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RESEARCH**

APPLICATION NUMBER:

200603

MEDICAL REVIEW(S)

Clinical Review - Addendum

NDA #200603-O1

Sponsor: Sunovion (formerly Dainippon, Sepracor)

Drug: Lurasidone

Formulation: 40 and 80 mg tablets

Drug category: Antipsychotic

Material submitted: Amendments to NDA 200603

Indication: Treatment of Schizophrenia

Date Review Completed: 10/27/2010

Clinical Reviewer: Cara Alfaro, Pharm.D.

Background

NDA 200603, lurasidone for the treatment of schizophrenia, was submitted in December 2009. The clinical review was completed on 9/10/2010 and signed off on 9/22/2010. Since that time, a number of additional amendments have been submitted to the NDA. Most of these amendments have been proposed changes in product labeling which have been negotiated in real time between the Division and the Sponsor.

During the review of the NDA, I was concerned regarding a number of patient cases that were suggestive of a hypersensitivity reaction – specifically one case of angioedema and several cases involving orofacial swelling (these are outlined in the clinical review). The Division requested that the Sponsor perform a more detailed review of potential hypersensitivity reactions and provide this additional analysis to the Division for review. This addendum addresses this additional analysis.

Hypersensitivity Analysis

The Sponsor submitted the results of the hypersensitivity analysis (SD-41). The Sponsor identified Standardized MedDRA Queries (SMQs) and high level terms (HLTs) which were the most appropriate to identify hypersensitivity-related events in the P2/3STC database (Phase 2/3 short term, placebo-controlled database):

SMQs: anaphylactic reaction, angioedema, severe cutaneous adverse reactions

HLTs: allergy to food, food additives, drugs and other chemicals

The Sponsor also submitted the list of 342 unique preferred terms contained within these SMQs and HLTs.

The search identified 131 subjects (n = 90 lurasidone, n = 41 placebo) with potential hypersensitivity-related events. Per the Sponsor, upon medical review, 63 of the 131 subjects had events that were deemed to be hypersensitivity-related – this was based on a review of the subject's case report form. The Sponsor included a listing of the potential events together with the annotated medical adjudication of each event.

Table 1: Number and Percentage of Subjects with Treatment-Emergent Hypersensitivity Events by Preferred Term in the Lurasidone P23STC Database

Preferred Term ^a	Lurasidone					
	Placebo (N=455)	20 mg (N=71)	40 mg (N=360)	80 mg (N=282)	120 mg (N=291)	All Lurasidone (N=1004)
Number of Subjects with ≥1 Treatment-Emergent Hypersensitivity Event	21 (4.6%)	2 (2.8%)	20 (5.6%)	10 (3.5%)	10 (3.4%)	42 (4.2%)
Rash	8 (1.8%)	1 (1.4%)	10 (2.8%)	4 (1.4%)	4 (1.4%)	19 (1.9%)
Pruritus	6 (1.3%)	1 (1.4%)	5 (1.4%)	2 (0.7%)	5 (1.7%)	13 (1.3%)
Dermatitis contact	3 (0.7%)	0	1 (0.3%)	1 (0.4%)	1 (0.3%)	3 (0.3%)
Rash pruritic	0	0	2 (0.6%)	0	1 (0.3%)	3 (0.3%)
Stomatitis	0	0	1 (0.3%)	1 (0.4%)	0	2 (0.2%)
Urticaria	1 (0.2%)	0	1 (0.3%)	1 (0.4%)	0	2 (0.2%)
Lip swelling	0	0	0	1 (0.4%)	0	1 (<0.1%)
Multiple allergies	0	0	1 (0.3%)	0	0	1 (<0.1%)
Pruritus generalized	1 (0.2%)	0	0	1 (0.4%)	0	1 (<0.1%)
Eye pruritus	1 (0.2%)	0	0	0	0	0
Flushing	1 (0.2%)	0	0	0	0	0
Rash maculo-papular	1 (0.2%)	0	0	0	0	0

^a Preferred terms are listed in descending order of frequency based on the All Lurasidone group.

The Sponsor indicated that the proportion of hypersensitivity-related events that were reported as severe was comparable for lurasidone (1/1004, 0.1%) and placebo-treated (1/455, 0.2%) subjects and there were no hypersensitivity-related events that were reported as serious for either lurasidone or placebo-treated subjects. Additionally, the proportion of subjects who discontinued study treatment due to hypersensitivity-related adverse events was comparable for lurasidone (2/1004, 0.2%) and placebo-treated (1/455, 0.2%) subjects.

The Sponsor concluded that, based on this analysis, there was no indication of an increased risk for hypersensitivity-related events, or increased severity or seriousness of such events, in subjects treated with lurasidone compared to placebo-treated subjects.

Reviewer's Comments

This reviewer noted that the Sponsor had not included 3 additional lurasidone-treated patients that could have experienced hypersensitivity reactions – 2 of these cases were not noted to have been adjudicated. One case was “swelling face”, this adverse event was noted in a table in the ISS. Two additional cases were noted in the JMP database for adverse events – these were noted under the verbatim term “non-dystonia tongue thickness” which was coded to the preferred term “tongue disorder” [this was not a term falling under the hypersensitivity rubric]. The Sponsor was asked to review these cases and submit the data to the Division.

The Sponsor provided further clinical information regarding these cases (SD-45):

Swelling Face

Subject D1050229-0017-00020 ([Narrative](#)), a 57-year-old white male was randomized in [Study D1050229](#) on July 31, 2008 and discontinued on September 15, 2008. The subject developed facial swelling on September 11, 2008, 42 days after initiating study drug (lurasidone 40 mg/day). The event was considered mild in intensity and lasted two days.

This subject had a history of chronic obstructive pulmonary disease (COPD). Additional reported adverse events at the time of this event were an upper respiratory infection (URI), exacerbation of COPD, weight gain, and pneumonitis. The URI symptoms were described as including nasal and chest congestion. The facial swelling resolved and no specific treatment for this adverse event was initiated. This case was included in the

assessment of all potential hypersensitivity-related events in the lurasidone database ([October 13, 2010](#)).

Based on the medical reviewer's judgment, this case was deemed not to be hypersensitivity related and therefore excluded from the list of subjects with reported hypersensitivity-related adverse events. The event was considered to be related to a combination of adverse events and not to be hypersensitivity related based on this subject's reported presentation, which included URI, exacerbation of COPD, and pneumonitis, as well as the mild and brief duration of facial swelling.

Non-Dystonia Thick Tongue

Subject D1050231-0032-00011 ([Narrative](#)), a 42-year-old black male was randomized in [Study D1050231](#) on March 10, 2008 and discontinued on July 30, 2008. The subject developed a "non-dystonia thick tongue" as well as "oculogyric crisis" (b) (6) following the initiation of study drug (lurasidone 40 mg/day). The "non-dystonia thick tongue" event lasted for 85 days, and the oculogyric crisis lasted for one day. The "non-dystonia thick tongue" was considered mild in intensity, and the "oculogyric crisis" was considered moderate in intensity.

Both adverse events were assessed by the investigator as possibly related to study drug. The subject was treated with intramuscular diphenhydramine (day of oculogyric event) and oral benztropine (day of events as well as approximately 50 days later for the subsequent 35 days). The adverse event of "non-dystonia thick tongue" (coded to tongue disorder) is deemed after medical review to be related to extrapyramidal syndrome (EPS) and not to be hypersensitivity related, based on its temporal association with a dystonic event (oculogyric crisis), lack of additional hypersensitivity symptoms and resolution prior to discontinuation of lurasidone treatment.

Non-Dystonia Tongue Thickness

Subject D1050231-032-00021, a 39-year-old black male, was randomized in [Study D1050231](#) on June 09, 2008 and discontinued on July 31, 2008. The subject developed a “non-dystonia tongue thickness” on (b) (6) which was (b) (6) prior to receiving the first dose of study medication (June 10, 2008). This non-treatment emergent adverse event resolved on the same day it occurred. Therefore, this non-treatment emergent adverse event was unrelated to lurasidone (or study) treatment and was not included in our analysis of potential hypersensitivity-related cases.

Conclusions

This reviewer agrees with the assessments of the Sponsor with regard to these three cases. Overall, it appears that the rate of hypersensitivity reactions was similar between lurasidone and placebo-treated subjects in the P2/3STC database. The case of angioedema, noted in the clinical review for the NDA, occurred in study D1050237 – a study that is not in the P2/3STC database.

Recommendations

The Sponsor has been asked to submit all cases of angioedema as 15 day safety reports as a post-marketing commitment.

This reviewer still has some concerns about orofacial swelling adverse events, some of these events occurred outside the P2/3STC database and led to patient discontinuation. Admittedly, events occurring in open-label extension studies or other uncontrolled studies are more difficult to interpret. However, it was interesting to this reviewer that the vast majority of these cases occurred in African American males. Two additional Phase 3 clinical trials have recently been completed. Safety data from these additional trials should be carefully reviewed to identify any additional safety signals (including hypersensitivity reactions) that should be included in product labeling.

Cara Alfaro, Pharm.D.
Clinical Analyst
Division of Psychiatry Products

10/27/2010

cc: Khin/Sohn/Laughren/Alfaro

Schedule of Activities

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/s/

CARA L ALFARO
10/27/2010

NI A KHIN
10/28/2010

The rate of hypersensitivity reactions was similar between lurasidone and placebo-treated subjects in the phase 2/3 short-term controlled trials. The sponsor has agreed to report any post-marketing cases of angiodema. We have reached labeling agreement with the sponsor (including the statement that angioedema has been observed with lurasidone in the contraindication section). The Division will be issuing an AP letter. We should continue to observe if there are any relevant post-marketing reports on this issue.

CLINICAL REVIEW

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Application Number 200603-O1
Priority or Standard Standard

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Division Division of Psychiatry
Products

Reviewer Name Cara L. Alfaro, Pharm.D.
Review Completion Date 9/10/2010

Established Name lurasidone
Trade Name TBD
Therapeutic Class Antipsychotic
Applicant Sepracor

Formulation 40, 80 and 120 mg tablets
Dosing Regimen 40 to 80 mg once daily,
up to 120 mg/day
Indication Treatment of
Schizophrenia
Intended Population Adults

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1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT

1.1 Recommendation on Regulatory Action

This reviewer recommends that a complete response action be taken on NDA 200603 for lurasidone in the treatment of schizophrenia.

The Sponsor submitted 4 double-blind, placebo-controlled, fixed-dose, 6-week studies to support the indication (see review for details). This reviewer considered Study D1050196 (lurasidone 80 mg) and Study D1050231 (lurasidone 40 mg, lurasidone 120 mg) to be positive in support of the indication. However, in one Phase 2 trial (D1050006), the discontinuation rate was very high (approximately 50% had discontinued by week 3), such that this reviewer believes that the results are not interpretable. The primary reason for discontinuation in all treatment groups was insufficient clinical response. Since this study was deemed uninterpretable, the Sponsor does not have duplication of efficacy data for the 40 mg and 120 mg doses. In the only trial that included three lurasidone doses (D1050229), 40 mg, 80 mg and 120 mg, the 80 mg dose was the only one demonstrating efficacy. This trial included both US and nonUS sites (~50% each), however, virtually no efficacy signal was demonstrated for lurasidone at any dose in the US sites and the placebo response was similar in both geographic regions.

A number of quality issues in the NDA submission (as detailed in the review) were noted during the review. Because of these issues, this reviewer does not feel that the Sponsor has adequately characterized the safety profile of lurasidone. One issue that needs to be further addressed is potential hypersensitivity reactions which have included one case of angioedema leading to respiratory failure and numbers of cases of edema, swollen face, swollen tongue, "thick" tongue, etc.

It is relevant that two additional Phase 3 trials have been completed since this NDA was filed (noted in review). Given the issues identified above, this reviewer considers it important to fully evaluate both the efficacy and safety of lurasidone with the addition of these trial data before a final action is taken.

1.2 Risk Benefit Assessment

Efficacy has not been established in this NDA submission. The safety profile is more similar to typical antipsychotics with significant akathisia, hyperprolactinemia, parkinsonian-adverse events and dystonias; many of which are dose-related. Lurasidone does not appear to have significant adverse impact on metabolic indices (glucose, lipids, weight, etc.). Lurasidone may be associated with potentially significant hypersensitivity reactions. A comprehensive risk:benefit assessment is premature at this time.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No recommendations at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

The Sponsor should conduct an adequately designed maintenance study for the treatment of schizophrenia. The Sponsor should also evaluate the efficacy of lower doses of lurasidone, e.g. 20 mg. In any future study, a more rigorous approach should also be implemented for evaluation of withdrawal syndromes including withdrawal dyskinesias.

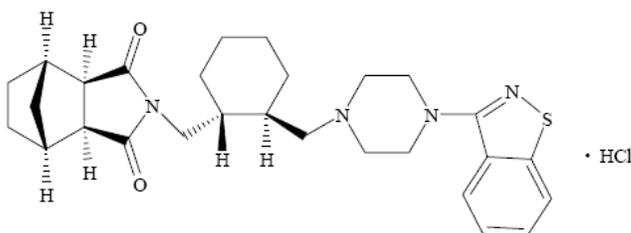
2 INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

Lurasidone hydrochloride is a new molecular entity with putative antipsychotic activity. The IND for lurasidone, IND 61,292, was filed in November 2000 by Dainippon Pharma America, Inc. Lurasidone was originally referred to as SM-13496 then as MK-3756 when Merck obtained Sponsorship. Sponsorship was transferred back to Dainippon and Sepracor became the Sponsor when the two companies merged.

The chemical name is (3*aR*,4*S*,7*R*,7*aS*)-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 structural formula is



Lurasidone exhibits in vitro receptor binding affinities similar to other currently marketed atypical antipsychotics, specifically high affinities for the D2 and 5-HT2A receptors.

At the time this review was finalized, the Sponsor was proposing alternative trade names for the product as prior submissions (b) (4) were found to be unacceptable by the Division of Medication Error Prevention and Analysis.

The Sponsor's proposed indication is for the treatment of schizophrenia in adults. The proposed dosing regimen is 40 to 80 mg once (b) (4) daily. Lurasidone should be given with a meal.

2.2 Currently Available Treatments for Proposed Indication

A number of "typical" and "atypical" antipsychotics are currently available for the treatment of schizophrenia in adults. Though not an exhaustive list, examples of typical antipsychotics include haloperidol, thioridazine, trifluoperazine. Atypical antipsychotics include olanzapine (Zyprexa), risperidone (Risperdal), quetiapine (Seroquel), aripiprazole (Abilify), ziprasidone (Geodon), and paliperidone (Invega), iloperidone (Fanapt), and asenapine (Saphris). Due to the risk of agranulocytosis, clozapine (Clozaril) is approved for treatment-resistant schizophrenia.

2.3 Availability of Proposed Active Ingredients in the United States

Lurasidone is not currently marketed in this country.

2.4 Important Safety Issues With Consideration to Related Drugs

Some of the relevant safety issues for the class of antipsychotics include extrapyramidal side effects (parkinsonism, dystonia, akathisia), tardive dyskinesia, neuroleptic malignant syndrome, hyperprolactinemia, orthostatic hypotension, weight gain, diabetes mellitus, hyperglycemia, hyperlipidemia, and leukopenia/neutropenia/agranulocytosis.

In general, the typical antipsychotics have been associated with more extrapyramidal side effects compared to the atypical antipsychotics, though the latter are not devoid of this adverse effect. The atypical antipsychotics have been associated more with weight gain, hyperglycemia and hyperlipidemia side effects compared to the typical antipsychotics. Within each class of typical or atypical antipsychotic, there are different propensities for patients to develop these adverse effects.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

IND 61,292 for the investigational use of lurasidone in the treatment of schizophrenia was submitted to the Division on November 15, 2000. Dainippon Sumitomo Pharma America, Inc. was the Sponsor at that time.

Merck became the Sponsor of IND 61,292 on September 30, 2005.

An End-of-Phase 2 meeting was held on September 26, 2006.

Some key points discussed at this meeting were:

1. The Sponsor had originally planned to study flexible dose lurasidone (40 – 120 mg) in three Phase 3 clinical trials. The Division strongly recommended that fixed dose designs be incorporated into the clinical

trials and that the Sponsor study all 3 doses of lurasidone in at least one if not all three of the planned 6-week studies.

2. The Sponsor stated that the approach of using PET D2 occupancy in combination with Phase 2 data to conclude that 20 mg is an ineffective dose and studying 3 doses (40, 80, 120 mg) across three efficacy and safety studies adequately explores the dose range and supports registration of lurasidone with the proposed dosage and administration for the treatment of schizophrenia. The Division stated that the approach of using PET D2 occupancy in combination with clinical data across studies is an adequate method to explore the dose response, particularly when the three lurasidone treatment arms are included in at least one study with placebo and an active comparator.
3. The Division commented that if the Sponsor hopes to include any information from secondary outcomes in labeling, they would need to identify key secondary outcomes in the protocols, obtain agreement with the Division on the selection of the key secondary outcomes, and have a plan for analyzing these key secondary outcomes incorporated in the SAPs. There would need to be replication before any such findings could be included in labeling. The Division recommended that the Sponsor select at least one functional measure as a key secondary. Factor scores such as the PANSS positive and negative symptoms subscales will not be acceptable as key secondaries, nor would a measure of depressive symptoms. The CGI-S score would be acceptable and would serve as a valid functional measure. The Sponsor indicated an interest in the CGI-S as their first key secondary (b) (4)

Merck transferred the sponsorship of IND 61,292 back to Dainippon on 2/23/2007.

On April 1, 2010, Dainippon Sumitomo Pharma America, Inc. and Sepracor Inc. officially merged. The surviving entity is Sepracor Inc.

2.6 Other Relevant Background Information

No other relevant background information was identified.

3 ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

Division of Scientific Investigations Inspections

The Division of Scientific Investigations (DSI) was consulted to inspect a number of clinical sites from the pivotal clinical trials. The following sites were chosen:

Site Number/Investigator Location	Protocol	Number of Subjects
Site #14/Robert Riesenberg Atlanta GA	D1050006	27
Site #17/Robert Riesenberg Atlanta GA	D1050231 D1050229	10 15
Site #15/Tram K. Tran-Johnson San Diego CA	D1050006	29
Site #37/Tram K. Tran-Johnson San Diego CA	D1050231	16
Site #465/Rodrigo Cordoba Bogotá Colombia	D1050231	14
Site #464/Laura Giraldo Bogotá Colombia	D1050231	12

The primary reason those U.S. sites were chosen was the numbers of subjects enrolled in the protocols and involvement in multiple protocols. In study D1050006, though there were 15 sites that enrolled subjects, sites 14 and 15 randomized nearly 40% of the total number of subjects. Additionally, these investigators enrolled subjects in 3 or 4 of the pivotal schizophrenia trials and it was thought important to ascertain whether any duplicate enrollment occurred across these trials (e.g. did any of the same patients enroll in more than one pivotal trial at each site?).

The sites in Colombia were chosen primarily due to their significant contribution to the overall efficacy signal in study D1050231. Though subjects in this study were enrolled in the U.S., India, Lithuania, Philippines and Columbia, the geographic region subgroup analyses showed robust results favoring lurasidone over placebo consistently in the Colombia region and not the other regions.

The Division of Scientific Investigations did not find any significant issues with any of the clinical sites that were inspected, no Form FDA 483s were issued. DSI also inspected Sepracor, with a focus on Protocols D1050006 and D1050196. No discrepancies or deficiencies were noted in the selection and training of clinical investigators, IRB processes or firm's responsibilities to contract research organizations. At the end of the inspection, the field investigator issued a 3-observation Form FDA 483 for 1) failure to ensure that the study was conducted in accordance with protocol or investigational plan, 2)

failure to maintain adequate written records of the disposition of an investigational drug and 3) lack of adequate records covering receipt and disposition of an investigational drug. Sepracor has addressed these issues with DSI. It is the opinion of DSI, and this reviewer, that these deficiencies are unlikely to have significant impact on the outcome of these clinical studies.

Other Submission Quality and Integrity Issues

During the review, there were a number of quality issues identified. It should be noted that this reviewer did not have time to perform a rigorous and comprehensive quality check on the data in the NDA, these issues were identified during the normal course of reviewing the submission. Additionally, this reviewer did not audit a certain proportion of CRFs in the submission, but rather referred to CRFs in the course of the review (e.g. when reviewing narratives) as noted below.

Missing Data

The Sponsor amended the NDA with additional data (7/30/2010, SD-X). The Sponsor had discovered that laboratory data from three clinical sites for Study D1050006 were not included in the original locked laboratory database. The laboratory data were missing for 27 patients (18% of the study population for that study). The Sponsor included revised tables for the CSR for that study, but had not intended to revise the ISS. Since it is very difficult to determine whether the data from these patients could affect the overall study results from data not integrated into the ISS, the Sponsor was asked to do this. Upon query, the Sponsor indicated that no other data were missing from these 27 patients (adverse event data, for example).

Concomitant Medications

This reviewer was interested in assessing the potential impact that concomitant lorazepam administration could have on the primary efficacy assessments since, at week 6, many patients in all treatment groups received this concomitant benzodiazepine in at least 3 of the pivotal trials. According to the protocols, efficacy assessments were not supposed to have been performed within 8 hours of receiving a dose of benzodiazepine. The Sponsor was asked to determine how many patients received a dose of lorazepam within 8 hours of the efficacy assessment. The Sponsor replied that they did not have that information (email communication). This seemed unusual to this reviewer in that, first of all, how can you determine whether a protocol violation occurred for data you do not appear to be collecting? It would seem, however, that some of this data would be available since approximately 20-30% of patients continued on inpatient status beyond 6 weeks (end of study).

Narratives

Overall, the narratives were poor and many omitted data relevant to the adverse events in question. In some cases, data was incorrect. In other cases, follow-up

seemed to not have been done for significant adverse events, or, if done, this information was not integrated into the narratives. A few examples are as follows:

Angioedema – this is perhaps one of the most egregious examples. This was a serious adverse event occurring in study D1050237. The narrative is approximately one paragraph long and discusses the chief complaint, administration of lorazepam, symptom persistence, subject request to go to the emergency room, hospitalization “for further treatment” and recovery. Virtually no details are provided. Though the concomitant medication section of the narrative does include medications administered coincident with the adverse event, this is in no way integrated in the narrative. Upon review of the CRF, it was noted that the patient required intubation with administration of multiple medications: propofol, suxamethonium, vecuronium, prednisone, etc. Also, noted in the CRF but not indicated anywhere in the narrative was the adverse event “respiratory failure” occurring during the same time period as the angioedema. In this reviewer’s opinion, this is entirely unacceptable in that it does not fully characterize the seriousness of the adverse event (though it was, appropriately, termed an SAE).

Incorrect Lab Values – the Sponsor was asked to perform an analysis of patient cases meeting criteria for Hy’s law. The reviewer had identified one potential case (“hepatitis infectious”) included in the narratives as an SAE/discontinuation due to adverse event. In the narrative, ALT and AST had increased from normal baseline to 276 and 224 U/L. Upon review of the laboratory data the Sponsor provided in response to the Hy’s analysis, it was noted that the ALT and AST had increased from normal baseline to 1720 and 1444 U/L (date same for lab draw). This reviewer looked at the corresponding JMP file for laboratory data and the values from the Hy’s report were in that file. This is very discouraging since it is unlikely that this reviewer would have found this discrepancy had the Sponsor not been asked to conduct this additional analysis. This reviewer does not make a habit of checking the accuracy of all laboratory data included in narratives with JMP files (although perhaps this is necessary). Fortunately, the correct laboratory data were in the JMP files, so overall analyses were likely not affected by this error.

Lack of clinical presentation – Many of the narratives lacked details regarding the clinical presentation of adverse events. For example, an adverse event of “rhabdomyolysis” only included CPK values. Notably, dystonic events (of which there were many), did not include many clinical descriptors – no mention of muscles or body areas affected. Also, though some narratives included treatments received, most did not state the route of administration. For a number of cases, treatments involved parenteral administration which is one indication of adverse event severity. CRFs did not include a space where

investigators could consistently describe the clinical presentation of the dystonic event, though this could have been included in a comments field.

Narratives not updated – Many of the narratives were not updated with relevant data that appeared elsewhere in the submission (CRF, CIOMS report). For example, a patient enrolled in study D1050237 had the adverse event “metrorrhagia on pregnancy” after having received lurasidone for ~160 days. The narrative describes some bleeding and a “local HCG test revealed a result of 340,08 mIU/mL (reference range not provided)”. The medical monitor was informed, the patient was withdrawn from the study and a new HCG test was performed with obstetric consult. “At the time of this report no more information was available”.

However, upon review of the CIOMS report, it was noted that the patient had a spontaneous abortion (considered a miscarriage by the clinical site), HCG in blood and echo confirmed that the patient was not pregnant. This information is quite relevant and should have been incorporated into the narrative.

Adverse Event Coding

A number of potential issues in coding verbatim terms to preferred terms were noted during the review. For example, one SAE coded “fall” was, according to the narrative, a jump from a freeway overpass. Though it is unclear what the motivation for the jump was (suicidal thoughts denied, auditory hallucinations denied), “fall” does not seem to capture the seriousness of the event.

Prolactin Laboratory Data

This reviewer had requested the Sponsor to submit a line listing of patients with prolactin concentrations meeting MAPLV criteria (> 5x ULN) and include prolactin concentrations from all study visits. When these data were evaluated, this reviewer found it odd that prolactin concentrations exhibited marked variability (e.g. 130 ng/ml on Day 7, 9 ng/ml on Day 9) in this fixed dose study (See Section 7.4.2 of review for more discussion). The Sponsor was not asked to address this issue.

Patient Disposition Issues

A recategorization of many study discontinuations was performed by this reviewer after evaluating the comment field in the subject termination/subject disposition listings. All recategorizations are included as footnotes in the subject disposition section of the study summaries – but include things such as recategorizing from “withdrawal of consent” to “adverse event” since the comment field indicated that discontinuation was due to a dystonic event. In general, this reviewer was surprised at the large percentage of patients included in the “withdrawal of consent” category. In this reviewer’s opinion, this category is not very informative. In a number of cases, the comment field indicated that discontinuation was due to an adverse event and this was not

being captured as such. It is likely that the investigator may have checked the “withdrawal of consent” box on the CRF and then wrote something in the comment line (such as “dystonia”). Clearly it seems that many of these subject dispositions were not vetted by the Sponsor.

This reviewer is very troubled by this lack of rigorous review and reclassification for subject disposition. As another example, for the angioedema case noted above (under narratives), the termination log in the electronic CRF was reviewed. The investigator had chosen “withdrawal of consent – family concerns” as the primary reason for patient discontinuation. This patient had experienced angioedema and respiratory failure. Given the trend noted by this reviewer, it seems likely that the Sponsor would capture this discontinuation as “withdrawal of consent” – the study report for this study was not included with the NDA submission, so this assumption cannot be validated.

Case Identification

The Sponsor was asked to perform an analysis of patient cases meeting criteria for Hy’s law since this analysis was not included in the NDA submission (request to Sponsor 6/2010). The Sponsor provided one case. However, this reviewer notes that another case potentially meeting criteria for Hy’s Law was submitted as a 15-day safety report to IND 61,292 for a patient participating in an ongoing clinical trial (D1050233) – the study drug was still blinded. This safety report was submitted to the Division in March 2010. The Sponsor noted in a safety update submitted to the IND on 8/5/10, that the study drug was unblinded in July and the patient was found to be taking quetiapine XR 600 mg/day. However, the fact that this case was not submitted is problematic.

In the example noted under “Narratives” for the adverse event “angioedema”, the investigator also noted respiratory failure. It should be noted that the investigator did not enter respiratory failure in the adverse event section of the CRF, but rather included this reason for administration of several concomitant medications in the concomitant medications section of the CRF. This should have been queried by a site auditor. So, the adverse event of respiratory failure was not captured as an SAE (two other cases of respiratory failure occurred in clinical trials). This patient also required endotracheal intubation which was also not captured as an SAE (there is one other patient case that required endotracheal intubation and this was captured as an SAE under the SOC Surgical and Medical Procedures).

This reviewer reviewed all the narratives submitted with the NDA – this would include only deaths, SAEs and discontinuations due to adverse events. In the course of this review, the narrative for patient #329002 who participated in study D1050049 was reviewed. This patient was noted to have experienced the SAE “akathisia”. However, upon review of the narrative, there was a comment about other adverse events the patient experienced while participating in the clinical

trial, one of which was “pancreatitis” with a start date a few days prior to the end of the clinical trial. The JMP file for labs was reviewed, and there was no listing for amylase or lipase (labs that were not routinely performed in the trials). The CRF for this patient was reviewed, and, the labs around the time of the “pancreatitis” adverse event included significant elevations in ALT (125 U/L), AST (392 U/L), LDH (647 U/L), and CPK (19484 U/L) [total bilirubin was WNL]. Additionally, the amylase and lipase concentrations obtained were in the normal range. Interestingly, the narrative states that this patient completed the double-blind portion of the protocol “without incident” on 12/30 – the labs given above were the end of study labs (12/30/02). This patient did not continue in the open-label extension study. Follow-up labs were available which indicated that labs normalized ~1/16/2003. All of these labs were in the JMP files. Though this reviewer could not confirm the adverse event “pancreatitis”, certainly the occurrence of this adverse event with a start date a few days prior to completion of the study would not be consistent with completing the study “without incident”.

Maintaining Study Blind

Though there may be the usual concerns with maintaining a blind due to adverse event profiles, this reviewer was concerned that the lab reports included in many of the CRFs included prolactin concentrations that reported the actual value rather than stating “blinded”. The actual laboratory reports were included with the CRFs only for the nonelectronic CRFs, electronic CRFs did not have any laboratory data included. It is unknown if someone at the site separated the report so that the investigator did not see the prolactin concentration (this lab appeared alone on a separate page). It is troublesome that the value was actually reported with the lab results.

3.2 Compliance with Good Clinical Practices

Protocols were reviewed and approved by Institutional Review Boards and informed consent was obtained from participants in the clinical trials. The Sponsor did not identify any site-specific issues and no sites were excluded from Sponsor’s analyses.

The Sponsor indicated that all studies were conducted in accordance with good clinical practices as required by FDA, ICH guidelines and SOPs for clinical investigation and documentation at Dainippon Sumitomo Pharmaceuticals America, Ltd. For those studies performed in nonUS sites, the studies were also conducted in accordance with country-specific and/or local laws and regulations governing clinical studies of investigational products. Compliance with these requirements also constitutes conformity with the ethical principles of the Declaration of Helsinki.

3.3 Financial Disclosures

Form 3454 (version 10/09) “Certification: Financial Interests and Arrangements of Clinical Investigators” was included in the submission. The Sponsor indicated

that they had not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21CFR54.2(a).

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry Manufacturing and Controls

The chemistry, manufacturing and controls data were reviewed by Shastri Bhamidipati, Ph.D. The reviewer considered the NDA approvable from a CMC perspective pending satisfactory responses from the Sponsor to several issues identified by the reviewer (communicated to Sponsor 8/20/10). The proposed acceptance criteria for dissolution testing (Q30NLT (b) (4)) of the drug product are considered not appropriate and a final recommendation by the Biopharmaceutical Reviewer is pending.

The Office of Compliance has not provided a final recommendation as to the acceptability of manufacturing and testing facilities for the drug product.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

The pharmacology/toxicology data was reviewed by Sonia Tabacova, Ph.D. At the time this review was completed, the pharmacology/toxicology review was not available. The review team held many status meetings during the course of this NDA and no significant issues were identified by the pharmacology/toxicology reviewer.

Carcinogenesis: Lifetime carcinogenicity studies were conducted in ICR mice and Sprague-Dawley rats. Lurasidone was administered orally at doses of 30 – 1200 mg/kg/day to male ICR mice, 30 – 650 mg/kg/day to female ICR mice and 3-50 mg/kg/day to Sprague-Dawley rats. In the mouse study, there was increased serum prolactin at all dose levels and increased incidences of masses in the pituitary and in the mammary glands of female mice at 30 mg/kg/day or higher. Vaginal mucification and vaginal, uterine and cervical atrophy were also observed at these dose levels in female mice. In rats, administration of lurasidone at doses of 12 mg/kg/day or 50/36 mg/kg/day showed an increase in incidence of mammary carcinomas for females and increased milk secretion for males at all dose levels. An increased absence of corpora lutea in the ovary and an increase in cornification of the vagina were noted at all doses in females.

Mutagenesis: Lurasidone was not genotoxic in the Ames test, the in vitro chromosomal aberration test in Chinese Hamster Lung cells or the in vivo mouse bone marrow micronucleus test.

hERG: Using a hERG expressing HEK293 cell line, effects on rapidly activated delayed rectifier potassium current (IKr) were investigated with a patch-clamp technique. Lurasidone showed a dose-dependent inhibitory effect (IC₅₀: 108 nmol/L = 57 ng/ml) on IKr.

4.4 Clinical Pharmacology

The clinical pharmacology data was reviewed by Kofi Kumi, Ph.D. At the time this review was completed, the clinical pharmacology review was not available. The review team held many status meetings during the course of this NDA and few issues were identified by the clinical pharmacology reviewer. One recent issue identified was a lack data at a Japanese site for one of the key bioequivalence studies, it is the understanding of this reviewer that this related to assay data. At the time this review was completed, this issue had not been resolved.

4.4.1 Mechanism of Action

Receptor binding studies (in vitro) indicate that lurasidone possesses high affinities for dopamine D₂ (K_i = 1.68 nmol/L), serotonin 5-HT_{2A} (K_i = 2.03 nmol/L), 5HT₇ (K_i = 0.495 nmol/L), 5-HT_{1A} (K_i = 6.75 nmol/L), and noradrenaline α _{2C} (K_i = 10.8 nmol/L) receptors.

A dopamine D₂ receptor occupancy study in healthy male volunteers evaluated single doses of 10 to 80 mg of lurasidone. The mean D₂ receptor occupancies were 41.3-43.3% for 10 mg, 51-54.8% for 20 mg, 63.1-67.5% for 40 mg, 77.4-84.3% for 60 mg and 72.9-78.9% for 80 mg.

4.4.2 Pharmacodynamics

Lurasidone has demonstrated putative antipsychotic effects in several animal models including inhibition of dopamine D₂ receptor-mediated behaviors and conditioned avoidance response in rats and mice, inhibition of serotonin t-HT₂ receptor-mediated behaviors in rats.

4.4.3 Pharmacokinetics

Lurasidone is rapidly absorbed after oral administration with t_{max} occurring at 1.3-1.8 hours. Lurasidone has linear pharmacokinetics at doses of 20 to 100 mg in healthy volunteers and at doses of 120 mg to 160 mg in patients with schizophrenia. In the presence of a low-fat meal/medium calorie meal, lurasidone C_{max} increased by 2.8-fold and AUC increased by 2.3-fold (relative to a fasted state). The mean apparent volume of distribution ranges from 3220 L and 4410 L. Lurasidone is highly bound (~99%) to serum proteins. The mean terminal elimination half-life of lurasidone ranged from 12.2 to 21 hours in healthy volunteers.

Lurasidone's activity is primarily due to the parent drug and, to a lesser extent, to the active metabolites ID-14283 and ID-14326 which represent 25% and 3% of the parent exposure, respectively. The major biotransformation pathways are oxidative *N*-dealkylation, hydroxylation of norbornane ring and *S*-oxidation.

Approximately 90% of a lurasidone dose was recovered with 9.2-19% in urine and 67-80% in feces, suggesting that lurasidone is primarily eliminated via non-renal pathways. Mean apparent clearance ranges from 175 L/hr to 244 L/hr. In vitro and in vivo data suggest that lurasidone is metabolized primarily by CYP3A4. Significant drug interactions are noted for coadministration with CYP3A4 inhibitors (e.g. ketoconazole) and CYP3A4 inducers (e.g. rifampin).

4.5 QT Interdisciplinary Review Team

The QT Interdisciplinary Review Team reviewed the thorough QT study D1050249 "A double-blind, double-dummy, active controlled, randomized, 3-arm parallel study to evaluate the effects of therapeutic and suprathreshold doses of MK-3756 (lurasidone) on QTc interval in male and female schizophrenic or schizoaffective patients". This trial evaluated the effects of lurasidone 120 mg and lurasidone 600 mg on the QT interval with ziprasidone 160 mg as an active control. The reviewer considered the results inconclusive due to the following reasons (taken from the QT IRT consult):

1. The primary endpoint was inadequately defined. The QT study used time-matched mean changes from baseline in QTcI (i.e. Δ QTc) as the primary endpoint. The primary variable is inappropriate because it does not account for between-day shifting for ECG signals, which can be pronounced with an 11 day difference between the observation day and baseline day. A time-matched, baseline-corrected, and placebo-adjusted QTc ($\Delta\Delta$ QTc) should be used as the primary variable in a parallel thorough QT study. However, this variable cannot be derived from the current trial because of the absence of the placebo arm.
2. Assay sensitivity was not established in the trial. The QT study used ziprasidone as active control. The results from ziprasidone arm has two limitations: the results were described by using Δ QTc rather than $\Delta\Delta$ QTc and, at the tested dose level, the QTc interval change appears to be larger than the small change defined by ICH E14 guidance.

This reviewer had comments relating to the overall conclusions of the QT IRT (see Section X) as well as general comments about the findings of this thorough QT study. The most significant issue is that inclusion of a placebo arm in a thorough QT study in schizophrenic patients is not feasible.

4.6 Division of Anti-Infective and Ophthalmology Products

Since lurasidone is known to bind to melanin, several protocols included ophthalmologic assessments such as slit lamp examinations, fundoscopic assessments and visual acuity assessments. Study D1050237, a 12 month double-blind study comparing lurasidone (40-120 mg/day, flexible dose) and

risperidone (2-6 mg/day, flexible dose) included these assessments; this was the clinical trial with the longest exposure to lurasidone with ophthalmologic assessments. The Division of Anti-Infective and Ophthalmology Products was consulted to evaluate ophthalmologic data from study D1050237. At the time this review was completed, results from this consult were not available.

4.7 Division of Reproductive and Urologic Products

Lurasidone is associated with a significant increase in prolactin concentration. Several protocols had included markers for bone turnover as well as DEXA scans. Study D1050237, a 12 month double-blind study comparing lurasidone (40-120 mg/day, flexible dose) and risperidone (2-6 mg/day, flexible dose) included these assessments; this was the clinical trial with the longest exposure to lurasidone with DEXA scans. The Division of Reproductive and Urologic Products was consulted to evaluate DEXA scan data, as well as any other clinical data related to risk for bone fractures, for study D1050237. At the time this review was completed, results from this consult were not available.

5 SOURCES OF CLINICAL DATA

5.1 Tables of Studies/Clinical Trials

Only studies involving human subjects are included in these tables, see pharmacology/toxicology and biopharmaceutics reviews for animal and *in vitro* studies.

The pivotal clinical trials submitted to support the proposed indication are noted with an asterisk in Table 1. Two Phase 3 acute clinical trials were ongoing at the time the NDA was submitted to the Division (see table below): Study D1001002 and Study D1050233. Study D1001002 includes treatment groups lurasidone 40 mg, lurasidone 80 mg, risperidone 4 mg and placebo. Study D1050233 includes treatment groups lurasidone 80 mg, lurasidone 160 mg, quetiapine XR 600 mg and placebo. Per recent correspondence with the Sponsor, study D1001002 completed subject participation on May 10, 2010. A total number of 460 patients were randomized to double-blind treatment. Data are being cleaned and remain blinded, database lock is planned for December 2010. Study D1050233 completed subject participation on June 15, 2010. A total of 488 patients were randomized to double-blind treatment. Data are being cleaned and remain blinded, the database lock is planned for July with preliminary results available in August 2010. The final clinical study report is expected October 2010.

