT)	12.686	12.079	105.03	98.40	112.10
Ln (Vz/F)	6348.333	6360.655	99.81	90.69	109.84

Test formulation = SM-13496 40 mg tablets, Reference formulation = SM-13496 20 mg tablets
**: Synonymous with k_{el}

Table 3C Results of the bioequivalence assessment

Dependent variable	Test formulation Median (hr)	Reference formulation Median (hr)	Median of difference (hr)	Lower limit of 90% confidence interval (hr)	Upper limit of 90% confidence interval (hr)
t_{max}	2	1.5	0.25	0.25	0.5

Test formulation = SM-13496 40 mg tablets, Reference formulation = SM-13496 20 mg tablets

This study was inspected by DSI. DSI recommended that because analytical deficiencies during the analysis of the samples at the analytical site (b) (4)), the integrity of the data could not be assured and the study should not be accepted (refer to Appendix for DSI report, (b) (4) Response and OCP comments). OCP agrees with DSI (See OCP response to DSI inspection in Appendix). This single dose study cannot be considered pivotal and determination of bioequivalence between the To be Marketed formulation and the Clinical Trial Material cannot be based solely on this study.

The sponsor submitted a multiple dose bioequivalence study comparing the Lurasidone 120 mg (3 x 40 mg) clinical trial formulation to Lurasidone 120 mg (1 x 120 mg) (b) (b) (4) This multiple dose study used the proposed highest strength, was conducted under fed conditions, with a replicate design and no washout between periods. ,Generally, multiple dose studies are not sensitive enough to detect differences in formulation. This study was not inspected by DSI.

This was an open-label, randomized, three-period, two-sequence crossover, repeated-dose, incomplete replicate design study to compare the bioavailability of two different lurasidone formulations (3 x 40 mg reference film-coated tablets (b) (4) (CTM) versus 120 mg test film-coated tablet (b) (4) (TBM) in a minimum of 52 subjects with schizophrenia, schizoaffective, or schizophreniform disorder. Fifty-five subjects were

randomized. The safety population included 54 subjects and the PK population included 48 subjects. The subjects were randomized to one of two possible treatment sequences as shown below

Sequence	Period 1	Period 2	Period 3
1	T	R	T
2	R	T	R

R: Reference formulation (3 x 40 mg tablets (b) (4); T: Test formulation (1 x 120 mg tablet (b) (4)

The results of the statistical determination of bioequivalence is provided in the table below.

Assessment of Bioequivalence for Steady State Serum Lurasidone Pharmacokinetic Parameters

		LS Means				
Parameter	N	Test	Reference	Ratio of Geometric LS Means (Test/Reference)	90% CI for Ratio of Geometric LS Means (%)	Estimate of Intra-Subject CV
C_{max}	48	110.74	109.50	101.14 %	(94.37, 108.39)	23.1 %
AUC_{tau}	48	623.87	628.54	99.26 %	(95.40, 103.27)	13.1 %

AUC_{tau} = area under the curve from time 0 extrapolated to tau; CI = Confidence interval C_{max} = maximum serum concentration; CV = Coefficient of variation; LS = Least square; N = Number of subjects included in the analysis; Reference = 3 x 40 mg film-coated tablets (b) (4) Test = 1 x 120 mg film-coated tablet (b) (4)

The steady state PK results demonstrate that the test formulation (1 x 120 mg film-coated tablet (b) (4) TBM) is bioequivalent to the reference formulation (3 x 40 mg film-coated tablets (b) (4) CTM).

The sponsor is requesting waiver for the Lurasidone 80 mg tablet strength. Refer to ONDQA Biopharmaceutics review for decision on biowaiver request.

2.9.3 What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendations need to be made regarding the administration of Lurasidone in relation to meals or meal types.

The pivotal food effect study was an open-label study to determine the effect of calories and fat content on the pharmacokinetics of repeated dose Lurasidone 120 mg to be marketed formulation in subjects with schizophrenia, schizoaffective disorder, or schizophreniform disorder. The study compared the steady-state pharmacokinetic (PK) profile of lurasidone 120 mg with meals of various calorie and fat content versus the fasted state. The following table contains the meal composition used in the study.

Meal Composition

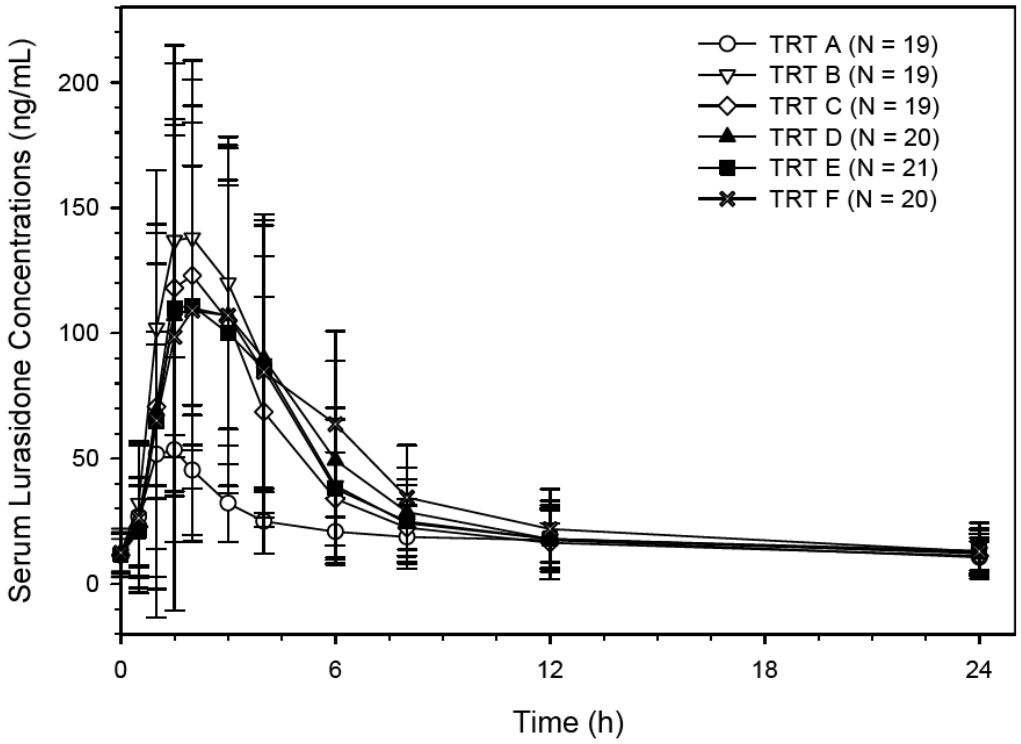
	Fat Content	
Calorie Content	Low (15% of total calories)	High (50% of total calories)
Low (350 calories)		Treatment A[a] and Treatment B
Medium (500 calories)	Treatment C	Treatment D
High (800 to 1000 calories)	Treatment E	Treatment F

Note: While the percent content of carbohydrate in all breakfasts varied across treatment, the protein content was approximately 15% of total calories.

[a.] Days 1 and 2 were fed conditions; and Days 3, 4, and 5 were fasted conditions.

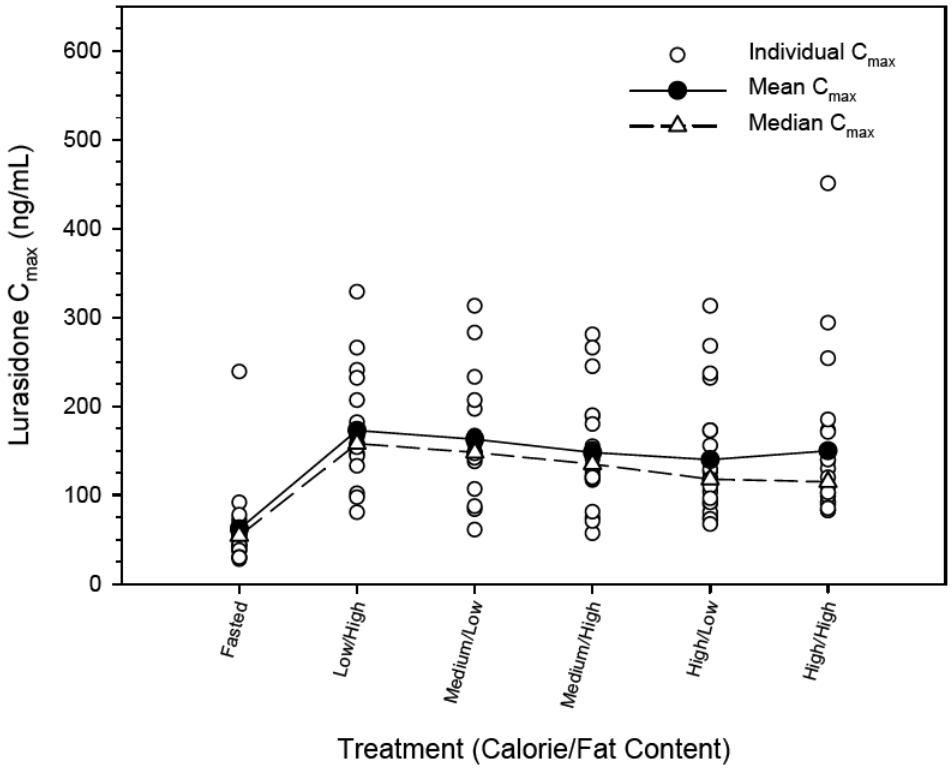
The following figure contains Mean (±SD) concentration-versus-time profiles for each treatment and scatter plots for Cmax and AUC of Lurasidone

Mean (±SD) Lurasidone serum concentration-time profiles after multiple-dose administration of 120 mg Lurasidone under fed (varying calories and fat content) and fasted conditions to subjects with schizophrenia