Phase 2 and 3 Clinical Trials:

Table 1. Acute Trials – Double-Blind, Placebo-Controlled

Protocol	Study Design	Subjects	Treatment Arms	Duration of Treatment
*D1050006 Regions: United States	MC, DB, R, fixed dose, PC-controlled, parallel group	Adults with schizophrenia N = 149 entered	Lurasidone 40 mg/day Lurasidone 120 mg/day Placebo	6 weeks
D1050049 Regions: United States	MC, DB, R, fixed-dose, PC and active-comparator controlled, parallel group	Adults with schizophrenia N = 356 entered	Lurasidone 20 mg/day Lurasidone 40 mg/day Lurasidone 80 mg/day Haloperidol 10 mg/day Placebo	6 weeks
*D1050196 Regions: United States	MC, DB, R, fixed-dose, PC controlled, parallel group	Adults with schizophrenia N = 180 entered	Lurasidone 80 mg/day Placebo	6 weeks
*D1050229 Regions: United States, France, India, Malaysia, Romania, Russia, Ukraine	MC, DB, R, fixed-dose, PC controlled, parallel group	Adults with schizophrenia N = 500 entered	Lurasidone 40 mg/day Lurasidone 80 mg/day Lurasidone 120 mg/day Placebo	6 weeks
*D1050231 Regions: United States, Columbia, India, Lithuania, Philippines	MC, R, DB, PC and active comparator controlled, parallel group	Adults with schizophrenia N = 478 entered	Lurasidone 40 mg/day Lurasidone 120 mg/day Olanzapine 15 mg/day Placebo	6 weeks
Ongoing Trials				
D1001002 (nonIND) Regions: Japan, Korea, Taiwan	MC, DB, R, PC and active-comparator controlled, parallel group	Adults with schizophrenia N = 460 entered	Lurasidone 40 mg/day Lurasidone 80 mg/day Risperidone 4 mg/day Placebo	6 weeks
D1050233 Regions: US, Colombia	MC, DB, R, PC and active-comparator controlled, parallel group	Adults with schizophrenia N = 488 entered	Lurasidone 80 mg/day Lurasidone 160 mg/day Quetiapine XR 600 mg/day Placebo	6 weeks

MC = multicenter, DB = double-blind, R = randomized, PC = placebo, PK = pharmacokinetics, DDI = drug-drug interaction, PD = pharmacodynamics

*Pivotal clinical trials

Source for ongoing clinical trials: Annual report (2/18/2010; SD-322)

Source: Table 5.2.1 (Tabular listing of all clinical studies), Table 3 (ISS), Table 2 (120-day Safety Update)

Table 2. Acute Trials - Open-Label/Active-Comparator-controlled/Uncontrolled

Protocol	Study Design	Subjects	Treatment Arms	Duration of Treatment
D1050254 Regions: United States	DB, R, active-controlled, fixed-dose, parallel group	Adults with schizophrenia N = 307 entered	Lurasidone titrated to 120 mg, MD Ziprasidone titrated to 80 mg BID, MD	21 days
D1001016 Regions: Japan	OL, uncontrolled, flexible dose	Adults with schizophrenia N = 70 entered	Lurasidone 20 – 80 mg MD	8 weeks
D1001001 Regions: Japan	R, DB, uncontrolled, parallel group	Adults with schizophrenia N = 208 entered	Lurasidone 20 mg MD Lurasidone 40 mg MD Lurasidone 80 mg	8 weeks
D1001017 Regions: Japan PK Study	Noncontrolled, OL, flexible-dose	Adults with schizophrenia	Lurasidone 20 – 80 mg/day	8 weeks

MC = multicenter, DB = double-blind, R = randomized, PC = placebo, PK = pharmacokinetics, DDI = drug-drug interaction, PD = pharmacodynamics

Source: Table 5.2.1 (Tabular listing of all clinical studies), Table 3 (ISS), Table 2 (120-day Safety Update)

Table 3. Long-term Trials - Open-Label/Active-Comparator Extension and other Long-term trials

Protocol	Study Design	Subjects	Treatment Arms	Duration of Treatment
D1001036 extension to D1001001 Region: Japan	MC, OL, flexible-dose, 12-month	Adults with schizophrenia N = 102 entered	Lurasidone 20 – 120 mg MD	52 weeks
D1001048 Region: Japan	MC, OL, flexible dose, 12-month study	Adults with schizophrenia N = 186 entered	Lurasidone 40 – 120 mg MD	52 weeks
D1050174 <i>Extension to D1050049</i>	MC, OL, dose-blinded, 6-month	Adults with schizophrenia N = 98 entered	Lurasidone 20 mg MD Lurasidone 40 mg MD Lurasidone 80 mg MD	26 weeks
D1050199 <i>extension to D1050196</i>	MC, OL, 12-month	Adults with schizophrenia N = 61 entered	Lurasidone 80 mg QD	52 weeks
Ongoing Studies				
D1050229E <i>Extension to D1050229</i>	MC, OL, 22-month	Adults with schizophrenia N = 251 entered	Lurasidone 40 – 120 mg QD	22 months
D1050231E	MC, OL, 6-month	Adults with schizophrenia	Lurasidone 40 – 120 mg QD	6 months

<i>Extension to D1050231</i>		N = 250 entered		
D1050234 <i>Patients who participated in D1050233</i>	MC, DB, R active comparator-controlled, 12-month	Adults with schizophrenia N = 240 planned, n = 148 entered	Lurasidone 40 – 160 mg/day Quetiapine XR 200 – 800 mg/day	12 months
D1050237	MC, DB, R active-comparator-controlled, 12-month	Adults with schizophrenia or schizoaffective disorder N = 605 entered	Lurasidone 40 – 120 mg/day Risperidone 2 – 6 mg/day	12 months (DB)
D1050237E Extension to D1050237	MC, OL, 6-month	Adults with schizophrenia N = 18 entered	Lurasidone 40 – 120 mg QD	6 months

MC = multicenter, DB = double-blind, R = randomized, PC = placebo, PK = pharmacokinetics, DDI = drug-drug interaction, PD = pharmacodynamics

Source: Table 5.2.1 (Tabular listing of all clinical studies), Table 3 (ISS), Table 2 (120-day Safety Update)

Phase 1 Clinical Trials

Table 4. Clinical Trials in Healthy Volunteers

Protocol	Study Design	Subjects	Treatment Arms	Duration of Treatment
S01P12 Food-Effect Study (Japan)	OL, crossover	Healthy volunteers	Lurasidone 20 mg single dose	1 day in each of 2 periods
D1050251 Bioavailability study	OL, R, 4-period crossover	Healthy volunteers	Lurasidone formulation A, 20 mg single dose Lurasidone formulation C, 20 mg single dose	1 day in each of 4 periods
D1050252 Bioavailability study	OL, R, 4-period, crossover	Healthy volunteers	Lurasidone formulation A, 20 mg single dose Lurasidone formulation D, 20 mg single dose Lurasidone formulation E, 20 mg single dose	1 day in each of 4 periods
D1050001 PK Study Single-ascending dose	DB, PC controlled, crossover	Healthy volunteers	Lurasidone 10 – 100 mg single dose Placebo	1 day in each of 2 or 3 periods
D1050002 PK Study Multiple doses	DB, PC controlled	Healthy volunteers	Lurasidone 40 mg/day Lurasidone 80 mg/day Placebo	8 days
D1050184 PK Study	OL, non-R	Healthy volunteers	[carbonyl- ¹⁴ C]-lurasidone 40 mg single dose	1 day
SM-071019	Single blind, PC	Healthy	Lurasidone 0.1 – 30 mg	1 day in each of

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PK Study (Japan)	controlled	volunteers	single dose	1 to 3 dose levels
S01P13 PK Study (Japan)	R, PC, single-blind	Healthy volunteers	Lurasidone 10 mg BID	7 days
D1050262 PK Study	OL, non-R	Healthy volunteers	[isothiazolyl-3- ¹⁴ C]-lurasidone 40 mg single dose	1 day
D1050253 PK Study Elderly	R, DB, PC controlled	Healthy volunteers	Lurasidone 20 mg/day	1 day
D1050264 PK Study Hepatic Impairment	OL	Hepatic impairment	Lurasidone 20 mg/day	1 day
D1050265 PK Study Renal Impairment	OL	Renal impairment	Lurasidone 40 mg/day	1 day
D1001049 PK Study Elderly (Japan)	OL, non-controlled, parallel-group, comparative	Healthy volunteers	Lurasidone 20 mg/day	1 day
D1050183 PK Study DDI	OL, 1-sequence, crossover	Healthy volunteers	Lurasidone 10 mg/day single dose Ketonazole 400 mg/day, multiple dose	
D1050250 PK Study DDI	R, PC controlled, partially-blinded, 2-period, fixed sequence	Healthy volunteers	Lurasidone 20 mg single dose Diltiazem 240 mg multiple dose	
D1050270 PK Study DDI	OL, 2-period, sequential	Healthy volunteers	Lurasidone 40 mg SD Rifampin 600 mg MD	
D1050246 PK Study DDI	R, DB, PC controlled, 2-period, crossover	Healthy volunteers	Lurasidone 40 mg MD Oral contraceptive QD MD	10 days
D1050180 PD Study Receptor occupancy	OL	Healthy volunteers	Lurasidone 10 – 80 mg SD	1 day
D1001013 PD Study qEEG	R, DB, crossover, PC controlled	Healthy volunteers	Lurasidone 20 and 40 mg SD	1 day in each of 3 periods

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(Japan)				
D1001053	R, OL, two period, cross-over study	Healthy volunteers	Lurasidone 40 mg SD	1 day
Bioequivalence Study				

MC = multicenter, DB = double-blind, R = randomized, PC = placebo, PK = pharmacokinetics, DDI = drug-drug interaction, PD = pharmacodynamics
 Source: Table 5.2.1 (Tabular listing of all clinical studies), Table 3 (ISS), Table 2 (120-day Safety Update)

Table 5. Clinical Trials in Patients with Schizophrenia

Protocol	Study Design	Subjects	Treatment Arms	Duration of Treatment
D1050263	OL, R, 3-period, 2-sequence, crossover, replicate-design	Adults with schizophrenia	Lurasidone 3 x 40 mg Lurasidone 120 mg	21 days
Bioequivalence Study				
D1050160	Single-blind, fixed-dose, and sequential dose-escalation	Adults with schizophrenia	Lurasidone 120 mg/day Lurasidone 140 mg/day Lurasidone 160 mg/day	6 days
PK Study MTD				
D1050217	R, DB, PC controlled	Adults with schizophrenia	Lurasidone 160 – 600 mg/day	6 to 8 days
PK Study MTD				
D1050269	OL, sequential	Adults with schizophrenia	Lurasidone 120 mg MD Midazolam 5 mg MD	8 days
PK Study DDI				
D1050247	OL, 2-period, sequential	Adults with schizophrenia or schizoaffective disorder	Lurasidone 120 mg MD Lithium 600 mg BID MD	16 days
PK Study DDI				
D1050279	OL, sequential	Adults with schizophrenia or schizoaffective disorder	Lurasidone 120 mg MD Digoxin 0.25 MD	8 days
PK Study DDI				
D1050249	R, DB, double-dummy, active-controlled, 3-arm parallel group	Adults with schizophrenia or schizoaffective disorder	Lurasidone 120 mg MD Lurasidone titrated to 600 mg MD Ziprasidone titrated to 80 mg BID, MD	11 days
Thorough QT study				
D1050267	R, OL, 6-way cross-over, repeat dose	Adults with schizophrenia or schizoaffective disorder	Lurasidone 120 mg MD	30 days
Food Effect				

MC = multicenter, DB = double-blind, R = randomized, PC = placebo, PK = pharmacokinetics, DDI = drug-drug interaction, PD = pharmacodynamics
 Source: Table 5.2.1 (Tabular listing of all clinical studies), Table 3 (ISS), Table 2 (120-day Safety Update)

5.2 Review Strategy

For the assessment of efficacy, this reviewer focused on the four pivotal clinical trials (D1050006, D1050196, D1050229, and D1050231). Study D1050049 was also reviewed, though this was a failed trial (neither lurasidone or active comparator, haloperidol, separated from placebo). These 5 clinical trials represent the Phase 2 and Phase 3 double-blind, placebo-controlled clinical trials in the lurasidone development program. Though there were a number of open label trials (some extension trials to the acute pivotal trials), due to the open-label design and lack of placebo group, efficacy cannot be readily established. Therefore the efficacy review focused only on double-blind, placebo-controlled studies.

Of note, two additional Phase 3 double-blind, placebo-controlled clinical trials were completed after the NDA was submitted (D1001002, D1050233). The results from these clinical trials were not available at the time this clinical review was completed.

All studies were used in the integrated safety analysis. Comprehensive safety data were not submitted for studies ongoing at the time the NDA was submitted – for those studies, the Sponsor did submit deaths and other serious adverse events.

Biometrics performed an assessment of efficacy for the pivotal studies from a statistical perspective with additional analyses as deemed necessary. Those additional analyses are included in the efficacy section of this review.

5.2 Discussion of Individual Studies/Clinical Trials

See Section 6.1.2 of the review.

6 REVIEW OF EFFICACY

Efficacy Summary

The Sponsor submitted four double-blind, placebo-controlled clinical trials to support the efficacy of lurasidone in the treatment of schizophrenia. All four clinical trials were 6 weeks in duration and adequately designed to assess the efficacy of lurasidone in the treatment of schizophrenia. All four trials included fixed doses of lurasidone and acceptable primary endpoints (BPRS derived from the PANSS or PANSS total score). One additional double-blind, placebo-controlled, active-comparator controlled study (D1050049) was a failed study in that neither lurasidone nor the active comparator (haloperidol) separated from placebo.

D1050006 was a Phase 2 trial in which 149 patients were randomized to lurasidone 40 mg/day, lurasidone 120 mg/day or placebo. All clinical sites were in the United States. The discontinuation rate in this study was 66%: 68% in the lurasidone 40 mg/day group, 59% in the lurasidone 120 mg/day group and 70%

in the placebo group. Though both lurasidone doses were statistically different from placebo on the primary outcome variable (change in BPRSd), due to the very high discontinuation rate, the overall interpretation of this study is problematic.

There is more to the interpretation of the efficacy signal in a clinical trial than the p-value. Reviewers would raise concern if a study was overpowered to find very small differences in a rating scale that were of dubious clinical relevance yet yielded a robust statistical difference. This reviewer has concerns about interpretation of the statistical results in study D1050006 with regard to the high discontinuation rate among all three treatment groups, the time course for discontinuation with ~50% discontinuing by study midpoint and the reasons for discontinuation which included primarily insufficient clinical response and “withdrawal of consent”, a category that is difficult to interpret and likely includes some patients with insufficient clinical response. This clinical trial was a small trial, ~50 patients per group. By week 6, 20 or fewer patients were present in each treatment group.

The discontinuation rate in this trial was much higher than in the other 3 pivotal trials. Patients enrolled in this trial were not more severely ill or more clinically symptomatic, in fact the mean BPRSd and PANSS total baseline scores were lower in this trial compared to the other 3 clinical trials (indicating a less symptomatic population in this trial). The only notable difference that this reviewer could find was that, compared to the other 3 clinical trials, significantly less concomitant lorazepam was used in this trial.

Due to the issues outlined above, this reviewer does not consider this clinical trial a positive one to support efficacy of lurasidone in the treatment of schizophrenia.

D1050196 was a Phase 2 trial in which 180 patients were randomized to lurasidone 80 mg/day or placebo. All clinical sites were in the United States. Lurasidone 80 mg/day separated from placebo on the primary endpoint, BPRSd (LOCF), and secondary endpoints including BPRSd (OC), BPRSd (MMRM – Division analysis), PANSS total score (LOCF), PANSS positive subscale score (LOCF) and CGI-S (LOCF).

D1050229 was a Phase 3 trial in which 500 patients were randomized to lurasidone 40 mg/day, lurasidone 80 mg/day, lurasidone 120 mg/day and placebo. This study included sites in the United States, Europe and Asia; 55% of patients enrolled were from sites in the United States. In this study, only the lurasidone 80 mg/day dose separated from placebo on the primary endpoint (PANSS Total Score, MMRM) and the key secondary endpoint (CGI-S, MMRM). Despite similar changes in PANSS total score in the placebo group between the US and Non-US subgroups, the difference between lurasidone and placebo in the US subgroup was -2 compared to -10.8 in the Non-US subgroup. LS means

in all four groups (lurasidone 40 mg, 80 mg, 120 mg and placebo) were similar in the US subgroup.

D1050231 was a Phase 3 trial in which 478 patients were randomized to lurasidone 40 mg/day, lurasidone 120 mg/day, olanzapine 15 mg/day or placebo. This study included sites in the United States, Europe, Asia and South America, 60% of patients enrolled were from sites in the United States. Both lurasidone doses (40 mg/day, 120 mg/day) and olanzapine 15 mg/day groups consistently separated from placebo on the primary endpoint (PANSS total score, MMRM) and the key secondary endpoint (CGI-S, MMRM). Though the Non-US subgroup exhibited more robust changes in the PANSS total score, the US subgroup did have greater LS mean changes in the lurasidone 40 and 120 mg/day group compared to placebo.

This reviewer is somewhat discouraged by the very frequent use of concomitant lorazepam in 3 of the pivotal trials (D1050196, D1050229 and D1050231). At week 6, 35-42% of patients in the lurasidone groups were receiving concomitant lorazepam compared to 35 – 49% in the placebo groups (mean daily doses of lorazepam were similar). In NDAs, Sponsors usually submit an overall table of concomitant medication use which is the frequency over the course of the clinical trial. It is unusual for a Sponsor to include the mean/median dose by week for a concomitant medication unless specifically asked to do so (they were asked to submit these data). Therefore, if a number of recent NDAs for this indication were sampled, it is unlikely that these data (mean/median dose of concomitant benzodiazepines) would be available for comparison purposes. It is somewhat disconcerting to this reviewer that similar percentages of patients are receiving concomitant lorazepam towards the end of the trials at similar mean/median daily doses. One would anticipate that more patients in the placebo group would be receiving concomitant lorazepam and at higher mean/median daily doses. The only one of the four pivotal trials that had much less use of concomitant lorazepam was study D1050006, the study in which the discontinuation rate was ~66%. In study D1050231, it is noted that the patients in the olanzapine 15 mg group also received concomitant lorazepam with the same frequency and mean/median daily dose as the other treatment groups. This reviewer did not ask the Sponsor to provide concomitant lorazepam use by US vs. Non-US geographic regions, so it is not known what, if any, impact differences in use may have had on the differences in efficacy noted between these regions (larger LS mean change and LS mean differences in Non-US vs. US sites). The Sponsor was asked to provide the numbers of patients who received lorazepam within 8 hours of the primary efficacy assessment and they did not have this information. One might speculate that, due to randomization, similar percentages of patients received lorazepam within 8 hours of the efficacy assessment in the treatment groups, but this cannot be verified.

In general, this reviewer does not believe that D1050006 is an interpretable study for reasons outlined above. Study D1050229 is, in the opinion of this reviewer, marginal since only one of three lurasidone doses separated from placebo and this dose did not exhibit a robust signal in the US subgroup analysis. This reviewer considered studies D1050196 and D1050231 to be positive studies in support of the efficacy of lurasidone 40 mg (D1050231), 80 mg (D1050196) and 120 mg (D1050231) in the treatment of schizophrenia. However, since the efficacy of these doses of lurasidone has not been replicated in the other studies, this reviewer would recommend a complete response action at this time.

It is also relevant to note that two Phase 3 clinical trials have recently been completed (D1001002 and D1050233). The final study report for D1050233 is estimated to be submitted in October 2010 and data from D1001002 should be available sometime after that. Study D1001002 (n = 460) evaluated the efficacy of lurasidone 40 mg, lurasidone 80 mg, risperidone 4 mg and placebo. Study D1050233 (n = 488) evaluated the efficacy of lurasidone 80 mg, lurasidone 160 mg, quetiapine XR 600 mg and placebo. Based on the marginal efficacy data presented in this NDA and the pending availability of significant clinical trial data (both efficacy and safety) it seems premature to recommend a final action at this time. These recently completed clinical trials provide more efficacy and safety data for the 40 mg/day, 80 mg/day and a higher dose, 160 mg/day. These clinical trials are placebo controlled and both also include an active comparator. It would seem prudent to review the efficacy data from these recently completed Phase 3 trials before taking a final action since the data submitted in this NDA, in this reviewer's opinion, do not support the efficacy of lurasidone in the treatment of schizophrenia.

Additionally, though the Sponsor appears to be studying higher doses of lurasidone for the treatment of schizophrenia (160 mg in the recently completed study as above), this reviewer does not believe that the Sponsor has adequately addressed the dose range for lower doses (e.g. 20 mg). In the EOP2 meeting, the Sponsor wanted concurrence with the Division that the approach of using PET D2 occupancy in combination with Phase 2 data to conclude that 20 mg is an ineffective dose and studying 3 doses (40, 80, 120 mg) across three efficacy and safety studies adequately explores the dose range and supports registration of lurasidone. The D2 receptor occupancy rates in one clinical study were 51-54.8% for the 20 mg dose, 63.1-67.5% for the 40 mg dose and higher occupancy rates for higher doses; so the PET data is not dramatically different between the 20 and 40 mg lurasidone doses. This reviewer could find only one double-blind, placebo-controlled clinical trial that included the lurasidone 20 mg dose (the failed D1050049 study). In this study, lurasidone 20 mg performed similar to lurasidone 40 mg; mean change from baseline in the PANSS total score was -7.1 (20 mg) and -7.2 (40 mg). One additional double-blind, but not placebo-controlled, study was conducted evaluating lurasidone 20 mg (n = 65), lurasidone 40 mg (n = 72) and lurasidone 80 mg (n = 58) (Study D1001001). The

lurasidone 20 mg group performed similarly to the lurasidone 80 mg group on the BPRS total score (mean change from baseline -2.1, lurasidone 20 mg; -3.0, lurasidone 80 mg) and on the PANSS total score (mean change from baseline -3.4, lurasidone 20 mg; -3.8, lurasidone 80 mg). Based on these data, this reviewer does not believe the lower dose of lurasidone have been adequately explored for efficacy and, since lurasidone is associated with significant EPS effects and prolactin elevation which appear to be dose-related (see Safety review), it would seem prudent to evaluate the efficacy of lower doses.

6.1 Studies Pertinent to Claim 1 – Treatment of Schizophrenia

6.1.1 Rationale for Selection of Studies for Review

The clinical review focused primarily on four pivotal clinical trials submitted to support the efficacy of lurasidone in the treatment of schizophrenia. All four clinical trials were 6 weeks in duration. Two of the clinical trials included 2 or more fixed doses of lurasidone compared to placebo: D1050006 (40 mg, 120 mg, PC) and D1050229 (40 mg, 80 mg, 120 mg, PC). One clinical trial included 1 fixed dose of lurasidone compared to placebo: D1050196 (80 mg, PC). One clinical trial included 2 fixed doses of lurasidone and an active comparator compared to placebo: D1050231 (40 mg, 120 mg, olanzapine 15 mg, PC).

One additional clinical trial is covered briefly in this section (D1050049). This 6 week clinical trial included 3 fixed doses of lurasidone (20 mg, 40 mg, 80 mg), an active comparator (haloperidol 10 mg) and placebo but was considered a failed trial in that none of the treatment arms separated from placebo on the primary outcome variable.

6.1.2 Study Summaries

Study 1 – D1050006

“A double-blind, randomized, fixed dose, placebo-controlled, parallel-group, 6-week, efficacy, safety, and tolerability study of two doses of SM-13496 [lurasidone] in patients with schizophrenia by DSM-IV criteria who are experiencing an acute exacerbation of symptoms”.

This study was conducted in 15 sites in the U.S.
Study conducted 2/6/2001 – 12/18/2001.

Methods/Study Design/Analysis Plan

Study D1050006 was a 6-week, multicenter, randomized, fixed dose, double-blind, parallel group, placebo-controlled Phase 2 trial. A screening period (up to 14 days) was followed by a single-blind placebo washout period (3 to 7 days) and a 6-week double-blind treatment period. Following the washout period, patients were randomized (1:1:1) to received lurasidone 40 mg/day, lurasidone 120

mg/day or placebo administered once daily. Patients randomized to lurasidone 40 mg/day began taking this dose on Day 1. Patients randomized to lurasidone 120 mg/day were titrated to this dose over a 6-day period starting with 80 mg/day on Day 1, 80 or 120 mg on Days 2-5 and 120 mg on Day 6. Study medication was taken with water in the morning, following breakfast. Patients remained hospitalized for at least the first 2 weeks of the double-blind treatment period. During the double-blind phase, study visits occurred on days 1, 3, 7, 14, 21, 28, 35 and 42.

Patients were eligible for the clinical trial if they met specific inclusion/exclusion criteria (see Appendix 9.5 for full criteria). Inclusion criteria included male or female; 18 to 64 years of age (inclusive); DSM-IV criteria for a primary diagnosis of schizophrenia as established by the SCID-CV, minimum duration of illness of at least 1 year; BPRSd total score of ≥ 42 (as extracted from the PANSS); a score of at least 4 on 2 or more items of the positive symptom subcluster on the PANSS; and CGI-S ≥ 4 at screening.

Allowable concomitant medications during the double-blind period included lorazepam (≤ 8 mg/24 hours), temazepam (≤ 30 mg/24 hours), zolpidem (≤ 10 mg/24 hours), chloral hydrate (≤ 1500 mg/24 hours) for no more than 5 consecutive days. Benztropine or biperiden (1-2 mg BID) were permitted for the treatment of EPS.

Efficacy Assessments included the PANSS, CGI-S and CGI-I. The primary endpoint was the BPRS extracted from the PANSS [BPRSd] which included items 2-9, 15-24 from the PANSS.

Analysis Plan

In order to detect a standardized treatment difference of 0.730 between a single lurasidone treatment group and the placebo group at 90% power (2-tailed) at an alpha level of 0.050 (2-sided), 40 subjects in each of the 3 treatment groups were required to assure adequate power of detection.

The statistical analyses were initially specified in the protocol. Further details of the planned statistical analysis were outlined in the statistical analysis plan that was finalized 9/6/2001 prior to unblinding of the treatment assignments.

The primary efficacy variable was the change from baseline in BPRS score derived from the PANSS (BPRSd) for the ITT population using the ANCOVA with treatment, investigator, and investigator-by-treatment interaction, including baseline BPRSd score as a covariate. Efficacy results were carried forward from Day 3 (LOCF-3) since ratings were not performed on days 1 or 2 in the protocol.

Results

Demographics

Demographic characteristics were fairly well balanced between the treatment groups. The majority of patients enrolled were males (> 70%) with a mean age of 39.6 years. The majority of patients enrolled were Caucasian or Black, a slightly greater percentage in the latter category.

Table 6. Patient Demographics (D1050006)

	Lurasidone 40 mg (n = 50)	Lurasidone 120 mg (n = 49)	Placebo (n = 50)
Gender (n, %)			
Male	36 (72%)	36 (73.5%)	42 (84%)
Female	14 (28%)	13 (26.5%)	8 (16%)
Age (years)			
Mean	39.8	41	38.1
Range	21 – 61	24 – 59	18 - 56
Race (n, %)			
Caucasian	20 (40%)	22 (44.9%)	20 (40%)
Black	25 (50%)	24 (49%)	25 (50%)
Asian	1 (2%)	0	1 (2%)
Hispanic	3 (6%)	3 (6.1%)	1 (2%)
Other	1 (2%)	0	3 (6%)

Source: Table 7.5.1 (CSR)

Baseline Characteristics

Baseline characteristics were fairly balanced between the treatment groups. The subtype of schizophrenia was predominantly paranoid subtype and the severity of symptoms, as measured by the PANSS and CGI-S, were similar between the groups. There was no information regarding how chronically ill these patients were (number of prior hospitalizations, etc.).

Table 7. Patient Baseline Characteristics (D1050006)

	Lurasidone 40 mg (n = 50)	Lurasidone 120 mg (n = 49)	Placebo (n = 50)
Schizophrenia subtype			
Disorganized	1 (2%)	0	1 (2%)
Paranoid	45 (90%)	44 (89.8%)	45 (90%)
Undifferentiated	4 (8%)	4 (8.2%)	4 (8%)
BPRSd Score (Mean, SD)	54.6 (9.1)	52.5 (7.6)	54.4 (8.3)
PANSS Total Score (Mean, SD)	92.8 (16.1)	89.6 (13.4)	93.3 (16.4)
CGI-S Score (Mean, SD)	4.8 (0.7)	4.7 (0.6)	4.6 (0.7)

Source: Table 7.6.1 (CSR)

Patient Disposition

Overall, 149 patients were randomized in this study (n = 50 lurasidone 40 mg, n = 50 lurasidone 120 mg, n = 50 placebo). It is noteworthy that 37% of the patients came from 2 of the 15 U.S. sites.

Sixty-six percent (98/149) of patients discontinued the study (Table 8). Reasons for discontinuation are provided in Table 8. A number of discontinuations were recategorized by this reviewer based on information in the subject termination log – see Table footnotes). Insufficient clinical response was a reason for discontinuation in 30% of patients receiving lurasidone 40 mg, 20% of patients receiving lurasidone 120 mg and 34% of patients receiving placebo.

Interestingly, the category “withdrawal of consent” included a large percentage of patients in all treatment groups (20-22%). In general, this category is not very informative and is difficult to interpret. Some of the reasons specified under the category of “withdrawal of consent” included: patient wanted to go home, patient left hospital unauthorized, patient decision – feels medication is not helping, patient left hospital, did not want to be an outpatient, patient no longer wanted to be hospitalized, patient did not like study medication, patient wanted to go home and end research, patient did not wish to continue with protocol.

Table 8. Patient Disposition (D1050006)

	Lurasidone 40 mg	Lurasidone 120 mg	Placebo
Randomized	50	49	50
Discontinued	34 (68%)	29 (59.2%)	35 (70%)
Reasons for discontinuation			
Insufficient clinical response	15 (30%)	10 (20%)	17 (34%)
Withdrawal of consent	11 (22%)	11 (22%)	10 (20%)
Adverse event	4 (8%)	5 (10%)	2 (4%)
Protocol violation*	2 (4%)	1 (2%)	4 (8%)
Lost to follow-up	2 (4%)	2 (4%)	2 (4%)

Sources: Table 7.1.1 in CSR, Data Listing 2 (subject termination log) in CSR

Recategorizations:

Adverse event to insufficient clinical response: “increased psychosis”, “worsening of schizophrenia”, “increased paranoia”, “increased somatic complaints most probably due to psychosis”, “incr in psychosis”, “SAE-acute exacerbation of paranoid schizophrenia”,

Withdrawal of consent to insufficient clinical response: “PI decision, lack of efficacy”, “due to lack of effect”, “lack of efficacy”

Withdrawal of consent to adverse event: “due to dystonia”

Other to adverse event: “abnormal lab values ALT = 94”

*Included noncompliance with protocol in this category (Sponsor classified as “other”)

Concomitant Medication Use

This reviewer focused primarily on concomitant medication use that may have impacted study results – specifically concomitant antipsychotic and benzodiazepine use. Concomitant use of medications for the treatment of EPS or akathisia are discussed elsewhere in the review (see Section 7.4.7).

According to the clinical study report, a total of 34 (68%) patients in the lurasidone 40 mg group, 23 (47%) patients in the lurasidone 120 mg group and 28 (56%) patients in the placebo group had taken concomitant antipsychotics during the clinical trial – though this may be an inflated number since some of

these patients could have received more than one antipsychotic (e.g. 2 prn doses of different antipsychotics) (Table 9).

Table 9. Concomitant Medications of Interest (D1050006)

	Lurasidone 40 mg (n = 50)	Lurasidone 120 mg (n = 49)	Placebo (n = 50)
Antidepressants			
Bupropion	0	1 (2%)	1 (2%)
Nefazodone	1 (2%)	0	0
Trazodone	1 (2%)	0	1 (2%)
Antipsychotics			
Chlorpromazine	1 (2%)	0	1 (2%)
Droperidol	3 (6%)	2 (4.1%)	4 (8%)
Fluphenazine HCl	0	0	1 (2%)
Fluphenazine decanoate	0	0	1 (2%)
Haloperidol	4 (8%)	2 (4.1%)	4 (8%)
Loxapine	1 (2%)	0	0
Olanzapine	9 (18%)	7 (14.3%)	10 (20%)
Perphenazine	2 (4%)	0	0
Quetiapine	3 (6%)	3 (6.1%)	2 (4.0%)
Risperidone	11 (22%)	8 (16.3%)	4 (8%)
Thiothixene	0	0	1 (2%)
Trifluoperazine	0	1 (2%)	0
Benzodiazepines			
Clonazepam	45 (90%)	43 (87.8%)	41 (82%)
Diazepam	2	1	0
Lorazepam	0	0	1
Temazepam	44	41	41
	15	13	11
BZD-related drugs			
Zolpidem	9 (18%)	7 (14.3%)	10 (20%)
Chloral hydrate			
	8 (16%)	4 (8.2%)	9 (18%)

Sources: Table 7.9.1 (CSR) and Table 26 (concomitant medication summary) (CSR)

The Sponsor provided further details of the concomitant antipsychotic use upon request (Amendment 12 to NDA). The Sponsor submitted a line listing for all subjects who took antipsychotic concomitant medications (Listing 1.1.1.3 in Amendment 12), however, the line listing and the tables in the clinical study report could not be reconciled. The line listing provided by the Sponsor did not include many of the concomitant antipsychotics included in the clinical study report. For example, according to Table 26 in the CSR, 9 (18%) of patients in the 40 mg group and 7 (14.3%) in the 120 mg group took concomitant olanzapine whereas the line listing indicates that 1 patient in the 40 mg group and 1 patient in the 120 mg group. The Sponsor was asked to reconcile these disparate results in concomitant antipsychotic use in this study.

In a response submitted as an amendment to the NDA, the Sponsor indicated that the reason for the different numbers was due to the different algorithms used to determine concomitant medication use. For study D1050006, the clinical study report used both the “prior medication” CRF page and the “concomitant medication” CRF page. For the “prior medication” page, medications were noted

as concomitant if 1) a medication's stop date was after the first study drug dose date and 2) the medication's ongoing status was "YES". For the "concomitant medication" CRF page, all medications recorded on this page were identified as concomitant regardless of start or stop dates (this particular algorithm was not used in the other 3 pivotal trials).

In the 7/25/10 response, the Sponsor indicated that according to the algorithm provided above, n = 63 (42.3%) of patients received concomitant antipsychotics during this trial. The data the Sponsor provided in the line listing (Amendment 12) used the same algorithm that the other 3 pivotal trials had used in their CSRs – a concomitant medication was defined as any recorded medication use with the exception of medication use that stopped before the first study drug dose date or started after the last study drug dose date. When using this algorithm, the Sponsor found that n = 10 (6.7%) of patients received concomitant antipsychotics and 8 of those 10 had received the concomitant antipsychotic on the last day of receiving the double-blind study drug.

It is unfortunate that the Sponsor had not questioned the very high concomitant antipsychotic medication use at the time the CSR was written. It is unknown whether the investigators for this study did not know what constituted a concomitant medication or whether investigators in the other pivotal trials made similar errors since these data in the CRFs from the other 3 trials were not used by the Sponsor to identify concomitant medication use.

The Sponsor was asked to provide the mean daily dose/week of concomitant benzodiazepine use for all of the treatment groups. The Sponsor provided these data as Amendment 12 to the NDA. The majority of concomitant benzodiazepines used in this clinical trial were lorazepam and temazepam. Table 10 summarizes the mean daily dose of lorazepam in each treatment group by study week. The percentage of patients receiving concomitant lorazepam varied by week – weeks 5 and 6 do not provide much data as the attrition was fairly high after week 3. The mean daily doses of lorazepam were fairly consistent between the treatment groups, importantly, the patients in the lurasidone groups were not receiving consistently higher mean doses of lorazepam compared to the placebo group.

Table 10. Concomitant Lorazepam Use – Mean Daily Dose (SD) By Week (D1050006)

	Lurasidone 40 mg (N = 50)	Lurasidone 120 mg (N = 49)	Placebo (N = 99)
Week 1			
n (%)	35 (70%)	25 (51%)	32 (64%)
Mean (SD)	1.29 (0.85)	1.64 (2.32)	1.24 (0.98)
Median	1.00	1.00	1.00
Week 2			
n (%)	22 (61%)	20 (54.1%)	19 (54.3%)
Mean (SD)	1.05 (0.82)	1.65 (2.59)	1.22 (1.18)
Median	0.80	1.00	0.86
Week 3			
n (%)	6 (23.1%)	7 (25%)	13 (44.8%)
Mean (SD)	0.88 (0.87)	1.18 (0.49)	1.22 (0.84)
Median	0.36	1.00	1.00
Week 4			
n (%)	5 (20.8%)	7 (30.4%)	4 (19%)
Mean (SD)	0.83 (0.74)	0.94 (0.62)	1.36 (0.62)
Median	0.43	1.00	1.07
Week 5			
n (%)	1 (5.9%)	3 (14.3%)	3 (15.8%)
Mean (SD)	0.86	0.90 (0.16)	1.26 (1.2)
Median	0.86	1.00	1.00
Week 6			
n (%)	2 (12.5%)	4 (19%)	1 (6.7%)
Mean (SD)	0.48 (0.269)	1.25 (0.66)	2.57
Median	0.48	1.00	2.57

Source: Post Hoc Table (Amendment 12 to NDA)

Important Protocol Violations

The clinical study report indicated that 16 protocol waivers were granted. The Sponsor was asked to provide more information regarding these waivers. The Sponsor responded that the 16 waivers were granted for 14 patients, n = 5 in the placebo group, n = 6 in the lurasidone 40 mg group and n = 2 in the lurasidone 120 mg group. These waivers included: prohibited antipsychotic medication during washout (2), hospitalization within 3 months prior to screening (6), positive urine drug screen (3), prohibited antihypertensive medication (1), abnormal ECG at screening (2), prohibited antidepressant medication (1), and abnormal eye exam at screening (1). It is unlikely that granting these specific waivers would have affected the efficacy evaluation.

In the clinical study report, the Sponsor indicated that only 2% of patients had protocol violations (3/149). To this reviewer, this seems like a very small number depending on the definition of protocol violation used. These 3 patients were discontinued from the study based on these violations. The protocol violations included not discontinuing olanzapine 72 hours prior to randomization, rescue medications given > 5 consecutive days, and patient could not keep scheduled

appointments. Based on the data available, the protocol violations are not anticipated to have influenced the overall results of this study.

Efficacy Results – Sponsor’s Results

Study Populations for Efficacy Analyses

	Lurasidone 40 mg (n = 50)	Lurasidone 120 mg (n = 49)	Placebo (n = 50)
ITT*	49	47	49
Completers	16	20	15

*ITT, Intent to Treat:: all subjects randomized, who received at least one dose of study medication, and had a baseline and at least one post-baseline efficacy measurement

Primary Analysis

Table 11. BPRSd: Change from Baseline to Endpoint: LOCF Analysis (D1050006)

	Lurasidone 40 mg (n = 49)	Lurasidone 120 mg (n = 47)	Placebo (n = 49)
Baseline mean (SD)	54.2 (8.93)	52.7 (7.61)	54.7 (8.13)
LS mean (SE)	-9.4 (1.58)	-11 (1.58)	-3.8 (1.57)
Difference between lurasidone and placebo 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	

Source: Table 8.1.1 (CSR)

*Dunnett’s adjusted p-value

Secondary Analyses

The Sponsor did not prespecify any key secondary analyses. The Sponsor did not provide any subscale analyses (PANSS positive subscale, etc.).

Table 12. BPRSd: Change from Baseline to Endpoint, OC Analysis (D1050006)

	Lurasidone 40 mg (n = 17)	Lurasidone 120 mg (n = 19)	Placebo (n = 17)
Baseline mean (SD)	54.2 (8.93)	52.7 (7.61)	54.7 (8.13)
LS mean (SE)	-17 (2.1)	-15 (2.1)	-9.9 (2.4)
Difference between lurasidone and placebo LS mean (SE)	-6.7 (3.1)	-4.9 (2.9)	
95% CI	(-13, -0.5)	(-11, 0.9)	
p-value	0.062	0.164	

Source: Table 7.1 (CSR)

Table 13. PANSS Total Score: Change from Baseline to Endpoint: LOCF Analysis (D1050006)

	Lurasidone 40 mg (n = 49)	Lurasidone 120 mg (n = 47)	Placebo (n = 49)
Baseline mean (SD)	92.2 (15.74)	90.0 (13.42)	93.9 (15.87)
LS mean (SE)	-14 (2.74)	-17 (2.73)	-6.2 (2.74)
Difference between lurasidone and placebo LS mean (SE)	-7.6 (3.67)	-11 (3.74)	
95% CI	(-15, -0.3)	(-18, -3.3)	
p-value	0.076	0.009	

Source: Table 8.2.1 (CSR)

Table 14. CGI-S: Change from Baseline to Endpoint, LOCF Analysis (D1050006)

	Lurasidone 40 mg (n = 49)	Lurasidone 120 mg (n = 47)	Placebo (n = 49)
Baseline mean (SD)	4.8 (0.72)	4.7 (0.62)	4.7 (0.66)
LS mean (SE)	-0.8 (0.15)	-0.8 (0.14)	-0.1 (0.14)
Difference between lurasidone and placebo LS mean (SE)	-0.7 (0.20)	-0.7 (0.20)	
95% CI	(-1.1, -0.3)	(-1.1, -0.3)	
p-value	0.002	0.001	

Source: Table 8.2.2 (CSR)

Efficacy Results – Additional Analyses by Division

The statistical reviewer provided additional analyses of the Sponsor's data including MMRM analysis of the primary endpoint (BPRSd) and LOCF analysis of the primary endpoint by visit.

Table 15. BPRSd Total Score: Mean Change from Baseline, MMRM analysis (D1050006)

Day	Lurasidone 40mg		Lurasidone 120 mg		Placebo	
	No	LS Mean (SE)	No	LS Mean (SE)	No	LS Mean (SE)
3	47	-4.6 (1.01)	44	-5.0 (1.01)	44	-3.2 (1.03)
7	47	-6.2 (1.34)	44	-6.9 (1.37)	44	-4.7 (1.37)
14	32	-11.0 (1.53)	37	-11.5 (1.44)	34	-5.5 (1.50)
21	26	-13.2 (2.00)	24	-10.0 (2.01)	26	-5.2 (2.00)
28	22	-12.5 (1.87)	23	-12.8 (1.83)	18	-6.5 (1.93)
35	17	-13.2 (1.88)	21	-12.7 (1.78)	15	-5.9 (1.92)
42	17	-13.4 (2.10)	19	-13.4 (2.00)	17	-4.1 (2.11)
LS Mean Diff. (SE)	-9.3 (2.95)		-9.2 (2.89)			
p-value (unadjusted)	0.0025		0.0022			

Source: Statistical Reviewer's Results

Table 16. BPRSd Total Score: Mean Change from Baseline by Visit, LOCF (D105006)

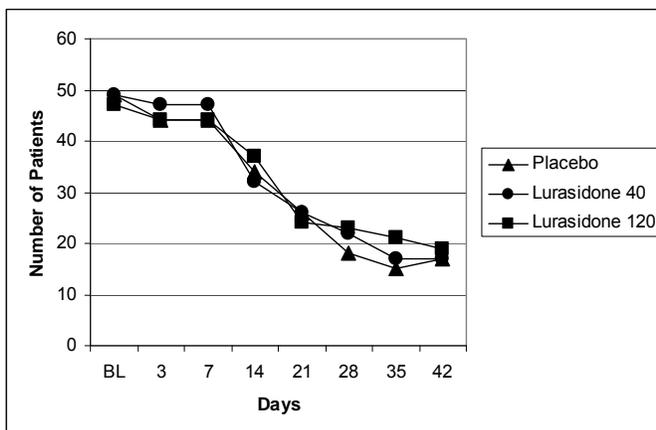
Day	Lurasidone 40 mg LS Mean (SE) p-value*	Lurasidone 120 mg LS Mean p-value*	Placebo LS Mean (SE) p-value*
3	-4.6 (1.01) 0.252	-5.0 (1.02) 0.150	-3.0 (1.04)
7	-5.6 (1.33) 0.452	-6.4 (1.32) 0.239	-4.3 (1.33)
14	-8.4 (1.50) 0.073	-10.4 (1.50) 0.007	-4.7 (1.49)
21	-10.1 (1.60) 0.014	-9.7 (1.60) 0.023	-4.7 (1.59)
28	-9.4 (1.57) 0.036	-10.6 (1.57) 0.008	-4.9 (1.56)
35	-9.4 (1.56) 0.024	-10.3 (1.56) 0.008	-4.6 (1.55)

Source: Statistical Reviewer's Results

*All p-values are lurasidone treatment group vs. placebo and unadjusted

Conclusions

In this Phase 2 study, 149 patients were randomized to one of three treatment arms and 51 (34%) completed the study. The drop-out rate was very high: 68% in the lurasidone 40 mg group, 59% in the lurasidone 120 mg group and 70% in the placebo group. The pattern of drop-outs is also potentially problematic in that ~50% had dropped out by the midpoint of the study (Day 21).



Source: Table 7.2 BPRS Summary Statistics by Visit for the Change from Baseline (CSR)

Approximately 40-50% of patients dropped out due to either insufficient clinical response or withdrawal of consent; this was consistent between all three groups. Since this was a Phase 2 study, thus a small study, loss of this many patients makes this study, in this reviewer's opinion, uninterpretable. This study certainly does not strongly support (in a pivotal way) efficacy of lurasidone at the doses administered in this study.

The prespecified primary endpoint in this trial was the change from baseline to endpoint in the BPRS-derived total score analyzed by LOCF. This analysis is problematic in the context of this many drop-outs – 50% dropping out by the midpoint of the trial. Although an MMRM approach might be used for further analysis, in this reviewer’s opinion, it is still problematic in that one is modeling data that is not present due to the high drop-out rate in a small study.

An exhaustive review of the drop-out rates for all development programs for schizophrenia cannot be completed within the deadline for this application. A selection of a few NDA submissions notes that, while it is not unusual to have high drop-out rates in schizophrenia clinical trials, these rates are in the range of 30-50% in drug treatment groups. Even within the context of the 4 pivotal trials that the Sponsor submitted to support the proposed indication, this clinical trial has the largest percentage of discontinuations. The discontinuation rate for the lurasidone groups in the 3 other pivotal clinical trials (30 – 45%) is more consistent with the discontinuation rates usually seen in these trials.

This Division has previously advised Sponsors that “at least 50% of patients assigned to active drug must complete to the nominal endpoint of the trial in order for it to be considered a completed trial” [advice letter to Sponsor for study in pediatric schizophrenia population]. Since this advice was given to a Sponsor who was evaluating a previously approved drug in a new population, it would seem unusual for this Division to accept a higher attrition rate in a clinical trial for a drug with no prior approval.