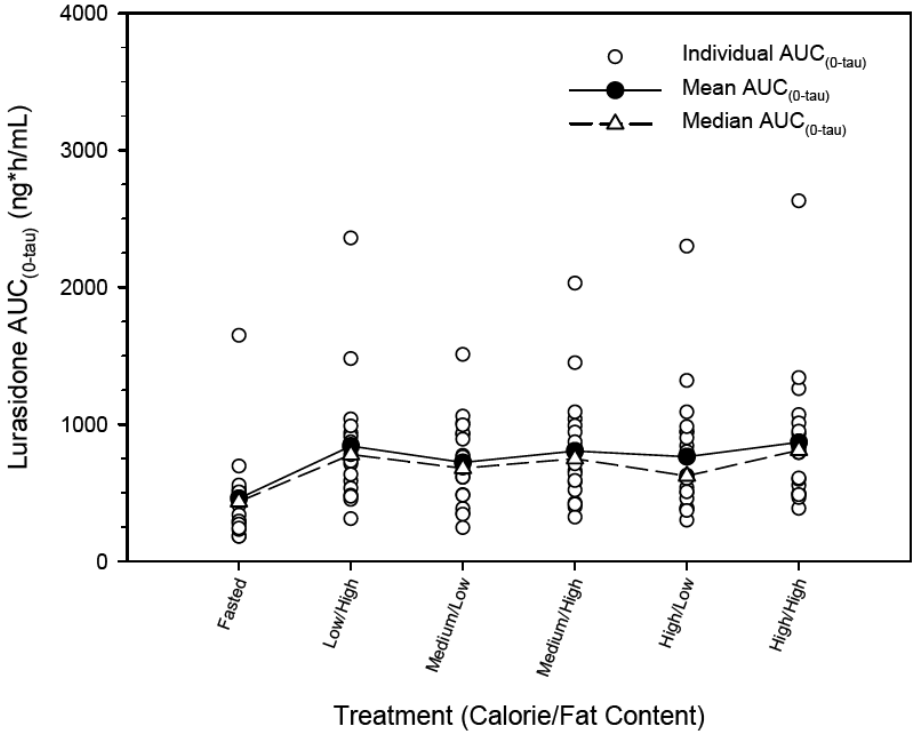


A = fasted; B = low-calorie/high-fat breakfast; C= medium-calorie/low-fat breakfast; D = medium-calorie/high-fat breakfast; E = high-calorie/low-fat breakfast; F = high-calorie/high-fat breakfast.

Scatter plots of Lurasidone Individual, mean and median Cmax after multiple dose administration of 120 mg Lurasidone under fed(various calories and fat content) and Fasted conditions to subjects with schizophrenia.



Scatter plots of Lurasidone individual, mean and median AUC after multiple dose administration of 120 mg Lurasidone under fed (various calories and fat content) and fasted conditions to subjects with schizophrenia.



The following table shows the point estimates and two-sided 90% CIs of the geometric mean ratio for lurasidone Cmax and AUC(0-tau) for each of the fed conditions (varying calories and fat content) compared to fasted conditions in subjects with schizophrenia. The 90% CIs of the geometric mean ratio of all fed to fasted comparisons fell outside of the 80% to 125% range for both AUC(0-tau) and Cmax. There was 1.6- 2.0-fold and 2.4-3.0-fold increase in AUC and Cmax, respectively.

Statistical comparison of Lurasidone Cmax and AUC after multiple-dose administration of 120 mg Lurasidone under Fed and Fasted conditions to subjects with schizophrenia

Parameter (Units) / Treatment	n	Geometric Least-squares Means	Pair	Ratio (%)	90% CI
$AUC_{(0\text{-}tau)}$ (ng·h/mL)					
Fasted (A)	19	390			
Low-calorie/ high-fat breakfast (B)	19	743	B/A	190.51	(175.41, 206.92)
Medium-calorie/ low-fat breakfast (C)	19	642	C/A	164.61	(151.56, 178.79)
Medium-calorie/ high-fat breakfast (D)	20	727	D/A	186.46	(171.69, 202.50)
High-calorie/ low-fat breakfast (E)	21	691	E/A	177.29	(163.31, 192.46)
High-calorie/ high-fat breakfast (F)	20	769	F/A	197.17	(181.62, 214.04)
C_{max} (ng/mL)					
Fasted (A)	19	52.9			
Low-calorie/ high-fat breakfast (B)	19	161	B/A	304.98	(267.60, 347.57)
Medium-calorie/ low-fat breakfast (C)	19	149	C/A	281.33	(246.85, 320.62)
Medium-calorie/ high-fat breakfast (D)	20	135	D/A	255.16	(223.98, 290.69)
High-calorie/ low-fat breakfast (E)	21	128	E/A	241.02	(211.70, 274.41)
High-calorie/ high-fat breakfast (F)	20	131	F/A	248.39	(218.13, 282.86)

CI = Confidence Interval. Inferential results are based on linear mixed model with fixed effects for treatment, period, sequence, and site; and subject nested within sequence as a random effect. Parameters were log-transformed prior to the analysis.

Food has a significant effect on lurasidone exposure. But there was no significant difference in exposure based on the caloric/fat content of the meal All clinical studies were conducted under fed conditions. Lurasidone should be administered with food. Two other food effect studies were submitted but the study was conducted using formulations that were not used in clinical trials or to-be marketed; hence results are not included in this review. Concentration-effect or dose-response relationship was not shown in the clinical studies. It is not clear therefore whether administration of lurasidone with food is essential. However, since the safety and efficacy program was conducted by administering Lurasidone with food, it is recommended that the Lurasidone should be taken with food.

2.10 Analytical Section

What bioanalytical methods are used to assess concentrations and is the validation complete and acceptable?

Validated bioanalytical methods were used to assay lurasidone and its relevant metabolites in serum, urine, and feces. Lurasidone, its metabolites (active metabolites ID-14283 and ID-14326, non-active 11614) and the stable labeled internal standards were extracted from human serum using (b) (4). After solvent evaporation under nitrogen, the residue was reconstituted and analyzed using liquid chromatography (LC) with tandem mass spectrometric detection (MS/MS). The validation method for determining serum Lurasidone concentrations and its metabolites are provided in the following tables. Also the comparisons of the various methods are presented.

The analytical method developed for the analysis of lurasidone and its metabolites was adequately validated and acceptable. However, when DSI inspected one of the analytical sites (b) (4)) quality control during the analysis of the samples were deficient. Refer to DSI report and OCP comments in the Appendix

Parameter	Validation Method for Determination of Serum Lurasidone (SM-13496) and Metabolites (ID-14283, ID-14326, and ID-11614), (b) (4) Report 7589-101[a] and 7589-133[a]											
	Serum Lurasidone			Serum ID-14283			Serum ID-14326			Serum ID-11614		
Method	LC/MS/MS			LC/MS/MS			LC/MS/MS			LC/MS/MS		
LLOQ, ng/mL	0.0200			0.0200			0.0200			0.100		
Linear Range, ng/mL	0.0200 – 10.0			0.0200 – 10.0			0.0200 – 10.0			0.100 – 10.0		
QC Samples ng/mL	0.0600	2.50	7.50	0.0600	2.50	7.50	0.0600	2.50	7.50	0.300	2.50	7.50
n (QC samples)	18	18	18	18	18	18	18	18	18	18	18	18
Inter-day accuracy, %	105.8	102.4	98.5	102.2	102.4	94.5	101.7	102.0	95.1	103.0	101.2	102.8
Inter-day Precision, RSD, %	5.6	5.7	3.3	6.4	8.0	4.9	5.5	5.6	5.0	3.5	3.8	3.5
Intra-day accuracy, %	107.2, 103.0, 107.3	105.2, 101.2, 100.4	100.0, 97.7, 98.0	101.7, 104.7, 100.2	107.6, 102.4, 97.6	96.4, 95.7, 91.3	104.5, 101.3, 99.3	106.4, 103.6, 96.8	96.4, 97.1, 91.6	105.0, 104.3, 99.3	102.8, 99.6, 101.2	106.4, 101.3, 100.5
Intra-day Precision, RSD, %	2.9, 5.6, 7.3	3.4, 2.2, 8.9	3.7, 2.7, 3.4	4.1, 9.3, 4.6	4.8, 11.2, 2.6	5.2, 4.6, 3.4	6.8, 5.1, 3.8	3.9, 5.8, 1.5	6.0, 3.4, 3.6	2.3, 3.4, 2.0	4.2, 2.4, 4.4	2.4, 2.9, 2.2
Freeze-thaw stability @ -10 to -30°C)												
RSD, %	11.8	-	10.1	5.0	-	6.9	8.1	-	8.2	6.0	-	4.7
Accuracy (%)	111.3	-	98.0	95.3	-	98.5	102.2	-	97.3	101.3	-	102.1
Bench top Stability at RT (24 hrs)												
RSD, %	9.9	-	2.5	4.4	-	4.2	5.6	-	5.2	5.4	-	2.9
Accuracy, %	111.2	-	91.9	99.0	-	94.1	101.8	-	93.5	96.7	-	98.3
Long term stability at -10 to -30°C (902 days)												
RSD, %	3.2	3.6	8.0	6.7	3.0	4.3	7.3	5.4	3.9	3.2	3.5	1.5
Accuracy, %	97.0	89.6	93.9	103.2	105.6	103.6	102.3	107.6	107.5	110.0	109.2	114.4
Recovery, %	72.4	77.0	70.2	66.6	69.0	64.6	68.3	73.5	65.8	24.1	29.0	27.4

[a] These validated methods were used in BA (b) (4) Reports 7589-102 (study D1050184), 7589-112 (study D1050217), 6438-665 (study D1050246), 7589-158 (study D1050247), 7589-132 (study D1050254), 6438-795 (study D1050262), 7589-153 (study D1050263), 8087-101 (study D1050264), 8087-100 (study D1050265), 7589-157 (study D1050269), 7589-159 (study D1050270), 7589-154 (study D1050279), 7589-119 (study D1050229), 7589-120 (study D1050231).