It is unclear why the discontinuation rate was so high in this clinical trial. Compared to the other clinical trials, these patients had similar severity of clinical symptoms as measured by baseline scores on PANSS or BPRSd. If anything, the patients in this study were slightly less symptomatic compared to patients in the other 3 pivotal trials when comparing the PANSS total scores at baseline. In this study, the range of mean baseline PANSS total scores in the treatment groups was 89 – 93 compared to 95 - 98 in the other studies. This reviewer did note one significant difference between this study and the other 3 pivotal trials and that is the use of concomitant lorazepam throughout the double-blind phase. Study D1050006 seemed to have much less use of concomitant lorazepam compared to the other studies – for example, at week 3 (when ~50% of patients had dropped from this trial), concomitant use of lorazepam was ~25% in the lurasidone groups and 45% in the placebo group. By comparison, at week 3 in the other trials, approximately 50 to 70% of patients were receiving concomitant lorazepam in each of the treatment groups (all lurasidone groups and placebo); and significant numbers of patients continued to receive concomitant medication until the end of the trial. Additionally, the mean daily dose and median daily dose of concomitant lorazepam was lower in this trial overall compared to the other 3 pivotal trials. For example, the mean (median) daily dose of lorazepam at week 3 for D1050006 was 0.88 (0.36) for lurasidone 40 mg, 1.18 (1.0) for lurasidone

120 mg and 1.22 (1.0) for placebo. For study D1050229, the mean (median) daily dose of lorazepam was 2.2 (1.57) for lurasidone 40 mg, 1.84 (1.64) for lurasidone 80 mg, 1.64 (1.29) for lurasidone 120 mg and 1.84 (1.64) for placebo.

Regardless of the reason, due to the high discontinuation rate in this small study, this reviewer cannot consider this a pivotal trial to support the efficacy of either the 40 mg/day or 120 mg/day dose of lurasidone in the treatment of schizophrenia.

Study 2 – D1050196

“A double-blind, fixed dose study of SM-13496 (lurasidone) and placebo in the treatment of schizophrenia”

This study was conducted in 22 sites in the U.S.
Study conducted 5/28/2004 – 12/6/2004

Methods/Study Design/Analysis Plan

Study D1050196 was a 6-week, multicenter, randomized, fixed dose, double-blind, parallel group, placebo-controlled Phase 2 trial. A 3 to 7 day single-blind placebo washout period was followed by a 6-week double-blind treatment period. Patients were randomized (1:1) to either lurasidone 80 mg/day (initiated at this dose) or placebo. Study medication was taken in the morning 30 minutes after breakfast.

Patients were hospitalized during the washout period and for the first 4 weeks of the double-blind treatment period (hospitalization could be extended). During the double-blind phase, study visits occurred on days 1, 3, 7, 14, 21, 28, 35 and 42.

Patients were eligible for the clinical trial if they met specific inclusion/exclusion criteria (see Appendix 9.5 for full criteria). Criteria were essentially the same as Study D1050006. Inclusion criteria included male or female; 18 to 64 years of age (inclusive); DSM-IV criteria for a primary diagnosis of schizophrenia as established by the SCID-CV; minimum duration of illness ≥ 1 year; BPRS total score of ≥ 42 (as extracted from the PANSS); a score of at least 4 on 2 or more items of the positive symptom subcluster on the PANSS; CGI-S ≥ 4 at screening.

Allowable concomitant medications during the double-blind period included lorazepam, temazepam, and zolpidem, the protocol outlined maximum doses/24 hours by week of the trial and whether inpatient or outpatient status. Benztropine was allowed for treatment of EPS.

Patients who participated in this study were eligible to enter a 1-year open-label extension study, D1050199.

Efficacy assessments included the PANSS, MADRS, and CGI-S. The primary endpoint was the BPRS extracted from the PANSS [BPRSd] which included items 2-9, 15-24 from the PANSS.

Analysis Plan

The sample size was determined to provide at least a 90% power to detect a 6-point difference between lurasidone and placebo. Based on the 2-sample t-test and assuming a standard deviation for change in BPRS of 10.5, 72 patients per group provide 92% power.

The statistical analyses were initially specified in the protocol. Further details of the planned statistical analysis were outlined in the statistical analysis plan that was finalized 9/9/2004 prior to unblinding of the treatment assignments.

The primary efficacy variable was the change from baseline to Day 42 LOCF in the BPRS total score (extracted from the PANSS) for the ITT population using ANCOVA with treatment group and study center as main effects and baseline BPRS as a covariate.

Results

Demographics

Demographic characteristics were fairly well balanced between the treatment groups. The majority of patients enrolled were males (> 75%). The majority of patients enrolled were Caucasian or Black, a greater percentage in the latter category.

Table 17. Patient Demographics (D1050196)

	Lurasidone 80 mg (n = 90)	Placebo (n = 90)
Gender		
Male	68 (75.6%)	70 (77.8%)
Female	22 (24.4%)	20 (22.2%)
Age (years)		
Mean	39.7 (9.91)	41.9 (9.78)
Range	(22 – 62)	(21 – 63)
Race		
Caucasian	35 (38.9%)	26 (28.9%)
Black	47 (52.2%)	56 (62.2%)
Asian	2 (2.2%)	1 (1.1%)
Hispanic	5 (5.6%)	7 (7.8%)
Other	1 (1.1%)	0

Source: Table 10.5.1 (CSR).

Baseline Characteristics

Baseline characteristics were fairly balanced between the treatment groups. The subtype of schizophrenia was predominantly paranoid subtype and the severity of symptoms, as measured by the PANSS and CGI-S, were similar between the

groups. There was no information regarding how chronically ill these patients were (number of prior hospitalizations, etc.).

Table 18. Patient Baseline Characteristics (D1050196)

	Lurasidone 80 mg (n = 90)	Placebo (n = 90)
Schizophrenia subtype		
Disorganized	4 (4.4%)	4 (4.4%)
Paranoid	73 (81.1%)	72 (80%)
Undifferentiated	13 (14.4%)	14 (15.6%)
BPRSd Score (Mean, SD)	55.1 (5.95)	56.1 (6.84)
PANSS Total Score (Mean, SD)	94.4 (10.9)	96 (11.59)
PANSS Positive Subscale Score	24.0 (3.76)	25.0 (4.17)
CGI-S Score (Mean, SD)	4.8 (0.71)	4.8 (0.67)
MADRS (Mean, SD)	14.2 (7.95)	14.5 (8.34)

Source: Table 10.5.1 and 10.6.1 (CSR).

Patient Disposition

Overall, 180 patients were randomized in this study (n = 90 lurasidone 80 mg, n = 90 placebo). Forty-five percent (81/180) of patients discontinued the study (Table 19). Reasons for discontinuation are provided in Table 19. A number of discontinuations were recategorized by this reviewer based on information in the subject completion/discontinuation log – see Table footnotes). Insufficient clinical response was a reason for discontinuation in 13% of patients receiving lurasidone 80 mg and 34% of patients receiving placebo. The second most frequent reason for study discontinuations was “withdrawal of consent”, a category that is not very informative and is difficult to interpret.

Table 19. Patient Disposition (D1050196)

	Lurasidone 80 mg	Placebo
Randomized	90	90
Discontinued	38 (42%)	43 (48%)
Reasons for discontinuation		
Insufficient clinical response	12 (13%)	31 (34%)
Withdrawal of consent	13 (14%)	8 (9%)
Lost to follow-up	2 (2%)	2 (2%)
Other*	2 (2%)	0
Protocol violation*	1 (1%)	1 (1%)
Adverse event	8 (9%)	1 (1%)

Sources: Table 10.1.1 (CSR) and Data Listing 2 subject completion/discontinuation log (CSR)

Recategorizations:

Other to insufficient clinical response: “worsening psychosis”

Withdrawal of consent to insufficient clinical response: “subject withdraws consent, no longer wants to participate, increased paranoia”, “lack of study drug effect”, “increasing paranoia”

Withdrawal of consent to lost to follow-up: “was discharged from hospital but never arrived at destination, lost to follow-up”

Withdrawal of consent to adverse event: “due to AE of glossospasm”, “nausea and vomiting”

Adverse event to insufficient clinical response: “severe psychotic deterioration”

Other to adverse event: “hospitalization/SAE”

*Other: “family situation”, noncompliance with protocol was recategorized from other to protocol violation.

Concomitant Medication Use

This reviewer focused primarily on concomitant medication use that may have impacted study results – specifically concomitant antipsychotic and benzodiazepine use. Concomitant use of medications for the treatment of EPS or akathisia are discussed elsewhere in the review (see Section 7.4.7).

According to the CSR, 9 (10%) of patients in the lurasidone group and 10 (11%) of patients in the placebo group had taken concomitant antipsychotics during the clinical trial. The Sponsor provided more information upon request (see concomitant medication use section of study D1050006). The Sponsor indicated that 10 (5.6%) of patients received concomitant antipsychotics during the clinical trial and 7 of those patients received the antipsychotic medication on the final day of double-blind study drug.

Table 20. Concomitant Medications of Interest (D1050196)

	Lurasidone 80 mg (n = 90)	Placebo (n = 90)
Antidepressants		
Escitalopram	1 (1.1%)	0
Antipsychotics		
Aripiprazole	1 (1.1%)	1 (1.1%)
Chlorpromazine	0	1 (1.1%)
Haloperidol	1 (1.1%)	1 (1.1%)
Loxapine	0	1 (1.1%)
Olanzapine	1 (1.1%)	2 (2.2%)
Quetiapine	4 (4.4%)	0
Risperidone	0	1 (1.1%)
Thiothixene	0	1 (1.1%)
Ziprasidone	2 (2.2%)	2 (2.2%)
Benzodiazepines		
Diazepam	0	1 (1.1%)
Lorazepam	76 (84.4%)	70 (77.8%)
Temazepam	30 (33.3%)	32 (35.6%)
BZD-related drugs		
Zaleplon	0	1 (1.1%)
Zolpidem	45 (50%)	37 (41%)

Sources: Table 30 (Summary of concomitant medications) (CSR)

The Sponsor was asked to provide the mean daily dose/week of concomitant benzodiazepine use for all of the treatment groups. The Sponsor provided these data as Amendment 12 to the NDA. The majority of concomitant benzodiazepines used in this clinical trial were lorazepam and temazepam. Table 21 summarizes the mean daily dose of lorazepam in each treatment group by study week. While the use of concomitant lorazepam did decrease over the course of the study, significant numbers of patients were requiring concomitant lorazepam during the final weeks of the trial. It is somewhat disconcerting that at week 5, 46% of patients in the lurasidone group were requiring concomitant lorazepam (mean dose 1.60 mg) compared to 57% of patients in the placebo

group (mean dose 1.37 mg). By week 6, 35% of patients in the lurasidone received concomitant lorazepam vs. 48% in the placebo group. Per protocol, benzodiazepines were not to be administered within 8 hours of the efficacy assessments. The Sponsor was asked to provide information regarding the numbers of patients in which lorazepam was administered within 8 hours of the primary efficacy assessment. The Sponsor responded that they did not have that information.

Table 21. Concomitant Lorazepam Use – Mean Daily Dose (SD) By Week (D1050196)

	Lurasidone 80 mg (N = 90)	Placebo (N = 90)
Week 1		
n (%)	62 (68.9%)	69 (76.7%)
Mean (SD)	1.84 (1.16)	2.02 (2.06)
Median	1.64	1.71
Week 2		
n (%)	57 (73.1%)	60 (72.3%)
Mean (SD)	1.81 (1.33)	1.71 (1.09)
Median	1.43	1.68
Week 3		
n (%)	44 (67.7%)	53 (69.7%)
Mean (SD)	1.59 (1.12)	1.62 (1.05)
Median	1.25	1.50
Week 4		
n (%)	38 (63.3%)	42 (60.9%)
Mean (SD)	1.50 (0.95)	1.73 (0.96)
Median	1.25	1.68
Week 5		
n (%)	26 (46.4%)	35 (57.4%)
Mean (SD)	1.59 (0.94)	1.37 (0.82)
Median	1.25	1.29
Week 6		
n (%)	18 (34.6%)	24 (48%)
Mean (SD)	1.66 (0.88)	1.57 (0.55)
Median	1.48	1.50

Source: Post Hoc Table (Amendment 12 to NDA)

Important Protocol Violations

The Sponsor indicated that there were 29 major protocol deviations occurring in 28 patients (15 in the lurasidone group and 13 in the placebo group). The most common were use of a prohibited medication during the study (6 patients in each group) and taking an improper dose of an allowed medication.

Of note, two patients in the lurasidone group had “non-zero serum concentration of lurasidone at baseline” and 3 patients had prior exposure to lurasidone (2 in

the placebo group).¹ The Sponsor was asked to clarify these cases and provided these data as Amendment 12 to the NDA. The three patients with prior exposure to lurasidone had been in prior lurasidone clinical trials, all three had been enrolled in the trials by different investigators (the same investigator had not enrolled the patient in two different clinical trials). This reviewer was concerned that these 3 patients, who may have shown response to lurasidone in prior clinical trials, may have been randomized to receive lurasidone in study D1050196 which could potentially impact the study results (though unlikely since so few had prior exposure). However, since it was confirmed that 2 of the 3 patients received placebo in study D1050196, this is not a concern for this reviewer.

Regarding the 2 patients with non-zero lurasidone serum concentrations at baseline, to the best of the Sponsor's knowledge, neither of these patients had participated in a prior clinical trial with lurasidone. One of these patients had a baseline lurasidone serum concentration close to the lower limit of quantification of the assay (0.02 ng/ml). The other patient had a baseline lurasidone serum concentration of 3.15 ng/ml which was close to the 5.23 ng/ml concentration achieved at week 1 of lurasidone dosing. The Sponsor stated that it could not be ruled out that this patient received active drug during the washout period. It is unlikely that these cases would have influenced the outcome of the study.

Efficacy Results – Sponsor's Results

Study Populations for Efficacy Analyses

	Lurasidone 80 mg (n = 90)	Placebo (n = 90)
ITT*	90	90
Completers	52	47

*ITT, Intent to Treat: all subjects who received at least 1 dose of study medication and at least 1 post-baseline efficacy assessment of the PANSS

Primary Efficacy Analysis

Table 22. BPRSd: Change from Baseline to Endpoint, LOCF Analysis (D1050196)

	Lurasidone 80 mg (n = 90)	Placebo (n = 90)
Baseline mean (SD)	55.1 (5.95)	56.1 (6.84)
LS mean (SE)	-8.9 (1.32)	-4.2 (1.36)
Difference between lurasidone and placebo LS mean	-4.68	
95% CI	(-8.3, -1.1)	
p-value	0.0118	

Source: Table 11.1.1 (CSR)

¹ Lurasidone group: patients 79001 (site 7), 159014 (site 15), 179012 (site 17); Placebo group: patients 179011 (site 17) and 239014 (site 23).

Secondary Analyses

The Sponsor did not prespecify any key secondary analyses.

Table 23. BPRSd: Change from Baseline to Endpoint, OC Analysis (D1050196)

	Lurasidone 80 mg (n = 52)	Placebo (n = 49)
Baseline mean	55.1 (5.95)	56.1 (6.84)
LS mean (SE)	-14.7 (1.49)	-9.7 (1.66)
Difference between lurasidone and placebo LS mean	-5.03	
95% CI	(-9.3, -0.7)	
p-value	0.0229	

Source: Table 11.2.1.1 (CSR)

Table 24. PANSS Total Score: Change from Baseline to Endpoint, LOCF Analysis (D1050196)

	Lurasidone 80 mg (n = 90)	Placebo (n = 90)
Baseline mean (SD)	94.4 (10.9)	96.0 (11.59)
LS mean (SE)	-14.1 (2.12)	-5.5 (2.17)
Difference between lurasidone and placebo LS mean (SE)	-8.57	
95% CI	(-14.4, -2.8)	
p-value	0.0040	

Source: Table 11.2.2.1 (CSR)

Table 25. PANSS Positive Subscale: Change from Baseline to Endpoint, LOCF (D1050196)

	Lurasidone 40 mg (n = 90)	Placebo (n = 90)
Baseline mean (SD)	24.0 (3.76)	25.0 (4.17)
LS mean (SE)	-4.3 (0.67)	-1.7 (0.70)
Difference between lurasidone and placebo LS mean (SE)	-2.63	
95% CI	(-4.5, -0.8)	
p-value	0.0060	

Source: Table 11.2.3.1 (CSR)

Similar efficacy findings were noted for the PANSS negative and general psychopathology subscales (data not shown).

Table 26. CGI-S: Change from Baseline to Endpoint, LOCF Analysis (D1050196)

	Lurasidone 40 mg (n = 90)	Placebo (n = 90)
Baseline mean (SD)	4.8 (0.71)	4.8 (0.67)
LS mean (SE)	-0.6 (0.11)	-0.2 (0.11)
Difference between lurasidone and placebo LS mean (SE)	-0.41	
95% CI	(-0.7, -0.1)	
p-value	0.0072	

Source: Table 11.2.7.1 (CSR)

Efficacy Results – Additional Analyses by Division

The statistical reviewer provided additional analyses of the Sponsor’s data including MMRM analysis of the primary endpoint (BPRSd).

Table 27. BPRS: Change from Baseline to Endpoint, MMRM Analysis (D1050196)

Day	Lurasidone 80 mg		Placebo		Treatment Difference: Lurasidone - Placebo	
	N	LS Mean (SE)	N	LS Mean (SE)	LS Mean	p-value
3	89	-3.7 (0.58)	88	-1.5 (0.59)	-2.2	0.0064
7	85	-5.3 (0.81)	87	-2.5 (0.82)	-2.8	0.0162
14	73	-7.5 (0.96)	82	-4.2 (0.94)	-3.3	0.0160
21	63	-10.5 (1.02)	71	-5.1 (0.99)	-5.4	0.0002
28	59	-10.7 (1.28)	65	-6.4 (1.24)	-4.3	0.0163
35	53	-11.4 (1.44)	58	-4.9 (1.38)	-6.4	0.0015
42	52	-11.3 (1.60)	49	-5.8 (1.55)	-5.6	0.0131

Source: Statistical Reviewer’s Results

Conclusions

In study D1050196, lurasidone 80 mg/day consistently separated from placebo at the 6 week endpoint on the primary endpoint, BPRSd (LOCF), and secondary endpoints including BPRSd (OC), BPRSd (MMRM – Division analysis), PANSS total score (LOCF), PANSS positive subscale score (LOCF) and CGI-S (LOCF). The discontinuation rate for this study (45%) was within expected attrition for schizophrenia trials. It is somewhat disconcerting to this reviewer that at week 5 and week 6, 46% and 35% of patients in the lurasidone group were receiving concomitant lorazepam. However, the frequency of concomitant use of lorazepam at weeks 5 and 6 were greater in the placebo group (57% and 48%) while the median doses between the groups were similar at those timepoints. The Sponsor was asked to provide the numbers of patients who received lorazepam within 8 hours of the primary efficacy assessment and they did not have this information, though this reviewer believes this data must be available. Though one might speculate that, due to randomization, similar percentages of

patients received lorazepam within 8 hours of the efficacy assessment in both treatment groups, but this cannot be verified.

This reviewer considers this clinical trial positive and supportive of the efficacy of lurasidone 80 mg/day in the treatment of schizophrenia.

Study 3 – D1050229

“A Phase 3, randomized, placebo-controlled, clinical trial to study the safety and efficacy of three doses of lurasidone HCl in acutely psychotic patients with schizophrenia”

This study was conducted in 48 foreign and U.S. sites: France (1), India (6), Malaysia (2), Romania (5), Russia (7), Ukraine (6), and U.S. (21).
Study conducted 10/26/2007 – 12/15/2008

Methods/Study Design/Analysis Plan

Study D1050229 was a 6 week, multicenter, randomized, fixed dose, double-blind, parallel group, placebo-controlled Phase 3 trial. A 3 to 7 day single-blind placebo washout period was followed by a 6 week double-blind treatment period. Patients were randomized (1:1:1:1) to lurasidone 40 mg/day, lurasidone 80 mg/day, lurasidone 120 mg/day or placebo. For the lurasidone 40 mg and 80 mg/day groups, dosing was initiated at the full dose. For the lurasidone 120 mg/day group, patients received 80 mg on days 1-3 then 120 mg thereafter. Study medications were taken once daily in the morning with a meal or within 30 minutes after eating. Patients were hospitalized during the washout period and weeks 1 through 3; patients were eligible for hospital discharge after completing 21 days of double-blind treatment if specific criteria were met. During the double-blind phase, study visits occurred on days 4, 7, 14, 21, 28, 35 and 42.

Patients were eligible for the clinical trial if they met specific inclusion/exclusion criteria (see Appendix 9.5 for full criteria). Inclusion criteria included male or female; 18 to 75 years of age (inclusive); DSM-IV criteria for a primary diagnosis of schizophrenia using the Mini-International Neuropsychiatric Interview Plus (MINI Plus); minimum duration of illness ≥ 1 year; PANSS total score ≥ 80 at screening/baseline; a score of ≥ 4 on two or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, unusual thought content and suspiciousness; CGI-S ≥ 4 at screening/baseline.

Allowable concomitant medications during the double-blind period included lorazepam (≤ 6 mg/day), zolpidem (≤ 10 mg/day), zolpidem CR (≤ 12.5 mg/day) and temazepam (≤ 30 mg/day). Benztropine, biperiden, diphenhydramine, propranolol or amantadine were allowed for treatment of EPS or akathisia.

Patients who participated in this study were eligible to enter a 22-month, open-label extension study, D1050229E.

Efficacy assessments included the PANSS, CGI-S, and the MADRS. The primary endpoint was the PANSS. The Sponsor prespecified a key secondary endpoint, the CGI-S.

Analysis Plan

The statistical analyses were initially specified in the protocol. Further details of the planned statistical analysis were outlined in the statistical analysis plan that was finalized 1/9/2009.

Several amendments to the protocol were made regarding the statistical analysis plan and the statistical reviewers provided input and guidance regarding changes in the statistical analysis plan (see statistical review for more comprehensive review).

Expected improvements in the PANSS were estimated from studies D1050006 and D1050196. Assuming lurasidone differed from placebo in the change from baseline in PANSS total score by 6.8, 8.0, and 10.0 for the 40 mg, 80 mg and 120 mg/day doses and assuming a standard deviation of 19.1, then 120 subjects per group provided 97.5% power (at the $\alpha = 0.05$ level, two-sided test) to reject the null hypothesis. The power calculation incorporated the Bonferroni's procedure for controlling pairwise differences to placebo (obtained by computer simulations).

The primary efficacy analysis was the change from baseline PANSS total score at week 6, as evaluated using a MMRM model (for the ITT population) under the assumption of an unstructured covariance matrix. The model included factors for pooled center, time, baseline PANSS total score, treatment, and treatment-by-time interaction.

The Hommel-based tree-gatekeeping procedure was applied to p-values from the MMRM analysis to control the family-wise Type I error rate at 5% by taking into account multiple doses and multiple primary and key secondary endpoints.

The Sponsor prespecified one key secondary endpoint, change from baseline in the CGI-S.

Results

Demographics

Demographic characteristics were fairly well balanced between the treatment groups. The majority of patients enrolled were males with a mean age of 38.8 years. Although the inclusion criteria indicated that patients 18 – 75 years of age could be enrolled, only 2 patients ≥ 65 years were enrolled. With regard to race,

approximately half of all patients in each group were White and approximately one third of all patients in each group were Black.

The groups were also balanced with regard to geographic region: Asia (15% lurasidone groups vs. 15% placebo group), Europe (30% lurasidone groups vs. 31% placebo group) and the United States (56% lurasidone groups vs. 54% placebo).

Table 28. Patient Demographics (D1050229)

	Lurasidone 40 mg (n = 124)	Lurasidone 80 mg (n = 121)	Lurasidone 120 mg (n = 124)	Placebo (n = 127)
Gender (n, %)				
Male	83 (67)	78 (64)	92 (74)	93 (73)
Female	41 (33)	43 (36)	32 (26)	34 (27)
Age (years)				
Mean	40.7 (11.1)	38.7 (9.5)	37.7 (11.2)	38.1 (9.8)
Range	18 - 72	19 - 62	18 - 65	20 - 64
Race (n, %)				
Asian	17 (14)	19 (16)	20 (16)	20 (16)
Black	49 (40)	40 (33)	41 (33)	38 (30)
Native Hawaiian or Other Pacific Islander	0	1 (< 1)	0	0
White	57 (46)	61 (50)	60 (48)	66 (52)
Other	1 (< 1)	0	3 (2)	3 (2)

Source: Table 14 (CSR)

Baseline Characteristics

Baseline characteristics were fairly balanced between the treatment groups. The subtype of schizophrenia was predominantly paranoid subtype and the severity of symptoms, as measured by the PANSS and CGI-S, were similar between the groups. The majority of patients ($\geq 55\%$) in each group had ≥ 4 prior hospitalizations for schizophrenia. The mean age at onset of schizophrenia was ~24 years.

Table 29. Patient Baseline Characteristics (ITT Population) (D1050229)

	Lurasidone 40 mg (n = 122)	Lurasidone 80 mg (n = 119)	Lurasidone 120 mg (n = 124)	Placebo (n = 124)
Schizophrenia subtype				
Disorganized	3 (2)	3 (3)	1 (< 1)	4 (3)
Paranoid	109 (89)	104 (87)	108 (87)	109 (88)
Undifferentiated	10 (8)	12 (10)	15 (12)	11 (9)
PANSS Total Score (Mean, SD)	96.5 (11.5)	96 (10.8)	96 (9.7)	96.8 (11.1)
PANSS Positive Subscale (Mean, SD)	26.3 (4.1)	25.8 (3.6)	26.2 (3.6)	25.7 (4.3)
CGI-S Score (Mean, SD)	5 (0.7)	4.9 (0.6)	4.9 (0.6)	4.9 (0.6)

Source: Table 15 (CSR)

Patient Disposition

Overall, 500 patients were randomized in this study: 125 to lurasidone 40 mg, 123 to lurasidone 80 mg, 124 to lurasidone 120 mg and 128 to placebo. Thirty-four percent (172/500) discontinued the study.

Table 30 depicts the patient disposition for this study. After reviewing the subject disposition listing, this reviewer recategorized a few of the reasons for discontinuation (see table footnotes for details). The most common reason for discontinuation was “insufficient clinical response”. The second most frequent reason for study discontinuations was “withdrawal of consent”, a category that is not very informative and is difficult to interpret. The most common reasons specified under the category “withdrawal of consent” included “personal reasons” and not wanting to continue on an inpatient basis.

Table 30. Patient Disposition (D1050229)

	Lurasidone 40 mg	Lurasidone 80 mg	Lurasidone 120 mg	Placebo
Randomized	125	123	124	128
Discontinued	41 (33%)	37 (30%)	39 (31%)	55 (43%)
Reasons for discontinuation				
Insufficient clinical response	20 (16%)	11 (9%)	20 (16%)	34 (27%)
Adverse event	9 (7%)	9 (7%)	7 (6%)	2 (2%)
Lost to follow-up	4 (3%)	2 (2%)	0	6 (5%)
Protocol violation	2 (2%)	0	1 (< 1%)	0
Withdrawal of consent	6 (5%)	14 (11%)	10 (8%)	13 (10%)
Administrative	0	1 (< 1%)	1 (< 1%)	0

Source: Table 11 (CSR), Listing 16.2.1.1 (subject disposition) (CSR)

Recategorizations: withdrawal of consent to adverse event: akathisia, “agitated on the inside”, insomnia, back pain, delusional ideas; administrative to protocol violation: poor compliance with study procedures, ethanol positive lab test, cocaine test positive; administrative to insufficient clinical response: hostile and uncooperative; adverse event to insufficient clinical response: psychotic decompensation, paranoid, lack of efficacy, acute exacerbation of schizophrenia

Concomitant Medication Use

This reviewer focused primarily on concomitant medication use that may have impacted study results – specifically concomitant antipsychotic and benzodiazepine use. Concomitant use of medications for the treatment of EPS or akathisia are discussed elsewhere in the review (see Section 7.4.7).

According to the CSR, 12 to 15% of patients in each treatment group received concomitant antipsychotics. The Sponsor provided more information upon request (see concomitant medication use section of study D1050006). The Sponsor indicated that 64 (12.9%) of patients received concomitant antipsychotics during the clinical trial and 60 of those patients received the antipsychotic medication on the final day of double-blind study drug.

Table 31. Concomitant Medications of Interest (D1050229)

	Lurasidone 40 mg (n = 124)	Lurasidone 80 mg (n = 121)	Lurasidone 120 mg (n = 124)	Placebo (n = 127)
Antidepressants				
Duloxetine	0	0	1 (< 1%)	0
Escitalopram	0	2 (2%)	0	1 (< 1%)
Sertraline	0	1 (< 1%)	0	0
Trazodone	1 (< 1%)	1 (< 1%)	0	0
Venlafaxine	0	0	1 (< 1%)	0
Antipsychotics				
Aripiprazole	1 (< 1%)	1 (< 1%)	0	2 (2%)
Chlorpromazine	0	2 (2%)	0	1 (< 1%)
Fluphenazine	3 (2%)	2 (2%)	2 (2%)	0
Haloperidol	3 (2%)	2 (2%)	2 (2%)	1 (< 1%)
Olanzapine	1 (< 1%)	3 (2%)	3 (2%)	0
Paliperidone	1 (< 1%)	1 (< 1%)	0	2 (2%)
Perphenazine	0	1 (< 1%)	0	1 (< 1%)
Quetiapine	5 (4%)	5 (4%)	10 (8%)	6 (5%)
Risperidone	2 (2%)	1 (< 1%)	3 (2%)	5 (4%)
Trifluoperazine	0	1 (< 1%)	0	0
Ziprasidone	0	1 (< 1%)	1 (< 1%)	0
Zuclopenthixol	0	0	1 (< 1%)	0
Benzodiazepines				
Diazepam	1 (< 1%)	2 (2%)	2 (2%)	3 (2%)
Lorazepam	81 (65%)	73 (60%)	83 (67%)	73 (57%)
Phenazepam	4 (3%)	2 (2%)	3 (2%)	3 (2%)
Temazepam	11 (9%)	9 (7%)	11 (9%)	13 (10%)
BZD-related drugs				
Zolpidem	41 (33%)	37 (31%)	47 (38%)	37 (29%)
Zopiclone	2 (2%)	2 (2%)	1 (< 1%)	0

Source: Table 14.1.5.2 (number and percentage of subjects with concomitant medications)

The Sponsor was asked to provide the mean daily dose/week of concomitant benzodiazepine use for all of the treatment groups. The Sponsor provided these data as Amendment 12 to the NDA. The majority of concomitant benzodiazepines used in this clinical trial were lorazepam and temazepam. Table 32 summarizes the mean daily dose of lorazepam in each treatment group by study week. Significant percentages of patients required concomitant lorazepam during the first few weeks of the study (~50% - 60%). Approximately 30 to 45% of patients were requiring concomitant lorazepam during weeks 5 and 6. Mean doses of lorazepam were ~1.5 to 2 mg/day. At week 5, similar percentages of patient in the lurasidone 40 mg/day group and placebo group were receiving concomitant lorazepam, fewer patients received lorazepam in the lurasidone 80 and 120 mg/day groups. By week 6, more patients received lorazepam in the lurasidone 40 mg/day group (and at higher mean and median daily dose) compared to the other treatment groups. At week 6, 37% of patients in all lurasidone groups were receiving lorazepam at a mean dose of 1.85 mg/day compared to 35.5% of patients in the placebo group

receiving a mean dose of 1.75 mg/day of lorazepam. Per protocol, benzodiazepines were not to be administered within 8 hours of the efficacy assessments. The Sponsor was asked to provide information regarding the numbers of patients in which lorazepam was administered within 8 hours of the primary efficacy assessment. The Sponsor responded that they did not have that information.

Table 32. Concomitant Lorazepam Use – Mean Daily Dose (SD) By Week (D1050229)

	Lurasidone 40 mg (N = 124)	Lurasidone 80 mg (N = 121)	Lurasidone 120 mg (N = 124)	Placebo (N = 99)
Week 1				
n (%)	73 (58.9%)	62 (51.2%)	72 (58.1%)	63 (49.6%)
Mean (SD)	1.84 (1.47)	1.93 (1.44)	1.82 (1.49)	1.77 (1.32)
Median	1.43	1.71	1.54	1.57
Week 2				
n (%)	67 (59.8%)	57 (52.8%)	57 (51.4%)	57 (48.3%)
Mean (SD)	2.01 (1.63)	1.72 (1.43)	1.79 (1.62)	1.74 (1.35)
Median	1.57	1.14	1.29	1.33
Week 3				
n (%)	58 (56.3%)	47 (48%)	54 (53.5%)	52 (49.1%)
Mean (SD)	2.20 (1.76)	1.84 (1.40)	1.64 (1.45)	1.84 (1.46)
Median	1.57	1.64	1.29	1.64
Week 4				
n (%)	48 (50%)	38 (40.4%)	39 (42.4%)	39 (41.9%)
Mean (SD)	2.21 (1.81)	1.91 (1.38)	1.67 (1.26)	1.74 (1.41)
Median	1.86	1.86	1.43	1.29
Week 5				
n (%)	43 (46.7%)	37 (39.8%)	31 (34.8%)	37 (45.1%)
Mean (SD)	2.23 (1.58)	1.81 (1.44)	2.0 (1.61)	1.50 (1.37)
Median	2.0	1.33	1.71	1.00
Week 6				
n (%)	38 (43.7%)	29 (32.2%)	30 (35.3%)	27 (35.5%)
Mean (SD)	1.97 (1.50)	1.75 (1.17)	1.80 (1.62)	1.75 (1.69)
Median	1.75	1.57	1.00	1.14

Source: Post Hoc Table (Amendment 12 to NDA)

Important Protocol Violations

Five patients received the incorrect double-blind treatment (2-40 mg group, 1-80 mg group and 2-placebo group), no further details were provided. Treatment group became unblinded in two cases (1-120 mg group, 1-placebo group), no further details were provided. These violations occurred in both lurasidone and placebo groups. It is unlikely that these few violations affected the overall study results.

Efficacy Results – Sponsor’s Results

Study Populations for Efficacy Analyses

	Lurasidone 40 mg (n = 125)	Lurasidone 80 mg (n = 123)	Lurasidone 120 mg (n = 124)	Placebo (n = 128)
ITT*	122	119	124	124
Completer	85	88	86	75

*ITT, Intent to Treat: all subjects randomized, who received at least one dose of study medication, and had a baseline and at least one post-baseline efficacy measurement

Primary Efficacy Analysis

Table 33. PANSS Total Score: Change from Baseline to Endpoint, MMRM Analysis (D1050229)

	Lurasidone 40 mg (n = 121)	Lurasidone 80 mg (n = 118)	Lurasidone 120 mg (n = 123)	Placebo (n = 124)
Baseline mean (SD)	96.5 (11.5)	96.0 (10.8)	96.0 (9.7)	96.8 (11.1)
Change from BL to Week 6. Estimate (SE)	-19.2 (1.7)	-23.4 (1.8)	-20.5 (1.8)	-17.0 (1.8)
Difference between lurasidone and placebo Estimate (SE)	-2.1 (2.5)	-6.4 (2.5)	-3.5 (2.5)	
95% CI	(-7, 2.8)	(-11.3, -1.5)	(-8.4, 1.4)	
p-value*	0.591	0.034	0.391	

Source: Table 18 (CSR)

*p-values were adjusted with Hommel-based tree-gatekeeping procedures. The unadjusted p-values were 0.394 (40 mg), 0.011 (80 mg) and 0.163 (120 mg).

Secondary Analyses

Key Secondary Analysis

Table 34. CGI-S: Change from Baseline to Endpoint, MMRM Analysis (D1050229)

	Lurasidone 40 mg (n = 122)	Lurasidone 80 mg (n = 119)	Lurasidone 120 mg (n = 124)	Placebo (n = 124)
Baseline mean (SD)	5.0 (0.7)	4.9 (0.6)	4.9 (0.6)	4.9 (0.6)
Change from Baseline to Week 6. Estimate (SE)	-1.1 (0.1)	-1.4 (0.1)	-1.2 (0.1)	-1.0 (0.1)
Difference between lurasidone and placebo Estimate (SE)	-0.1 (0.1)	-0.4 (0.1)	-0.2 (0.1)	
95% CI	(-0.4, 0.1)	(-0.7, -0.1)	(-0.5, 0.1)	
p-value*	0.591	0.034	0.543	

Source: Table 22 (CSR)

*p-values were adjusted with Hommel-based tree-gatekeeping procedures. The unadjusted p-values were 0.365 (40 mg), 0.005 (80 mg) and 0.169 (120 mg).

The change in CGI-S from baseline to endpoint was also analyzed via ITT-LOCF and a completers (observed cases) analysis. The LOCF analysis showed

efficacy for the lurasidone 80 mg group ($p = 0.001$ – not adjusted) but not the lurasidone 40 mg group ($p = 0.237$) or the lurasidone 120 mg group ($p = 0.113$). The completers analysis did not show efficacy for any of the lurasidone groups compared to placebo (all groups $p > 0.3$ vs. placebo, not adjusted).

Table 35. PANSS Total Score: Change from Baseline to Endpoint By Visit, MMRM Analysis (D1050229)

	Lurasidone 40 mg	Lurasidone 80 mg	Lurasidone 120 mg	Placebo
Day 4				
Change from BL (Estimate)	-4.3	-4.2	-4.3	-3.2
Treatment Difference (Estimate)	-1.1	-1.0	-1.0	
p-value (vs. placebo)*	0.241	0.296	0.263	
Week 1				
Change from BL (Estimate)	-7.2	-8.3	-8.2	-6.3
Treatment Difference (Estimate)	-1.0	-2.0	-1.9	
p-value (vs. placebo)*	0.433	0.113	0.122	
Week 2				
Change from BL (Estimate)	-10.8	-12.9	-12.7	-9.4
Treatment Difference (Estimate)	-1.5	-3.5	-3.4	
p-value (vs. placebo)*	0.360	0.031	0.036	
Week 3				
Change from BL (Estimate)	-14.5	-16.4	-16.1	-11.8
Treatment Difference (Estimate)	-2.7	-4.6	-4.3	
p-value (vs. placebo)*	0.156	0.018	0.026	
Week 4				
Change from BL (Estimate)	-16.2	-19.1	-18.0	-14.1
Treatment Difference (Estimate)	-2.2	-5.1	-3.9	
p-value (vs. placebo)*	0.301	0.017	0.062	
Week 5				
Change from BL (Estimate)	-17.6	-21.2	-19.5	-15.3
Treatment Difference (Estimate)	-2.3	-5.9	-4.2	
p-value (vs. placebo)*	0.304	0.010	0.064	
Week 6				
Change from BL (Estimate)	-19.2	23.4	-20.5	-17.0
Treatment Difference (Estimate)	-2.1	-6.4	-3.5	
p-value (vs. placebo)*	0.394	0.011	0.163	

Source: Table 14.2.1.1 (CSR)

*unadjusted for multiple comparisons

Table 36. PANSS Total Score: Change from Baseline to Endpoint, LOCF Analysis (D1050229)

	Lurasidone 40 mg (n = 121)	Lurasidone 80 mg (n = 118)	Lurasidone 120 mg (n = 124)	Placebo (n = 124)
Baseline mean (SD)	96.6 (11.5)	95.6 (10.2)	95.8 (9.5)	96.8 (11.1)
LS mean (SE)	-17.4 (1.6)	-20.8 (1.6)	-18.5 (1.6)	-14.7 (1.6)
Difference between lurasidone and placebo Estimate (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	

Source: Table 19 (CSR)

*P-values versus placebo, p-values comparing lurasidone groups, LS means, and CIs are from an ANCOVA with treatment and pooled center as fixed factors and baseline value as a covariate, unadjusted

Table 37. PANSS Total Score: Change from Baseline to Endpoint, OC Analysis (D1050229)

	Lurasidone 40 mg (n = 85)	Lurasidone 80 mg (n = 88)	Lurasidone 120 mg (n = 86)	Placebo (n = 75)
Baseline mean (SD)	97.2 (11.3)	96.1 (9.9)	95.6 (9.7)	95.1 (9.7)
LS mean (SE)	-24 (1.5)	-24.9 (1.5)	-27.1 (1.5)	-25.2 (1.6)
Difference between lurasidone and placebo Estimate (SE)	1.2 (2.1)	0.3 (2.1)	-1.9 (2.1)	
95% CI	(-3, 5.4)	(-3.9, 4.4)	(-6.1, 2.3)	
p-value*	0.568	0.893	0.370	

Source: Table 19 (CSR)

*P-values versus placebo, p-values comparing lurasidone groups, LS means, and CIs are from an ANCOVA with treatment and pooled center as fixed factors and baseline value as a covariate, unadjusted

Table 38. PANSS Positive Subscale Score: Change from Baseline to Endpoint, MMRM Analysis (D1050229)

	Lurasidone 40 mg (n = 121)	Lurasidone 80 mg (n = 118)	Lurasidone 120 mg (n = 123)	Placebo (n = 124)
Baseline mean (SD)	26.3 (4.1)	25.8 (3.6)	26.2 (3.6)	25.7 (4.3)
Change from BL to Week 6. Estimate (SE)	-6.5 (0.6)	-8.6 (0.6)	-7.5 (0.6)	-5.3 (0.6)
Difference between lurasidone and placebo Estimate (SE)	-1.2 (0.9)	-3.3 (0.9)	-2.3 (0.9)	
95% CI	(-2.9, 0.5)	(-5.0, -1.6)	(-4.0, -0.6)	
p-value*	0.153	< 0.001	0.018	

Source: Table 14.2.1.5 (CSR)

*Hommel-adjusted p-value

Analyses by Geographic Subgroup

This study was conducted in 48 foreign and U.S. sites: France (1), India (6), Malaysia (2), Romania (5), Russia (7), Ukraine (6), and U.S. (21). One of the analyses provided by the Sponsor compared the results between the US and Non-US sites. The numbers of subjects were fairly well balanced between these geographic regions with n = 268 in US sites and n = 218 in Non-US sites.

When evaluating the PANSS (LOCF) results for US sites, none of the lurasidone treatment groups separate from placebo, two of the lurasidone doses perform (numerically) worse than placebo. By contrast, the lurasidone treatment groups separate from placebo for 2 of the 3 dose groups in the Non-US sites. These differences in efficacy are based largely on the effect size of lurasidone – the LS mean differences for the placebo group are similar in the US and Non-US sites. [Also see geographic region analyses, MMRM in *Efficacy Results – Additional Analyses by Division section that follow*].

Table 39. PANSS Total Score: Change from Baseline to Endpoint by Geographic Region, LOCF Analysis (D1050229)

US

	Lurasidone 40 mg (n = 69)	Lurasidone 80 mg (n = 63)	Lurasidone 120 mg (n = 69)	Placebo (n = 67)
Baseline Mean (SD)	96 (11.7)	94.7 (10.7)	95.7 (8.9)	94.9 (10.4)
LS mean (SE)	-14.5 (2.1)	-17.1 (2.2)	-14.9 (2.1)	-15.1 (2.1)
Difference between lurasidone and placebo Estimate (SE)	0.6 (3.0)	-2.0 (3.0)	0.2 (3.0)	
95% CI	(-5.2, 6.5)	(-8.0, 3.9)	(-5.6, 6.0)	
p-value*	0.829	0.503	0.943	

Non-US (Europe and Asia)

	Lurasidone 40 mg (n = 52)	Lurasidone 80 mg (n = 55)	Lurasidone 120 mg (n = 54)	Placebo (n = 57)
Baseline Mean (SD)	97.2 (11.5)	96.7 (9.5)	95.9 (10.3)	98.9 (11.7)
LS mean (SE)	-20.3 (2.5)	-24.5 (2.4)	-22.3 (2.5)	-13.7 (2.4)
Difference between lurasidone and placebo Estimate (SE)	-6.5 (3.5)	-10.8 (3.4)	-8.6 (3.4)	
95% CI	(13.4, 0.3)	(-17.5, -4.1)	(-15.4, -1.8)	
p-value*	0.061	0.002	0.013	

Source: Table 21 (CSR)

*P-values versus placebo, p-values comparing lurasidone groups, LS means, and CIs are from an ANCOVA with treatment and pooled center as fixed factors and baseline value as a covariate, not adjusted

The sites in Europe had 35-39 patients per treatment group. In the geographic region subanalysis (LOCF), the treatment difference (lurasidone vs. placebo) was -8.3 for lurasidone 40 mg ($p = 0.046$), -10.6 for lurasidone 80 mg ($p = 0.011$) and -7.5 for lurasidone 120 mg ($p = 0.075$). The sites in Asia were the smallest with 16 – 19 patients per treatment group. The treatment difference was -1.5 for lurasidone 40 mg ($p = 0.821$), -11.1 for lurasidone 80 mg ($p = 0.081$) and -10.2 for lurasidone 120 mg ($p = 0.105$).

The change in CGI-S from baseline showed a similar pattern as the PANSS in the geographic region subanalyses (Table 40).

Table 40. CGI-S: Change from Baseline to Endpoint by Geographic Region, LOCF (D1050229)

US

	Lurasidone 40 mg (n = 70)	Lurasidone 80 mg (n = 64)	Lurasidone 120 mg (n = 70)	Placebo (n = 67)
Baseline Mean (SD)	5 (0.8)	4.9 (0.7)	4.9 (0.7)	4.8 (0.7)
LS mean (SE)	-0.7 (0.1)	-0.9 (0.1)	-0.7 (0.1)	-0.7 (0.1)
Difference between lurasidone and placebo Estimate (SE)	0.0 (0.2)	-0.2 (0.2)	0.0 (0.2)	
95% CI	(-0.3, 0.4)	(-0.5, 0.2)	(-0.3, 0.4)	
p-value*	0.917	0.351	0.917	

Non-US

	Lurasidone 40 mg (n = 52)	Lurasidone 80 mg (n = 55)	Lurasidone 120 mg (n = 54)	Placebo (n = 57)
Baseline Mean (SD)	4.9 (0.6)	4.9 (0.5)	4.9 (0.5)	5.1 (0.4)
LS mean (SE)	-1.2 (0.1)	-1.5 (0.1)	-1.3 (0.1)	-0.7 (0.1)
Difference between lurasidone and placebo Estimate (SE)	-0.4 (0.2)	-0.8 (0.2)	-0.6 (0.2)	
95% CI	(-0.8, -0.0)	(-1.2, -0.4)	(-1.0, -0.2)	
p-value*	0.028	< 0.001	0.004	

Source: Table 24 (CSR)

*P-values versus placebo, p-values comparing lurasidone groups, LS means, and CIs are from an ANCOVA with treatment and pooled center as fixed factors and baseline value as a covariate

In the geographic region subanalysis for Europe (LOCF), the treatment difference (lurasidone vs. placebo) was -0.7 for lurasidone 40 mg ($p = 0.006$), -0.8 for lurasidone 80 mg ($p < 0.001$) and -0.7 for lurasidone 120 mg ($p = 0.010$) [all unadjusted]. In the geographic region subanalysis for Asia, the treatment difference was 0.1 for lurasidone 40 mg ($p = 0.749$), -0.7 for lurasidone 80 mg ($p = 0.038$) and -0.4 for lurasidone 120 mg ($p = 0.117$).

Efficacy Results – Additional Analyses by Division

As with the geographic subgroup analysis (LOCF) performed by the Sponsor, the MMRM analysis for the primary efficacy variable (PANSS Total Score) yielded similar results. While the LS mean change in the placebo group is *slightly* greater in the US subgroup compared to the Non-US subgroup, none of the lurasidone treatment groups differ substantially from placebo in the former.

Table 41. PANSS Total Score: LS Mean Change from Baseline by Geographic Subgroup, MMRM Analysis (D1050229)

	Lurasidone 40mg	Lurasidone 80mg	Lurasidone 120mg	Placebo
US	-17.0 (2.4)	-20.1 (2.4)	-17.3 (2.4)	-18.1 (2.4)
Non-US	-22.1 (2.6)	-27.1 (2.5)	-24.3 (2.6)	-16.5 (2.6)

Source: Statistical Reviewer's Results

The pharmacometric reviewer evaluated the serum concentrations between geographic regions and noted that the lurasidone concentrations were higher for each fixed dose group in the Non-US sites compared to the US sites for patients completing the clinical trial (Table 42).

Although there were differences in serum concentrations between the geographic regions, this does not explain the discrepancy in effect between the regions. The 40 mg dose in the non-US sites performed more robustly on the PANSS total score-LOCF (Table 39) than the 120 mg dose in the US sites: LS mean -20.3 vs. -14.9, LS mean difference from placebo -6.5 vs. 0.2.

Table 42. Lurasidone AUC by Geographic Region (D1050229)

	Mean (SD) AUC ng*hr/ml		
	Lurasidone 40 mg	Lurasidone 80 mg	Lurasidone 120 mg
US	0.30 (0.33)	0.62 (0.73)	0.83 (0.86)
NonUS	0.40 (0.29)	0.77 (0.57)	1.06 (1.23)

Source: Pharmacometric Reviewer's Results
 Sample sizes US: n = 64 (40 mg), 58 (80 mg), 64 (120 mg)
 Sample sizes non-US: n = 48 (40 mg), 49 (80 mg), 52 (120 mg)

Conclusions

In study D1050229, lurasidone 80 mg/day consistently separated from placebo on the primary endpoint (PANSS Total Score, MMRM), the key secondary endpoint (CGI-S, MMRM) and other secondary endpoints such as PANSS total score (LOCF) and PANSS positive subscale score (MMRM); while the lurasidone 40 mg/day and lurasidone 120 mg/day doses did not separate from placebo on any of these measures except for the PANSS positive subscale score (only 120 mg/day).

It is somewhat disconcerting to this reviewer that at week 6, similar percentages of patients are receiving concomitant lorazepam - 37% in the lurasidone groups (combined) vs. 35% in the placebo group. The mean dose of lorazepam at week 6 was 1.85 mg/day for the lurasidone groups (combined) and 1.75 mg/day for the placebo group. The Sponsor was asked to provide the numbers of patients who received lorazepam within 8 hours of the primary efficacy assessment and they did not have this information, though this reviewer believes this data must be available. Though one might speculate that, due to randomization, similar percentages of patients received lorazepam within 8 hours of the efficacy assessment in the treatment groups, but this cannot be verified.

Upon examination of the geographic subgroup analysis, none of the lurasidone treatment groups separated from placebo in the US subgroup which comprised > 50% of the study sample. Though it is not unusual for geographic differences to be noted in clinical trials, in the experience of this Division, these differences are largely due to a greater placebo effect in the U.S. sites compared to the Non-US

sites. In study D1050229, there were similar treatment effects in the placebo groups for the US and Non-US sites. This findings was consistent in the geographic subgroup analysis for the PANSS total score (LOCF and MMRM) and the key secondary variable, CGI-S (LOCF). This reviewer did not ask the Sponsor to provide concomitant lorazepam data for US vs. non-US regions, so the extent to which this may or may not contribute to overall differences in efficacy cannot be determined.

Though one might consider that subgroup analyses may be problematic from a power perspective, 268 patients were in the ITT US population translating to 63 – 69 patients per treatment group. This number/treatment group was slightly larger than the Phase 2 study D1050006 (~50/treatment group).

The pharmacometrics reviewer noted that the serum concentrations of lurasidone were higher in the Non-US sites compared to the US sites for every dose group. However, as noted in that section of the review, this does not explain the discrepancy in efficacy since the 40 mg dose of lurasidone in the Non-US sites had a greater effect (e.g. decrease in PANSS total score) compared to the 120 mg dose in the US sites. Though the pharmacometrics reviewer commented that the differences in concentrations between the US and Non-US sites may be due to differences in baseline weights (higher mean weight in US sites), in the opinion of this reviewer, CYP3A4 (or other isozymes) activity would likely be more of a contributing factor in overall concentrations achieved. CYP3A4 activity differences, if present between the two populations, was not ascertained in these studies.

In the opinion of this reviewer, the overall efficacy data from this clinical trial are marginal. Overall, only the lurasidone 80 mg/day group separated from placebo, the 40 mg/day and 120 mg/day lurasidone groups did not. In the US subgroup analysis, all of the lurasidone groups as well as placebo had similar LS means and the mean difference between lurasidone 80 mg/day and placebo was -2.0 points on the PANSS total score. Due to the discrepancies in lurasidone 80 mg effect sizes between the US and Non-US groups, this reviewer considers the overall efficacy of lurasidone in this clinical trial to be only marginal.

Study 4 – D1050231

“A Phase 3, randomized, placebo- and active comparator-controlled clinical trial to study the safety and efficacy of two doses of lurasidone HCl in acutely psychotic patients with schizophrenia”

This study was conducted in 52 foreign and U.S. sites: Columbia (5), India (14), Lithuania (4), Philippines (4), and U.S. (25).
Study conducted 1/18/2008 – 6/16/2009

Methods/Study Design/Analysis Plan

Study D1050231 was a 6 week, multicenter, randomized, fixed dose, double-blind, parallel group, placebo- and active comparator Phase 3 trial. A 3 to 7 day single-blind placebo washout period was followed by a 6 week double-blind treatment period. Patients were randomized (1:1:1:1) to lurasidone 40 mg/day, lurasidone 120 mg/day, olanzapine 15 mg/day or placebo. Patients randomized to lurasidone 40 mg or 120 mg/day were initiated at the full dose. Patients randomized to olanzapine received 10 mg/day for the first 7 days and 15 mg/day thereafter. Study medications were taken once daily in the morning by mouth with a meal or within 30 minutes after eating.

Patients were hospitalized during the washout period and weeks 1 through 3; patients were eligible for hospital discharge after completing 21 days of double-blind treatment if specific criteria were met. During the double-blind phase, study visits occurred on days 4, 7, 14, 21, 28, 35 and 42.

Patients were eligible for the clinical trial if they met specific inclusion/exclusion criteria (see Appendix 9.5 for full criteria). Inclusion criteria included male or female; 18 to 75 years of age (inclusive); DSM-IV criteria for a primary diagnosis of schizophrenia using the MINI Plus; minimum duration of illness ≥ 1 year; PANSS total score > 80 at screening/baseline; a score of ≥ 4 on 2 or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, unusual thought content, and suspiciousness; CGI-S ≥ 4 at screening/baseline.

Allowable concomitant medications during the double-blind period included lorazepam (≤ 6 mg/day), zolpidem (≤ 10 mg/day), zolpidem CR (≤ 12.5 mg/day) and temazepam (≤ 30 mg/day). Benztropine, biperiden, diphenhydramine, propranolol or amantadine were allowed for treatment of EPS or akathisia.

Patients who participated in this study were eligible to enter a 6-month, open-label extension study, D1050231E.

Efficacy assessments included the PANSS, CGI-S and MADRS. The primary endpoint was the PANSS. The Sponsor prespecified a key secondary endpoint, the CGI-S.

Analysis Plan

The statistical analyses were initially specified in the protocol. Further details of the planned statistical analysis were outlined in the statistical analysis plan that was finalized on 7/6/2009.

Several amendments to the protocol were made regarding the statistical analysis plan and the statistical reviewers provided input and guidance regarding changes

in the statistical analysis plan (see statistical review for more comprehensive review).

Expected improvements in the PANSS were estimated from studies D1050006 and D1050196. Assuming lurasidone differed from placebo in the change from baseline in PANSS total score by 6.8, 8.0, and 10.0 for the 40 mg, 80 mg and 120 mg/day doses and assuming a standard deviation of 19.1, then 120 subjects per group provided 97.5% power (at the $\alpha = 0.05$ level, two-sided test) to reject the null hypothesis. The power calculation incorporated the Bonferroni's procedure for controlling pairwise differences to placebo (obtained by computer simulations).

The primary efficacy analysis was the change from baseline PANSS total score at week 6, as evaluated using a MMRM model (for the ITT population) under the assumption of an unstructured covariance matrix. The model included factors for pooled center, time, baseline PANSS total score, treatment, and treatment-by-time interaction.

The Hommel-based tree-gatekeeping procedure was applied to p-values from the MMRM analysis to control the family-wise Type I error rate at 5% by taking into account multiple doses and multiple primary and key secondary endpoints.

Results

Demographics

Demographic characteristics were fairly well balanced between the treatment groups. The majority of patients enrolled were males with a mean age of 37.7 years. Although the inclusion criteria indicated that patients 18 – 75 years of age could be enrolled, only 2 patients ≥ 65 years were enrolled. With regard to race, approximately 1/3 of all patients in each group were White, 1/3 were Black and 1/4 were Asian.

The groups were also balanced with regard to geographic region: Asia (~24% all groups), Europe (~6%), United States (~60%) and South America (10%).

Table 43. Patient Demographics (D1050231)

	Lurasidone 40 mg (n = 119)	Lurasidone 120 mg (n = 118)	Olanzapine 15 mg (n = 122)	Placebo (n = 116)
Gender (n, %)				
Male	93 (78)	93 (79)	95 (78)	90 (78)
Female	26 (22)	25 (21)	27 (22)	26 (22)
Age (years)				
Mean (SD)	37.7 (11)	37.9 (11.2)	38.3 (10.2)	36.9 (11.3)
Range	18 - 63	18 - 68	19 - 62	18 - 64
Race (n, %)				
American Indian or Native Alaskan	0	1 (< 1)	1 (< 1)	0
Asian	31 (26)	27 (23)	30 (25)	28 (24)
Black	39 (33)	36 (31)	44 (36)	41 (35)
Native Hawaiian or Other Pacific Islander	0	0	0	1 (< 1)
White	44 (37)	48 (41)	41 (34)	37 (32)
Other	5 (4)	6 (5)	6 (5)	9 (8)

Source: Table 14 (CSR)

Baseline Characteristics

Baseline characteristics were fairly balanced between the treatment groups. The subtype of schizophrenia was predominantly paranoid subtype and the severity of symptoms, as measured by the PANSS and CGI-S, were similar between the groups. The majority of patients ($\geq 55\%$) in each group had ≥ 4 prior hospitalizations for schizophrenia. The mean age at onset of schizophrenia was ~24 years.

Table 44. Patient Baseline Characteristics (ITT Population) (D1050231)

	Lurasidone 40 mg (n = 119)	Lurasidone 120 mg (n = 118)	Olanzapine 15 mg (n = 122)	Placebo (n = 114)
Schizophrenia subtype				
Disorganized	2 (2)	3 (3)	5 (4)	8 (7)
Paranoid	106 (89)	105 (89)	100 (82)	98 (86)
Undifferentiated	11 (9)	10 (8)	17 (14)	8 (7)
PANSS Total Score (Mean, SD)	96.6 (10.7)	97.9 (11.3)	96.3 (12.2)	95.8 (10.8)
PANSS Positive Subscale (Mean, SD)	25.6 (4.0)	25.9 (3.6)	25.6 (4.1)	26.4 (4.0)
CGI-S Score (Mean, SD)	5 (0.7)	5 (0.6)	4.9 (0.7)	4.9 (0.7)

Source: Table 15 (CSR), Table 19 (CSR), Table 22 (CSR), Table 14.2.1.8 (CSR)

Patient Disposition

Overall, 478 patients were randomized in this study: 120 to lurasidone 40 mg, 119 to lurasidone 120 mg, 123 to olanzapine 15 mg and 116 to placebo. Thirty-eight percent (180/578) discontinued the study. Table 45 depicts the patient disposition for this study. After reviewing the subject disposition listing, this reviewer recategorized a few of the reasons for discontinuation (see table

footnotes for details). The most common reason for discontinuation was “insufficient clinical response”. The second most frequent reason for study discontinuations was “withdrawal of consent”, a category that is not very informative and is difficult to interpret. Some of the reasons specified under the category of “withdrawal of consent” included: death in the family, wanted to leave hospital, no longer wanted to participate in study, family issues, wanted to go back on old medications, did not like the way it made him feel, no longer wanted to be an inpatient.

Table 45. Patient Disposition (D1050231)

	Lurasidone 40 mg	Lurasidone 120 mg	Olanzapine 15 mg	Placebo
Randomized	120	119	123	116
Discontinued	43 (36%)	53 (45%)	39 (32%)	45 (39%)
Reasons for discontinuation				
Insufficient clinical response	20 (17%)	14 (12%)	11 (9%)	22 (19%)
Adverse event	5 (4%)	12 (10%)	9 (7%)	6 (5%)
Lost to follow-up	1 (< 1%)	2 (2%)	1 (< 1%)	2 (2%)
Protocol violation	3 (2%)	0	2 (2%)	1 (< 1%)
Withdrawal of consent	14 (12%)	25 (21%)	15 (12%)	12 (10%)
Administrative	0	0	1 (< 1%)	2 (2%)

Sources: Table 11 (CSR), Listing 16.2.1.1 (CSR)

Recategorizations:

adverse event to insufficient clinical response: “insufficient clinical response”, “psychosis”, “exacerbation of schizophrenia symptoms”, “symptom recurrence”, “worsening of schizophrenia”, “worsening of schizophrenic symptoms”, “worsening of psychotic agitation”, “increased psychosis”

withdrawal of consent to insufficient clinical response: “too paranoid and agitated, hallucinating”, “subject withdrew consent due to lack of therapeutic response”, “withdrew consent secondary to lack of study drug effect”, “withdrew consent secondary to determination that patient too unstable to continue study as outpatient”, “lack of efficacy”, “subject withdrew consent secondary to delusions”

withdrawal of consent to adverse event: “chose to withdraw due to elevated blood sugar”, “patient was unable to tolerate adverse events like dizziness, epigastric pain, dragging sensation in the limbs, nausea and vomiting”

administrative to protocol violation: “protocol noncompliance”, “pt. didn’t take medication”

Adverse event to protocol violation: “substance abuse”

Concomitant Medication Use

This reviewer focused primarily on concomitant medication use that may have impacted study results – specifically concomitant antipsychotic and benzodiazepine use. Concomitant use of medications for the treatment of EPS or akathisia are discussed elsewhere in the review (see Section 7.4.7).

According to the CSR, 10% of patients in the lurasidone 40 mg group, 11% of patients in the lurasidone 120 mg group, 7% of patients in the olanzapine group and 5% of patients in the placebo group received concomitant antipsychotics during the double-blind phase of the trial. The Sponsor provided more information upon request (see concomitant medication use section of study D1050006). The Sponsor indicated that 39 (8.2%) of patients received concomitant antipsychotics during the clinical trial and 35 of those patients received the antipsychotic medication on the final day of double-blind study drug.

Table 46. Concomitant Medications of Interest (D1050231)

	Lurasidone 40 mg (n = 119)	Lurasidone 120 mg (n = 118)	Olanzapine 15 mg (n = 122)	Placebo (n = 116)
Antidepressants				
Trazodone	0	2 (2%)	0	0
Venlafaxine	1 (< 1%)	0	0	0
Antipsychotics				
Aripiprazole	1 (< 1%)	0	1 (< 1%)	0
Chlorpromazine	0	1 (< 1%)	0	0
Fluphenazine	1 (< 1%)	0	0	0
Haloperidol	1 (< 1%)	2 (2%)	3 (2%)	1 (< 1%)
Olanzapine	2 (2%)	3 (3%)	1 (< 1%)	1 (< 1%)
Paliperidone	1 (< 1%)	0	0	0
Quetiapine	3 (3%)	5 (4%)	1 (< 1%)	2 (2%)
Risperidone	3 (3%)	4 (3%)	3 (2%)	3 (3%)
Trifluoperazine	0	1 (< 1%)	0	0
Ziprasidone	1 (< 1%)	0	0	0
Benzodiazepines				
Alprazolam	2 (2%)	1 (< 1%)	0	2 (2%)
Clonazepam	1 (< 1%)	0	0	0
Diazepam	0	1 (< 1%)	1 (< 1%)	0
Lorazepam	86 (72%)	94 (80%)	79 (65%)	83 (72%)
Temazepam	17 (14%)	10 (8%)	15 (12%)	13 (11%)
BZD-related drugs				
Zolpidem	60 (50%)	51 (43%)	52 (43%)	52 (45%)

Source: Table 14.1.5.2 (CSR)

The Sponsor was asked to provide the mean daily dose/week of concomitant benzodiazepine use for all of the treatment groups. The Sponsor provided these data as Amendment 12 to the NDA. The majority of concomitant benzodiazepines used in this clinical trial were lorazepam and temazepam. Table 47 summarizes the mean daily dose of lorazepam in each treatment group by study week. Significant percentages of patients required concomitant lorazepam during the first few weeks of the study (~60% - 70%). Surprisingly, 40 to 50% of patients were requiring concomitant lorazepam during weeks 5 and 6. Mean doses of lorazepam were ~1.5 to 2 mg/day. The frequency of use as well as the mean daily dose were fairly similar between the study groups. By week 6, 42% of patients in all lurasidone groups (combined) were receiving a mean dose of 1.59 mg/day of lorazepam compared to 49% of patients in the placebo group receiving 2.08 mg/day of lorazepam and 36.4% of patients in the olanzapine group receiving 1.96 mg/day of lorazepam. Per protocol, benzodiazepines were not to be administered within 8 hours of the efficacy assessments. The Sponsor was asked to provide information regarding the numbers of patients in which lorazepam was administered within 8 hours of the primary efficacy assessment. The Sponsor responded that they did not have that information.

Table 47. Concomitant Lorazepam Use – Mean Daily Dose (SD) By Week (D1050231)

	Lurasidone 40 mg (N = 119)	Lurasidone 120 mg (N = 118)	Olanzapine 15 mg (N = 122)	Placebo (N = 116)
Week 1				
n (%)	73 (61.3%)	82 (69.5%)	71 (58.2%)	75 (64.7%)
Mean (SD)	1.74 (1.22)	2.01 (1.43)	1.85 (1.37)	1.88 (1.53)
Median	1.43	1.93	2.00	1.57
Week 2				
n (%)	71 (64%)	71 (67%)	65 (56.0%)	63 (60%)
Mean (SD)	1.77 (1.15)	1.94 (1.46)	2.04 (1.37)	2.08 (1.61)
Median	1.71	1.50	2.00	1.71
Week 3				
n (%)	63 (59.4%)	59 (66.3%)	58 (53.2%)	55 (57.9%)
Mean (SD)	1.82 (1.32)	1.75 (1.32)	2.06 (1.31)	1.96 (1.49)
Median	1.71	1.29	2.00	1.57
Week 4				
n (%)	53 (56.4%)	50 (63.3%)	50 (48.5%)	46 (54.1%)
Mean (SD)	1.91 (1.36)	1.57 (1.30)	1.93 (1.34)	1.98 (1.54)
Median	2.0	1.21	2.00	1.86
Week 5				
n (%)	41 (47.7%)	39 (54.2%)	43 (45.3%)	41 (53.2%)
Mean (SD)	1.74 (1.24)	1.54 (1.31)	1.81 (1.32)	1.92 (1.60)
Median	1.50	1.14	2.00	1.57
Week 6				
n (%)	30 (38%)	31 (46.3%)	32 (36.4%)	36 (48.6%)
Mean (SD)	1.64 (1.17)	1.53 (1.42)	1.96 (1.22)	2.08 (1.54)
Median	1.13	1.20	2.00	1.88

Source: Post Hoc Table (Amendment 12 to NDA)

Important Protocol Violations

Violation of inclusion/exclusion criteria occurred in 11 patients (3-lurasidone groups, 3-olanzapine, 5-placebo). No further details were provided. Three patients were discontinued from the trial for protocol violations including positive toxicology screen (n = 2) and patient reported history of seizure. It is unlikely that these few violations affected the overall study results.

Efficacy Results – Sponsor’s Results

Study Populations for Efficacy Analyses

	Lurasidone 40 mg (n = 120)	Lurasidone 120 mg (n = 119)	Olanzapine 15 mg (n = 123)	Placebo (n = 116)
ITT*	119	118	122	114
Completer	77	66	84	71

*ITT, Intent to Treat: all subjects randomized, who received at least one dose of study medication, and had a baseline and at least one post-baseline efficacy measurement

Primary Efficacy Analysis

Table 48. PANSS Total Score: Change from Baseline to Endpoint: MMRM Analysis (D1050231)

	Lurasidone 40 mg (n = 118)	Lurasidone 120 mg (n = 118)	Olanzapine 15 mg (n = 121)	Placebo (n = 114)
Baseline mean (SD)	96.6 (10.7)	97.9 (11.3)	96.3 (12.2)	95.8 (10.8)
Change from BL to Week 6. Estimate (SE)	-25.7 (2)	-23.6 (2.1)	-28.7 (1.9)	-16 (2.1)
Difference between lurasidone and placebo Estimate (SE)	-9.7 (2.9)	-7.5 (3.0)	-12.6 (2.8)	
95% CI	(-15.3, -4.1)	(-13.4, -1.7)	(-18.2, -7.1)	
p-value*	0.002	0.022	< 0.001	

Source: Table 18 (CSR), Table 14.2.1.3 (CSR)

*For lurasidone vs. placebo comparisons, p-values were adjusted with Hommel-based tree-gatekeeping procedures; p-values without adjustment were < 0.001 (40 mg) and 0.011 (120 mg).

Key Secondary Analysis

Table 49. CGI-S: Change from Baseline to Endpoint: MMRM Analysis (D1050231)

	Lurasidone 40 mg (n = 119)	Lurasidone 120 mg (n = 118)	Olanzapine 15 mg (n = 122)	Placebo (n = 114)
Baseline mean (SD)	5.0 (0.7)	5.0 (0.6)	4.9 (0.7)	4.9 (0.7)
Change from Baseline to Week 6. Estimate (SE)	-1.5 (0.1)	-1.4 (0.1)	-1.5 (0.1)	-1.1 (0.1)
Difference between lurasidone and placebo Estimate (SE)	-0.4 (0.1)	-0.3 (0.1)	-0.5 (0.1)	
95% CI	(-0.7, -0.1)	(-0.6, -0.0)	(-0.8, -0.2)	
p-value*	0.011	0.040	< 0.001	

Source: Table 22 (CSR), Table 14.2.2.3 (CSR)

**For lurasidone vs. placebo comparisons, p-values were adjusted with Hommel-based tree-gatekeeping procedures; p-values without adjustment were 0.006 (40 mg) and 0.040 (120 mg).

Table 50. PANSS Total Score: Change from Baseline to Endpoint by Visit, MMRM Analysis (D1050231)

	Lurasidone 40 mg	Lurasidone 120 mg	Olanzapine 15 mg	Placebo
Day 4				
Change from BL (Estimate)	-5.1 (0.7)	-5.4 (0.7)	-6.1 (0.7)	-4.8 (0.7)
Treatment Difference (Estimate)	-0.2 (1.0)	-0.6 (1.0)	-1.3 (0.9)	
p-value (vs. placebo)*	0.80	0.56	0.166	
Week 1				
Change from BL (Estimate)	-10.1 (0.9)	-8.8 (0.9)	-10.5 (0.9)	-7.0 (1.0)
Treatment Difference (Estimate)	-3.1 (1.3)	-1.7 (1.3)	-3.5 (1.3)	
p-value (vs. placebo)*	0.022	0.201	0.008	
Week 2				
Change from BL (Estimate)	-15.1 (1.2)	-13.6 (1.3)	-15.8 (1.2)	-10.4 (1.2)
Treatment Difference (Estimate)	-4.6 (1.7)	-3.2 (1.8)	-5.4 (1.7)	
p-value (vs. placebo)*	0.008	0.073	0.002	
Week 3				
Change from BL (Estimate)	-18.4 (1.5)	-17.9 (1.6)	-20.9 (1.5)	-11.4 (1.6)
Treatment Difference (Estimate)	-7.0 (2.2)	-6.5 (2.2)	-9.5 (2.2)	
p-value (vs. placebo)*	0.002	0.004	< 0.001	
Week 4				
Change from BL (Estimate)	-21.2 (1.7)	-21.3 (1.8)	-24.5 (1.6)	-13.1 (1.7)
Treatment Difference (Estimate)	-8.1 (2.4)	-8.2 (2.5)	-11.4 (2.4)	
p-value (vs. placebo)*	< 0.001	< 0.001	< 0.001	
Week 5				
Change from BL (Estimate)	-24.0 (1.9)	-24.6 (2.0)	-27.0 (1.8)	-15.0 (1.9)
Treatment Difference (Estimate)	-8.9 (2.7)	-9.6 (2.8)	-11.9 (2.7)	
p-value (vs. placebo)*	0.001	< 0.001	< 0.001	
Week 6				
Change from BL (Estimate)	-25.7 (2.0)	-23.6 (2.1)	-28.7 (1.9)	-16.0 (2.1)
Treatment Difference (Estimate)	-9.7 (2.9)	-7.5 (3.0)	-12.6 (2.8)	
p-value (vs. placebo)*	< 0.001	0.011	< 0.001	

Source: Table 14.2.1.1 (CSR)

*unadjusted for multiple comparisons

Table 51. PANSS Total Score: Change from Baseline to Endpoint: LOCF Analysis (D1050231)

	Lurasidone 40 mg (n = 119)	Lurasidone 120 mg (n = 118)	Olanzapine 15 mg (n = 122)	Placebo (n = 114)
Baseline mean (SD)	96.4 (10.5)	97.9 (11.3)	96.3 (12.2)	95.8 (10.8)
LS mean (SE)	-23.1 (1.7)	-20 (1.7)	-26.7 (1.7)	-15.2 (1.7)
Difference between lurasidone and placebo Estimate (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	

Source: Table 19 (CSR)

*p-values versus placebo, p-values comparing lurasidone groups, LS means, and CIs are from an ANCOVA with treatment and pooled center as fixed factors and baseline value as a covariate, not adjusted for multiple comparisons

Table 52. PANSS Total Score: Change from Baseline to Endpoint: OC Analysis (D1050231)

	Lurasidone 40 mg (n = 79)	Lurasidone 120 mg (n = 68)	Olanzapine 15 mg (n = 87)	Placebo (n = 73)
Baseline mean (SD)	96.6 (10.7)	98.1 (10.8)	95.6 (11.1)	93.6 (9.3)
LS mean (SE)	-30.5 (1.7)	-27.3 (1.9)	-30.8 (1.6)	-23.6 (1.8)
Difference between lurasidone and placebo Estimate (SE)	-6.9 (2.5)	-3.7 (2.6)	-7.2 (2.4)	
95% CI	(-11.8, -2.0)	(-8.8, 1.5)	(-11.9, -2.4)	
p-value*	0.006	0.161	0.003	

Source: Table 19 (CSR)

*p-values versus placebo, p-values comparing lurasidone groups, LS means, and CIs are from an ANCOVA with treatment and pooled center as fixed factors and baseline value as a covariate, not adjusted for multiple comparisons

Table 53. PANSS Positive Subscale Score: Change from Baseline to Endpoint, MMRM

	Lurasidone 40 mg (n = 118)	Lurasidone 120 mg (n = 118)	Olanzapine 15 mg (n = 121)	Placebo (n = 114)
Baseline Mean (SD)	25.6 (4.0)	25.9 (3.6)	25.6 (4.1)	26.4 (4.0)
Change from Baseline to Week 6. Estimate (SE)	-7.7 (0.7)	-7.5 (0.7)	-9.3 (0.7)	-5.4 (0.7)
Difference between lurasidone and placebo Estimate (SE)	-2.3 (1.0)	-2.2 (1.0)	-3.9 (1.0)	
95% CI	(-4.3, -0.4)	(-4.2, -0.1)	(-5.8, -2.0)	
p-value* vs. placebo	0.035	0.035	< 0.001	

Source: Tables 14.2.1.3, 14.2.1.5, 14.2.1.8 (CSR)

*Hommel adjusted

Analyses by Geographic Subgroup

This study was conducted in 52 foreign and U.S. sites: Columbia (5), India (14), Lithuania (4), Philippines (4), and U.S. (25). One of the analyses provided by the Sponsor compared the results between the US and Non-US sites.

Approximately 60% of patients were in US sites compared to Non-US sites: n = 281 in US sites and n = 190 in Non-US sites.

When evaluating the PANSS (LOCF) results for US, the lurasidone 40 mg and olanzapine 15 mg groups separate from placebo; but all three groups have greater LS mean changes compared to placebo. The LS mean change in the placebo group was fairly small. Similar to study D1050229, the lurasidone groups (and olanzapine) had a much greater LS mean change compared to the US sites while the LS mean change in the placebo group was also greater in the Non-US sites compared to the US sites. Interestingly, the lurasidone 120 mg/day group does not separate from placebo in either of these geographic subgroups but does separate from placebo in the primary analysis. When evaluating

countries separately, it does appear that South America contributes significantly to the overall positive results in the Non-US region analysis (Table 55).
 [Also see geographic region analyses, MMRM in *Efficacy Results – Additional Analyses by Division section that follow*].

Table 54. PANSS Total Score: Change from Baseline to Endpoint by Geographic Region: LOCF Analysis (D1050231)

US

	Lurasidone 40 mg (n = 69)	Lurasidone 120 mg (n = 72)	Olanzapine 15 mg (n = 73)	Placebo (n = 67)
Baseline Mean (SD)	93.5 (8.3)	95.7 (9.4)	94.6 (10.4)	93.6 (9.7)
LS mean (SE)	-16.2 (2)	-14.2 (2)	-20 (2)	-10.5 (2)
Difference between lurasidone and placebo Estimate (SE)	-5.7 (2.8)	-3.8 (2.8)	-9.6 (2.8)	
95% CI	(-11.3, -0.1)	(-9.3, 1.8)	(-15.1, -4.0)	
p-value*	0.046	0.183	< 0.001	

Non-US (Europe, Asia, South America)

	Lurasidone 40 mg (n = 49)	Lurasidone 120 mg (n = 46)	Olanzapine 15 mg (n = 48)	Placebo (n = 47)
Baseline Mean (SD)	100.5 (11.9)	101.3 (13)	98.9 (14.3)	98.9 (11.6)
LS mean (SE)	-30.7 (3)	-26.7 (3.1)	-34.9 (3)	-20.2 (3.1)
Difference between lurasidone and placebo Estimate (SE)	-10.5 (4.3)	-6.5 (4.4)	-14.7 (4.3)	
95% CI	(-18.9, -2.1)	(-15.1, 2.1)	(-23.2, -6.2)	
p-value*	0.015	0.138	< 0.001	

Source: Table 14.2.1.3.1 (CSR), Table 14.2.1.3.2 (CSR)

*p-values vs. placebo, LS means, and CIs are from an ANCOVA with treatment and pooled center as fixed factors and baseline value as a covariate; not adjusted for multiple comparisons

Table 55. PANSS Total Score: Change from Baseline to Endpoint by Country, LOCF Analysis (D1050231)

	Lurasidone 40 mg	Lurasidone 120 mg	Olanzapine 15 mg	Placebo
Europe				
n	7	7	7	8
Treatment Diff (SE)	1.1 (8.9)	-11.9 (8.8)	-20 (8.8)	
p-value	0.906	0.188	0.034	
South America				
n	12	12	12	12
Treatment Diff (SE)	-23.9 (8.1)	-20 (8)	-20 (8)	
p-value	0.005	0.017	0.017	
Asia				
n	30	27	29	27
Treatment Diff (SE)	-6.8 (5.8)	0.7 (6.0)	-11.2 (5.9)	
p-value	0.246	0.911	0.061	

Source: Table 14.2.1.3.1 (CSR)

*P-values versus placebo, p-values comparing lurasidone groups, LS means, and CIs are from an ANCOVA with treatment and pooled center as fixed factors and baseline value as a covariate

The CGI-S (LOCF) analyses by geographic region showed similar results to the PANSS total score analyses.

Table 56. CGI-S: Change from Baseline to Endpoint by Geographic Region, LOCF Analysis (D1050231)

US

	Lurasidone 40 mg (n = 70)	Lurasidone 120 mg (n = 72)	Olanzapine 15 mg (n = 74)	Placebo (n = 67)
Baseline Mean (SD)	4.8 (0.7)	4.9 (0.7)	4.8 (0.7)	4.7 (0.7)
LS mean (SE)	-0.9 (0.1)	-0.8 (0.1)	-1.1 (0.1)	
Difference between lurasidone and placebo Estimate (SE)	-0.2 (0.2)	-0.1 (0.2)	-0.4 (0.2)	
95% CI	(-0.5, 0.1)	(-0.5, 0.2)	(-0.7, -0.1)	
p-value*	0.181	0.411	0.022	

Non-US

	Lurasidone 40 mg (n = 49)	Lurasidone 120 mg (n = 46)	Olanzapine 15 mg (n = 48)	Placebo (n = 47)
Baseline Mean (SD)	5.2 (0.6)	5.1 (0.5)	5.1 (0.6)	5.1 (0.6)
LS mean (SE)	-1.6 (0.2)	-1.4 (0.2)	-1.8 (0.2)	
Difference between lurasidone and placebo Estimate (SE)	-0.5 (0.2)	-0.4 (0.2)	-0.7 (0.2)	
95% CI	(-0.9, -0.1)	(-0.8, 0.1)	(-1.2, -0.3)	
p-value*	0.028	0.107	0.001	

Source: Table 14.2.2.3.2 (CSR)

*P-values versus placebo, p-values comparing lurasidone groups, LS means, and CIs are from an ANCOVA with treatment and pooled center as fixed factors and baseline value as a covariate; unadjusted for multiple comparisons

Additional Analyses by Division

The statistician provided an MMRM analysis for the geographic subgroups (US vs. Non-US) for the primary endpoint, PANSS total score. A similar pattern is noted with both analyses, greater overall treatment effects in all groups (including placebo) in the Non-US sites compared to the US sites. In the US subgroup, the lurasidone treatment groups had a greater LS mean change compared to placebo in contrast to the results from D1050229.

Table 57. PANSS Total Score: LS Mean Change from Baseline by Geographic Subgroup, MMRM Analysis (D1050231)

	Lurasidone 40mg	Lurasidone 120mg	Olanzapine 15mg	Placebo
US	-20.0 (2.3)	-17.5 (2.4)	-23.0 (2.1)	-12.8 (2.3)
Non-US	-32.5 (3.1)	-32.6 (3.5)	-36.2 (3.2)	-21.2 (3.4)

Source: Statistical Reviewer's Results

The pharmacometrics reviewer evaluated the serum concentrations between geographic regions and noted that the lurasidone concentrations were higher in each dose group in the Non-US sites compared to the US sites for patients completing the clinical trial (Table 58).

Although there were differences in serum concentrations between the geographic regions, this does not explain the discrepancy in effect between the regions. On the PANSS total score-LOCF (Table 54) The 40 mg dose in the non-US sites performed more robustly than the 120 mg dose in the US sites: LS mean -30.7 vs. -14.2, LS mean difference from placebo -10.5 vs. -3.8.

Table 58. Lurasidone AUC by Geographic Region (D1050231)

	Mean (SD) AUC ng*hr/ml	
	Lurasidone 40 mg	Lurasidone 120 mg
US	0.27 (0.23)	0.71 (0.42)
NonUS	0.50 (0.32)	1.26 (0.88)

Source: Pharmacometrics Reviewer's Results
 Sample sizes US: n = 61 (40 mg), n = 63
 Sample sizes non-US: n = 48, n = 40

Conclusions

In study D1050231, the lurasidone 40 mg/day, lurasidone 120 mg/day and olanzapine 15 mg/day groups consistently separated from placebo on the primary endpoint (PANSS total score, MMRM) and the key secondary endpoint (CGI-S, MMRM). There was less consistency of results with other secondary endpoints such as the PANSS LOCF and PANSS OC analyses. All treatment groups also separated from placebo on the secondary endpoint, PANSS positive subscale score (MMRM).

It is somewhat disconcerting to this reviewer that at week 6 similar percentages of patients are receiving concomitant lorazepam in the lurasidone and placebo groups - 42% lurasidone groups (combined) vs. 49% in the placebo group. The lorazepam mean dose was 1.60 mg/day for the lurasidone groups (combined) and 2.1 mg/day for the placebo group. In the olanzapine group, 36% of patients were receiving concomitant lorazepam at week 6 at a mean dose of 1.96 mg/day. The Sponsor was asked to provide the numbers of patients who received lorazepam within 8 hours of the primary efficacy assessment and they did not have this information, though this reviewer believes this data must be available. Though one might speculate that, due to randomization, similar percentages of patients received lorazepam within 8 hours of the efficacy assessment in the treatment groups, but this cannot be verified.

Interestingly, when evaluating the geographic subgroups, lurasidone 120 mg/day does not separate from placebo in either the US or Non-US subgroups. In general, greater treatment differences were noted in the Non-US subgroup compared to the US subgroup even though the LS mean change in the placebo group was also greater in the Non-US subgroup. When evaluating the signal in the US subgroup, the lurasidone groups had a larger LS mean change compared to the placebo group. The olanzapine 15 mg group was the only comparison to placebo to reach statistical significance in the US subgroup.

The pharmacometrics reviewer noted that the serum concentrations of lurasidone were higher in the Non-US sites compared to the US sites for every dose group. However, as noted in that section of the review, this does not explain the discrepancy in efficacy since the 40 mg dose of lurasidone in the Non-US sites had a greater effect (e.g. decrease in PANSS total score) compared to the 120 mg dose in the US sites. Though the pharmacometrics reviewer commented that the differences in concentrations between the US and Non-US sites may be due to differences in baseline weights (higher mean weight in US sites), in the opinion of this reviewer, CYP3A4 (or other isozymes) activity would likely be more of a contributing factor in overall concentrations achieved. CYP3A4 activity differences, if present between the two populations, was not ascertained in these studies.

This reviewer considers study D1050231 positive in support of the efficacy of lurasidone 40 mg/day and lurasidone 120 mg/day in the treatment of schizophrenia.

Study 5 – D1050049

“A 6-week, double-blind, randomized, fixed dose, parallel-group study of the efficacy and safety of three dose levels of SM-13496 (lurasidone) compared to placebo and haloperidol in patients with schizophrenia who are experiencing an acute exacerbation of symptoms”

This study was a failed study, neither the active-control (haloperidol) nor lurasidone separated from placebo on the primary efficacy variable. It is summarized *briefly* here for completeness.

This study was conducted in 33 sites in the U.S.
 Study conducted August 26, 2002 – May 15, 2003

Methods/Study Design/Analysis Plan

Study D1050049 was a 6-week, multicenter, randomized, fixed-dose, double-blind, parallel group, placebo- and active comparator trial. Patients were hospitalized during the washout period and the first 3 weeks of the double-blind phase of the study. Patients were randomized (1:1:1:1) to lurasidone 20 mg, lurasidone 40 mg, lurasidone 80 mg, haloperidol 10 mg or placebo.

Inclusion criteria included male or female; 18 – 64 years of age (inclusive); DSM-IV criteria for a primary diagnosis of schizophrenia as established by SCID-CV; BPRS \geq 42 at screening and baseline; a score of \geq 4 in 2 or more items of the positive subcluster on the PANSS; \geq 4 on the CGI-S at baseline.