LLOQ = lower limit of quantitation; QC = quality control; RSD = relative standard deviation; hr = hours

Parameter	Validation Method for Determination of Serum Lurasidone (SM-13496) and Metabolites (ID-14283, ID-14326, and ID-11614), (b) (4) Report 8200-092[a]											
	Serum Lurasidone			Serum ID-14283			Serum ID-14326			Serum ID-11614		
Method	LC/MS/MS			LC/MS/MS			LC/MS/MS			LC/MS/MS		
LLOQ, ng/mL	0.0200			0.0200			0.0200			0.0200		
Linear Range, ng/mL	0.0200 – 10.0			0.0200 – 10.0			0.0200 – 10.0			0.0200 – 10.0		
QC Samples ng/mL	0.0600	2.50	7.50	0.0600	2.50	7.50	0.0600	2.50	7.50	0.0600	2.50	7.50
n (QC samples)	18	18	18	18	18	18	18	18	18	18	18	18
Inter-day accuracy, %	100.3	100.0	92.7	102.8	106.0	100.0	103.5	106.4	99.5	103.5	104.4	102.1
Inter-day Precision, RSD, %	3.5	2.4	2.2	4.1	2.7	2.2	3.3	2.7	2.2	2.8	2.3	1.9
Intra-day accuracy, %	102.3, 97.7, 101.0	100.0, 101.2, 99.2	92.3, 93.5, 92.1	100.7, 104.0, 103.8	106.0, 105.6, 106.8	101.2, 99.3, 99.6	105.5, 103.0, 102.0	106.0, 105.6, 106.8	99.7, 98.9, 99.6	103.8, 103.2, 103.8	103.2, 106.0, 104.0	101.3, 103.6, 101.6
Intra-day Precision, RSD, %	3.9, 1.6, 3.2	2.0, 2.9, 2.5	2.2, 2.4, 1.9	2.9, 4.9, 4.0	1.5, 4.4, 1.6	1.2, 3.2, 1.7	1.7, 2.8, 4.6	2.9, 3.5, 1.8	1.7, 3.0, 2.1	2.2, 3.0, 3.7	1.2, 2.9, 2.0	0.8, 1.7, 2.2
Freeze-thaw stability @ -10 to -30°C												
RSD, %	4.7	-	1.8	4.3	-	3.1	2.8	-	3.6	2.9	-	2.1
Accuracy (%)	101.3	-	96.4	105.5	-	103.3	107.3	-	102.1	106.0	-	103.7
Bench top Stability at RT (26 hrs)												
RSD, %	4.3	-	2.9	3.4	-	3.8	3.6	-	4.1	3.3	-	4.3
Accuracy, %	99.7	-	96.9	107.3	-	103.1	107.3	-	102.9	106.8	-	104.9
Long term stability at -10 to -30°C (163 days)												
RSD, %	2.5	1.6	1.7	3.0	2.2	2.0	5.0	1.8	1.9	3.7	1.3	1.4
Accuracy, %	100.7	98.0	94.3	105.2	104.8	102.3	105.7	103.2	100.9	104.3	104.0	101.7
Recovery, %	89.3	88.2	86.2	72.4	72.0	72.7	79.8	79.0	78.3	47.0	44.3	45.6

[a] This validated method was used in BA (b) (4) eport 7589-122 (Study D1050237)
LLOQ = lower limit of quantitation; QC = quality control; RSD = relative standard deviation; hr = hours

Parameter	Validation Method for Determination of Serum Lurasidone (SM-13496) and Metabolites (ID-14283, ID-14326, and I 11614), (b) (4) Report KPTK/S99/19010											
	Serum Lurasidone			**Serum ID-14283**			**Serum ID-14326**			**Serum ID-11614**		
Method	LC/MS/MS			LC/MS/MS			LC/MS/MS			LC/MS/MS		
LLOQ, ng/mL	0.0200			0.0200			0.0200			0.1		
Linear Range, ng/mL	0.0200 – 10.0			0.0200 – 10.0			0.0200 – 10.0			0.1 – 10.0		
QC Samples ng/mL	0.0206	1.03	10.3	0.0190	0.95	9.52	0.0200	1.000	9.98	0.11	1.10	11
n (QC samples)	5	5	5	5	5	5	5	5	5	5	5	5
Inter-day accuracy, %	8.2	2.8	-3.2	2.4	2.9	-3.2	2.5	6.6	-4.5	2.1	10.9	2.7
Inter-day Precision, RSD, %	10.8	4.2	5.5	14.7	3.7	8.7	18.3	8.0	6.8	12.4	7.0	4.1
Intra-day accuracy, %	16.4	5.1	4.5	6.2	9.3	1.5	-3.6	13.7	0.4	-13.7	5.6	-0.
Intra-day Precision, RSD, %	4.4	5.8	1.6	14.7	6.9	2.4	10.9	5.8	4.0	5.8	3.9	4.4
Freeze-thaw stability @ -20°C (two cycles)												
RSD, %	--	7.9	7.7	--	2.7	-1.9	--	-7.3	3.7	--	10.7	4.1
Trueness (%)	--	9.6	13.8	--	13.3	0.4	--	-2.8	-0.5	--	14.2	4.2
Stability of Reconstituted Extract in Autosampler, 48 hrs												
RSD, %	--	6.2	-5.2	--	-5.0	-4.4	--	-5.4	-3.5	--	7.9	5.5
Accuracy, %	--	7.9	0.1	--	4.7	-2.2	--	5.8	-1.3	--	11.2	5.5
Long term stability at -20 (3 weeks)												
RSD, %	--	11.3	-5.8	--	-8.8	-3.1	--	-9.4	-5.0	--	13.9	2.8
Accuracy, %	--	13.1	-0.4	--	0.6	-0.8	--	1.3	-2.8	--	17.5	2.8
Recovery, %	--	157.4	166.8	--	65.5	67.5	--	66.7	76.1	--	54.0	72

[a] This validated method was used for study D1050001 (b) (4) BA Report KPTK/S99/19030), D1050002 (b) (4) BA Report KPTK/S99/19050), D1050160 (b) (4) BA Report P01-1906), D1050180 (b) (4) BA Report P02-1910), D1050183 (b) (4) BA Report P04-1914), D1050196 (P04-1915), D1050049 (P02-1917), D1050174 (P02-1908), D1050199 (P04-1916).