Table 59. Patient Disposition (D1050049)

	Lurasidone 20 mg	Lurasidone 40 mg	Lurasidone 80 mg	Haloperidol 10 mg	Placebo
Randomized	71	69	71	73	72
Discontinued	44 (62%)	39 (56%)	40 (56%)	43 (59%)	36 (50%)
Reasons for discontinuation					
Insuff. clinical response	24 (34%)	16 (23.2%)	10 (14.1%)	13 (17.8%)	13 (18.1%)
Adverse event	1 (1.4%)	8 (11.6%)	7 (9.9%)	11 (15.1%)	4 (5.6%)
Lost to follow-up	2 (2.8%)	1 (1.4%)	0	2 (2.7%)	1 (1.4%)
Protocol violation	1 (1.4%)	3 (4.3%)	0	1 (1.4%)	3 (4.2%)
Withdrawal of consent	14 (20%)	11 (15.9%)	22 (31%)	13 (17.8%)	14 (19.4%)
Other	2 (3%)	0	1 (1.4%)	3 (4.1%)	1 (1.4%)

Primary Efficacy Analysis

Table 60. BPRSd Total Score: Change from Baseline to Endpoint: LOCF Analysis (D1050049)

	Lurasidone 20 mg (n = 71)	Lurasidone 40 mg (n = 67)	Lurasidone 80 mg (n = 71)	Haloperidol 10 mg (n = 72)	Placebo (n = 72)
Baseline mean (SD)	55.4 (0.86)	54.8 (0.93)	54.5 (0.87)	56.1 (0.93)	56.8 (0.99)
Change from BL to Week 6. Mean (SE)	-5.0 (1.38)	-5.2 (1.44)	-8.0 (1.40)	-9.8 (1.37)	-7.9 (1.38)
Difference between lurasidone and placebo Estimate	2.93	2.75	-0.04	-1.82	
95% CI	(-1.8, 7.7)	(-2.1, 7.6)	(-4.8, 4.7)	(-6.5, 2.9)	
p-value*	0.357	0.437	1.000	0.747	

Source: Table 8.1.1 (CSR)

The OC analysis of the primary efficacy variable showed an adjusted mean change of ~-13 to -14 points in each of the 5 treatment groups. No statistically significant differences were found between any of the treatment groups and placebo.

Table 61. PANSS Total Score: Change from Baseline to Endpoint: LOCF Analysis (D1050049)

	Lurasidone 20 mg (n = 71)	Lurasidone 40 mg (n = 67)	Lurasidone 80 mg (n = 71)	Haloperidol 10 mg (n = 72)	Placebo (n = 72)
Baseline mean (SD)	94.7 (1.58)	93.2 (1.87)	93.1 (1.64)	94.3 (1.61)	96.5 (1.82)
Change from BL to Week 6. Mean (SE)	-7.1 (2.31)	-7.2 (2.42)	-13.6 (2.34)	-16 (2.29)	-12.3 (2.32)
Difference between lurasidone and placebo Estimate	5.18	5.09	-1.28	-3.69	
95% CI	(-1.2, 11.5)	(-1.4, 11.6)	(-7.7, 5.1)	(-10, 2.6)	
p-value*	0.109	0.126	0.694	0.252	

Source: Table 8.2.2.1 (CSR)

Table 62. CGI-S: Change from Baseline to Endpoint: LOCF Analysis (D1050049)

	Lurasidone 20 mg (n = 71)	Lurasidone 40 mg (n = 67)	Lurasidone 80 mg (n = 71)	Haloperidol 10 mg (n = 72)	Placebo (n = 72)
Baseline mean (SD)	4.7 (0.09)	4.8 (0.10)	4.7 (0.09)	4.8 (0.09)	4.8 (0.08)
Change from BL to Week 6. Mean (SE)	-0.5 (0.11)	-0.4 (0.12)	-0.8 (0.12)	-0.8 (0.12)	-0.7 (0.11)
Difference between lurasidone and placebo Estimate	0.21	0.25	-0.09	-0.12	
95% CI	(-0.1, 0.5)	(-0.1, 0.6)	(-0.4, 0.2)	(-0.4, 0.2)	
p-value*	0.179	0.128	0.595	0.463	

Source: Table 8.2.3.1 (CSR)

Conclusions

Study D1050049 was considered a failed trial by the Sponsor since neither the lurasidone treatment groups nor the active comparator, haloperidol 10 mg, separated from placebo. This reviewer concurs with this assessment.

6.1.3 Crosscutting Issues

6.1.3.1 Subgroup Analyses

The Sponsor did not include subgroup analyses for gender, race or age for the two Phase 2 pivotal trials, D1050006 and D1050196. These analyses were provided for the two Phase 3 pivotal trials, D1050229 and D1050231.

Study D1050229. The subgroup analysis for gender did not indicate differential response (treatment*subgroup interaction p-value = 0.447). The subgroup analysis for age (< 55, \geq 55 years) did not indicate differential response (treatment*subgroup interaction p-value = 0.857), though the numbers of patients in the \geq 55 years of age cells were very small. The subgroup analysis for race did not indicate differential response (treatment*subgroup interaction p-value = 0.342), though the numbers of patients in the Native Hawaiian/Other Pacific Islander and Other categories were very small ($n \leq 3$ /cell, data not shown in table). Interestingly, Asians had a much greater decrease in PANSS total score in all groups (lurasidone, olanzapine and placebo) compared to Whites and Blacks. The subgroup analysis for ethnicity did not indicate a differential response, however, the numbers of patients who were Hispanic/Latino were very small ($n \leq 7$ /cell).

The Sponsor conducted subgroup analyses for gender, race and age separately for the Phase 3 trials, D1050229 and D1050231 and those results are in the efficacy result sections for those studies. The Integrated Summary of Efficacy also included analyses for these subgroups for pooled data for the 4 pivotal trials (D1050006, D1050196, D1050229, D1050231).

For gender, there was no treatment by gender interaction according to the MMRM model. The change in baseline was similar between males and females for all treatment groups (Table 63). For race, there was also no treatment by race interaction according to the MMRM model; however, the change from baseline was numerically larger in the treatment groups for the Non-White/Non-Black racial category compared to the White and Black racial categories. The Sponsor did not perform a similar analysis for age since only 3 patients were \geq 65 years of age. The Sponsor did use an MMRM model with age as a continuous covariate along with terms for treatment, study protocol, pooled site within site, visit, baseline score, treatment by age and treatment by age by visit.

There was no significant age by treatment effect noted for PANSS total score at week 6.

Table 63. PANSS Total Score – Mean Change (SD) from Baseline to Endpoint (LOCF): By Gender, Age, and Race (D1050229)

	Lurasidone 40 mg (N = 122)	Lurasidone 80 mg (N = 119)	Lurasidone 120 mg (N = 124)	Placebo (N = 124)
Male				
n	81	75	91	90
Mean Change (SD)	-15.7 (17.9)	-21 (17.9)	-16.2 (18.2)	-14.3 (21.4)
Female				
n	40	43	32	34
Mean Change (SD)	-20.9 (18.5)	-20.1 (13.3)	-22.6 (17.1)	-14.7 (20.4)
Age ≥ 55				
n	10	4	9	6
Mean Change (SD)	-18 (18.3)	-18.3 (9.5)	-24.6 (16.6)	-21.5 (21.2)
Age < 55				
n	111	114	114	118
Mean Change (SD)	-17.3 (18.3)	-20.8 (16.5)	-17.4 (18.2)	-14.1 (21.1)
White				
n	55	59	60	66
Mean Change (SD)	-16.4 (17.6)	-21.6 (16.7)	-15.5 (17.1)	-12.6 (21.5)
Black				
n	49	39	40	36
Mean Change (SD)	-18.1 (19.3)	-17.1 (15.2)	-16.9 (17.3)	-17.8 (20.7)
Asian				
n	16	19	20	19
Mean Change (SD)	-19 (17.9)	-26.5 (15.6)	-26.8 (21.4)	-16.8 (20.9)

Source: Tables 14.2.1.18, 14.2.1.19, 14.2.1.20 (CSR)

Study D1050231. The subgroup analysis for gender did not indicate differential response (treatment*subgroup interaction p-value = 0.708). The subgroup analysis for age (< 55, ≥ 55 years) did not indicate differential response (treatment*subgroup interaction p-value = 0.501), though the numbers of patients in the ≥ 55 years of age cells were very small. The subgroup analysis for race did not indicate differential response (treatment*subgroup interaction p-value = 0.857), though the numbers of patients in the other racial categories (American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, Other) were very small (n ≤ 9/cell, data not shown in table). Although there was not a differential response statistically, it did appear that Asians had a much greater decrease in PANSS total score in all groups (lurasidone, olanzapine and placebo) compared to Whites and Blacks. The subgroup analysis for ethnicity did not indicate a differential response, however, the numbers of patients who were Hispanic/Latino were very small (n ≤ 7/cell).

Table 64. PANSS Total Score: Mean Change (SD) from Baseline to Endpoint LOCF Analysis - By Gender, Age, and Race (D1050231)

	Lurasidone 40 mg (N = 119)	Lurasidone 120 mg (N = 118)	Olanzapine 15 mg (N = 122)	Placebo (N = 114)
Male n	92	93	94	88
Mean Change (SD)	-22.9 (21.9)	-18.4 (18.1)	-26.6 (20.1)	-13.4 (21.0)
Female n	26	25	27	26
Mean Change (SD)	-20.6 (20.6)	-24.8 (24.2)	-22.8 (18.1)	-14.7 (24.7)
Age ≥ 55 n	6	10	6	7
Mean Change (SD)	-14.8 (13.2)	-18.4 (21.6)	-18 (16.6)	-13.9 (11.0)
Age < 55 n	112	108	115	107
Mean Change (SD)	-22.8 (21.9)	-19.9 (19.5)	-26.1 (19.8)	-13.7 (22.4)
White n	43	48	40	36
Mean Change (SD)	-19.3 (21.8)	-16 (18.8)	-23.5 (16)	-12.2 (18)
Black n	39	36	44	41
Mean Change (SD)	-16.7 (15.3)	-19.2 (15.7)	-20.4 (19.4)	-12 (17.3)
Asian n	31	27	30	27
Mean Change (SD)	-30.5 (22.1)	-24.4 (20.7)	-33.7 (20.3)	-21.9 (27.8)

Source: Tables 14.2.1.18, 14.2.1.19, 14.2.1.20 (CSR)

Subgroup analyses for geographic regions were performed for the two pivotal Phase 3 studies (D1050229 and D1050231) – the other two Phase 2 pivotal studies (D1050006 and D1050196) were performed in the United States only. Since these geographic subgroup analyses had some impact on the overall conclusions reached by this reviewer, those analyses are covered in the sections specific to those clinical trials (see Efficacy Results sections).

6.1.3.2 Dose Response and Concentration Response

Dose Response

The Sponsor indicated that there did not appear to be a consistent dose-dependent response across the 40, 80, 120 mg dose range. In the ISE, the Sponsor indicated that pairwise comparisons between lurasidone fixed-dose groups for PANSS total score and CGI-S based on the pooled dataset, using both MMRM and ANCOVA models indicated no efficacy differences between the lurasidone dose groups.

Table 65 provides the LS mean change from baseline in BPRSd total score or PANSS total score by study by either LOCF or MMRM analyses. In this crude comparison, there is no consistent trend for a dose response for lurasidone.

The pharmacometrics reviewer conducted a more comprehensive review of dose response and did not find a consistent relationship between lurasidone dose and changes in efficacy endpoints.

Table 65. BPRSd and PANSS Total Scores: LS Mean Change from Baseline in Each Pivotal Study

	Lurasidone 40 mg	Lurasidone 80 mg	Lurasidone 120 mg	Placebo
D1050006				
BPRSd (LOCF)*	-9.4		-11	-3.8
BPRSd (MMRM)	-13.4		-13.4	-4.1
PANSS (LOCF)	-14		-17	-6.2
D1050196				
BPRSd (LOCF)*		-8.9		-4.2
PANSS (LOCF)		-14.1		-5.5
D1050229				
PANSS (MMRM)*	-19.2	-23.4	-20.5	-17.0
PANSS (LOCF)	-17.4	-20.8	-18.5	-14.7
US Sites	-14.5	-17.1	-14.9	-15.1
Non-US Sites	-20.3	-24.5	-22.3	-13.7
D1050231				
PANSS (MMRM)*	-25.7	-	-23.6	-16
PANSS (LOCF)	-23.1	-	-20	-15.2
US Sites	-16.2	-	-14.2	-10.5
Non-US Sites	-30.7	-	-26.7	-20.2

*Primary efficacy variable

Concentration Response

The pharmacometrics reviewer found a trend in changes in PANSS total scores and higher lurasidone AUC in study D1050231 but not in study D1050229 in those patients who completed the clinical trials (see pharmacometrics review).

6.1.3.3 Key Secondary Variables

Two of the pivotal trials, D1050229 and D1050231, had prespecified a key secondary variable, the CGI-S. Based on prior conversations the Division had with the Sponsor, the Division considers the CGI-S to be an acceptable key secondary variable for purposes of product labeling as there is little redundancy with the primary variable, the PANSS total score.

For study D1050229, as with the primary efficacy endpoint, one dose of lurasidone (80 mg/day) separated from placebo on the key secondary variable, the CGI-S. For study D1050231, both doses of lurasidone (40 mg and 120 mg) separated from placebo on the primary efficacy endpoint as well as the key secondary variable, the CGI-S. If study D1050229 is deemed a positive clinical trial, the Sponsor will have replicated the CGI-S findings in two studies though there is no dose replication.

6.1.3.4 Effect Size

Table 65 (above) provides a summary of LS mean changes from baseline. Table 66 (below) provides a summary of the LS mean difference between lurasidone groups and placebo (and active comparator and placebo) as a crude estimate of effect sizes in the clinical trials.

The effect sizes that were statistically significantly different from placebo are consistent with effect sizes noted in clinical trials in schizophrenia for approved antipsychotics. Though the effect sizes for D1050006 are consistent with the other pivotal trials were positive efficacy findings were noted, issues with high discontinuation rates complicates the interpretation of that study (see discussion in study summary section and conclusions sections).

Of note, in the only pivotal trial to include an active comparator, olanzapine 15 mg exhibited a larger effect size compared to both lurasidone 40 mg/day and lurasidone 120 mg/day groups.

Table 66. LS Mean Difference Between Lurasidone and Active Comparator and Placebo

	Lurasidone 40 mg	Lurasidone 80 mg	Lurasidone 120 mg	Olanzapine 15 mg
D1050006				
BPRSd (LOCF)*	-5.6**	-	-6.7**	-
BPRSd (MMRM)	-9.3**	-	-9.2**	-
PANSS (LOCF)	-7.6	-	-11**	-
D1050196				
BPRSd (LOCF)*	-4.7**	-	-	-
PANSS (LOCF)	-8.6**	-	-	-
D1050229				
PANSS (MMRM)*	-2.1	-6.4**	-3.5	-
PANSS (LOCF)	-2.7	-6.1**	-3.8	-
US Sites	0.6	-2.0	0.2	-
Non-US Sites	-6.5	-10.8**	-8.6**	-
D1050231				
PANSS (MMRM)*	-9.7**	-	-7.5**	-12.6**
PANSS (LOCF)	-7.9**	-	-4.8	-11.4**
US Sites	-5.7	-	-3.8	-9.6**
Non-US Sites	-10.5**	-	-6.5	-14.7**

*Primary efficacy variable

**Statistically significant vs. placebo

6.1.3.4 Long-Term Efficacy

The Sponsor has not conducted a maintenance trial. The long-term data included in this NDA are primarily to evaluate the safety and tolerability of lurasidone and include several open-label extension studies 6 – 22 months in duration. A number of these studies were ongoing at the time this NDA was submitted.

6.1.3.5 Pediatric Development

The incidence of schizophrenia is low in children 10 – 17 and rare in children < 10 years of age. At the EOP2 meeting in September 2006, the Division granted a waiver for clinical studies with lurasidone in the (b) (4) year old pediatric population and a deferral for clinical studies with lurasidone in the (b) (4) year old adolescent population until after approval of lurasidone in the treatment of adult patients with schizophrenia.

The Pediatric Review Committee (PeRC) will be meeting on September 22, 2010 to review the requests for waiver and deferral.

6.1.4 Efficacy Conclusions – Treatment of Schizophrenia

The Sponsor submitted four double-blind, placebo-controlled clinical trials to support the efficacy of lurasidone in the treatment of schizophrenia. All four clinical trials were 6 weeks in duration and adequately designed to assess the efficacy of lurasidone in the treatment of schizophrenia. All four trials included fixed doses of lurasidone and acceptable primary endpoints (BPRS derived from the PANSS or PANSS total score). One additional double-blind, placebo-controlled, active-comparator controlled study (D1050049) was a failed study in that neither lurasidone nor the active comparator (haloperidol) separated from placebo.

D1050006 was a Phase 2 trial in which 149 patients were randomized to lurasidone 40 mg/day, lurasidone 120 mg/day or placebo. All clinical sites were in the United States. The discontinuation rate in this study was 66%: 68% in the lurasidone 40 mg/day group, 59% in the lurasidone 120 mg/day group and 70% in the placebo group. Though both lurasidone doses were statistically different from placebo on the primary outcome variable (change in BPRSd), due to the very high discontinuation rate, the overall interpretation of this study is problematic.

There is more to the interpretation of the efficacy signal in a clinical trial than the p-value. Reviewers would raise concern if a study was overpowered to find very small differences in a rating scale that were of dubious clinical relevance yet yielded a robust statistical difference. This reviewer has concerns about interpretation of the statistical results in study D1050006 with regard to the high discontinuation rate among all three treatment groups, the time course for discontinuation with ~50% discontinuing by study midpoint and the reasons for discontinuation which included primarily insufficient clinical response and “withdrawal of consent”, a category that is difficult to interpret and likely includes some patients with insufficient clinical response. This clinical trial was a small trial, ~50 patients per group. By week 6, 20 or fewer patients were present in each treatment group.

The discontinuation rate in this trial was much higher than in the other 3 pivotal trials. Patients enrolled in this trial were not more severely ill or more clinically symptomatic, in fact the mean BPRSd and PANSS total baseline scores were lower in this trial compared to the other 3 clinical trials (indicating a less symptomatic population in this trial). The only notable difference that this reviewer could find was that, compared to the other 3 clinical trials, significantly less concomitant lorazepam was used in this trial.

Due to the issues outlined above, this reviewer does not consider this clinical trial a positive one to support efficacy of lurasidone in the treatment of schizophrenia.

D1050196 was a Phase 2 trial in which 180 patients were randomized to lurasidone 80 mg/day or placebo. All clinical sites were in the United States. Lurasidone 80 mg/day separated from placebo on the primary endpoint, BPRSd (LOCF), and secondary endpoints including BPRSd (OC), BPRSd (MMRM – Division analysis), PANSS total score (LOCF), PANSS positive subscale score (LOCF) and CGI-S (LOCF).

D1050229 was a Phase 3 trial in which 500 patients were randomized to lurasidone 40 mg/day, lurasidone 80 mg/day, lurasidone 120 mg/day and placebo. This study included sites in the United States, Europe and Asia; 55% of patients enrolled were from sites in the United States. In this study, only the lurasidone 80 mg/day dose separated from placebo on the primary endpoint (PANSS Total Score, MMRM) and the key secondary endpoint (CGI-S, MMRM). Despite similar changes in PANSS total score in the placebo group between the US and Non-US subgroups, the difference between lurasidone and placebo in the US subgroup was -2 compared to -10.8 in the Non-US subgroup. LS means in all four groups (lurasidone 40 mg, 80 mg, 120 mg and placebo) were similar in the US subgroup.

D1050231 was a Phase 3 trial in which 478 patients were randomized to lurasidone 40 mg/day, lurasidone 120 mg/day, olanzapine 15 mg/day or placebo. This study included sites in the United States, Europe, Asia and South America, 60% of patients enrolled were from sites in the United States. Both lurasidone doses (40 mg/day, 120 mg/day) and olanzapine 15 mg/day groups consistently separated from placebo on the primary endpoint (PANSS total score, MMRM) and the key secondary endpoint (CGI-S, MMRM). Though the Non-US subgroup exhibited more robust changes in the PANSS total score, the US subgroup did have greater LS mean changes in the lurasidone 40 and 120 mg/day group compared to placebo.

This reviewer is somewhat discouraged by the very frequent use of concomitant lorazepam in 3 of the pivotal trials (D1050196, D1050229 and D1050231). At week 6, 35-42% of patients in the lurasidone groups were receiving concomitant lorazepam compared to 35 – 49% in the placebo groups (mean daily doses of

lorazepam were similar). In NDAs, Sponsors usually submit an overall table of concomitant medication use which is the frequency over the course of the clinical trial. It is unusual for a Sponsor to include the mean/median dose by week for a concomitant medication unless specifically asked to do so (they were asked to submit these data). Therefore, if a number of recent NDAs for this indication were sampled, it is unlikely that these data (mean/median dose of concomitant benzodiazepines) would be available for comparison purposes. It is somewhat disconcerting to this reviewer that similar percentages of patients are receiving concomitant lorazepam towards the end of the trials at similar mean/median daily doses. One would anticipate that more patients in the placebo group would be receiving concomitant lorazepam and at higher mean/median daily doses. The only one of the four pivotal trials that had much less use of concomitant lorazepam was study D1050006, the study in which the discontinuation rate was ~66%. In study D1050231, it is noted that the patients in the olanzapine 15 mg group also received concomitant lorazepam with the same frequency and mean/median daily dose as the other treatment groups. This reviewer did not ask the Sponsor to provide concomitant lorazepam use by US vs. Non-US geographic regions, so it is not known what, if any, impact differences in use may have had on the differences in efficacy noted between these regions (larger LS mean change and LS mean differences in Non-US vs. US sites). The Sponsor was asked to provide the numbers of patients who received lorazepam within 8 hours of the primary efficacy assessment and they did not have this information. One might speculate that, due to randomization, similar percentages of patients received lorazepam within 8 hours of the efficacy assessment in the treatment groups, but this cannot be verified.

In general, this reviewer does not believe that D1050006 is an interpretable study for reasons outlined above. Study D1050229 is, in the opinion of this reviewer, marginal since only one of three lurasidone doses separated from placebo and this dose did not exhibit a robust signal in the US subgroup analysis. This reviewer considered studies D1050196 and D1050231 to be positive studies in support of the efficacy of lurasidone 40 mg (D1050231), 80 mg (D1050196) and 120 mg (D1050231) in the treatment of schizophrenia. However, since the efficacy of these doses of lurasidone has not been replicated in the other studies, this reviewer would recommend a complete response action at this time.

It is also relevant to note that two Phase 3 clinical trials have recently been completed (D1001002 and D1050233). The final study report for D1050233 is estimated to be submitted in October 2010 and data from D1001002 should be available sometime after that. Study D1001002 (n = 460) evaluated the efficacy of lurasidone 40 mg, lurasidone 80 mg, risperidone 4 mg and placebo. Study D1050233 (n = 488) evaluated the efficacy of lurasidone 80 mg, lurasidone 160 mg, quetiapine XR 600 mg and placebo. Based on the marginal efficacy data presented in this NDA and the pending availability of significant clinical trial data (both efficacy and safety) it seems premature to recommend a final action at this

time. These recently completed clinical trials provide more efficacy and safety data for the 40 mg/day, 80 mg/day and a higher dose, 160 mg/day. These clinical trials are placebo controlled and both also include an active comparator. It would seem prudent to review the efficacy data from these recently completed Phase 3 trials before taking a final action since the data submitted in this NDA, in this reviewer's opinion, do not support the efficacy of lurasidone in the treatment of schizophrenia.

Additionally, though the Sponsor appears to be studying higher doses of lurasidone for the treatment of schizophrenia (160 mg in the recently completed study as above), this reviewer does not believe that the Sponsor has adequately addressed the dose range for lower doses (e.g. 20 mg). In the EOP2 meeting, the Sponsor wanted concurrence with the Division that the approach of using PET D2 occupancy in combination with Phase 2 data to conclude that 20 mg is an ineffective dose and studying 3 doses (40, 80, 120 mg) across three efficacy and safety studies adequately explores the dose range and supports registration of lurasidone. The D2 receptor occupancy rates in one clinical study were 51-54.8% for the 20 mg dose, 63.1-67.5% for the 40 mg dose and higher occupancy rates for higher doses; so the PET data is not dramatically different between the 20 and 40 mg lurasidone doses. This reviewer could find only one double-blind, placebo-controlled clinical trial that included the lurasidone 20 mg dose (the failed D1050049 study). In this study, lurasidone 20 mg performed similar to lurasidone 40 mg; mean change from baseline in the PANSS total score was -7.1 (20 mg) and -7.2 (40 mg). One additional double-blind, but not placebo-controlled, study was conducted evaluating lurasidone 20 mg (n = 65), lurasidone 40 mg (n = 72) and lurasidone 80 mg (n = 58) (Study D1001001). The lurasidone 20 mg group performed similarly to the lurasidone 80 mg group on the BPRS total score (mean change from baseline -2.1, lurasidone 20 mg; -3.0, lurasidone 80 mg) and on the PANSS total score (mean change from baseline -3.4, lurasidone 20 mg; -3.8, lurasidone 80 mg). Based on these data, this reviewer does not believe the lower dose of lurasidone have been adequately explored for efficacy and, since lurasidone is associated with significant EPS effects and prolactin elevation which appear to be dose-related (see Safety review), it would seem prudent to evaluate the efficacy of lower doses.

7 REVIEW OF SAFETY

Safety Summary

In reviewing the submission, one case of respiratory failure and one case of a patient meeting criteria for Hy's law were found that were not identified by the Sponsor. Due to these oversights and other issues within the submission outlined in Section 3.1 of this review, this reviewer does not have confidence that the Sponsor has adequately characterized the safety profile of lurasidone. One key recommendation that this reviewer will have is that all of the clinical data be reviewed in detail, including review of all CRFs, and that these data be

recompiled into an ISS. It is also the recommendation of this reviewer that this recompiled ISS include the two recently completed Phase 3 clinical trials, D1001002 and D1050233, the latter study including a higher dose of lurasidone than was studied in the pivotal trials (160 mg). Analysis of safety data from D1001002 and D1050233 would be important to assess the risk of hypersensitivity reactions that may be associated with lurasidone and analysis of data from D1050233 would evaluate the safety of 160 mg compared to lower doses of lurasidone.

At the time this review was completed, consults to evaluate the bone density data and the ophthalmologic findings had not been completed.

Overarching Summary

A more detailed summary of safety findings is presented in the paragraphs that follow. In general, this reviewer was concerned with one death occurring in a patient receiving lurasidone. Additional signals of concern were the 3 cases of respiratory failure (2 cases had other contributing factors) and a potential signal for hypersensitivity that was not adequately explored by the Sponsor. A number of patients experienced adverse events related to orofacial and peripheral swelling, including the case of angioedema that led to respiratory failure. Other significant safety findings included a significant EPS signal that is dose-related for akathisia and likely dose-related for parkinsonian adverse events but coding was somewhat problematic. There was also a significant signal for dystonic events, a number that led to discontinuation from the clinical trials and requiring treatment with parenteral medications.

The most remarkable laboratory finding was dose-related increases in prolactin concentration. There did not appear to be a significant QT prolongation signal in either the clinical trials or the thorough QT study. There was also a signal for orthostatic hypotension.

The Sponsor submitted safety data for > 2600 subjects who received lurasidone in Phase 1, 2 and 3 studies in single doses ranging from 0.1 – 100 mg, repeated doses up to 600 mg/day for less than one week, repeated doses up to 120 mg/day for 6 weeks of treatment and up to 120 mg/day for 12 months of treatment. This includes > 480 healthy volunteers and > 2300 patients with schizophrenia. In the Phase 2/3 studies, 500 patients had a cumulative exposure > 24 weeks and 225 patients had a cumulative exposure > 52 weeks. In the Phase 2/3 studies, the primary lurasidone doses administered were 20 mg, 40 mg, 80 mg and 120 mg.

This safety summary focuses primarily on findings of the Phase 2/3 studies, though Phase 1 studies were also reviewed and are included in the body of the review. The Phase 2/3 short term controlled studies (P2/3STC) pooled data provide placebo comparisons – this data includes the 4 pivotal trials (D1050006, D1050049, D1050229 and D1050231) and one failed trial (D1050049). These 5 6-week clinical trials also included active comparators (haloperidol in D1050049,

olanzapine in D1050231). The Phase 2/3 all pooled data (P2/3ALL) included all data from all Phase 2 and 3 clinical trials, controlled and uncontrolled.

Of note, two Phase 3 clinical trials were recently completed (see Table 1 in review for details). Study D1001002 (n = 460) includes treatment groups lurasidone 40 mg, lurasidone 80 mg, risperidone 4 mg and placebo. Study D1050233 (n = 488) includes treatment groups lurasidone 80 mg, lurasidone 160 mg, quetiapine XR 600 mg and placebo. Though SAEs were included in the NDA for these studies which were ongoing at the time the NDA was submitted, comprehensive safety data have not been submitted to the Division.

Deaths

A total of 18 deaths occurred in the clinical trials, all Phase 2/3 trials. Thirteen of the deaths were in patients receiving lurasidone and 2 deaths remain blinded to study drug. Of these 15 deaths, 4 were “sudden death” with only 1 of these 4 having autopsy results. These sudden deaths included one case of massive GI hemorrhage due to a large gastroduodenal ulcer (per autopsy), one case confounded by administration of IM haloperidol at the time of the event, one case of possible MI or PE (unconfirmed) and one case in which post-mortem CT scans of the head and chest revealed venous bleeding in the brainstem and pericardial bleeding (no cause of death was noted). In the 3 cases in which patients were receiving lurasidone, deaths occurred after receiving lurasidone for 24 days, 210 days and 360 days. In the one case in which the patient received blinded study medication, the death occurred after receiving study medication for > 150 days. In this reviewer’s opinion, the most troubling of the sudden death cases is the case with the CT findings of venous bleeding in the brainstem and pericardial bleeding – this is the patient who received lurasidone for the fewest number of days (24) prior to the event “sudden death”.

One additional death in a lurasidone-treated patient was reclassified from sudden death to hypertensive heart disease based on autopsy findings of cardiovascular disease. Autopsy results for a case of MI occurring in a patient on blinded medication also revealed cardiovascular disease. There were also 4 cases of completed suicide occurring in the Phase 2/3 trials. No pattern for these deaths was evident based on reviewing lurasidone dose, duration of treatment, demographics or concomitant medications (e.g. CYP3A4 inhibitors).

Nonfatal Serious Adverse Events

In the P2/3STC studies, approximately 5% of patients in the lurasidone treatment groups and placebo groups experienced SAEs. The most common serious adverse events were psychotic disorder/schizophrenia occurring with similar frequencies in the lurasidone (4%) and placebo (3.3%) groups.

The Sponsor identified 2 cases of respiratory failure occurring in the Phase 2/3ALL clinical trials. In the course of the review, one additional case of

respiratory failure was noted that appeared related to the SAE angioedema that was reported by the Sponsor. Of these 3 cases, two required endotracheal intubation. Though there were confounds and/or contributing factors in two of these cases, none were identified in the angioedema case. In the case that was associated with angioedema, angioedema occurred on Day 2 of receiving lurasidone (80 mg). This patient was receiving a number of concomitant medications (including amlodipine for hypertension), but had been receiving these medications since 2005 – this event occurred in 2009. Interestingly, the narrative lists “drug hypersensitivity” as a concomitant illness with no other clinical information (preexisting?).

Discontinuations due to Adverse Events

Approximately 21 cases of dystonia as an SAE and/or discontinuation due to adverse event were identified. Nine of these cases were treated with parenteral administration of anticholinergics, antihistamines and/or benzodiazepines.

Common Adverse Events

Adverse events occurring in $\geq 5\%$ of patients treated with lurasidone and with an incidence $>$ placebo included akathisia (15%), nausea (12%), sedation (11.9%), somnolence (10.7%), insomnia (8.4%), dyspepsia (7.6%), agitation (6.4%), and anxiety (6.3%). Due to issues of coding adverse events (splitting/lumping), frequencies for parkinsonian-related adverse events and dystonias were difficult to determine. Dystonias (as a preferred term) occurred in 3.5% of patients in the lurasidone groups, 0.7% of patients in the placebo group and 12.5% of patients in the comparator haloperidol 10 mg group. However, rates of dystonia are higher if other dystonia-related preferred terms are included such as oculogyric crisis, oromandibular dystonia and torticollis. Similarly, parkinsonian adverse events occurred in 4.9% of patients in the lurasidone groups, 0.4% of patients in the placebo group and 0 patients in the haloperidol 10 mg group (though 18% experienced “extrapyramidal disorder” in the haloperidol group, coding differences). Determining the frequency of parkinsonian-related adverse events was difficult since there was potential splitting for preferred terms tremor, cogwheel rigidity, bradykinesia, drooling, etc. Additionally, there were some issues with coding and identification of parkinsonian-related adverse events (discussed further in the review) which may have led to underreporting of these adverse events.

Examining the dose-relatedness of adverse events, there appeared to be an increase in frequency with increasing dose for akathisia (up to 22% in the 120 mg group), sedation and somnolence. Though there was not a clear dose-relationship to parkinsonian adverse events, however, most of the preferred terms related to this adverse event were highest in the lurasidone 120 mg group.

A number of adverse events occurred in the clinical trials program that could be related to hypersensitivity reactions. Though there were some cases of rash and

pruritis, this reviewer was more concerned regarding cases related to swelling and edema. In addition to the SAE of angioedema which may have resulted in respiratory failure, the following adverse events were noted in the P2/3ALL studies: swelling face, eyelid swelling, swollen tongue, lip swelling, peripheral edema and edema. There were also cases of “tongue thickening” mapped to the preferred term “tongue disorder” and it was not clear whether these were consistent with tongue swelling (some specifically state not related to dystonia). A more comprehensive analysis of these adverse events should be conducted by the Sponsor.

Laboratory Analysis

Chemistry

In the P2/3STC studies, the only significant finding for mean change from baseline analyses was for prolactin. The mean change from normal baseline prolactin was 8.9 ng/ml in the lurasidone group, 0.2 ng/ml in the placebo group and 16.7 ng/ml in the haloperidol 10 mg group. As expected, prolactin elevations were more significant in female patients with mean increases of 19.8 ng/ml in the lurasidone group, 1.7 ng/ml in the placebo group and 40.5 ng/ml in the haloperidol 10 mg group. There was a dose-related increase in prolactin with mean changes of 4.5 ng/ml in the 20 mg dose, 5.9 ng/ml in the 40 mg dose, 9.8 ng/ml in the 80 mg dose and 12.9 ng/ml in the 120 mg dose. Similar dose-related patterns were noted for both male and female patients. The frequency of prolactin > 5x ULN was 3.6% in the lurasidone group compared to 0.7% in the placebo group.

In the evaluation of LFTs for mean change from baseline and markedly abnormal results, no significant differences between lurasidone and placebo were noted. The Sponsor was asked to perform an analysis of cases meeting criteria for Hy’s Law and identified one case. The Sponsor indicated that this case was thought to be due to infectious hepatitis, this was not confirmed. [Of note, the second case identified by this reviewer was later unblinded and patient was receiving comparator drug].

Metabolic Indices

The mean change in fasting glucose in the P2/3STC trials was 1.4 mg/dL in the lurasidone group, 0.6 mg/dL in the placebo group and 9.0 mg/dL in the olanzapine 15 mg group. Mean increases were not noted in the total cholesterol (fasting), LDL cholesterol (fasting) or triglycerides (fasting) indices for the lurasidone group.

There was not a strong association of increases in mean glucose by dose for lurasidone, the highest mean increases were 2.9 mg/dL in the 40 mg group and 2.2 mg/dL in the 120 mg group (a decrease in mean fasting glucose was noted in the 80 mg group).

When evaluating shift data for fasting glucose, normal to high shifts (< 100 to ≥ 126 mg/dL) occurred in 6.1% of patients in the lurasidone group, 3.7% of patients in the placebo group and 8.2% of patients in the olanzapine 15 mg group. Shifts from impaired to high fasting glucose (≥ 100 and < 126 to ≥ 126 mg/dL) occurred in 13.9% of patients in the lurasidone group, 12.3% of patients in the placebo group and 31.8% of patients in the olanzapine group. There were no statistically significant differences in these parameters between the treatment groups. Shifts in lipids were similar between the lurasidone and placebo groups.

Weight

In the P2/3STC studies (6 weeks), lurasidone was associated with a 0.75 kg mean increase in weight compared to a 0.26 kg mean increase in the placebo group and a 4.1 kg mean increase in the olanzapine 15 mg group. The increase in weight did not appear to be related to lurasidone dose, the greatest increase was 1.14 kg in the 80 mg group. A categorical weight increase of $\geq 7\%$ was noted in 5.6% of patients in the lurasidone group, 4% of patients in the placebo group and 34.4% of patients in the olanzapine 15 mg group.

In the P2/3ALL studies (up to 52 weeks), the categorical weight increase of $\geq 7\%$ was 11.9% at week 24 ($n = 480$), 14.8% at week 36 ($n = 277$), and 17.7% at week 52 ($n = 192$); however, more patients had $\geq 7\%$ weight decrease at these timepoints. Patients with the greatest mean increase in weight were those with BMI < 18.5 kg/m²: 2.0 kg at week 24, 2.8 kg at week 36 and 3.3 kg at week 52; though the sample sizes for this BMI category were very small (≤ 18 at each timepoint). All other BMI groups were associated with a mean decrease in weight.

There were no notable signals with respect to hematology parameters.

Vital signs

Mean change from baseline for vital signs was not remarkable. Standing pulse increased by 1.3 bpm in the lurasidone group and 2.6 bpm in the placebo group. Standing SBP decreased by 0.1 mmHg in the lurasidone group and increased by 1.0 mm Hg in the placebo group. However, there were differences when mean change in vital signs was evaluated by lurasidone dose (see review for data for all doses). There was a dose related increase in sitting pulse (-1.1 bpm 20 mg, 1.4 bpm 120 mg) and standing pulse (0.7 bpm 40 mg, 2.1 bpm 120 mg). There was a dose related decrease in sitting SBP (2.2 mm Hg 20 mg, -1.3 mm Hg 120 mg). A decrease in standing SBP was noted only in the lurasidone 120 mg group (-0.7 mm Hg).

Since three of the P2/3STC trials included vital sign assessments for orthostatic hypotension, the Sponsor was asked to provide this analysis. For the two large Phase 3 trials (D1050229 and D1050231), vital signs were obtained after 5 minutes sitting, 1 minute standing and 3 minutes standing. The Sponsor did not specify which of the standing measurements were used in this analysis. In this

analysis, 1.3% of patients in the lurasidone group met criteria for orthostatic hypotension compared to 0.9% of patients in the placebo group. There appeared to be a dose relationship in that the 40 mg dose was similar to placebo and the 80 mg and 120 mg groups were associated with a 1.4% and 1.7% frequency of orthostatic hypotension.

ECG

In the P2/3STC database, there were no cases of QTcF > 500 (0/973). The Sponsor conducted a thorough QT study evaluating lurasidone 120 mg, lurasidone 600 mg (supratherapeutic dose) and ziprasidone 160 mg. The QT Interdisciplinary Review Team evaluated the data (see their consult and further comments in this review). The thorough QT study did not identify significant QT-prolonging effects of lurasidone – maximal mean Δ QTcI was 7.5 msec (90% CI 3.3, 11.7) at 2 hours post dose for lurasidone 120 mg and 5.2 msec (90% CI 1.1, 9.2) at 8 hours post dose for lurasidone 600 mg.

7.1 Methods

The data cut-off dates for the ISS were July 1, 2009 for data entered in the lurasidone clinical trial databases, and September 1, 2009 for deaths and SAEs. The data cut-off date for all data in the Safety Update (submitted April 28, 2010) was December 1, 2009.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

All of the safety data available from all clinical trials were used in assessments of safety (see Section 5.1). In the ISS, the Sponsor pooled data from Phase 1 studies (individual studies listed in footnote to Table 67) and Phase 2/3 studies as indicated in Table 67. Overall, 359 healthy subjects and 284 patients with schizophrenia were exposed to lurasidone in Phase 1 trials, 1004 patients were exposed to lurasidone in Phase 2 short-term placebo-controlled trials (P2/3STC). A total of 2096 patients were exposed to lurasidone in all Phase 2/3 clinical trials (P23ALL).

The safety data included in the NDA do not include comprehensive safety data from two recently completed Phase 3 clinical trials: non IND study D1001002 (4-arm study [2-lurasidone arms], n = 460 randomized) and D1050233 (4-arm study [2-lurasidone arms], n = 488 randomized) (See Table 1). Several ongoing studies were also not included in the integrated database: D1050234 (12 month study, see Table 3), and 3 studies in bipolar depression (D1050235, D1050236 and D1050256). For these recently completed and ongoing studies, the Sponsor submitted deaths (including narratives) and serious adverse events (many events still blinded).

Table 67. Pooled Datasets in ISS

	Lurasidone	Placebo	Active Comparator
Phase 1 Studies			
Healthy volunteers (P1HV)	359	73	
Schizophrenia (P1SCH)	284	16	
All Phase 1 Studies	643	89	
Phase 2/3 Studies			
Short Term DB PC (P2/3STC)	1004	455	194
D1050006	99	50	
D1050049	209	72	72 (haloperidol)
D1050196	90	90	
D1050229	369	127	
D1050231	237	116	122 (olanzapine)
Long Term DB Active Comparator Controlled (P2/3LTC)	190	-	85
D1050237	190	-	85 (risperidone)
Uncontrolled (P2/3UC)	752*	-	
D1001001	203	-	
D1001016	69	-	
D1001017	20	-	
D1001036	0	-	
D1001048	182	-	
D1050174	46	-	
D1050199	31	-	
D1050229E	59	-	
D1050231E	133	-	
D1050237E	9	-	
Short-term Other (P2/3STO)**	150	-	151
D1050254	150	-	151 (ziprasidone)
		-	
All Phase 2/3 Studies (P2/3ALL)	2096	455	430

Source: Table 3 (120-Day Safety Update)

P1HV: D1001013, D1001049, D1050001, D1050002, D1050180, D1050183, D1050184, D1050246, D1050250, D1050251, D1050252, D1050253, D1050262, D1050264, D1050265, D1050270, S01P12, S01P13, SM-071019, D1001053

P1SCH: D1050160, D1050217, D1050247, D1050249, D1050263, D1050269, D1050279, D1050267

*n = 752 new lurasidone exposures, n = 400 lurasidone re-exposures

**P23STO: D1050254 (3-week, R, DB trial)

7.1.2 Categorization of Adverse Events

Adverse events were coded using MedDRA Version 11.1.

The JMP file for adverse events was reviewed with an emphasis on the verbatim to preferred term coding. In general, it appeared that most verbatim terms were appropriately coded to preferred terms.

Some terms potentially relating to dystonic-type events may not have been captured in appropriate preferred terms. One example is the verbatim term “upgoing eyes (EPS)” which was mapped to the preferred term eye rolling. This reviewer had some difficulty with verbatim terms such as “thick tongue” and “tongue swelling”. Since there was no context for these events, it is unknown if they were dystonic in nature or a hypersensitivity reaction or some other reaction – most of these were mapped to preferred terms oromandibular dystonia or tongue disorder.

This reviewer was somewhat concerned that not all adverse events were adequately captured from the clinical trials. A thorough review of all CRFs is not possible within the time constraints for NDA review, and this would also assume that CRFs capture all events noted in source documents which are not included in NDA submissions. This reviewer did note two examples of adverse events that were not reported (see Section 3.1 of review). One example was a case of respiratory failure that was not reported as an SAE (it was reported as angioedema and the case narrative description of the event did not include pertinent details such as respiratory failure and endotracheal intubation). Another example was when this reviewer asked for an analysis of all patient cases meeting criteria for Hy’s Law. The Sponsor failed to include a case that had been reported in a 15-day safety report submitted to the IND (61,292) that occurred a few months prior to this request for information. The latter case was blinded to medication treatment assignment at the time the 15-day safety report and updates were submitted to the IND; this case was recently unblinded and the patient was not taking lurasidone. However, the issue of adverse event identification and categorization are still problematic to this reviewer.

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

See Section 7.1.1.

7.2 Adequacy of Safety Assessments

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

The Sponsor has proposed (b) (4) 40 (b) (4) mg/day of lurasidone in the treatment of schizophrenia.

In the Phase 1 studies conducted in healthy volunteers, 323 subjects received lurasidone (n = 202 lurasidone < 30 mg, n = 110 lurasidone 40 mg, n = 35 lurasidone 60 – 100 mg) and 73 subjects received placebo.

In the Phase 1 studies conducted in patients with schizophrenia, 258 patients received lurasidone (n = 162 lurasidone 120 mg, n = 96 lurasidone > 120 mg) and 16 patients received placebo. The majority of the data for lurasidone > 120 mg/day came from MTD studies (D1050160, D1050217) and the thorough QT study (D1050249). The dose breakdown for the > 120 mg/group was 140 mg (n = 8), 160 mg (n = 13), 200 mg (n = 5), 240 mg (n = 7), 280 (n = 6), 320 mg (n = 7), 400 mg (n = 6), 520 mg (n = 7), titration to 600 mg (n = 37).

The exposure for lurasidone doses ≥ 40 mg/day in patients in Phase 1 and Phase 2/3 trials are in Tables 68 and 69 respectively. In the Phase 2/3 trials, 503 patients had cumulative exposure ≥ 24 weeks and 225 patients had cumulative exposure ≥ 52 weeks. These exposures fall within the ICH guidelines for chronically administered drugs: 1500 patients overall: 300-600 patients for 6 months and 100 patients for 1 year.

Table 68. Exposure to ≥ 40 mg/day Lurasidone (P1SCH)

Duration of Exposure	Lurasidone > 40 mg/day (N = 258)
1 day	10
2 days	9
3-6 days	70
≥ 7 days	195

Source: Table 5.1.1.2 (ISS-Safety Update)

Table 69. Exposure to ≥ 40 mg/day Lurasidone (P2/3ALL)

Duration of Exposure	Lurasidone > 40 mg/day (N = 1900)
1-6 days	175
7-20 days	323
21-41 days	341
42-62 days	327
63-83 days	83
84-111 days	70
112-167 days	78
168-223 days	141
224-279 days	90
280-363 days	47
≥ 364 days	225

Source: Table 6 (ISS-Safety Update)

The modal lurasidone dose summary is provided in Table 70.

Table 70. Lurasidone Modal Dose (P2/3ALL)

	Lurasidone (N = 2095)
> 0 to < 40 mg	159 (7.6%)
40 to < 60 mg	520 (24.8%)
60 to < 80 mg	62 (3.0%)
80 to < 120 mg	779 (37.2%)
120 mg	571 (27.3%)
Flexible (80 – 120 mg)	4 (< 1%)

Source: Table 4 (ISS-safety update)

7.2.2 Explorations for Dose Response

Three of the four pivotal clinical trials included fixed dose designs evaluating 2 or more doses of lurasidone compared to placebo and/or an active comparator:

D1050006: lurasidone 40 mg vs. Lurasidone 120 mg vs. Placebo

D1050229: lurasidone 40 mg, lurasidone 80 mg, lurasidone 120 mg, placebo

D1050231: lurasidone 40 mg, lurasidone 120 mg, placebo, olanzapine 15 mg

One other clinical trial, considered a failed trial since neither lurasidone nor the active comparator separated from placebo, also included multiple fixed doses of lurasidone:

D1050049: lurasidone 20 mg, lurasidone 40 mg, lurasidone 80 mg, placebo, haloperidol 10 mg

Dose response is discussed in the corresponding safety sections of this review.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

The clinical trials programs included usual routine clinical testing at screening, baseline, at various timepoints during studies and at the end of study:

Hematology: RBC, hemoglobin, hematocrit, platelet, MCV, MCHC, WBC with differential,

Chemistry: AST, ALT, GGT, LDH, alkaline phosphatase, bilirubin (total), albumin, protein, bicarbonate, BUN, calcium, chloride, creatinine, phosphate, potassium, sodium, CPK, glucose, HbA1c, total cholesterol, LDL, HDL, triglycerides

Urinalysis: pH, specific gravity, ketones, bilirubin, blood, leukocyte esterase, nitrite, protein, glucose, RBC, WBC

Hormone assessments: prolactin, TSH (screening), testosterone

Markers for bone turnover: C-telopeptide (serum and urine), N-telopeptide, procollagen type 1 amino-terminal propeptide, osteocalcin, 25-hydroxy vitamin D3, deoxypyridinilone, bone-specific alkaline phosphatase, parathyroid hormone and testosterone (free and total).

Other: C-reactive protein (Study D1050237) and insulin (Study D1050237)

DEXA scans (Study D1050237)

Ophthalmologic evaluations – slit lamp, fundoscopic evaluation, visual acuity (Study D1050237)

ECGs – 12 lead

Vital signs – vital signs were assessed in the clinical trials. Three of the clinical trials (D1050196, D1050229 and D1050231) included assessments for orthostatic hypotension.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to the comprehensive review by Biopharmaceutics.

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

Some of the relevant safety issues for the class of antipsychotics include extrapyramidal side effects (parkinsonism, dystonia, akathisia), tardive dyskinesia, neuroleptic malignant syndrome, QT prolongation, hyperprolactinemia, orthostatic hypotension, weight gain, diabetes mellitus, hyperglycemia, hyperlipidemia, and leukopenia/neutropenia/agranulocytosis. The clinical trials included appropriate assessments for these adverse events.

7.3 Major Safety Results

7.3.1 Deaths

Phase 1 Studies

No deaths occurred in the Phase 1 studies.

Phase 2/3 Studies

In the initial ISS [database cut-off date 9/1/2009], 16 deaths were reported. In the Safety Update [database cut-off date 12/1/2009], 2 additional deaths were reported. These two additional deaths occurred in an ongoing study and are not included in the Safety Update integrated database.

As of 12/1/2009, a total of eighteen deaths occurred in the clinical trials (Tables 71 and 72): 13 deaths in patients receiving lurasidone, 1 death in a patient receiving olanzapine (bronchopneumonia), 1 death in a patient receiving ziprasidone (cardiac arrest), 1 death in a patient who did not receive study drug (choking) and 2 deaths in patients who received blinded study medication (blind not broken as studies are ongoing). The last two cases listed in Table 71 occurred > 30 days after the last dose of study medication.

No further deaths have been submitted to IND 61,292 ([REDACTED] (b) (4) [REDACTED]) as of the date this review was completed.

Four deaths were classified under the preferred term “sudden death”, 3 occurred in patients taking lurasidone and one occurred in a patient taking blinded study med (blind not broken as study ongoing). Brief narratives for these cases of “sudden death” are included in Appendix 9.6.1. Only one of these cases had autopsy results available. In this case (D1050237-0020-00036), the autopsy indicated that death was due to a massive GI hemorrhage due to a large gastroduodenal ulcer with contributing factor of cocaine use. For the 3 cases in which autopsies were not performed, one patient received IM haloperidol around the time of the event (D1001048-0000-00039); one patient was elderly (73 yrs., D1050237-0410-00001) and it was hypothesized that sudden death may have been due to an MI or PE (neither confirmed); in the other case (D1001002-0107-0004) post-mortem CT scans of the head and chest revealed venous bleeding in the brainstem and pericardial bleeding (no specific cause of death noted). In the 3 cases in which patients were receiving lurasidone, deaths occurred after receiving lurasidone for 24 days, 210 days and 360 days. In the one case in which the patient received blinded study medication, the death occurred after receiving study medication for > 150 days. In this reviewer’s opinion, the most troubling of the sudden death cases is D1001002-0107-0004 with the CT findings of venous bleeding in the brainstem and pericardial bleeding – this is the patient who received lurasidone for the fewest number of days (24) prior to the event “sudden death”.

Two other cases deserve further comment. In the hypertensive heart disease case (D1050237-0017-00030), this was first classified as “sudden death” and then reclassified based on autopsy findings of hypertensive cardiovascular disease specifically diffuse ventricular interstitial fibrosis and mild arteriolonephrosclerosis. In the case of myocardial infarction (D1050233-0058-00002) in the patient receiving blinded medication, the autopsy indicated that death was due to probable cardiac arrhythmia due to congenital artery anomaly (hypoplasia of the right coronary artery) with contributing factor of cardiomegaly (530 grams). Brief narratives for these cases are in Appendix 9.6.1.

For the cases of sudden death, the reviewer also evaluated concomitant medications, specifically evaluating if CYP3A4 inhibitors may have been initiated - no instances were found.

All deaths occurred in both genders, different races, different lurasidone doses and different durations of exposure to lurasidone; no consistent pattern was noted.

The Sponsor calculated that, based on the Safety Update integrated database (which did not include all deaths), 0.43% of all lurasidone-treated patients died (9/2096) and the death rate was approximately 1.44 deaths per 100 patient-years (9 deaths/624.0 subject years). This estimate does not include the 4 additional deaths in the integrated database that occurred in ongoing clinical trials.

Table 71. Deaths Occurring in Lurasidone-Treated Patients (All Clinical Trials)

Study Patient No.	Gender, Age, Race	Treatment	Preferred Term (verbatim term)	Day of Death (relative to start of study)	Last Day of Study Med Prior to Death	Autopsy
D1001048 0000-00039	M, 59, Asian	Lurasidone flexible dose	Sudden death (sudden death)	(b) (6)	360	No
D1001048 0000-00044	M, 35, Asian	Lurasidone flexible dose	Completed suicide (suicide)		168	No
D1050229 0127-00007	F, 40, Asian	Lurasidone flexible dose	Thermal burns (accidental burns)		81	No
D1050237 0017-00030	M, 52, White	Lurasidone flexible dose	Hypertensive heart disease		61	Yes
D1050237 0410-00001	F, 73, White	Lurasidone flexible dose	Sudden death (Sudden death)		210	No
D1001048 0000-00065	M, 29, Asian	Lurasidone flexible dose	Completed suicide (suicide)		24	No
D100148 0000-00072	F, 41, Asian	Lurasidone flexible dose	Septic shock (septic shock)		124	Yes
D1001048 0000-00098	M, 63, Asian	Lurasidone flexible dose	Completed suicide (suicide)		223	No
D1050229 0013-00009	M, 42, Black	Lurasidone flexible dose	Road traffic accident Traumatic brain injury (car accident, brain injury secondary to car accident)		495	Yes
D1001002	F, 49, Asian	Lurasidone	Sudden death		24	No

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(b) (6)

0107-0004		80 mg				
D1050237 0587-0003	F, 31, Asian	Lurasidone 80 mg	Completed suicide		unknown	No
D1050229 0005-00011*	M, 58, White	Lurasidone flexible dose	Lung neoplasm malignant Metastatic neoplasm		211	No
D1050231 0011-00001*	M, 50, White	Lurasidone 40 mg	Accidental overdose (heroin overdose, accidental)		32	No

Source: Table 64 (ISS), Table 14 (Safety Update), Table 6.4.1.7 (Safety Update), Table 6.4.1.3 (ISS)
 Subject narratives (ISS, Safety Update)

*Deaths occurred > 30 days after discontinuing lurasidone

Table 72. Deaths Occurring in Clinical Trials (P2/3ALL) - *Blinded*

Study Patient No.	Gender, Age, Race	Treatment	Preferred Term	Day of Death (relative to start of study)	Last Day of Study Med Prior to Death	Autopsy?
D1050233 0058-00002	F, 46	Blinded	Myocardial infarction Per autopsy: Probable cardiac arrhythmia due to congenital coronary artery anomaly (hypoplasia of right coronary artery). Contributing factor cardiomegaly (530 g).	(b) (6)	20	Yes
D1050237 0020-00036	M, 44, White	Blinded	Sudden death Per autopsy – Massive gastrointestinal hemorrhage due to large gastroduodenal ulcer. Contributing factor, cocaine use.		≥ 151	Yes

Source: Table 64 (ISS), Table 14 (Safety Update), Table 6.4.1.7 (Safety Update), Table 6.4.1.3 (ISS)
 Subject narratives (ISS, Safety Update)

7.3.2 Nonfatal Serious Adverse Events

Phase 1 Studies

In the Phase 1 studies in healthy volunteers, one subject receiving placebo had two non-treatment emergent SAEs resulting from a motor vehicle accident.

In the Phase 1 studies in patients with schizophrenia, two patients had SAEs. One patient receiving lurasidone 120 mg had an asymptomatic increase in CPK from 403 U/L [elevated at baseline] to 2636 U/L [maximum elevation] noted on day 11; CPK still elevated as of last available lab value (1808 U/L ~day 34). Another patient receiving placebo experienced the SAEs “schizophrenia” and “suicidal ideation”.

Phase 2/3 Studies

Refer to Section 7.3.4 for more discussion of nonfatal SAEs.

In the P2/3STC studies, approximately 5% of patients in the lurasidone treatment groups and the placebo groups experienced serious adverse events. The most common serious adverse events were psychotic disorder/schizophrenia occurring with similar frequencies in the lurasidone (4%) and placebo (3.3%) groups.

Table 73. Serious Adverse Events (P2/3STC)

	Lurasidone (N = 1004)	Placebo (N = 455)
Cardiac Disorders	0	1 (0.2)
Acute MI	0	1 (0.2)
Angina Pectoris	0	1 (0.2)
Gastrointestinal Disorders	0	1 (0.2)
Hematemesis	0	1 (0.2)
Hepatobiliary Disorders	0	1 (0.2)
Cholecystitis	0	1 (0.2)
Infections and Infestations	1 (< 0.1)	0
Staph infection	1 (< 0.1)	0
Investigations	0	2 (0.4)
Blood CPK increased	0	1 (0.2)
Blood LDH increased	0	1 (0.2)
Neoplasms Benign, Malignant and Unspecified	1 (< 0.1)	0
Uterine leiomyoma	1 (< 0.1)	0
Nervous System Disorders	2 (0.2)	1 (0.2)
Complex partial seizures	1 (< 0.1)	0
Syncope	1 (< 0.1)	0
Grand mal convulsion	0	1 (0.2)
Psychiatric Disorders	44 (4.4)	19 (4.2)
Schizophrenia	30 (3.0)	10 (2.2)
Psychotic disorder	10 (1.0)	5 (1.1)

Suicidal ideation	4 (0.4)	1 (0.2)
Agitation	1 (< 0.1)	2 (0.4)
Anxiety	1 (< 0.1)	0
Substance abuse	1 (< 0.1)	0
Panic attack	0	1 (0.2)
Respiratory, Thoracic and Mediastinal Disorders	0	1 (0.2)
COPD	0	1 (0.2)

Source: Table 67 (ISS)

Table 74. Serious Adverse Events in All Studies (P2/3ALL)

	Lurasidone (N = 2096)
Cardiac Disorders	5 (0.2%)
Angina pectoris	1 (< 0.1%)
Coronary artery disease	1 (< 0.1%)
Hypertensive heart disease	1 (< 0.1%)
Pericardial effusion	1 (< 0.1%)
Sinus tachycardia	1 (< 0.1%)
Gastrointestinal Disorders	1 (< 0.1%)
Vomiting	1 (< 0.1%)
General Disorders and Administration Site Conditions	2 (< 0.1%)
Sudden death	2 (< 0.1%)
Hepatobiliary Disorders	1 (< 0.1%)
Jaundice	1 (< 0.1%)
Infections and Infestations	10 (0.5)
Bronchopneumonia	1 (< 0.1%)
Gastritis viral	1 (< 0.1%)
Hepatitis infectious	1 (< 0.1%)
Orchitis	1 (< 0.1%)
Perineal abscess	1 (< 0.1%)
Pneumonia	2 (< 0.1%)
Pulmonary tuberculosis	1 (< 0.1%)
Sepsis	1 (< 0.1%)
Septic shock	1 (< 0.1%)
Staphylococcal infection	1 (< 0.1%)
Bronchitis	1 (< 0.1%)
Injury, Poisoning and Procedural Complications	9 (0.4%)
Accidental overdose	1 (< 0.1%)
Clavicle fracture	1 (< 0.1%)
Fall	1 (< 0.1%)
Femur fracture	1 (< 0.1%)
Foot fracture	1 (< 0.1%)
Intentional overdose	1 (< 0.1%)
Lower limb fracture	1 (< 0.1%)
Lumbar vertebral fracture	1 (< 0.1%)
Pelvic fracture	1 (< 0.1%)
Rib fracture	1 (< 0.1%)
Spinal cord injury	1 (< 0.1%)
Thermal burn	1 (< 0.1%)
Open fracture	1 (< 0.1%)
Traumatic brain injury	1 (< 0.1%)

Investigations	1 (< 0.1%)
Blood glucose increased	1 (< 0.1%)
Metabolism and Nutrition Disorders	3 (0.1%)
Hypokalemia	1 (< 0.1%)
Hyponatremia	1 (< 0.1%)
Polydipsia	1 (< 0.1%)
Musculoskeletal and Connective Tissue Disorders	3 (0.1%)
Musculoskeletal weakness	1 (< 0.1%)
Musculoskeletal chest pain	1 (< 0.1%)
Osteoarthritis	1 (< 0.1%)
Neoplasms Benign, Malignant and Unspecified	3 (0.1%)
Gastric cancer	1 (< 0.1%)
Hepatic cancer metastatic	1 (< 0.1%)
Uterine leiomyoma	1 (< 0.1%)
Nervous System Disorders	17 (0.8%)
Cerebrovascular accident	3 (0.1%)
Convulsion	3 (0.1%)
Neuroleptic malignant syndrome	2 (< 0.1%)
Syncope	1 (< 0.1%)
Akathisia	2 (< 0.1%)
Bradykinesia	1 (< 0.1%)
Complex Partial Seizures	1 (< 0.1%)
Drooling	1 (< 0.1%)
Dystonia	1 (< 0.1%)
Parkinsonism	1 (< 0.1%)
Tremor	1 (< 0.1%)
Headache	1 (< 0.1%)
Poor quality sleep	2 (< 0.1%)
Pregnancy, Puerperium and Perinatal Conditions	1 (< 0.1%)
Abortion, spontaneous	1 (< 0.1%)
Psychiatric Disorders	163 (7.8)
Schizophrenia	102 (4.9%)
Psychotic disorder	33 (1.6%)
Suicidal ideation	8 (0.4%)
Agitation	3 (0.1%)
Completed suicide	3 (0.1%)
Depression	3 (0.1%)
Suicidal behavior	2 (< 0.1%)
Suicide attempt	2 (< 0.1%)
Abnormal behavior	1 (< 0.1%)
Acute psychosis	1 (< 0.1%)
Aggression	1 (< 0.1%)
Anxiety	1 (< 0.1%)
Conduct disorder	1 (< 0.1%)
Delusion	1 (< 0.1%)
Delusion of reference	1 (< 0.1%)
Paranoia	1 (< 0.1%)
Self injurious behavior	1 (< 0.1%)
Stress	1 (< 0.1%)
Substance abuse	1 (< 0.1%)
Schizophrenia, paranoid type	1 (< 0.1%)
Renal and Urinary Disorders	1 (< 0.1%)
Renal failure	1 (< 0.1%)
Reproductive System and Breast Disorders	2 (< 0.1%)

Metrorrhagia	1 (< 0.1%)
Prostatitis	1 (< 0.1%)
Respiratory, Thoracic and Mediastinal Disorders	6 (0.3%)
COPD	2 (< 0.1%)
Acute respiratory failure	1 (< 0.1%)
Hydropneumothorax	1 (< 0.1%)
Pulmonary mass	1 (< 0.1%)
Respiratory failure	1 (< 0.1%)
Skin and Subcutaneous Tissue Disorders	2 (< 0.1%)
Angioedema	1 (< 0.1%)
Rash maculopapular	1 (< 0.1%)
Rash pruritic	1 (< 0.1%)
Social Circumstances	1 (< 0.1%)
Physical assault	1 (< 0.1%)
Surgical and Medical Procedures	1 (< 0.1%)
Endotracheal intubation	1 (< 0.1%)
Vascular Disorders	1 (< 0.1%)
Hypotension	1 (< 0.1%)

Source: Table 15 (Safety Update), adapted, Table 6.3.1.5 (Safety Update)

As of December 1, 2009, there were 72 subjects with at least one SAE reported but not included in the Safety Update Integrated Database; 24 of these cases were “new” and occurred since the September 1, 2009 data cut-off date for subjects with SAEs not included in the ISS Integrated Database. These events were not included in the Safety Update Integrated Database because the subjects were ongoing in a double-blind study at the time of the database cut-off (December 1, 2009) or the SAEs occurred during an ongoing study that did not contribute data to the Safety Update Integrated Database (D1050233, D1050234, D1001002 [all schizophrenia]; D1050235, D1050236, D1050256 [bipolar depression]).

Ten of the 72 subjects had not received any study drug when the SAE occurred. *The majority of the cases (54) are still blinded.* The majority of the cases were related to the underlying disorder (“psychotic disorder”, “schizophrenia”, “acute psychosis). Other SAEs included pre-eclampsia/premature birth (occurring 7 months after discontinuation of lurasidone 80 mg – see Section 7.6.2), suicidal behavior, acute MI/cardiomyopathy (on blinded drug x ~1 month), suicidal ideation, syncope, oculogyric crisis, NMS, and rhabdomyolysis.

7.3.3 Dropouts and/or Discontinuations

Phase 1 Studies

In the Phase 1 studies in healthy volunteers, four (1.4%) of subjects discontinued due to adverse events; all of these volunteers participated in study D1050002 and all received lurasidone 80 mg. One subject experienced disturbance in attention, nausea, restlessness and anxiety, one subject experienced nausea, insomnia, disturbance in attention, anxiety, nervousness and restlessness; one

subject experienced anxiety, disturbance in attention and abnormal dreams and one subject experienced insomnia, agitation, disturbance in attention and restlessness.

In the Phase 1 studies in patients with schizophrenia, 17 (6.6%) of patients receiving lurasidone and one (6.3%) of patients receiving placebo experienced adverse events that led to study discontinuation. See Section 7.2.1 for discussion of doses in the lurasidone > 120 mg group.

Table 75. Subjects with Adverse Events Leading to Discontinuation (P1SCH)

	Lurasidone 120 mg (N = 162)	Lurasidone > 120 mg (N = 96)	Placebo (N = 16)
Gastrointestinal Disorder	1 (0.6%)	4 (4.2%)	0
Nausea	0	4 (4.2%)	0
Vomiting	1 (0.6%)	3 (3.1%)	0
Stomach discomfort	0	1 (1.0%)	0
Investigations	1 (0.6%)	0	0
ECG Abnormal	1 (0.6%)	0	0
Musculoskeletal and Connective Tissue Disorders	0	2 (2.1%)	0
Muscle tightness	0	1 (1.0%)	0
Musculoskeletal stiffness	0	1 (1.0%)	0
Nervous System Disorders	0	9 (9.4%)	1 (6.3%)
Sedation	0	4 (4.2%)	0
Akathisia	0	3 (3.1%)	1 (6.3%)
Dystonia	0	3 (3.1%)	0
Depressed level of consciousness	0	1 (1.0%)	0
Dysarthria	0	1 (1.0%)	0
Extrapyramidal disorder	0	1 (1.0%)	0
Psychiatric Disorders	0	4 (4.2%)	1 (6.3%)
Anxiety	0	2 (2.1%)	0
Restlessness	0	2 (2.1%)	0
Claustrophobia	0	1 (1.0%)	0
Schizophrenia	0	1 (1.0%)	0
Agitation	0	0	1 (6.3%)

Source: Table 16 (ISS)

Phase 2/3 Studies

Table 76. Subjects with Adverse Events Leading to Discontinuation (P2/3STC)*

	Lurasidone 40 mg (N = 360)	Lurasidone 80 mg (N = 282)	Lurasidone 120 mg (N = 291)	Placebo (N = 455)
Cardiac Disorders	1 (0.3%)	1 (0.4%)	2 (0.7%)	2 (0.4%)
Angina pectoris	0	0	1 (0.3%)	1 (0.2%)
Sinus bradycardia	0	1 (0.4%)	0	1 (0.2%)
Sinus tachycardia	0	0	1 (0.3%)	0
Ventricular extrasystoles	1 (0.3%)	0	0	0
Eye Disorders	0	0	1 (0.3%)	0
Vision blurred	0	0	1 (0.3%)	0
Gastrointestinal Disorders	0	5 (1.8%)	1 (0.3%)	2 (0.4%)
Nausea	0	3 (1.1%)	0	0
Vomiting	0	1 (0.4%)	1 (0.3%)	0
Diarrhea	0	1 (0.4%)	0	0
Lip swelling	0	1 (0.4%)	0	0
General Disorders and Administration Site Conditions	0	0	2 (0.7%)	0
Fatigue	0	0	2 (0.7%)	0
Infections and Infestations	0	0	1 (0.3%)	0
Pneumonia	0	0	1 (0.3%)	0
Investigations	3 (0.8%)	2 (0.7%)	4 (1.4%)	5 (1.1%)
Blood CPK increased	1 (0.3%)	1 (0.4%)	2 (0.7%)	2 (0.4%)
Blood prolactin increased	1 (0.3%)	0	1 (0.3%)	0
ALT increased	1 (0.3%)	0	0	0
Protein total increased	1 (0.3%)	0	0	0
Transaminases increased	0	0	1 (0.3%)	0
Weight increased	0	1 (0.4%)	0	0
Metabolism and Nutrition Disorders	0	0	1 (0.3%)	0
Hyperkalemia	0	0	1 (0.3%)	0
Musculoskeletal and Connective Tissue Disorders	0	0	1 (0.3%)	0
Rhabdomyolysis	0	0	1 (0.3%)	0
Nervous System Disorders	9 (2.5%)	10 (3.5%)	12 (4.1%)	1 (0.2%)
Akathisia	5 (1.4%)	5 (1.8%)	7 (2.4%)	0
Dystonia	0	4 (1.4%)	3 (1.0%)	0
Dizziness	1 (0.3%)	1 (0.4%)	0	0
Sedation	1 (0.3%)	1 (0.4%)	0	0
Complex partial seizures	1 (0.3%)	0	0	0
Dyskinesia	0	1 (0.4%)	0	0
Extrapyramidal disorder	0	0	1 (0.3)	0
Headache	1 (0.3%)	0	0	0
Sciatica	0	1 (0.4%)	0	0
Somnolence	0	0	1 (0.3)	0
Psychiatric Disorders	18 (5.0%)	7 (2.5%)	20 (6.9%)	17 (3.7%)
Schizophrenia	7 (1.9%)	2 (0.7%)	8 (2.7%)	5 (1.1%)
Psychotic disorder	4 (1.1%)	2 (0.7%)	7 (2.4%)	11 (2.4%)
Agitation	4 (1.1%)	0	1 (0.3%)	1 (0.2%)
Anxiety	0	2 (0.7%)	1 (0.3%)	0
Insomnia	1 (0.3%)	1 (0.4%)	0	0
Substance abuse	2 (0.6%)	0	0	0

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Confusional state	0	0	1 (0.3%)	0
Hallucination, auditory	1 (0.3%)	0	0	0
Hostility	0	0	1 (0.3%)	0
Nightmare	0	0	1 (0.3%)	0
Restlessness	0	0	1 (0.3%)	0
Suicidal ideation	0	0	1 (0.3%)	0
Suspiciousness	0	1 (0.4%)	0	0
Skin and Subcutaneous Tissue Disorders				
Disorders	0	1 (0.4%)	1 (0.3%)	1 (0.2%)
Hyperhidrosis	0	1 (0.4%)	0	0
Pruritis	0	0	1 (0.3%)	0
Rash	1 (0.3%)	0	0	0
Vascular Disorders				
Hypotension	0	1 (0.4%)	1 (0.3%)	0
Orthostatic hypotension	0	1 (0.4%)	0	0
	0	0	1 (0.3%)	0

*No subjects randomized to lurasidone 20 mg (N = 71) discontinued due to adverse events.

Source: Table 73 (ISS)

In the P2/3ALL studies, 21.4% (449/2096) of patients discontinued due to an adverse event.

Table 77. Subjects with Adverse Events Leading to Discontinuation (P2/3ALL)

	Lurasidone (N = 2096)
Blood and Lymphatic System Disorders	1 (< 0.1%)
Neutropenia	1 (< 0.1%)
Cardiac Disorders	11 (0.5%)
Angina pectoris	1 (< 0.1%)
Arrhythmia	1 (< 0.1%)
Bradycardia	1 (< 0.1%)
Coronary artery disease	1 (< 0.1%)
Palpitations	1 (< 0.1%)
Pericardial effusion	1 (< 0.1%)
Sinus arrhythmia	1 (< 0.1%)
Sinus bradycardia	1 (< 0.1%)
Sinus tachycardia	1 (< 0.1%)
Supraventricular extrasystoles	1 (< 0.1%)
Ventricular extrasystoles	1 (< 0.1%)
Eye Disorders	3 (0.1%)
Cataract*	1 (< 0.1%)
Presbyopia	1 (< 0.1%)
Vision blurred	1 (< 0.1%)
Gastrointestinal Disorders	34 (1.6%)
Nausea	16 (0.8%)
Vomiting	10 (0.5%)
Stomach discomfort	4 (0.2%)
Constipation	2 (< 0.1%)
Diarrhea	2 (< 0.1%)
Abdominal distension	1 (< 0.1%)
Abdominal pain upper	1 (< 0.1%)
Dyspepsia	1 (< 0.1%)
Gastritis	1 (< 0.1%)

Lip swelling	1 (< 0.1%)
Swollen tongue	1 (< 0.1%)
General Disorders and Administration Site Conditions	16 (0.8%)
Fatigue	7 (0.3%)
Asthenia	2 (< 0.1%)
Malaise	2 (< 0.1%)
Chest discomfort	1 (< 0.1%)
Chest pain	1 (< 0.1%)
Gait disturbance	1 (< 0.1%)
Irritability	1 (< 0.1%)
Sudden death	1 (< 0.1%)
Hepatobiliary Disorders	1 (< 0.1%)
Jaundice	1 (< 0.1%)
Infections and Infestations	4 (0.2%)
Pneumonia	2 (< 0.1%)
Hepatitis infectious	1 (< 0.1%)
Upper respiratory tract infection	1 (< 0.1%)
Injury, Poisoning and Procedural Complications	5 (0.2%)
Accidental overdose	1 (< 0.1%)
Lumbar vertebral fracture	1 (< 0.1%)
Multiple drug overdose	1 (< 0.1%)
Rib fracture	1 (< 0.1%)
Spinal cord injury	1 (< 0.1%)
Thermal burn	1 (< 0.1%)
Investigations	21 (1.0%)
Blood CPK increased	7 (0.3%)
Blood bilirubin increased	2 (< 0.1%)
ALT increased	1 (< 0.1%)
Blood prolactin increased	1 (< 0.1%)
Blood glucose increased	1 (< 0.1%)
Blood lactate dehydrogenase increased	1 (< 0.1%)
Blood prolactin abnormal	1 (< 0.1%)
Blood urine present	1 (< 0.1%)
EEG abnormal	1 (< 0.1%)
GGT increased	1 (< 0.1%)
Hepatic enzyme increased	1 (< 0.1%)
Protein total increased	1 (< 0.1%)
Transaminases increased	1 (< 0.1%)
Weight increased	1 (< 0.1%)
Weight decreased	1 (< 0.1%)
Metabolism and Nutrition Disorders	5 (0.2%)
Decreased appetite	2 (< 0.1%)
Anorexia	1 (< 0.1%)
Hyponatremia	1 (< 0.1%)
Polydipsia	1 (< 0.1%)
Musculoskeletal and Connective Tissue Disorders	10 (0.5%)
Muscular weakness	2 (< 0.1%)
Rhabdomyolysis	2 (< 0.1%)
Joint stiffness	1 (< 0.1%)
Muscle rigidity	1 (< 0.1%)
Musculoskeletal discomfort	1 (< 0.1%)
Osteoarthritis	1 (< 0.1%)
Torticollis	1 (< 0.1%)
Musculoskeletal stiffness	1 (< 0.1%)

Nervous System Disorders	95 (4.5%)
Akathisia	35 (1.7%)
Dystonia	13 (0.6%)
Somnolence	11 (0.5%)
Dizziness	5 (0.2%)
Headache	4 (0.2%)
Sedation	5 (0.2%)
Tremor	4 (0.2%)
Dyskinesia	3 (0.1%)
Cerebrovascular accident	3 (0.1%)
Extrapyramidal disorder	3 (0.1%)
Convulsion	3 (0.1%)
Paresthesia	2 (< 0.1%)
Tardive dyskinesia	1 (< 0.1%)
Bradykinesia	1 (< 0.1%)
Complex partial seizures	1 (< 0.1%)
Disturbance in attention	1 (< 0.1%)
Loss of consciousness	1 (< 0.1%)
Neuroleptic malignant syndrome	1 (< 0.1%)
Parkinsonism	1 (< 0.1%)
Psychomotor hyperactivity	1 (< 0.1%)
Sciatica	1 (< 0.1%)
Pregnancy, Puerperium and Perinatal Conditions	2 (< 0.1%)
Pregnancy	2 (< 0.1%)
Psychiatric Disorders	259 (12.4%)
Schizophrenia	148 (7.1%)
Psychotic disorder	37 (1.8%)
Insomnia	14 (0.7%)
Agitation	11 (0.5%)
Anxiety	8 (0.4%)
Hallucination, auditory	5 (0.2%)
Depression	4 (0.2%)
Completed suicide	3 (0.1%)
Confusional state	3 (0.1%)
Restlessness	3 (0.1%)
Suicidal ideation	3 (0.1%)
Abnormal behavior	2 (< 0.1%)
Aggression	2 (< 0.1%)
Delusion	2 (< 0.1%)
Hallucination	2 (< 0.1%)
Substance abuse	2 (< 0.1%)
Suicide attempt	2 (< 0.1%)
Suspiciousness	2 (< 0.1%)
Tension	2 (< 0.1%)
Acute psychosis	1 (< 0.1%)
Antisocial behavior	1 (< 0.1%)
Apathy	1 (< 0.1%)
Bruxism	1 (< 0.1%)
Conduct disorder	1 (< 0.1%)
Depressed mood	1 (< 0.1%)
Dermatillomania	1 (< 0.1%)
Drug abuse	1 (< 0.1%)
Hostility	1 (< 0.1%)
Hypochondriasis	1 (< 0.1%)

Impatience	1 (< 0.1%)
Loose associations	1 (< 0.1%)
Mania	1 (< 0.1%)
Nightmare	1 (< 0.1%)
Self injurious behavior	1 (< 0.1%)
Sleep disorder	1 (< 0.1%)
Somatic hallucination	1 (< 0.1%)
Stress	1 (< 0.1%)
Suicidal behavior	1 (< 0.1%)
Thinking abnormal	1 (< 0.1%)
Reproductive System and Breast Disorders	3 (0.1%)
Erectile dysfunction	1 (< 0.1%)
Galactorrhea	1 (< 0.1%)
Metrorrhagia	1 (< 0.1%)
Respiratory, Thoracic and Mediastinal Disorders	4 (0.2%)
Acute respiratory failure	1 (< 0.1%)
COPD	1 (< 0.1%)
Hyperventilation	1 (< 0.1%)
Respiratory failure	1 (< 0.1%)
Skin and Subcutaneous Tissue Disorders	3 (0.1%)
Hyperhidrosis	1 (< 0.1%)
Pruritis	1 (< 0.1%)
Rash	1 (< 0.1%)
Social Circumstances	1 (< 0.1%)
Physical assault	1 (< 0.1%)
Vascular Disorders	3 (0.1%)
Hypotension	2 (< 0.1%)
Hypertension	1 (< 0.1%)

Source: Table 17 (ISS-Safety Update), Table 6.2.1.6 (ISS-Safety Update)

*Per narrative, cataract noted at end of study visit for D1050049, patient receiving haloperidol. Results of evaluation not received until after patient started open-label lurasidone, patient was discontinued from study.

7.3.4 Significant Adverse Events

Respiratory failure

The reviewer reviewed all narratives for the SAEs occurring in the P2/3ALL studies. There were two cases of respiratory failure noted (one noted as acute respiratory failure) (see Narratives for D1001001-00484 and D1001018-0072 in Appendix 9.6.2). One case (D1001018-0072) involved a 41 YOAF who died secondary to septic shock noted on autopsy. The second case (D1001001-00484) was also associated with a “high” blood concentration of nitrazepam, though the concentration was not included in the narrative.

However, in the course of the NDA review, this reviewer noted one additional case of respiratory failure (see Narrative for D1050237-0027-00046 in Appendix 9.6.2). This third case was reported as “angioedema”, an SAE, but the Sponsor failed to note that this case also resulted in respiratory failure with endotracheal intubation (See Section 3.1 of review). Angioedema occurred on Day 1 of receiving lurasidone 80 mg, respiratory failure occurring on Day 2. The clinical description of the event for this case was extremely brief and only mentioned angioedema, hospitalization and recovery; though the concomitant medications

section of the narrative did list medications administered for respiratory failure and intubation (these terms were not included in the narrative) The investigator had not recorded respiratory failure as an adverse event in the CRF, but had recorded concomitant medications with the reason for administration “respiratory failure” in the concomitant medication section of the CRF.

This reviewer did not identify any other confounds in that patient case. This patient was receiving a number of concomitant medications (including amlodipine for hypertension), but had been receiving these medications since 2005 – this event occurred in 2009. Interestingly, the narrative lists “drug hypersensitivity” as a concomitant illness with no other clinical information (preexisting?).

The Sponsor should more comprehensively review the risk of respiratory failure (including assessment of hypersensitivity risk in general) with lurasidone.

Suicidality

There were four cases of completed suicide occurring in the clinical trials, all patients were taking lurasidone at the time of the event. In the P2/3STC database, suicidal ideation (as an adverse event) occurred in 0.4% (4/1004) of patients receiving lurasidone and 0.2% (1/455) of patients receiving placebo.

The Sponsor stated that they applied the Columbia Classification Algorithm of Suicidal Assessment (C-CASA) across all clinical trials with lurasidone. For the P2/3ALL database, the following frequencies were noted for lurasidone²: suicidal ideation (0.7%, 14/2094), completed suicide (0.2%, 4/2094), suicide attempt (0.1%, 3/2094), suicide behavior (0.1%, 3/2094), self-injurious behavior (< 0.1%, 2/2094). The Sponsor did not provide any further analysis comparing these results to placebo or any historical data.

Of note, the Sponsor was asked to include the Columbia Suicidality Severity Rating Scale (C-SSRS) to their clinical trials in January 2009. At that time, all of the pivotal clinical trials had been completed or were near completion. Therefore, the C-SSRS was applicable only to the open-label extensions to those clinical trials. The NDA did not include any information regarding C-SSRS ratings obtained in the clinical trials either in the original submission or the 120-day safety update.

Convulsions

Four cases of convulsions occurred in the clinical trials database (one occurred in study D1050237 that was ongoing at the time the NDA was submitted). Brief narratives for these cases is in Appendix 9.6.3. These event of convulsions occurred at 10, 16, 60 and 310 days after initiating lurasidone. 310, 16 days, 10,

² The 120-day update did not include an update for the C-CASA analysis. This reviewer added a few cases that the Sponsor had mentioned that were not included in the IDB since they were reported after the cut-off date for the ISS.

60 days. Three of these cases were SAEs, one case was a discontinuation due to adverse event. None of these cases described a prior history of seizures. One case of complex partial seizures occurred in the clinical trials program.

Cerebrovascular accidents

Two CVAs were identified by the Sponsor (50 YOM, 50 YOF), in both of these cases there appeared to have been a prior history of CVA that the investigator was not aware of at the time the patients were enrolled (see Narratives in Appendix 9.6.4).

One case of stroke was identified by the Sponsor (see Narrative in Appendix 9.6.4). The stroke occurred in a 50 YOM after receiving lurasidone for 45 days, this patient experienced a second stroke ~17 days after discontinuing lurasidone.

Dystonia

Approximately 21 cases of dystonia as an SAE and/or discontinuation due to adverse event were identified by the Sponsor. Nine of these cases were treated with parenteral administration of anticholinergics, antihistamines and/or benzodiazepines (see Table 84 in section 7.4.1).

Rhabdomyolysis and Neuroleptic Malignant Syndrome

There were two cases of rhabdomyolysis identified in the clinical trials database, both patients were discontinued due to this adverse event. Upon review of the cases, despite a limited narrative for both, it is not clear that these were cases of rhabdomyolysis since narratives describe predominantly an increase in CPK without associated clinical symptoms consistent with rhabdomyolysis.

One case was a 40 YO BM receiving lurasidone 20 mg. At the end of the double-blind study (D1050049), his CPK was elevated at 776 U/L (reference range < 18 – 198 U/L), he had been receiving lurasidone 20 mg/day. Approximately 2 weeks later, while receiving the same dose of lurasidone, his CPK was 28,450 U/L with elevations in LFTs noted (data not provided) and lurasidone was discontinued. Prior to the elevation in CPK, the patient experienced proteinuria and hematuria (details not provided). The patient went to the hospital for evaluation but was not admitted for treatment. Repeat CPK (~1 week later) = 551 U/L. The narrative states that the “rhabdomyolysis was an inference based on the CPK level and not on clinical symptomatology or confirmatory myoglobin measures in serum or urine”.

The second case occurred in a 58 YOM who was noted to have a CPK = 1157 U/L (reference range 0-174 U/L) on day 7 of receiving lurasidone 120 mg. The patient discontinued lurasidone on ~day 13. There are no other clinical details regarding “rhabdomyolysis” in the narrative.

Two cases of neuroleptic malignant syndrome were identified in the P2/3ALL database. One patient was a 61 YO AF receiving lurasidone 40 mg who had a CPK = 3283 with diaphoresis and fever (39°C) and BP 184/104 mmHg without

muscle rigidity after receiving lurasidone for 5 days. Based on the elevation in CPK, a diagnosis of NMS was made. In the second case, the patient had been discontinued from the clinical study due to worsening of schizophrenia and was receiving risperidone when the diagnosis of NMS was made (CPK was WNL at end of clinical study).

Rash/Lip Swelling/Tongue Swelling

Refer to Section 7.4.6 (Immunogenicity) for discussion of these adverse events.