LLOQ = lower limit of quantitation; QC = quality control; RSD = relative standard deviation; hr = hours

3. Appendix

3.1 Proposed Label with OCP edits
3.2 DSI Reports
3.3 OCP comments on DSI Reports

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60 pages have been withheld in full immediately following this page as B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200603	ORIG-1	SEPRACOR INC	Lurasidone HCl

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

/s/

HYOJONG KWON

09/09/2010

This memo is an addendum to the previous EIR cover memo. The firm's revised SOP is not included in the addendum due to large file size.

3.3 OCP Response to DSI Inspection Report.

Study Title: An Open-Label, Randomized, Single-Dose, 2-Period, Crossover Study to Determine the Bioequivalence of Two Different SM-13496 Formulations of 40 mg tablet (b) (4) and 20 mg (b) (4)) in Healthy Young Adult Subjects

Background

OCP requested that Division of Scientific Investigation (DSI) inspect the above pivotal bioequivalence study conducted in Japan. After the inspection DSI issued Form 483 and numerated the deficiencies they observed. The analytical site ((b) (4) Research Center) responded to the deficiencies. DSI recommended that the study should not be accepted. The following is OCP evaluation of the DSI responses submitted on 8/16/10 and 9/9/10. The DSI reports are attached in Appendix.

DSI Observation 1:

The clinical site failed to randomly select and retain reserve samples of test and reference products, as required under 21 CFR 320.38. In the firm's written response to FDA Form 483, they explained that the study was conducted to comply with the Japanese regulation, which did not require the retention of reserve samples at the site. However, DSI cannot assure the authenticity of the test and reference products used in Study D1001053 without the reserve samples.

OCP Comment: (b) (4) *indicated that "by the time the Sponsor included or decided to include the study into the US NDA, this study had been started and according to protocol all samples had been returned to the Sponsor". OCP accepts the* (b) (4) *(Analytical site) explanation. .*

DSI Observation 2:

The quality control samples (QCs) (0.04, 0.5, 8 nq/mL) and calibration standards (0.02, 0.05, 0.1, 0.2, 0.5, 1, 2, 5 and 10 ng/mL) for SM-13496 (lurasidone HCl) used in the analytical runs were not representative of SM-13496 concentrations observed in study samples.

- The maximum observed concentration of SM-13496 was 111.98 nq/mL before 20-fold dilution.

DSI indicated that they cannot assure the accuracy of the concentration data without a validation of accuracy of dilution

OCP Comment: (b) (4) *indicated that the results of the following experiments would be submitted by January 2011. 1) Evaluation of dilution factors of 10-fold and 20-fold 2) freeze/thaw stability below -65°C and 3) matrix effect.*

OCP accepts the time line for submission of the validation of the dilution at the (b) (4) *site. OCP will conditionally accept the validity of the 10- and 20-fold dilution since according to DSI* (b) (4) *had validated previously a 100-fold dilution which was acceptable but not representative of the dilution used in this analysis.*

It must also be noted that another analytical site (b) (4)*) used by the sponsor (Dainippon) to determine lurasidone and its metabolite concentrations demonstrated that there is no matrix effect* (b) (4)*study no. 7589-101) when lurasidone is mixed with the matrix (plasma).*

DSI Observation 3:

Failure to evaluate integrity of dilution applied to study samples.
Approximately 47% (378 out of 792) study samples were diluted 10-fold or 20-fold but there was no dilution QC in a run or evaluation of dilution factors (10 or 20) in method validation.

OCP comment: Refer to OCP response to Observation 2

DSI Observation 4:

QCs were not treated under the same conditions as study samples. Study samples were stored below 65°C prior to extraction, whereas QCs were freshly prepared on the day of extraction.

The sponsor stated in their response to FDA Form 483 that the bioequivalence samples from Study 01001053 were stored frozen with a controlled temperature -65°C or below. The 12-month frozen sample stability was established at both -20°C and -80°C. Therefore, the study samples stored at -65°C for a duration shorter than 12 months should be able to be reliably quantified with either frozen QCs or freshly prepared QCs, although frozen QCs might better mimic the study samples.

DSI accepted their explanation (refer to (b) (4) responses in the Appendix).

OCP comment: OCP accepts (b) (4) *explanation and concurs with DSI.*

DSI Observation 5:

Lack of documentation to ensure the condition of processed samples prior to analysis.

Specifically, the processed samples (extracts) were transferred to a different building for analysis, however there was no record documenting the duration and range of storage conditions between completion of processing (extraction) and analysis.

OCP comment: (b) (4) *did not document the duration and range of storage conditions of the extracts from the completion extraction until analysis. Therefore,* (b) (4) *should provide stock solution and bench top stability of lurasidone in their January 2011 submission.*

DSI Observation 6:

a) Failure to conduct appropriate method validation experiments. - For example: Freeze/thaw stability was evaluated at -20°C, whereas study samples were stored below -65°C
(b) Bench-top stability, stock solution stability and matrix effect for SM-13496 were not evaluated
(c) Recovery of SM-13496 was excessive (mean recovery was over 150%) in a validation experiment but the experiment was not investigated or repeated.
(d) Failure to prepare independent stock solutions for calibrators and QCs
(e) Dilution linearity was not evaluated. A dilution factor of 100 was evaluated in pre-study method validation, whereas study samples were diluted 10- and 20-fold before analysis
(f) Manual chromatogram integration was applied to all prestudy method validation, except for partial validation conducted in 2008 to evaluate precision/accuracy, selectivity, LLOQ and post-preparative stability

In response to this observation, (b) (4) indicated that data supporting the stability of samples at lower temperatures were derived from long term stability tests where stability at -20°C and -80°C were established at 373 and 363 days, respectively. (b) (4) has committed to conduct an experiment to provide information on the freeze/thaw cycles below -65°C and would submit the results in the January 2011 submission.

DSI has requested the sponsor conduct the following experiments to support accuracy: 1) recovery of SM 13496 2) incurred sample reproducibility (ISR).

OCP comment:
The sponsor should submit the results of the experiments in the January 2011 submission.

At this time the sponsor has no answer as to why recovery was high (150%). They plan to implement processes requiring investigation and documentation when recovery exceeds 120%.

DSI Observation 7:

Failure to use an acceptable calibration curve in batch 090804a. Specifically, the batch 090804a was calculated with calibration curve from batch 090803a

OCP Evaluation: (b) (4) *recalculated concentrations of subject samples in batch 090804a using its own calibration curve. DSI accepted the recalculated concentrations. OCP accepts the recalculated concentrations. The sponsor was requested to determine again whether the 2 x 20*

mg is bioequivalent to 40 mg lurasidone using the recalculated concentrations. The two formulations were found to be bioequivalent after the recalculation.

DSI Observation 8:

Failure to evaluate assay reproducibility of incurred samples

DSI requested the sponsor conduct an experiment to evaluate the incurred sample reproducibility (ISR). The results should be submitted with the January 2011 submission.

OCP Evaluation: OCP has no objection to DSI recommendation

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/s/

KOFI A KUMI
10/26/2010

VENKATESH A BHATTARAM
10/26/2010

JOGARAO V GOBBURU
10/26/2010

RAMAN K BAWEJA
10/26/2010

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	200-603	**Reviewer:** Houda Mahayni, Ph.D.	
Submission Date:	12/30/09 and 10/26/10		
Division:	DPP	**Team Leader:** Angelica Dorantes, Ph.D.	
Sponsor:	Dainippon Sumitomo Pharma America, Inc.	**Supervisor:** Patrick J. Marroum, Ph.D.	
Trade Name:	(SM-13496)	**Date Assigned:**	3/1/10
Generic Name:	Lurasidone HCl	**Date of Review:**	8/3/10
Indication:	Treatment of patients with schizophrenia	**Type of Submission:** New Drug Application	
Formulation/strengths	Film-Coated Tablet/ 40 mg, 80 mg, and 120 mg		
Route of Administration	Oral		

SUBMISSION:

Lurasidone hydrochloride (HCl) is a psychotropic agent for the treatment of patients with schizophrenia.

During the development of lurasidone tablets, different formulations were evaluated. The original sponsor of the Investigational New Drug Application (IND) was Sumitomo Pharmaceuticals America, Ltd. (Known today as Dainippon Sumitomo Pharma America, Inc.). Sumitomo Pharmaceuticals America, Ltd., transferred the sponsorship of the IND application to Merck Research Laboratories (MRL). Dainippon Sumitomo Pharma America, Inc. (DSPA) reacquired the development rights for lurasidone on March 30, 2007. Table 1 summarizes the Dainippon Sumitomo Pharma Co., Ltd. (DSP) formulations compared to the MRL formulations.
As noted in the table, the DSP Group B formulation was the same as MRL Group A formulation, and all other formulations were not equivalent as they consisted of different formulation compositions.

Table 1: Index of Formulation Equivalency between DSP and MRL Formulations

DSP Formulation Group (DL%)	MRL Formulation Group (DL%)
Pre-A (N/A)[a]	- -
A (b) (4)	-
B	A (b) (4)
-	C
-	D
-	E
C (b) (4)	-

[a] DSP Group pre-A represents several formulations.
DL = drug load; DSP = Dainippon Sumitomo Pharma Corporation, Limited; MRL = Merck Research Laboratories; NA = not applicable.
Source: D1050251, D1050252, D1050263, and S01P12.

DSP Groups pre-A, A and B were formulations developed prior to MRL IND sponsorship. During MRL IND sponsorship, DSP provided the DSP Group B formulation for the conduct of studies during this period of time, which MRL designated as MRL Group A formulation. Also, during the MRL IND sponsorship, MRL Groups C, D, and E, were developed in an effort to reduce tablet size and to minimize the food effect.