7.3.5 Submission Specific Primary Safety Concerns

Since lurasidone binds to melanin, clinical trials had included comprehensive ophthalmologic assessments including fundoscopic evaluation, slit-lamp examinations, and visual acuity assessments. The Sponsor was asked to continue these assessments in the 12-month double-blind study D1050237 that included a lurasidone flexible dose arm and a risperidone flexible dose arm (see Section 7.4.5). The Division of Anti-Infective and Ophthalmology Products was consulted to review the data from study D1050237. At the time this clinical review was being finalized, the consult had not been completed.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Phase 1 Studies

Healthy volunteers (P1NON)

The most common adverse events ($\geq 10\%$) occurring in any lurasidone group (≤ 30 mg, 40 mg, 60 – 100 mg) included nausea, fatigue, blood prolactin increased, somnolence, headache, akathisia, disturbance in attention, restlessness, anxiety, and abnormal dreams.

Schizophrenia (P1SCH)

Table 78. Adverse Events Reported in $\geq 2\%$ of Lurasidone-treated Subjects (P1SCH)

	Lurasidone 120 mg (N = 162)	Lurasidone > 120 mg (N = 96)	Placebo (N = 16)
Eye Disorders	6 (3.7%)	4 (4.2%)	0
Vision blurred	5 (3.1%)	4 (4.2%)	0
Gastrointestinal Disorders	64 (39.5%)	41 (42.7%)	6 (37.5%)
Nausea	18 (11.1%)	24 (25.0%)	2 (12.5%)
Vomiting	15 (9.3%)	19 (19.8%)	1 (6.3%)
Dyspepsia	22 (13.6%)	10 (10.4%)	0
Constipation	7 (4.3%)	6 (6.3%)	0
Diarrhea	3 (1.9%)	7 (7.3%)	2 (12.5%)

Dry mouth	10 (6.2%)	0	0
Abdominal pain	7 (4.3%)	2 (2.1%)	0
Stomach discomfort	2 (1.2%)	3 (3.1%)	1 (6.3%)
Toothache	4 (2.5%)	1 (1.0%)	0
General Disorders and Administration Site Conditions	6 (3.7%)	19 (19.8%)	1 (6.3%)
Fatigue	1 (0.6%)	9 (9.4%)	0
Pain	3 (1.9%)	4 (4.2%)	0
Irritability	1 (0.6%)	3 (3.1%)	1 (6.3%)
Asthenia	0	2 (2.1%)	0
Investigations	2 (1.2%)	5 (5.2%)	1 (6.3%)
Blood CPK increased	1 (0.6%)	3 (3.1%)	0
Musculoskeletal and Connective Tissue Disorders	20 (12.3%)	19 (19.8%)	2 (12.5%)
Back pain	7 (4.3%)	5 (5.2%)	0
Arthralgia	5 (3.1%)	1 (1.0%)	0
Muscle tightness	0	5 (5.2%)	0
Musculoskeletal pain	0	4 (4.2%)	0
Muscle spasms	1 (0.6%)	2 (2.1%)	1 (6.3%)
Musculoskeletal stiffness	0	3 (3.1%)	1 (6.3%)
Bone pain	0	2 (2.1%)	0
Nervous System Disorders	147 (90.7%)	69 (71.9%)	7 (43.8%)
Somnolence	130 (80.2%)	19 (19.8%)	1 (6.3%)
Akathisia	67 (41.4%)	17 (17.7%)	2 (12.5%)
Headache	17 (10.5%)	22 (22.9%)	3 (18.8%)
Dystonia	28 (17.3%)	8 (8.3%)	0
Sedation	2 (1.2%)	32 (33.3%)	3 (18.8%)
Extrapyramidal disorder	14 (8.6%)	5 (5.2%)	0
Dizziness	6 (3.7%)	8 (8.3%)	2 (12.5%)
Tremor	2 (1.2%)	3 (3.1%)	0
Dyskinesia	0	1 (1.0%)	0
Tardive dyskinesia	1 (0.6%)	1 (1.0%)	0
Psychiatric Disorders	66 (40.7%)	51 (53.1%)	12 (75%)
Anxiety	40 (24.7%)	28 (29.2%)	8 (50%)
Insomnia	30 (18.5%)	18 (18.8%)	4 (25%)
Restlessness	3 (1.9%)	30 (31.3%)	2 (12.5%)
Schizophrenia	7 (4.3%)	4 (4.2%)	4 (25%)
Agitation	1 (0.6%)	3 (3.1%)	1 (6.3%)
Depressed mood	2 (1.2%)	2 (2.1%)	0
Bruxism	0	2 (2.1%)	0
Reproductive System and Breast Disorders	2 (1.2%)	2 (2.1%)	0
Dysmenorrhea	1 (0.6%)	2 (2.1%)	0
Respiratory, Thoracic and Mediastinal Disorders	4 (2.5%)	4 (4.2%)	1 (6.3%)
Dyspnea	2 (1.2%)	2 (2.1%)	0
Skin and Subcutaneous Tissue Disorders	11 (6.8%)	3 (3.1%)	0
Rash*	4 (2.5%)	1 (1.0%)	0
Vascular Disorders	7 (4.3%)	0	0
Hot flush	4 (2.5%)	0	0

Source: Table 6.1.2.2 (ISS)

*Reviewer also included "rash, generalized" (n = 1) in this category.

Phase 2/3 Studies

Because of the way dystonias were classified as adverse events, the overall rate of “dystonias” is potentially underestimated in Table 79. If one included the following adverse events as dystonias: torticollis (n = 4), oculogyric crisis (n = 2), eye rolling (n = 2, see Section 7.1.2), tongue spasm (n = 1), and oromandibular dystonia (n = 2); the rate for dystonias in the lurasidone group increases from 3.5% to 4.6% (46/1004).

Table 79. Adverse Events Reported in $\geq 2\%$ of Lurasidone-treated Subjects (Phase 2/3STC)

	All Lurasidone (N = 1004)	Placebo (N = 455)
Blood and Lymphatic System Disorders	3 (0.3)	2 (0.4)
Anemia	2 (0.2)	0
Cardiac Disorders	25 (2.5)	13 (2.9)
Tachycardia	13 (1.3)	5 (1.1)
Eye Disorders	40 (4.0)	10 (2.2)
Vision Blurred	18 (1.8)	1 (0.2)
Gastrointestinal Disorders	353 (35.2)	136 (29.9)
Nausea	120 (12.0)	27 (5.9)
Vomiting	80 (8.0)	26 (5.7)
Dyspepsia	76 (7.6)	27 (5.9)
Constipation	52 (5.2)	27 (5.9)
Toothache	33 (3.3)	16 (3.5)
Diarrhea	32 (3.2)	20 (4.4)
Stomach discomfort	24 (2.4)	11 (2.4)
Salivary hypersecretion	21 (2.1)	2 (0.4)
Dry mouth	20 (2.0)	8 (1.8)
Abdominal pain, upper	19 (1.9)	6 (1.3)
General Disorders and Administration Site Conditions	88 (8.8)	41 (9.0)
Fatigue	36 (3.6)	13 (2.9)
Pain	17 (1.7)	13 (2.9)
Infections and Infestations	112 (11.2)	58 (12.7)
Nasopharyngitis	18 (1.8)	8 (1.8)
Upper Respiratory Tract Infection	17 (1.7)	14 (3.1)
Urinary Tract Infection	14 (1.4)	5 (1.1)
Tinea Pedis	10 (1.0)	2 (0.4)
Investigations	92 (9.2)	38 (8.4)
Weight increased	24 (2.4)	9 (2.0)
Blood CPK increased	16 (1.6)	6 (1.3)
Metabolism and Nutrition Disorders	37 (3.7)	19 (4.2)
Decreased appetite	18 (1.8)	5 (1.1)
Musculoskeletal and Connective Tissue Disorders	157 (15.6)	62 (13.6)
Back pain	38 (3.8)	14 (3.1)
Musculoskeletal stiffness	33 (3.3)	12 (2.6)
Pain in extremity	25 (2.5)	16 (3.5)
Arthralgia	22 (2.2)	14 (3.1)
Musculoskeletal pain	11 (1.1)	1 (0.2)
Musculoskeletal chest pain	5 (0.5)	2 (0.4)
Nervous System Disorder	520 (51.8)	152 (33.4)

Headache	177 (17.6)	82 (18.0)
Akathisia	151 (15.0)	15 (3.3)
Sedation	119 (11.9)	25 (5.5)
Somnolence	107 (10.7)	21 (4.6)
Parkinsonism	49 (4.9)	2 (0.4)
Dizziness	46 (4.6)	12 (2.6)
Dystonia	35 (3.5)	3 (0.7)
Tremor	30 (3.0)	10 (2.2)
Extrapyramidal disorder	20 (2.0)	7 (1.5)
Dyskinesia	18 (1.8)	9 (2.0)
Psychiatric Disorders	257 (25.6)	92 (20.2)
Insomnia	84 (8.4)	30 (6.6)
Agitation	64 (6.4)	14 (3.1)
Anxiety	63 (6.3)	15 (3.3)
Schizophrenia	44 (4.4)	17 (3.7)
Restlessness	26 (2.6)	7 (1.5)
Psychotic disorder	20 (2.0)	16 (3.5)
Reproductive System and Breast Disorders	20 (2.0)	9 (2.0)
Dysmenorrhea	11 (1.1)	3 (0.7)
Respiratory, Thoracic and Mediastinal Disorders	81 (8.1)	30 (6.6)
Cough	26 (2.6)	13 (2.9)
Oropharyngeal pain	24 (2.4)	12 (2.6)
Nasal congestion	24 (2.4)	4 (0.9)
Skin and Subcutaneous Tissue Disorders	69 (6.9)	30 (6.6)
Rash	20 (2.0)	10 (2.2)
Pruritis	14 (1.4)	7 (1.5)

Source: Table 50 (ISS), Table 6.1.2.3 (ISS)

Table 80 provides frequencies of adverse events by lurasidone dose. Potential dose-related adverse events include akathisia, sedation and somnolence (the latter two terms will need to be combined by the Sponsor due to overlap/similarity in terms). Due to difficulties in mapping of adverse event terms related to parkinsonian adverse events (e.g. splitting and lumping), it is more difficult to determine a dose-relationship. However, in nearly all categories related to parkinsonian adverse events, the frequency is highest in the lurasidone 120 mg group (see Table 83).

Table 80. Adverse Events Reported in $\geq 5\%$ of Subjects (P2/3STC) – By Dose

	Lurasidone 20 mg (N = 71)	Lurasidone 40 mg (N = 360)	Lurasidone 80 mg (N = 282)	Lurasidone 120 mg (N = 291)	Placebo (N = 455)
Headache	15 (21.1)	74 (20.6)	43 (15.2)	45 (15.5)	82 (18.0)
Akathisia*	4 (5.6)	41 (11.4)	42 (14.9)	64 (22.0)	15 (3.3)
Nausea	8 (11.3)	39 (10.8)	36 (12.8)	37 (12.7)	27 (5.9)
Sedation*	8 (11.3)	38 (10.6)	37 (13.1)	36 (12.4)	25 (5.5)
Somnolence*	3 (4.2)	33 (9.2)	29 (10.3)	42 (14.4)	21 (4.6)
Insomnia	6 (8.5)	31 (8.6)	22 (7.8)	25 (8.6)	30 (6.6)
Vomiting	5 (7.0)	19 (5.3)	29 (10.3)	27 (9.3)	26 (5.7)
Dyspepsia	8 (11.3)	24 (6.7)	22 (7.8)	22 (7.6)	27 (5.9)
Agitation	7 (9.9)	32 (8.9)	8 (2.8)	17 (5.8)	14 (3.1)
Anxiety	2 (2.8)	29 (8.1)	13 (4.6)	19 (6.5)	15 (3.3)
Constipation	2 (2.8)	14 (3.9)	21 (7.4)	15 (5.2)	27 (5.9)

Source: Table 51 (ISS)

*Potential relationship to lurasidone dose

Table 81. Adverse Events Reported in $\geq 1\%$ of Lurasidone-treated Subjects (P2/3ALL)

	All Lurasidone (N = 2096)
Gastrointestinal Disorders	759 (36.2%)
Nausea	288 (13.7%)
Vomiting	207 (9.9%)
Constipation	93 (4.4%)
Dyspepsia	95 (4.5%)
Diarrhea	80 (3.8%)
Salivary hypersecretion	55 (2.6%)
Toothache	59 (2.8%)
Dry mouth	46 (2.2%)
Stomach discomfort	46 (2.2%)
General Disorders and Administrative Site Conditions	239 (11.4%)
Fatigue	69 (3.3%)
Pyrexia	43 (2.1%)
Infections and Infestations	386 (18.4%)
Nasopharyngitis	177 (8.4%)
Upper respiratory tract infection	47 (2.2%)
Investigations	445 (21.2%)
Blood prolactin increased	97 (4.6%)
Weight increased	77 (3.7%)
Blood CPK increased	69 (3.3%)
Weight decreased	67 (3.2%)
Metabolism and Nutritional Disorders	134 (6.4%)
Decreased appetite	64 (3.1%)
Musculoskeletal and Connective Tissue Disorders	282 (13.5%)
Back pain	64 (3.1%)
Musculoskeletal stiffness	60 (2.9%)
Nervous System Disorders	1019 (48.6%)
Akathisia	295 (14.1%)
Headache	287 (13.7%)
Somnolence	254 (12.1%)

Sedation	179 (8.5%)
Dizziness	98 (4.7%)
Tremor	87 (4.2%)
Parkinsonism	87 (4.2%)
Dystonia	66 (3.1%)
Dyskinesia	51 (2.4%)
Extrapyramidal disorder	44 (2.1%)
Psychiatric Disorders	792 (37.8%)
Insomnia	303 (14.5%)
Schizophrenia	257 (12.3%)
Anxiety	128 (6.1%)
Agitation	93 (4.4%)
Restlessness	59 (2.8%)
Psychotic disorder	54 (2.6%)
Respiratory, Thoracic and Mediastinal Disorders	183 (8.7%)
Cough	49 (2.3%)

Source: Table 60 ISS and Table 9 ISS update

Extrapyramidal Side Effects (Akathisia, Parkinsonism, and Dyskinesias)

The frequency of akathisia was higher than placebo and was dose related (Table 80) with 22% of patients in the lurasidone 120 mg group exhibiting experiencing akathisia. It is difficult to ascertain the incidence of parkinsonian symptoms in these clinical trials due to lumping and splitting of terms. Some terms seem to be lumping – e.g. parkinsonism, extrapyramidal disorder, while others seemed to be split – e.g. tremor, bradykinesia, drooling. The Sponsor did not capture “salivary hypersecretion” as an EPS-related term, though this seems similar to “drooling” to this reviewer and the latter term was captured as an EPS-related term. Gait disturbance was also not necessarily captured adequately when mapping from verbatim terms – some cases where the gait was parkinsonian-like (e.g. “decrease arm swing during walk” mapped to preferred term “gait disturbance” with other adverse events consistent with EPS, “shuffling gait”). In the parkinsonism-related terms, the most frequently reported adverse events were “parkinsonism”, “tremor”, “salivary hypersecretion” and “extrapyramidal disorder” (Table 82). Lurasidone was associated with parkinsonian adverse events. Interestingly, “parkinsonism” was noted in 4.9% of patients in the lurasidone groups compared to 0 in the haloperidol group while “extrapyramidal disorder” was noted in only 2% of patients in the lurasidone groups compared to 18% of patients in the haloperidol group – again, issues with lumping and splitting likely evident as well as differences in overall coding of verbatim terms. The dose-relationship of lurasidone and parkinsonian adverse events is not as clear, perhaps due to some of the coding issues described. “Parkinsonism” was present in 0 patients in the 20 mg group, 5.3% in the 40 mg group, 1.8% in the 80 mg group and 8.6% in the 120 mg group. In nearly all parkinsonism-related categories, the highest frequencies were in the lurasidone 120 mg group. There were very few discontinuations due to parkinsonian adverse events.

Table 82. Extrapyramidal Symptoms (including dyskinesias), Number (%) of Patients with at least one EPS Adverse Event: P2/3STC

	All Lurasidone (N = 1004)	Placebo (N = 455)	Haloperidol 10 mg (N = 72)	Olanzapine 15 mg (N = 122)
<i>Akathisia-related</i>				
Akathisia	151 (15%)	15 (3.3%)	14 (19.4%)	9 (7.4%)
Restlessness	26 (2.6%)	7 (1.5%)	3 (4.2%)	4 (3.3%)
<i>Dystonia-related</i>				
Dystonia	35 (3.5%)	3 (0.7%)	9 (12.5%)	1 (0.8%)
Oculogyric Crisis	2 (0.2%)	0	1 (1.4%)	1 (0.8%)
Oromandibular dystonia	5 (0.5%)	0	3 (4.2%)	1 (0.8%)
Eye Rolling*	2 (0.2%)	1 (0.2%)	0	0
Torticollis	4 (0.4%)	0	0	0
Tongue Spasm	1 (< 0.1%)	0	0	0
<i>Parkinsonian-related</i>				
Parkinsonism	49 (4.9%)	2 (0.4%)	0	7 (5.7%)
Tremor	30 (3.0%)	10 (2.2%)	5 (6.9%)	7 (5.7%)
Salivary Hypersecretion*	21 (2.1%)	2 (0.4%)	3 (4.2%)	0
Extrapyramidal disorder	20 (2.0%)	7 (1.5%)	13 (18.1%)	0
Drooling	7 (0.7%)	2 (0.4%)	1 (1.4%)	0
Muscle rigidity	7 (0.7%)	2 (0.4%)	0	1 (0.8%)
Cogwheel rigidity	5 (0.5%)	0	0	0
Bradykinesia	2 (0.2%)	0	0	0
Psychomotor Retardation	2 (0.2%)	0	0	0
Hypokinesia	0	0	1 (1.4%)	0
Gait disturbance*	2 (0.2%)	0	0	0
<i>Dyskinesia-related</i>				
Tardive dyskinesia	0	3 (0.7%)	0	2 (1.6%)
Trismus	1 (< 0.1%)	0	0	0
Bruxism*	4 (0.4%)	2 (0.4%)	0	1 (0.8%)

Source: Table 57 (ISS) , Table 6.1.2.3 (ISS)

*Due to issues in AE coding (see Section), these terms are included since they were suggestive of EPS. For gait disturbance, only verbatim terms “decrease arm swing during walk” and “shuffling gait” were included in this preferred term for EPS assessment.

Table 83. Extrapyrimal Symptoms, Number (%) of Patients \geq 1 EPS Adverse Event *By Dose*: P2/3STC

	Lurasidone 20 mg (N = 71)	Lurasidone 40 mg (N = 360)	Lurasidone 80 mg (N = 282)	Lurasidone 120 mg (N = 291)
<i>Akathisia-related</i>				
Akathisia	4 (5.6%)	41 (11.4%)	42 (14.9%)	64 (22.0%)
Restlessness	1 (1.4%)	14 (3.9%)	3 (1.1%)	8 (2.7%)
<i>Dystonia-related</i>				
Dystonia	0	12 (3.3%)	12 (4.3%)	11 (3.8%)
Oculogyric Crisis	0	2 (0.6%)	0	0
Oromandibular dystonia	0	2 (0.6%)	0	3 (1.0%)
Eye Rolling*	0	0	1 (0.4%)	1 (0.3%)
Torticollis	0	0	0	4 (1.4%)
Tongue spasm	0	0	1 (0.4%)	0
<i>Parkinsonian-related</i>				
Parkinsonism	0	19 (5.3%)	5 (1.8%)	25 (8.6%)
Tremor	1 (1.4%)	10 (2.8%)	4 (1.4%)	15 (5.2%)
Salivary Hypersecretion*	1 (1.4%)	4 (1.1%)	5 (1.8%)	11 (3.8%)
Extrapyrimal disorder	3 (4.2%)	6 (1.7%)	8 (2.8%)	3 (1.0%)
Drooling	0	3 (0.8%)	1 (0.4%)	3 (1.0%)
Muscle rigidity	0	1 (0.3%)	2 (0.7%)	4 (1.4%)
Cogwheel rigidity	0	2 (0.6%)	0	3 (1.0%)
Bradykinesia	0	0	0	2 (0.7%)
Psychomotor Retardation	0	0	0	2 (0.7%)
Hypokinesia	0	0	0	0
Gait disturbance*	1 (1.4%)	1 (0.3%)	0	0
<i>Dyskinesia-related</i>				
Tardive dyskinesia	0	0	0	0
Trismus	0	0	0	1 (0.3%)
Bruxism*	0	2 (0.6%)	2 (0.7%)	0

Source: Table 57 (ISS) , Table 6.1.2.3 (ISS)

*Due to issues in AE coding (see Section), these terms are included since they were suggestive of EPS. For gait disturbance, only verbatim terms “decrease arm swing during walk” and “shuffling gait” were included in this preferred term for EPS assessment.

The narratives for SAEs and discontinuations for adverse events were reviewed and a number of discontinuations were due to dystonic events. In general, the clinical presentation of the dystonic events were not available and were not documented in either the narratives or the case report forms. The type of dystonia (when described), demographics of the patients, dose of lurasidone and day of onset (relative to lurasidone dose initiation) are included in Table 84. Twenty-one cases of “dystonia” were identified in the available narratives, two of these (tongue swelling, oculogyric movement) were identified as SAEs. It is unclear from the narrative whether the tongue swelling was a dystonic event as categorized or an allergic reaction, the event was treated with benztropine,

diphenhydramine and medroxyprogesterone (dosepak). For the patient with the oculogyric movement, data are still blinded and the patient could have been receiving lurasidone or risperidone.

Three of these 21 cases occurred in an MTD trial and patients received ≥ 200 mg lurasidone. Three of these 21 cases had adverse event onset later than would be expected for a dystonic event (days 44, 56 and 161) and all of these events also had another event of tardive dyskinesia occurring at about the same time as the “dystonic” event. In the 18 cases where the race was specified, 8 cases occurred in Black/African American patients. Sixteen of the 21 cases (76%) occurred in males and 8 of the cases occurred in patients ≤ 30 years of age. Nine of the cases were treated with medications administered parenterally.

Table 84. Serious Adverse Events and Discontinuations due to Adverse Events – *Dystonias* (P2/3ALL)

Study	Patient Demographics	Severity, Clinical Presentation	Treatment Received	Lurasidone Dose	Onset of Dystonia (relative to lurasidone dosing)
D1050006	40 YOWF #0014-00086	Moderate Not available	Benztropine (oral)	40 mg	Day 7
D1050196	22 YOBM #0004-09003	Moderate Not available	Benztropine (IM and oral)	80 mg	Day 1
D1050199	40 YOF #0004-09005	Severe Not available	Benztropine (oral)	80 mg	Day 4
D1050217*	46 YOF, Asian #0001-00708	Moderate Not available	None documented	520 mg*	Day 3
D1050217*	55 YOBM #0001-00807	Moderate Not available	Benztropine (IM) Lorazepam (IM)	200 mg*	Day 1
D1050217*	39 YOBM #0001-00809	Severe Not available	Benztropine (IM) Lorazepam (IM)	200 mg*	Day 1
D1050229	24 YOWM #0016-00003	Severe Not available	Benztropine (IM and oral)	80 mg	Day 2
D1050229	41 YOBM #0016-00009	Severe Not available	Trihexyphenidyl (oral) Diphenhydramine (IM)	80 mg	Day 2
D1050229	45 YOM Native Hawaiiin/Other Pacific Islander #0020-00010	Moderate No details	Benztropine (IM and oral)	80 mg	Day 19
D1050229	39 YOWM #0176-00001	Moderate Torsion dystonia	Trihexyphenidyl (oral) Phenazepam (oral)	120 mg	Day 2
D1050231	24 YOWM #0027-00017	Severe Bilateral jaw muscles, facial muscles	Benztropine (oral)	120 mg	Day 10
D1050231	31 YOWM #0029-00017	Moderate Bilateral jaw	Benztropine (oral)	120 mg	Day 2

		clenching, lateral movement of jaw			
D1050247	47 YOWM #0001-00110	Moderate Not available	Benztropine (IM and oral)	120 mg	Day 5
D1050231E	18 YOBM #0027-00020	Severe Torticollis	Benzotropine (oral) Diphenhydramine (IV)	80 mg	Day 13
D1050237	20 YOBM #0027-00050	Moderate "Tongue was swelling"	Benzotropine (oral) Diphenhydramine (IV) Medroxyprogesterone (oral)	80 mg	Day 3
D1050237	28 YOBF #0052-00008	Mild Jaw and tongue	Benzotropine (oral)	120 mg	Day 161 Tardive dyskinesia also noted
D1050237	26 YOM #0406-00005	Mild Tongue, mouth and jaw	Orphenadrine (oral)	40 mg	Day 56 Tardive dyskinesia also noted
D1050237	37 YOBM #0406-00006	Moderate	Ibuprofen (oral)**	80 mg	Day 44 Tardive dyskinesia also noted
D1050237	23 YOM #0566-00009	Moderate Oculogyric movement	Study drug dose reduced	Lurasidone or risperidone***	Day 5
D1001036	40 YOF, Asian #00483	Severe Not available	Biperidin (oral)	40 mg	Day 10
D1050267	49 YOWM #110	Mild Not available	Benzotropine (oral)	120 mg	Day 1

Source: Narratives and CRFs provided in ISS and ISS-safety update

*Maximum tolerated dose protocol

**Not a usual treatment for EPS

***Treatment was still blinded at time narrative constructed. Reviewer looked at other listings and datasets available for this study and could not locate patient.

Tardive Dyskinesia - P2/3ALL and D1050237

Since tardive dyskinesia is an adverse event unlikely to be exhibited in a 6-week trial, the clinical trials up to 52 weeks were evaluated.

The AIMS scores were only provided as change from baseline to LOCF, not matched timepoints by week. The mean change to LOCF endpoint was 0.1 (1.5). The incidence of a normal baseline AIMS to abnormal at LOCF endpoint was 2.5% (40/1580).

In D1050237, the incidence of a normal baseline AIMS to abnormal at LOCF endpoint was 2.7% (5/186) in the lurasidone group and 1.2% (1/83) in the risperidone group.

Interestingly, those percentages of normal to abnormal shifts were similar to the data from P2/3STC. The percentage of patients who worsened on the AIMS Global Severity Score was also consistent in the P2/3STC and P2/3ALL databases and was around 6-7%.

For these data, however, it would be important to look at completers at various timepoints over the 52 week exposure matched to their baseline scores to evaluate a tardive dyskinesia signal.

7.4.2 Laboratory Findings

In this section, laboratory findings are displayed in the following order: chemistry, metabolic parameters (glucose, lipids, etc.), and hematology.

Phase 1 Studies

Chemistry

Mean Change from Baseline

Healthy volunteers (P1NON)

There were no notable safety signals in the mean change from baseline laboratory assessments. Of interest, mean change from baseline for CPK was mean decreases (-24 U/L for all lurasidone group). The mean change for prolactin was -1.1 ng/ml (lurasidone \leq 30 mg), 30.2 ng/ml (lurasidone 40 mg) and 17.1 ng/ml (lurasidone 60-100 mg). The maximum prolactin concentration was 501 ng/ml noted in the lurasidone 40 mg group. The mean change in prolactin concentration for males was -1.1, -0.1 and 17.1 ng/ml for the three lurasidone dose groups. The mean change in prolactin concentration for females was -1.2 (\leq 30 mg) and 87 ng/ml (40 mg), no females received 60-100 mg lurasidone. The subject with the 501 ng/ml prolactin concentration was female.

Schizophrenia (P1SCH)

Table 85. Chemistry: Mean Change from Baseline to LOCF Endpoint (P1SCH)

	Lurasidone 120 mg (N = 162)	Lurasidone > 120 mg (N = 96)	Placebo (N = 16)
AST (U/L) Mean Change (SD)	0.4 (5.2)	-0.7 (9.1)	-0.4 (5.7)
ALT (U/L) Mean Change (SD)	-0.2 (10.2)	-2.1 (15.5)	7.4 (9.6)
GGT (U/L) Mean Change (SD)	NA	-1.6 (6.4)	1.6 (15.1)
LDH (U/L) Mean Change (SD)	9.6 (29.4)	-3.0 (13.9)	-12.8 (24.1)
Alkaline Phos (U/L) Mean Change (SD)	0.7 (9.6)	-0.8 (8.2)	-4.6 (7.1)
Bilirubin (mg/dL) Mean Change (SD)	-0.01 (0.18)	0.01 (0.25)	-0.04 (0.22)
Albumin (g/dL) Mean Change (SD)	0.02 (0.30)	0.07 (0.28)	-0.15 (0.39)
Protein (g/dL) Mean Change (SD)	0.0 (0.52)	0.01 (0.50)	-0.34 (0.59)
Bicarbonate (mEq/L) Mean Change (SD)	-0.7 (2.8)	-1.4 (2.1)	NA
BUN (mg/dL) Mean Change (SD)	0.09 (3.1)	-0.17 (3.0)	-0.56 (2.1)
Calcium (mg/dL) Mean Change (SD)	-0.03 (0.36)	0.02 (0.37)	-0.06 (0.43)
Chloride (mEq/L) Mean Change (SD)	-0.5 (3.2)	-0.8 (3.1)	1.4 (2.1)
Creatinine (mg/dL) Mean Change (SD)	0.10 (0.12)	0.12 (0.13)	-0.02 (0.10)
Phosphate (mg/dL) Mean Change (SD)	0.28 (0.51)	0.27 (0.55)	0.37 (0.29)
Potassium (mEq/L) Mean Change (SD)	-0.14 (0.38)	-0.14 (0.32)	-0.21 (0.32)
Sodium (mEq/L) Mean Change (SD)	0.3 (3.8)	-1.0 (3.3)	1.0 (2.0)
CPK (U/L) Mean Change (SD) Median Change	47 (206.7) 18	98.3 (158.2) 38	ND
Prolactin (ng/ml) Mean Change (SD)	11.1 (23.6)	11.7 (24.3)	3.3 (8.6)
<i>Males</i> n Mean Change	98 8.3 (11.4)	51 7.1 (9.7)	12 0.5 (4.6)
<i>Females</i> n Mean Change	32 19.6 (42.5)	10 35 (51.8)	3 14.1 (13.2)

Source: Table 7.1.1.2 ISS

Phase 2/3 Studies

In the original NDA submission, laboratory data from 27 patients participating in study D1050006 were inadvertently not included (Sponsor alerted Division in August 2010). Sponsor submitted these data including a revised ISS. The data in the following tables include those 27 patients.

The most significant finding when evaluating the mean change from baseline is the increase in prolactin concentration in the lurasidone group. This increase in prolactin was also dose related (also see Table 86). CPK elevations were also noted and appeared to be dose-related but unexpectedly low in the lurasidone 120 mg group compared to other doses. The placebo group, however, was associated with a larger mean increase in CPK.

There was a slight increase in phosphate in the 120 mg group. The maximum value for a patient was 5.4 mg/dL and this value was recorded at baseline, presumably prior to lurasidone administration. However, the median values were still higher in the 120 mg group.

Table 86. Chemistry: Mean Change from Baseline to LOCF Endpoint (P2/3STC)

	Lurasidone 20 mg (N = 71)	Lurasidone 40 mg (N = 360)	Lurasidone 80 mg (N = 282)	Lurasidone 120 mg (N = 291)	All Lurasidone (N = 1004)	Placebo (N = 455)
AST (U/L) Mean Change (SD)	-1.3 (8.9)	-1.0 (13.8)	1.4 (19.6)	-1.6 (10.0)	-0.5 (14.5)	2.3 (27.6)
ALT (U/L) Mean Change (SD)	-3.2 (14.3)	-2.9 (24.3)	-0.2 (24.6)	-2.1 (21.8)	-1.9 (23.1)	1.0 (31.1)
GGT (U/L) Mean Change (SD)	ND	-2.9 (19.4)	-4.6 (25.1)	-2.2 (14.6)	-3.0 (19.0)	-2.1 (15.0)
LDH (U/L) Mean Change (SD)	1.4 (26.1)	3.0 (49.1)	2.0 (41.4)	1.3 (44.2)	2.1 (44.2)	11.4 (79.2)
Alkaline Phos (U/L) Mean Change (SD)	-1.2 (11.9)	-2.3 (12.6)	-1.6 (14.8)	-2.4 (11.2)	-2.0 (12.8)	-0.8 (11.9)
Bilirubin (mg/dL) Mean Change (SD)	0.08 (0.28)	0.03 (0.21)	0.03 (0.25)	0.01 (0.25)	0.03 (0.24)	0.06 (0.22)
Albumin (g/dL) Mean Change (SD)	0.12 (0.36)	0.03 (0.31)	0.05 (0.29)	0.03 (0.29)	0.04 (0.30)	0.06 (0.32)
Protein (g/dL) Mean Change (SD)	0.04 (0.54)	-0.01 (0.52)	-0.03 (0.49)	0.01 (0.48)	-0.01 (0.50)	0.01 (0.49)
Bicarbonate (mEq/L) Mean Change (SD)	ND	-0.4 (3.0)	-0.5 (3.8)	-0.1 (3.2)	-0.3 (3.4)	-0.4 (3.0)
BUN (mg/dL) Mean Change (SD)	-0.37 (3.73)	-0.30 (3.88)	-0.21 (3.75)	-0.36 (3.48)	-0.30 (3.72)	0.03 (3.79)
Calcium (mg/dL) Mean Change (SD)	0.06 (0.46)	-0.03 (0.46)	-0.03 (0.43)	0.01 (0.46)	-0.01 (0.45)	0.03 (0.45)
Chloride (mEq/L) Mean Change (SD)	0.6 (3.4)	0.3 (3.2)	0.1 (3.5)	-0.1 (2.8)	0.1 (3.2)	0.7 (2.9)
Creatinine (mg/dL) Mean Change (SD)	0.03 (0.13)	0.04 (0.14)	0.06 (0.13)	0.07 (0.14)	0.06 (0.14)	0.03 (0.14)
Phosphate (mg/dL) Mean Change (SD)	-0.14 (0.72)	-0.03 (0.65)	-0.04 (0.67)	0.11 (0.68)	0.00 (0.67)	-0.06 (0.7)
Potassium (mEq/L) Mean Change (SD)	-0.06 (0.40)	-0.13 (0.45)	-0.08 (0.42)	-0.07 (0.39)	-0.09 (0.42)	-0.09 (0.42)

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Sodium (mEq/L) Mean Change (SD)	0.1 (3.7)	-0.0 (3.5)	-0.2 (3.1)	0.1 (2.6)	-0.0 (3.2)	0.4 (2.8)
CPK (U/L) Mean Change (SD) Median Change	17.6 (253) 15	47.1 (325) 15	151 (1581) 15	4.9 (381) 9	61.3 (881) 12.5	188 (2016) 14
C-Reactive Protein* (mg/dL) Mean Change (SD)	ND	0.05 (0.63)	ND	-0.03 (0.40)	0.01 (0.53)	0.08 (0.53)
Prolactin (ng/ml) Mean Change (SD)	4.2 (26.2)	2.2 (25.5)	6.5 (31.1)	11.1 (31.1)	6.1 (29)	-3.0 (17.2)
<i>Males</i> n Mean Change	51 0.0 (13.6)	252 1.6 (13.3)	181 2.8 (16.3)	214 6.4 (16.3)	698 3.3 (15.3)	328 -1.6 (10.8)
<i>Females</i> n Mean Change	19 15.3 (44.0)	99 4.0 (43.1)	78 15 (50.2)	70 25.5 (53.6)	266 13.7 (48.7)	102 -7.5 (29.1)

Source: Table 82 (ISS), Table 7.1.1.3 (ISS), Table 85 (ISS), Table 7.1.1.3 (Amendment SD-28)

ND = not done

*C-reactive protein was collected in study D1050231 only (n = 234 for lurasidone groups, n = 114 for placebo group)

Table 87. Chemistry: Mean Change from Baseline to Weeks 24, 36, 52 – P2/3ALL

	Week 24	Week 36	Week 52
AST (U/L) n Mean Change (SD)	186 -0.7 (11.9)	215 -0.3 (15.7)	193 0.3 (13.9)
ALT (U/L) n Mean Change (SD)	186 -5.1 (21.9)	216 -3.9 (26.1)	193 -2.5 (18.6)
GGT (U/L) n Mean Change (SD)	140 -1.8 (19.8)	204 -1.6 (26.4)	185 -2.3 (24.9)
LDH (U/L) n Mean Change (SD)	182 6.9 (64.9)	215 3.4 (34.0)	193 4.4 (36.9)
Alkaline Phos (U/L) n Mean Change (SD)	185 -1.1 (16.8)	216 3.9 (53.6)	193 2.3 (43.5)
Bilirubin (mg/dL) n Mean Change (SD)	185 0.03 (0.25)	216 0.05 (0.22)	193 0.05 (0.26)
Albumin (g/dL) n Mean Change (SD)	177 0.09 (0.30)	58 0.06 (0.26)	48 0.04 (0.29)
Protein (g/dL) n Mean Change (SD)	185 0.02 (0.51)	216 0.04 (0.46)	193 0.00 (0.44)
Bicarbonate (mEq/L) n Mean Change (SD)	131 -0.3 (4.3)	46 0.3 (5.0)	40 -0.7 (3.3)
BUN (mg/dL) n Mean Change (SD)	185 0.06 (4.11)	216 -0.05 (4.03)	193 -0.24 (3.26)
Calcium (mg/dL)			

n	177	58	48
Mean Change (SD)	0.00 (0.48)	-0.19 (0.49)	-0.15 (0.51)
Chloride (mEq/L)			
n	186	216	193
Mean Change (SD)	1.4 (3.7)	-0.0 (3.0)	0.0 (3.1)
Creatinine (mg/dL)			
n	185	216	193
Mean Change (SD)	0.07 (0.15)	0.07 (0.12)	0.07 (0.10)
Phosphate (mg/dL)			
n	177	56	48
Mean Change (SD)	-0.04 (0.67)	-0.05 (0.57)	-0.02 (0.69)
Potassium (mEq/L)			
n	185	214	193
Mean Change (SD)	-0.08 (0.41)	0.03 (0.44)	0.03 (0.44)
Sodium (mEq/L)			
n	186	216	193
Mean Change (SD)	-0.3 (2.6)	-0.5 (2.4)	-0.7 (2.5)
CPK (U/L)			
n	185	215	193
Mean Change (SD)	-9.5 (390.2)	10.6 (158.6)	9.0 (188.1)
Median Change	13.0	3.0	-4.0
Prolactin (ng/ml)			
n	188	175	191
Mean Change (SD)	-1.1 (26.7)	-21.8 (44.5)	-15.7 (41.4)
<i>Males</i>			
n	115	105	123
Mean Change	-0.2 (14.2)	-9.0 (19.6)	-5.6 (22.2)
Median Change	-1.6	-5.2	-3.4
Range	-31, 111	-70, 65	-72, 127
<i>Females</i>			
n	73	70	68
Mean Change	-2.5 (39.0)	-41.0 (61.6)	-33.8 (58.8)
Median Change	-2.4	-14.9	-7.9
Range	-104, 143	-244, 22	-236, 67

Source: Table 126 (ISS), Table 7.1.1.5 (ISS)

Markedly Abnormal Post-Baseline Values

Phase 1 Studies

The definitions for markedly abnormal values are listed with the analyte in Table 88.

There was one case of increased amylase noted in narrative for a subject who discontinued due to AE in the Phase 1 studies. Interestingly, the patient was noted to have participated in protocol S01P13, a healthy volunteer study, but the narrative states that the patient had schizophrenia. This 21 YOAM (S01P13-00002) received lurasidone 20 mg for 3 days when an increase in amylase was noted. Baseline amylase was elevated at 177 IU/L (normal range: 32 – 12 IU/L), Day 1 = 317 IU/L, Day 3 = 268 IU/L (discontinued subject). The highest amylase noted was 473 IU/L on day 7, 4 days after discontinuation of lurasidone and

resolved by day 19. No clinical symptoms were noted in narrative. Pancreatic enzymes were not routinely evaluated in the clinical trials.

Phase 2/3 Studies

There was one other case of acute pancreatitis occurring in a patient (D1050049-0032-09002), however, lab values for the day this adverse event was noted were not in the CRF or narrative. Amylase and lipase obtained 4 days after the onset date of this adverse event were within normal limits.

The most significant finding for markedly abnormal chemistry labs were for prolactin, consistent with the mean change from baseline data for this analyte.

Table 88. Chemistry: Patients with Markedly Abnormal Post-Baseline Laboratory Values (P2/3STC)

	Lurasidone 20 mg (N = 71)	Lurasidone 40 mg (N = 360)	Lurasidone 80 mg (N = 282)	Lurasidone 120 mg (N = 291)	All Lurasidone (N = 1004)	Placebo (N = 455)
AST (≥ 3x ULN)	0/71	3/353 (0.8%)	3/270 (1.1%)	2/283 (0.7%)	8/977 0.8%	4/439 (0.9%)
ALT (≥ 3x ULN)	0/71	3/353 (0.8%)	3/270 (1.1%)	2/283 (0.7%)	8/977 (0.8%)	5/439 (1.1%)
Alkaline Phosp (≥ 3x ULN)	0/71	0/353	0/270	0/283	0/977	0/439
Bilirubin (≥ 2 mg/dL)	0/71	1/353 (0.3%)	2/270 (0.7%)	3/284 (1.1%)	6/978 (0.6%)	4/439 (0.9%)
Albumin (< 50% LLN)	0/71	0/344	0/270	0/275	0/960	0/430
BUN (≥ 30 mg/dL)	0/71	3/353 (0.8%)	0/270	2/283 (0.7%)	5/977 (0.5%)	4/439 (0.9%)
Calcium < 8.4 mg/dL	1/71 (1.4%)	4/353 (1.1%)	2/270 (0.7%)	1/283 (0.4%)	8/977 (0.8%)	2/439 (0.5%)
> 11.5 mg/dL	0/71	0/353	1/270 (0.4%)	1/283 (0.4%)	2/977 (0.2%)	0/439
Chloride < 90 mEq/L	0/71	1/353 (0.3%)	2/270 (0.7%)	1/283 (0.4%)	4/977 (0.4%)	1/439 (0.2%)
> 115 mEq/L	4/71 (5.6%)	1/353 (0.3%)	0/270	0/283	5/977 (0.5%)	1/439 (0.2%)
Creatinine (≥ 2 mg/dL)	0/71	0/353	0/270	0/283	0/977	1/439 (0.2%)
Potassium < 3 mEq/L	0/71	1/352 (0.3%)	0/270	0/283	1/976 (0.1%)	0/438
> 5.5 mEq/L	0/71	2/352 (0.6%)	5/270 (1.9%)	2/283 (0.7%)	9/976 (0.9%)	8/438 (1.8%)
Sodium < 130 mEq/L	1/71 (1.4%)	4/353 (1.1%)	2/270 (0.7%)	2/284 (0.7%)	9/978 (0.9%)	2/439 (0.5%)
> 150 mEq/L	5/71 (7.0%)	1/353 (0.3%)	0/270	0/284	6/978 (0.6%)	2/439 (0.5%)
LDH > 3x ULN	0/71	0/352	0/270	0/284	0/977	2/439 (0.5%)
CPK > 3x ULN	9/71 (12.7%)	35/353 (9.9%)	28/270 (10.4%)	27/284 (9.5%)	99/978 (10.1%)	46/439 (10.5%)

Prolactin > 5x ULN	2/70 (2.9%)	12/351 (3.4%)	9/259 (3.5%)	12/284 (4.2%)	35/964 (3.6%)	3/431 (0.7%)
Males	0/51	3/252 (1.2%)	5/181 (2.8%)	5/214 (2.3%)	13/6698 (1.9%)	2/329 (0.6%)
Females	2/19 (10.5%)	9/99 (9.1%)	4/78 (5.1%)	7/70 (10.0%)	22/266 (8.3%)	1/102 (1.0%)
C-Reactive Protein* > 0.79 mg/dL	ND	21/119 (17.6%)	ND	14/115 (12.2%)	35/234 (15.0%)	18/114 (15.8%)

Source: Table 7.1.4.3 (ISS), Table 7.1.4.3 (Amendment SD-30).