After reacquiring IND sponsorship from MRL, DSPA utilized the DSP Group B formulation for the conduct of the clinical studies demonstrating the efficacy and safety of lurasidone. The DSP Group C Formulation was developed in order to optimize the intended market formulation.

BIOPHARMACEUTIC INFORMATION:

The intended market formulation (DSP Group C formulation) has a (b) (4) (DL), and will be provided as film-coated tablets in 40 mg, 80 mg, and 120 mg dosage strengths. The manufacturing process is identical for all dosage strengths. The core tablets of the three product strengths are (b) (4). However, there is difference in the color of the film coat. The 40 mg (b) (4) tablets are white to off-white film-coat; whereas, the 80 mg tablets are coated with pale green color. The tablet compositions are provided in Table 2.

Table 2: Composition of Lurasidone 40 mg, 80 mg (b) (4) Tablets

Component	% w/w	Quantity (mg)		Function	Specification
		40 mg	80 mg		
					(b) (4)
Lurasidone HCl	25	40	80	API	DMF 16059 (Module 1.4)
Mannitol, USP					USP
Pregelatinized Starch, NF					NF
Croscarmellose Sodium, NF					NF
Hypromellose (b) (4) USP					USP
Magnesium Stearate, NF					NF
(b) (4)					USP
					(b) (4)
OPADRY® (b) (4)					(b) (4) (Module 1.4)
Yellow Ferric Oxide, NF					NF
FD&C Blue No. 2 Aluminum Lake					CFR*
Carnauba Wax, NF					NF
(b) (4)					USP
Total Tablet Weight	-	162.61	324.328		

(b) (4)

Dissolution Method Development

Lurasidone HCl is poorly soluble in aqueous media. The solubility of lurasidone HCl was measured in a series of solvent systems and buffers. The results obtained are shown in Table 3. Since degradation of lurasidone HCl was observed to varying degrees in the solubility studies performed in 0.1N HCl, this medium was not judged to be an acceptable choice.

14 pages have been withheld in full immediately following this page as B4 (CCI/TS)

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/s/

HOUDA MAHAYNI
10/26/2010

PATRICK J MARROUM
10/27/2010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

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Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**200603**	**Brand Name**	(b) (4)
OCP Division (I, II, III, IV, V)	**I**	**Generic Name**	**Lurasidone**
Medical Division	DPP	**Drug Class**	**Atypical Antipsychotic**
OCP Reviewer	**Kofi Kumi**	**Indication(s)**	**Treatment of Schizophrenia**
OCP Team Leader	**Raman Baweja**	**Dosage Form**	**Tablets (40 mg, 80 mg, 120 mg)**
Pharmacometrics Reviewer	**Atul Bhattaram**	**Dosing Regimen**	**40 or 80 mg daily**
Date of Submission	**12/30/09**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**9/11/10**	**Sponsor**	**Dainippon Sumitomo Pharma America (DPSA)**
Medical Division Due Date	**9/18/10**	**Priority Classification**	**Standard**
PDUFA Due Date	**10/30/10**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies	**x**	**43**		**26 Clin Pharm/Biopharm studies (plus 2 provided in 120 day update)**
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**	**25**		**Bioanalytical Reports**
I. Clinical Pharmacology	**x**			
Mass balance:	**x**	**2**		
Isozyme characterization:	**x**	**14**		**In vitro studies**
Blood/plasma ratio:	**x**	**1**		**In vitro studies**
Plasma protein binding:	**x**	**3**		**In vitro studies**
Pharmacokinetics (e.g., Phase I) -	**x**			
Healthy Volunteers-				
single dose:	**x**	**3**		
multiple dose:	**x**	**2**		
Patients-				
single dose:				
multiple dose:	**x**	**3**		
Dose proportionality -				
fasting / non-fasting single dose:	**x**	**1**		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**x**	**4**		
In-vivo effects of primary drug:	**x**	**3**		
In-vitro:	**x**	**4**		

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Subpopulation studies -				
ethnicity:	**x**	**1**		**POPPK**
gender:	**x**	**1**		**POPPK**
pediatrics:				**Waiver/defer**
geriatrics:	**x**	**2**		
renal impairment:	**x**	**1**		
hepatic impairment:	**x**	**2**		
PD -				
Phase 2:	**x**	**2**		
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**x**	**3**		**Receptor occupancy/QT studies**
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	**x**	**4**		
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -	**x**	**3**		
solution as reference:				
alternate formulation as reference:	**x**	**3**		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:	**x**	**1**		
Food-drug interaction studies	**x**	**2**		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				**N/A**
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	**x**			**Waiver/Deferral Request**
Literature References	**x**			
Total Number of Studies		**40**		**(26 Human + 14 in vitro CPB studies)**

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			
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	x			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	legible so that a substantive review can begin?				
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)?				
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?				
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?				
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.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Reviewing Clinical Pharmacologist Kofi Kumi, Ph.D. Date 3/1/10

Team Leader/Supervisor Raman Baweja, Ph.D. Date 3/1/10

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200603	ORIG-1	DAINIPPON SUMITOMO PHARMA AMERICA INC	Lurasidone HCl

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/s/

KOFI A KUMI
03/01/2010

RAMAN K BAWEJA
03/01/2010