*C-reactive protein was collected in study D1050231 only (n = 234 for lurasidone groups, n = 114 for placebo group)

The Sponsor did not include an analysis of patient cases meeting criteria for Hy’s Law and was asked to provide this analysis. The definition for meeting criteria for Hy’s Law, according to the Guidance for Industry “Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009”, are:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo.
2. Among trial subjects showing such ALT/AST elevations, often with elevations much greater than 3x ULN, one or more subjects also show elevation of serum total bilirubin to > 2x ULN, without initial findings of cholestasis (elevated serum AP).
3. No other reason can be found to explain the combination of the increased ALT/AST and total bilirubin, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

Table 89 lists the the incidence of ALT/AST \geq 3x ULN (which was the MAPLV definition) across all studies.

Table 89. ALT/AST > 3x ULN Across Study Populations

	Lurasidone	Placebo	Ziprasidone	Haloperidol	Olanzapine	Risperidone
P1NON	0/302	1/73	-	-	-	-
P1SCH	0/278	0/16	-	-	-	-
P2/3STC	13/960 (1.4%)	6/430 (1.4%)	-	1/70 (1.4%)	10/122 (8.2%)	-
P2/3LTC	2/158 (1.3%)	-	-	-	-	0/67

Source: Amendment SD-23 to NDA

There was one patient (27 YOM, Asian; #0131-00007) who participated in D1050229 who discontinued from the extension phase of this study due to elevations in ALT/AST > 3x ULN and total bilirubin > 2x ULN. This patient had received lurasidone 120 mg/day in D1050229 and had completed that study. Increases in LFTs and total bilirubin were noted 44 days after beginning the open-label extension study (D1050229E). At visit 11 (44 days after beginning the

open-label extension), ALT = 1720 U/L, AST = 1444 U/L, total bilirubin = 7.7 mg/dL (the patient was discontinued from the study a few days after visit 11 labs were obtained). At visit 10 (the month prior), ALT, AST and total bilirubin had been within normal limits. This patient tested negative for Hepatitis B surface antigen and Hepatitis C antibody at the time of the event. Hepatitis A surface antigen or other markers of hepatic viral infection were not obtained. Based on the patient's clinical presentation (jaundice, decrease in appetite, generalized weakness, fever, chills, vomiting) and illness course, liver function test values, and the prevalence of infectious hepatitis in the region (Tirupati, India), the investigator reported this event as infectious hepatitis. According to the narrative, liver function tests normalized 3 months later.

[Of note, the original narrative for this case included in the NDA submission contained much lower ALT/AST values – in the 200s (see Section 3.1 of this review for more details). This reviewer did note that the laboratory data in the JMP file did contain the higher values submitted with the Hy's law analysis (> 1000 U/L). However, a review of the lab data for the P2/3ALL dataset (Table 7.1.1.5 ISS) had a maximum value for AST = 1105 U/L and ALT = 1491 U/L; both of which are lower than the reported values in this case. Therefore, it is unclear whether these data were included in the overall assessment of the effects of lurasidone on LFT parameters in the P2/3ALL dataset].

Prolactin

Per request, the Sponsor performed an additional analysis for mean change in prolactin from baseline to endpoint, but to include only those patients with baseline prolactin concentrations in the normal range. Overall, the increase in prolactin was slightly higher for those patients with normal baseline prolactin. The effects on prolactin for lurasidone 120 mg were similar, though slightly less, compared to haloperidol 10 mg.

Table 90. Prolactin: Mean Change from Baseline in Patients with Normal Prolactin at Baseline (P2/3STC)

	All Lurasidone (N = 1004)	Placebo (N = 455)	Haloperidol 10 mg (N = 72)	Olanzapine 15 mg (N = 122)
Prolactin, ng/ml (All) (n)	947	421	63	121
Mean Change (SD)	6.3 (29.2)	-2.7 (16.8)	19.0 (32.3)	4.2 (14.0)
Median Change	1.1	-0.5	8.5	3.7
<i>Males (n)</i>	688	322	52	94
Mean Change (SD)	3.3 (15.3)	-1.5 (10.7)	11.0 (12.1)	2.8 (8.6)
Median Change	1.0	-0.4	8.2	3.2
<i>Females (n)</i>	259	99	11	27
Mean Change (SD)	14.2 (49.2)	-6.6 (28.7)	56.5 (62.1)	9.1 (24.5)
Median Change	1.5	-1.4	27.6	8.5
Prolactin, ng/ml (Normal BL) (n)	795	348	52	96
Mean Change (SD)	8.9 (28.6)	0.6 (8.6)	16.7 (27.1)	6.7 (11.3)
Median Change	1.6	-0.1	8.5	4.4
<i>Males (n)</i>	583	272	43	75
Mean Change (SD)	4.9 (14.0)	0.2 (7.0)	11.7 (11.4)	4.8 (5.9)
Median Change	1.5	-0.2	8.4	3.7
<i>Females (n)</i>	212	76	9	21
Mean Change (SD)	19.8 (48.7)	1.7 (12.9)	40.5 (56.8)	13.6 (20.2)
Median Change	2.3	0.4	12.6	9.6

Source: Table 7.1.1.3 (ISS), Table 85 (ISS) and Table 1 Amendment SD-28 to NDA
 These data do not include the 27 patients from D1050006

Table 91. Prolactin: Mean (SD) and Median Change from Baseline in All Patients and Patients with Normal Prolactin at Baseline by Dose (P2/3STC)

	Lurasidone 20 mg (N = 71)	Lurasidone 40 mg (N = 360)	Lurasidone 80 mg (N = 282)	Lurasidone 120 mg (N = 291)
Prolactin, ng/ml (All) (n)	70	342	259	276
Mean Change (SD)	4.2 (26.2)	2.4 (25.7)	6.5 (31.1)	11.3 (31.5)
Median Change	-1.1	0.3	1.1	3.4
<i>Males (n)</i>	51	246	181	210
Mean Change (SD)	1.0 (13.6)	1.6 (13.4)	2.8 (16.3)	6.4 (16.5)
Median Change	-1.2	0.5	0.9	3.1
<i>Females (n)</i>	19	96	78	66
Mean Change (SD)	15.3 (44.0)	4.3 (43.7)	15 (50.2)	27.1 (54.7)
Median Change	-0.7	-0.8	2.0	7.1
Prolactin, ng/ml (Normal BL) (n)	60	286	216	233
Mean Change (SD)	4.5 (22.1)	5.9 (24.2)	9.8 (30.4)	12.9 (32.7)
Median Change	-0.9	0.7	2.0	3.4
<i>Males (n)</i>	43	207	152	181
Mean Change (SD)	2.1 (13.1)	3.9 (12.1)	4.2 (13.4)	7.5 (16.4)
Median Change	-1.1	0.9	1.4	3.1
<i>Females (n)</i>	17	79	64	52
Mean Change (SD)	10.6 (36.0)	11.2 (41.4)	23 (49.7)	31.7 (58.7)
Median Change	-0.7	0.2	5.6	7.9

Source: Table 7.1.1.3 (ISS), Table 85 (ISS) and Table 1 Amendment SD-28 to NDA

The Sponsor was also asked to provide a listing for all patients with prolactin concentrations meeting MAPLV (> 5x ULN) for the P2/3STC studies. In the P2/3STC studies, 34 lurasidone-treated patients had a prolactin elevation > 5x ULN on at least one occasion (Table 92). Sixty-two percent of the cases (21/34) occurred in female patients and 12 of those cases (12/21) occurred in African American females. Of the 34 cases, 22 patients had a maximum prolactin concentration \geq 100 and < 199 ng/ml, 5 patients had a maximum prolactin concentration \geq 200 and < 299 ng/ml and 2 patients had a maximum prolactin concentration > 300 ng/ml (315.7 and 393.3 ng/ml).

This reviewer asked for these data for a number of reasons. One is that the frequency of patients meeting criteria for MAPLV (> 5x ULN in this case) does not tell you how high the elevations were nor does it tell you the pattern of the elevation – was it one isolated elevation, a trend to increase over time, or an elevation with resolution.

However, upon review of these data, this reviewer questions the accuracy of the assay used in determining the prolactin concentrations. In general, prolactin concentrations are not subject to wide fluctuations without some intervening substance (such as drug effects). This reviewer focused on the P2/3STC data since these were fixed dose trials and would not introduce the confound of changing lurasidone dose on prolactin as might be encountered in the open-label/extension studies. However, some of the fluctuations in prolactin concentration are unusual (Table 93). The Sponsor was not asked to address this issue.

Table 92. Prolactin Concentrations > 5x ULN in Patients Receiving Lurasidone (P2/3STC)

Study	Patient Demographics	Lurasidone Dose	Prolactin (ng/ml)*		
			Baseline	End of Study	Maximum
D1050006	43 YOWF	40 mg	11.4	267.1 (D13)	267.1 (D13)
	43 YOWF	40 mg	11.7	8.6 (D9)	130.2 (D7)
	47 YOWM	120 mg	4.5	27 (D44)	96.7 (Wk D2)
	44 YOWM	120 mg	11.0	10.8 (D42)	97.7 (D7)
	32 YOBF	120 mg	44.3**	78.3 (D17)	250.4 (D7)
	40 YOBF	40 mg	15.4	103.8 (D11)	393.3 (D7)
	44 YOBF	40 mg	11.1	8.7 (D42)	98.1 (D14)
	40 YOBF	120 mg	9.5	315.7 (D42)	315.7
	44 YOWF	120 mg	22.3	73.6 (D42)	145.8 (D7)
D1050049	38 YOBF	80 mg	17.9	15.6 (D8)	132.1 (D4)
	57 YOWF	40 mg	9.0	198.5 (D15)	198.5
	47 YOBF	20 mg	24.5**	152.3 (D16)	152.3
	49 YOWF	20 mg	6.0	141.7 (D42)	141.7
	41 YOBF	40 mg	63.9**	107.0 (D42)	160 (D7)
	41 YOM	80 mg	3.0	7.6 (D42)	100.4 (D3)
	46 YOBF	80 mg	19.5**	103.3 (D42)	103.3
	47 YOBF	80 mg	7.8	104 (D13)	104

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	46 YOBF	40 mg	13.8	131 (D33)	131
D1050229	23 YOBF	120 mg	6.8	92.9 (D42)	145.4 (D14)
	44 YOBF	80 mg	3.3	170.3 (D42)	170.3
	45 YOBF	80 mg	3.3	170.3 (D42)	170.3
	45 YOWM	120 mg	4.3	138.1 (D10)	138.1
	49 YOBF	40 mg	2.2	107.8 (D40)	107.8
	54 YOBF	80 mg	10.8	285.8 (D42)	285.8
	49 YOBF	120 mg	8.4	170 (D42)	170
	30 YOWM	80 mg	2.9	1.9 (D42)	111.2 (D15)
	39 YOBF	120 mg	8.5	12 (D42)	97.8 (D6)
	30 YOAM	80 mg	57.3**	47.2 (D42)	97.1 (D8)
	40 YOAF	40 mg	19	3 (D42)	268 (D7)
	45 YOBF	80 mg	7	157.8 (D4)	157.8
D1050231	25 YOBF	40 mg	3.4	9.1 (D42)	101.3 (D16)
	38 YOBF	120 mg	69**	47.7 (D42)	187.8 (D8)
	49 YOBF	120 mg	4.2	224.1 (D12)	224.1
	25 YOAF	40 mg	4.2	13.3 (D15)	199.7 (D14)
	33 YOAF	40 mg	9.3	7.8 (D42)	146 (D7)

Source: Listing 16.7.1.1.8 Amendment SD-28 to NDA

*Reference ranges used: females 1.39 – 24.2 ng/ml and 2.8 – 29.2 ng/ml; Males 2.1 – 17.7 ng/ml and 1.61 – 18.77 ng/ml

**Elevated baseline

Table 93. Prolactin Fluctuations Noted in Patients with MAPLV (> 5x ULN).

	Prolactin Concentration (ng/ml)		
D1050006 0014-00086	Day 7 = 130.2	Day 9 = 8.6	
D1050006 0015-00113	Day 7 = 250.4	Day 11 = 12.2	Day 17 = 78.3
D1050006 0015-00115	Day 7 = 393.3	Day 11 = 103.9	
D1050049 0002-09001	Day 4 = 132.1	Day 8 = 15.6	
D1050049 0013-09007	Day 4 = 100.4	Day 7 = 5.8	
D1050229 0018-00002	Day 6 = 123.7	Day 13 = 13.3	
D1050229 0018-00019	Day 6 = 97.8	Day 13 = 0.9	

Source: Amendment SD-28 to NDA

Metabolic Parameters

Mean Change from Baseline

Phase 1 Studies

Fasting glucose and lipid parameters were not evaluated in the Phase 1 studies.

Phase 2/3 Studies

In the 6-week studies (P2/3STC), there was a mean increase in fasting glucose of 1.4 mg/dL in the lurasidone group compared to a 0.6 mg/dL increase in the placebo group. There was no obvious dose-relationship in the lurasidone group,

mean increases in fasting glucose were highest in the 40 mg group (2.9 mg/dL) and the 120 mg group (2.2 mg/dL) (Table 95). None of the lurasidone doses were statistically significantly different from placebo.

Table 94. Glucose (fasting), HbA1c, Lipids (fasting): Mean Change (SD) from Baseline to LOCF Endpoint (P2/3STC)

	All Lurasidone (N = 1004)	Placebo (N = 455)	Olanzapine 15 mg (N = 122)
Glucose (fasting), mg/dL	1.4 (23.6)*	0.6 (22.1)	9.0 (31.7)
HbA1c (%)	0.02 (0.32)*	-0.02 (0.36)	0.18 (0.57)
Insulin (mU/L)	-2.52 (27.9)	-2.46 (46)	5.94 (30.81)
Total Cholesterol (fasting), mg/dL	-8.5 (29.6)*	-9.3 (29.9)	9.0 (31.7)
LDL Cholesterol (fasting), mg/dL	-4.1 (22.3)*	-3.0 (25.1)	3.0 (25.9)
Triglycerides (fasting), mg/dL			
Mean Change (SD)	-14.8 (78.5)*	-19.4 (82.0)	55.8 (114.6)
Median Change	-8.0	-8.0	26
HDL, mg/dL	-0.9 (8.7)**	-2.4 (8.4)	-1.9 (9.3)

Source: Table 7.2.1.1 (ISS), Table 7.3.1.1 (ISS), Table 7.1.1.3 (ISS)

*Insulin was collected in study D1050231 only

* p < 0.05 vs. olanzapine, ** p < 0.05 vs. placebo

Table 95. Glucose (fasting), HbA1c, Lipids (fasting): Mean Change (SD) from Baseline to Endpoint (LOCF) *By Dose* (P2/3STC)

	Lurasidone 20 mg (N = 71)	Lurasidone 40 mg (N = 360)	Lurasidone 80 mg (N = 282)	Lurasidone 120 mg (N = 291)
Glucose (fasting) mg/dL	-1.9 (19.2)	2.9 (23.7)	-0.3 (26.9)	2.2 (20.2)
HbA1c (%)	-0.01 (0.29)	-0.01 (0.30)	0.04 (0.34)	0.05 (0.32)
Insulin (mU/L)*	ND	-3.18 (31.1)	ND	-1.83 (24.3)
Total Cholesterol (fasting), mg/dL	-11.4 (36.9)	-8.9 (30.2)	-9.9 (28.4)	-5.0 (27.1)
LDL Cholesterol (fasting), mg/dL	NA	-4.0 (23.1)	-4.7 (23.5)	-3.6 (20.4)
Triglycerides (fasting), mg/dL	-31.7 (108.1)	-12.8 (76.7)	-19.2 (76.3)	-5.2 (69.4)
HDL mg/dL	0	-0.6 (8.6)	-1.1 (8.4)	-0.9 (9.1)

Source: Table 7.1.1.3 (ISS), Table 7.2.1.1 (ISS), Table 7.3.1.1 (ISS)

*Insulin was collected in study D1050231 only

Table 96. Glucose (fasting): Mean Change (SD) from Baseline to LOCF Endpoint By Week (P2/3STC)

Glucose, fasting (mg/dL)	All Lurasidone (N = 1004)	Placebo (N = 455)	Olanzapine 15 mg (N = 122)
Baseline			
n	887	398	118
Mean (SD)	96.6 (23.9)	96.1 (24.3)	93.8 (16.8)
Week 2			
n	196	85	8
Mean Change (SD)	0.8 (19.0)*	-2.8 (22.5)	26.3 (61.3)
Week 4			
n	600	266	94
Mean Change (SD)	1.7 (19.9)**	-1.8 (19.2)	7.8 (26.1)
Week 6			
n	497	220	80
Mean Change (SD)	0.5 (23.2)*	-0.8 (22.7)	10.1 (34.4)

Source: Table 7.2.1.1 (ISS)

* p < 0.02 vs. olanzapine

** p < 0.02 vs. placebo, p = 0.006 vs. olanzapine

Table 97. Glucose (fasting): Mean Change (SD) from Baseline to LOCF Endpoint (LOCF) By Week, By Dose (P2/3STC)

Glucose fasting (mg/dL)	Lurasidone 20 mg (N = 71)	Lurasidone 40 mg (N = 360)	Lurasidone 80 mg (N = 282)	Lurasidone 120 mg (N = 291)
Week 2				
n	53	64	60	19
Mean Change (SD)	-3.2 (15.5)	0.5 (15.2)	4.2 (24.7)	1.6 (18.1)
Week 4				
n	37	218	185	160
Mean Change (SD)	-3.7 (17.1)	2.2 (19.8)	2.7 (23.7)	1.2 (15.0)
Week 6				
n	24	171	164	138
Mean Change (SD)	-3.5 (22.6)	3.5 (26.3)	-2.2 (23.7)	0.6 (17.6)

Source: Table 7.2.1.1 (ISS)

The mean change in fasting glucose by baseline glucose status is presented in Table 98. The mean change in fasting glucose in those patients with normal baseline glucose is difficult to interpret since there was a significant mean increase in fasting glucose in the placebo group for some unknown reason.

Table 98. Glucose (fasting): Mean Change (SD) from Baseline to LOCF Endpoint By Baseline Glucose (P2/3STC)

	All Lurasidone (N = 1004)	Placebo (N = 455)	Olanzapine 15 mg (N = 122)
Baseline Glucose Normal (< 100 mg/dL)	n = 656* 5.7 (17.2)	n = 298 6.3 (16.4)	n = 90 10 (23.9)
Baseline Glucose Impaired (100 – 125 mg/dL)	n = 187 -3.8 (20.2)	n = 81 -7.4 (17.3)	n = 22 12.1 (52)
Diabetic (> 126 mg/dL)	n = 61 -16 (59)	n = 26 -31.9 (48.3)	n = 6 7 (81.9)

Source: Table 7.2.2.1 (ISS)

*Sample sizes for baseline glucose status are the numbers of patients with glucose data available

There were not consistent, important changes in the mean change from baseline for metabolic parameters in the P2/3ALL database.

Table 99. Glucose and Lipids: Mean Change (SD) from Baseline to Weeks 24, 36 and 52 (P2/3ALL)

	All Lurasidone		
	Week 24	Week 36	Week 52
Glucose (fasting) mg/dL			
n	173	210	189
Mean Change	1.1 (19.7)	0.1 (15.5)	-0.6 (14.6)
HbA1c (%)			
n	149	212	184
Mean Change	-0.05 (0.47)	0.07 (0.31)	0.08 (0.30)
Insulin (mU/L)*			
n	38	20	17
Mean Change (SD)	-2.10 (13.4)	18.5 (48.6)	-5.7 (14.1)
Total Cholesterol (fasting)			
n	173	212	186
Mean Change	-5.3 (34.5)	-2.5 (29.1)	-6.7 (29.9)
LDL Cholesterol (fasting)			
n	123	53	43
Mean Change	1.7 (24.1)	-1.3 (33.0)	-1.7 (28.8)
Triglycerides (fasting)			
n	173	212	186
Mean Change	-15.1 (99.9)	-0.3 (104.7)	-7.4 (75.3)
HDL (fasting)			
n	123	54	43
Mean Change	-0.5 (9.2)	1.6 (11.3)	1.6 (11.5)

Source: Table 127 (ISS)

*Insulin data collected only in studies D1050231 and D1050237

Shift Data

There were no differences in the fasting glucose shift data between lurasidone and placebo (or between lurasidone and olanzapine). Shift changes in lipid parameters in the lurasidone group were similar or less than those in the placebo group. There were no dose-related shift changes in lipid parameters (data not shown).

Table 100. Glucose (fasting) Shift Data (P2/3STC)

	All Lurasidone			Placebo			Olanzapine 15 mg		
	N	n	(%)	N	n	(%)	N	n	(%)
Increase by ≥ 10 mg/dL									
Any Baseline	841	322	38.3%	379	136	35.9%	113	55	48.7%
Normal Baseline	583	257	43.3%	272	109	40.1%	85	44	51.8%
Impaired Baseline	187	46	24.6%	81	20	24.7%	22	9	40.9%
Post Baseline ≥ 140	853	72	8.4%	383	19	5.0%	115	13	11.3%
Post Baseline ≥ 200	853	15	1.8%	383	4	1.0%	115	4	3.5%
Post Baseline ≥ 300	853	4	0.5%	383	1	0.3%	115	1	0.9%
Normal to High (< 100 to > 126 mg/dL)	593	36	6.1%	272	10	3.7%	85	7	8.2%
Impaired to High (≥ 100 and < 126 to ≥ 126 mg/dL)	187	26	13.9%	81	10	12.3%	22	7	31.8%
Normal/Impaired to High (< 126 to ≥ 126 mg/dL)	780	62	7.9%	353	20	5.7%	107	14	13.1%

Source: Table 7.2.4.1 (ISS)

There were no differences in HbA1c shifts to $\geq 6.1\%$ between the lurasidone and placebo groups. There was a suggestion of a dose-related shift in HbA1c $> 6.1\%$: lurasidone 20 mg 6.5%, 40 mg 8.2%, 80 mg 9.3%, and 120 mg 5.9%, though none statistically different from the shift in the placebo group (5.0%). No patients in the placebo or lurasidone groups had shifts $\geq 8.0\%$.

Table 101. HbA1c, Shift to $\geq 6.1\%$ (P2/3STC)

	All Lurasidone			Placebo			Olanzapine 15 mg		
	N	n	(%)	N	n	(%)	N	n	(%)
Normal to $> 6.1\%$ (< 6.1 to ≥ 6.1)	659	51	7.7%	302	15	5.0%	90	7	7.8%

Source: Table 7.3.3.1 (ISS)

Table 102. Cholesterol (fasting) Shift Changes (P2/3STC)

	All Lurasidone			Placebo			Olanzapine 15 mg		
	N	n	(%)	N	n	(%)	N	n	(%)
Increase by \geq 40 mg/dL	764	50	6.5%*	346	24	6.9%	105	14	13.3%
Normal to High ($<$ 200 to \geq 240 mg/dL)	443	4	0.9%*	195	3	1.5%	58	2	3.4%
Borderline to High (\geq 200 and $<$ 240 to \geq 240)	207	36	17.4%	100	16	16%	32	7	21.9%
Normal/Borderline to High ($<$ 240 to \geq 240)	650	40	6.2%	295	19	6.4%	90	9	10%
Normal to Borderline/High ($<$ 200 to \geq 200)	443	71	16%	195	31	15.9%	58	15	25.9%

Source: Table 7.3.3.1 (ISS)

*p < 0.05 vs. olanzapine

Table 103. LDL (fasting) Shift Changes (P2/3STC)

	All Lurasidone			Placebo			Olanzapine 15 mg		
	N	n	(%)	N	n	(%)	N	n	(%)
Increase by \geq 30 mg/dL	555	40	7.2%	270	28	10.4%	105	12	11.4%
Normal to High ($<$ 100 to \geq 160 mg/dL)	213	0	0	106	1	0.9%	39	0	0
Borderline to High (\geq 100 and $<$ 160 to \geq 160)	293	19	6.5%	139	12	8.6%	52	4	7.7%
Normal/Borderline to High ($<$ 160 to \geq 160)	506	19	3.8%	245	13	5.3%	91	4	4.4%
Normal to Borderline/High ($<$ 100 to \geq 100)	213	46	21.6%	106	29	27.4%	39	14	35.9%

Source: Table 7.3.3.1 (ISS)

Table 104. Triglycerides (fasting) Shift Changes (P2/3STC)

	All Lurasidone			Placebo			Olanzapine 15 mg		
	N	n	(%)	N	n	(%)	N	n	(%)
Increase to $>$ 500 mg/dL	750	9	1.2%	340	2	0.6%	105	4	3.8%
Increase to $>$ 1000 mg/dL	764	0	0	346	0	0	105	1	1.0%
Normal to High ($<$ 150 to \geq 200 mg/dL)	472	15	3.2%*	222	12	5.4%	76	14	18.4%
Normal to Very High ($<$ 150 to \geq 500)	472	1	0.2%	222	1	0.5%	76	0	0
Borderline to High (\geq 150 and $<$ 200 to \geq 200)	126	35	27.8%	50	12	24.0%	17	7	41.2%
Borderline to Very High (\geq 150 and $<$ 200 to \geq 500)	126	2	1.6%	50	0	0	17	0	0
Normal/Borderline to High ($<$ 200 to \geq 200)	598	50	8.4%*	272	24	8.8%	93	21	22.6%
Normal/Borderline to Very High ($<$ 200 to \geq 500)	598	3	0.5%	272	1	0.4%	93	0	0
Normal to Borderline/High/Very High ($<$ 150 to \geq 150)	472	69	14.6%*	222	36	16.2%	76	29	38.2%

Source: Table 7.3.3.1 (ISS)

*p < 0.001 vs. olanzapine

Table 105. HDL (fasting) Shifts to < 40 mg/dL (P2/3STC)

	All Lurasidone			Placebo			Olanzapine 15 mg		
	N	n	(%)	N	n	(%)	N	n	(%)
Normal to Low (> 40 to < 40)	397	40	10.1%*	202	29	14.4%	78	17	21.8%

Source: Table 7.3.3.1 (ISS)

*p < 0.007 vs. olanzapine

The increase in mean change in fasting glucose noted in P2/3STC did not appear to increase with duration of therapy in the P2/3ALL database. The data from D1050237 show greater mean increases in fasting glucose at weeks 36 and 52, but these are based on data from very few patients. The LOCF endpoint data was consistent between P2/3ALL and D1050237.

Table 106. Glucose (fasting): Mean Change (SD) from Baseline to LOCF Endpoint (P2/3ALL)

	Lurasidone (N = 2094)
Baseline n Mean (SD)	1842 94.1 (20.8)
Week 2 n Mean Change (SD)	694 0.3 (15.8)
Week 4 n Mean Change (SD)	1026 1.0 (17.9)
Week 6 n Mean Change (SD)	656 1.0 (23.9)
Week 8 n Mean Change (SD)	524 -0.2 (15.9)
Week 12 n Mean Change (SD)	561 0.2 (16.4)
Week 24 n Mean Change (SD)	173 1.1 (19.7)
Week 36 n Mean Change (SD)	210 0.1 (15.5)
Week 52 n Mean Change (SD)	189 -0.6 (14.6)
Endpoint (LOCF) n Mean Change (SD)	1624 1.6 (22.6)

Source: Table 7.2.1.3 (ISS)

Table 107. Glucose (fasting): Mean Change (SD) from Baseline to Endpoint (Study D1050237)

	Lurasidone (N = 190)	Risperidone (N = 85)
Baseline		
n	180	75
Mean (SD)	93.4 (14.3)	94.8 (28.9)
Week 12		
n	59	25
Mean Change (SD)	0.3 (12.9)	3.3 (17.2)
Week 24		
n	29	15
Mean Change (SD)	-1.9	4.5 (12.7)
Week 36		
n	15	11
Mean Change (SD)	5.6 (20.7)	4.1 (12.3)
Week 52		
n	16	9
Mean Change (SD)	3.8 (12.2)	12.8 (24.3)
Endpoint (LOCF)		
n	108	46
Mean Change (SD)	1.1 (16.0)	4.1 (23.4)

Source: Table 7.2.1.2 (ISS)

There were no notable changes in urinalysis data for the lurasidone group.

Table 108. Urinalysis: Values at Baseline and LOCF Endpoint (P2/3STC)

	All Lurasidone (N = 1004)		Placebo (N = 455)		Olanzapine 15 mg (N = 122)	
	Baseline	Endpoint	Baseline	Endpoint	Baseline	Endpoint
pH mean	6.04	6.01	6.07	.0	6.22	6.19
Specific gravity mean	1.0187	1.0185	1.0184	1.0199	1.0176	1.0165
Ketones abnormal	12/983 (1.2%)	17/957 (1.8%)	3/444 (0.7%)	18/429* (4.2%)	3/122 (2.5%)	3/121 (2.5%)
Urobilinogen abnormal	0/982	0/957	1/444 (0.2%)	3/428 (0.7%)	0/122	0/121
Bilirubin abnormal	5/983 (0.5%)	2/959 (0.2%)	1/444 (0.2%)	7/429 (1.6%)	0/122	0/121
Blood abnormal	71/969 (7.3%)	65/954 (6.8%)	25/443 (5.6%)	23/427 (5.4%)	15/122 (12.3%)	8/121 (6.6%)
Leukocyte esterase abnormal	61/693 (8.8%)	59/676 (8.7%)	29/331 (8.8%)	34/320 (10.6%)	10/122 (8.2%)	10/121 (8.3%)
Nitrite abnormal	38/979 (3.9%)	40/959 (4.2%)	13/443 (2.9%)	20/429 (4.7%)	8/122 (6.6%)	7/121 (5.8%)
Protein	52/980	57/953	25/442	34/427	10/122	9/121

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abnormal	(5.3%)	(6.0%)	(5.7%)	(8.0%)	(8.2%)	(7.4%)
Glucose	10/980	14/953	5/444	4/427	0/122	3/121
abnormal	(1.0%)	(1.5%)	(1.1%)	(0.9%)		(2.5%)
RBC	26/252	35/286	5/93	17/119	7/50	4/48
abnormal	(10.3%)	(12.2%)	(5.4%)	(14.3%)	(14.0%)	(8.3%)
WBC	63/268	51/292	30/107	20/124	11/50	10/48
abnormal	(23.5%)	(17.5%)	(28.0%)	(16.1%)	(22.0%)	(20.8%)

Source: Table 7.5.1.3 (ISS)

*Sponsor indicated that all were trace to +1 ketones, 2 occurred in association with 3+ glucosuria suggesting the presence of early ketoacidosis. In all but one instance, the high ketones were associated with a urine specific gravity > 1.020; in 5 cases, the urine specific gravity was > 1.030 suggesting presence of dehydration.

Hematology

Mean Change from Baseline

Phase 1 Studies

Healthy Volunteers (P1NON)

There were no significant changes in RBC or WBC indices.

Schizophrenia (P1SCH)

A mean increase in platelets was evident in both lurasidone groups compared to placebo, this was not consistent with P2/3STC data.

Table 109. Hematology: Mean Change (SD) from Baseline to LOCF Endpoint (P1SCH)

	Lurasidone 120 mg (N = 162)	Lurasidone > 120 mg (N = 96)	Placebo (N = 16)
RBC (x10E6/ μ L)	-0.20 (0.29)	-0.24 (0.29)	-0.40 (0.31)
Hemoglobin (g/dL)	-0.49 (0.84)	-0.48 (0.80)	-1.08 (0.87)
Hematocrit (%)	-1.35 (2.62)	-1.47 (2.59)	-3.27 (2.58)
Platelet (x10E3/ μ L)	7.0 (39.1)	4.2 (25.2)	-4.8 (35.6)
MCV (fL)	0.19 (1.17)	-0.05 (1.52)	0.37 (1.43)
MCHC (g/dL)	-0.13 (0.51)	0.35 (0.69)	0.07 (0.58)
WBC (x10E3/ μ L)	0.51 (1.63)	0.17 (1.40)	-0.46 (1.54)
Neutrophils (%)	-0.40 (8.08)	-0.43 (10.57)	-3.41 (9.84)
Monocytes (%)	0.16 (2.06)	-0.28 (2.49)	-0.28 (1.83)
Lymphocytes (%)	0.36 (6.57)	0.17 (8.60)	3.82 (7.73)
Eosinophils (%)	-0.06 (2.71)	-0.03 (1.56)	-0.01 (2.49)
Basophils (%)	-0.08 (0.60)	-0.03 (0.42)	-0.12 (0.34)

Source: Table 22, Table 23 (ISS)

There were no notable changes in hematology parameters.

Table 110. Hematology: Mean Change (SD) from Baseline to LOCF Endpoint (P2/3STC)

	All Lurasidone (N = 1004)	Placebo (N = 455)	Olanzapine 15 mg (N = 122)
RBC (x10E6/ μ L)	-0.04 (0.29)	-0.01 (0.28)	-0.17 (0.27)
Hemoglobin (g/dL)	-0.11 (0.85)	-0.03 (0.79)	-0.49 (0.79)
Hematocrit (%)	-0.58 (2.81)	-0.32 (2.59)	-1.56 (2.41)
Platelet (x10E3/ μ L)	-1.1 (49.3)	-0.2 (43.3)	-14.4 (44.2)
MCV (fL)	-0.57 (2.25)	-0.60 (2.0)	-0.18 (1.81)
MCHC (g/dL)	0.25 (0.94)	0.20 (0.86)	0.06 (0.77)
WBC (x10E3/ μ L)	0.01 (1.86)	-0.15 (1.68)	-0.05 (1.90)
Neutrophils (%)	0.20 (8.72)	1.04 (10.38)	-0.04 (10.36)
Monocytes (%)	-0.00 (2.16)	0.01 (3.13)	0.35 (2.55)
Lymphocytes (%)	-0.14 (7.40)	-0.61 (8.57)	-0.95 (7.84)
Eosinophils (%)	-0.08 (2.11)	-0.39 (1.93)	0.46 (3.27)
Basophils (%)	-0.00 (0.51)	-0.03 (0.48)	0.06 (0.52)

Source: Table 87 (ISS), Table 88 (ISS)

Markedly Abnormal Post-Baseline Values

Table 111. Hematology: Markedly Abnormal Post-Baseline Lab Values (P2/3STC)

	All Lurasidone (N = 1004)	Placebo (N = 455)	Olanzapine 15 mg (N = 122)
Low WBC ($\leq 2.8 \times 10^3 / \mu\text{L}$)	5/959 (0.5%)	2/429 (0.5%)	2/121 (1.7%)
High WBC ($\geq 16 \times 10^3 / \mu\text{L}$)	16/959 (1.7%)	3/429 (0.7%)	4/121 (3.3%)
Low Hematocrit			
Male ($\leq 37\%$)	27/697 (3.9%)	4/329 (1.2%)	3/94 (3.2%)
Female ($\leq 32\%$)	4/262 (1.5%)	4/98 (4.1%)	3/27 (11.1%)
Low Hemoglobin			
Male ($\leq 11.5 \text{ g/dL}$)	10/697 (1.4%)	0/330	1/94 (1.1%)
Female ($\leq 9.5 \text{ g/dL}$)	1/262 (0.4%)	4/99 (4.0%)	2/27 (7.4%)
High Platelets ($\geq 700 \times 10^3 / \mu\text{L}$)*	2/958 (0.2%)	1/426 (0.2%)	0/120
High Eosinophils ($\geq 10\%$)	42/881 (4.8%)	14/389 (3.6%)	12/121 (9.9%)

Source: Table 90 (ISS)

*No patients had markedly abnormal low platelets ($\leq 75 \times 10^3 / \mu\text{L}$)

7.4.3 Vital Signs

Mean Change from Baseline

Phase 1 Studies

The Sponsor did not include mean change from baseline vital signs data for Phase 1 studies in the ISS. Included were the markedly abnormal values as indicated in that respective section.

Phase 2/3 Studies

Mean change from baseline for vital signs was not remarkable. Standing pulse increased by 1.3 bpm in the lurasidone group and 2.6 bpm in the placebo group. Standing SBP decreased by 0.1 mmHg in the lurasidone group and increased by 1.0 mm Hg in the placebo group. However, there were differences when mean change in vital signs was evaluated by lurasidone dose. There was a dose related increase in sitting pulse (-1.1 bpm 20 mg, 1.4 bpm 120 mg) and standing pulse (0.7 bpm 40 mg, 2.1 bpm 120 mg). There was a dose related decrease in sitting SBP (2.2 mm Hg 20 mg, -1.3 mm Hg 120 mg). A decrease in standing SBP was noted only in the lurasidone 120 mg group (-0.7 mm Hg).

Table 112. Vital Signs: Mean Change (SD) from Baseline to LOCF Endpoint (P2/3STC)

	All Lurasidone (N = 1004)	Placebo (N = 455)	Olanzapine 15 mg (N = 122)
Pulse, sitting (bpm)	0.4 (12.1)	0.5 (13.2)	4.3 (13.3)
Pulse, standing (bpm)	1.3 (13.2)	2.6 (12.4)	4.6 (12.1)
Pulse, supine (bpm)	0.4 (12.5)	-0.5 (12.6)	NA
SBP, sitting (mmHg)	0.2 (12.5)	0.6 (12.7)	1.6 (12.3)
SBP, standing (mmHg)	-0.1 (11.3)	1.0 (11.2)	3.2 (14.6)
SBP, supine (mmHg)	1.3 (14.8)	-0.4 (13.0)	NA
DBP, sitting (mmHg)	0.2 (9.3)	0.8 (9.5)	1.2 (9.7)
DBP, standing (mmHg)	0.5 (8.5)	0.9 (9.3)	1.3 (10.6)
DBP, supine (mmHg)	0.9 (10.6)	0.1 (10.1)	NA
Body temperature (°C)	0.02 (0.44)	0.06 (0.42)	-0.09 (0.48)

Source: Table 9.1.1.1 (ISS)

Table 113. Vital Signs: Mean Change (SD) from Baseline to LOCF Endpoint By Dose (P2/3STC)

	Lurasidone 20 mg (N = 71)	Lurasidone 40 mg (N = 360)	Lurasidone 80 mg (N = 282)	Lurasidone 120 mg (N = 291)
Pulse, sitting (bpm)	-1.1 (10.5)	-0.0 (12.4)	0.3 (11.8)	1.4 (12.3)
Pulse, standing (bpm)	NA	0.7 (13.2)	0.8 (13.6)	2.1 (12.8)
Pulse, supine (bpm)	-0.7 (9.4)	0.6 (13.3)	1.3 (13.4)	-1.7 (11.3)*
SBP, sitting (mmHg)	2.2 (13.5)	0.8 (12.1)	0.3 (12.9)	-1.3 (12.4)
SBP, standing (mmHg)	NA	0.0 (11.1)	0.4 (11.3)	-0.7 (11.6)
SBP, supine (mmHg)	2.9 (14.3)	-0.2 (14.4)	2.4 (15.1)	-0.7 (15.0)*
DBP, sitting (mmHg)	0.1 (10.1)	0.3 (9.3)	0.4 (9.7)	-0.1 (8.8)
DBP, standing (mmHg)	NA	1.1 (8.0)	0.3 (9.1)	0.1 (8.4)
DBP, supine (mmHg)	-0.9 (9.8)	1.2 (10.8)	2.2 (10.3)	-1.7 (11.8)*

Source: Table 9.1.1.1 (ISS)

*supine pulse, supine SBP and supine DBP only available for 49/291 (17%) patients due to differences in protocol designs

Markedly Abnormal Post-Baseline Values

The definitions for markedly abnormal post-baseline values are in the footnotes for the tables.

Phase 1 Studies

Healthy volunteers (P1NON)

The most notable changes were: standing pulse high which included 17.1% lurasidone \leq 30 mg, 0 lurasidone 40 mg, 16% lurasidone 60-100 mg and 0 for the placebo group; standing SBP low 22% lurasidone < 30 mg, 0 in lurasidone 40 mg and 60-100 mg and 3.2% placebo and standing DBP low 34% lurasidone < 30 mg, 0 in lurasidone 40 mg and 60-100 mg and 9.7% placebo.

Schizophrenia (P1SCH)

Vital signs were assessed in sitting and/or supine positions only.

Table 114. Vital Signs: Markedly Abnormal* Post-Baseline Assessments (P1SCH)

	Lurasidone 120 mg (N = 162)	Lurasidone > 120 mg (N = 96)	Placebo (N = 16)
Pulse, sitting (bpm)			
Low	0/8	0/66	0/16
High	0/8	1/66 (1.5%)	0/16
Pulse, supine (bpm)			
Low	2/109 (1.8%)	0/15	ND
High	0/109	0/15	ND
SBP, sitting (mmHg)			
Low	0/8	0/66	0/16
High	0/8	0/66	0/16
SBP, supine (mmHg)			
Low	5/138 (3.6%)	1/44 (2.3%)	ND
High	0/138	0/44	ND
DBP, sitting (mmHg)			
Low	1/8 (12.5%)	4/66 (6.1%)	0/16
High	0/8	0/66	0/16
DBP, supine (mmHg)			
Low	8/138 (5.8%)	1/44 (2.3%)	ND
High	1/138 (0.7%)	0/44	ND

Source: Table 27 (ISS), Table 9.2.1.2 (ISS)

* Pulse: Low \leq 50 and \geq 15 bpm decrease from baseline; High \geq 120 and \geq 15 bpm increase from baseline
 SBP: Low \leq 90 and \geq 20 mmHg decrease from baseline; High \geq 180 and \geq 20 mmHg increase from baseline
 DBP: Low \leq 50 and \geq 15 mmHg decrease from baseline; High \geq 105 and \geq 15 mmHg increase from baseline
 ND = not done

The only potential dose-related signal in the markedly abnormal post-baseline assessments was in the low standing SBP category: 0.4% (40 mg), 2.4% (80 mg), 4.1% (120 mg).

Table 115. Vital Signs: Markedly Abnormal* Post-Baseline Assessments (P2/3STC)

	All Lurasidone (N = 1004)	Placebo (N = 455)	Olanzapine 15 mg (N = 122)
Pulse, sitting (bpm)			
Low	5/907 (0.6%)	2/360 (0.6%)	1/122 (0.8%)
High	8/907 (0.9%)	3/360 (0.8%)	1/122 (0.8%)
Pulse, standing (bpm)			
Low	3/690 (0.4%)	0/329	0/122
High	27/690 (3.9%)	8/329 (2.4%)	4/122 (3.3%)
Pulse, supine (bpm)			
Low	2/396 (0.5%)	2/211 (0.9%)	NA
High	5/396 (1.3%)	0/211	
SBP, sitting (mmHg)			
Low	19/907 (2.1%)	5/360 (1.4%)	2/122 (1.6%)
High	1/907 (0.1%)	2/360 (0.6%)	0/122
SBP, standing (mmHg)			
Low	16/690 (2.3%)	8/329 (2.4%)	1/122 (0.8%)
High	0/690	2/329 (0.6%)	0/122
SBP, supine (mmHg)			
Low	5/396 (2.3%)	7/211 (3.3%)	NA
High	3/396 (0.8%)	3/211 (1.4%)	
DBP, sitting (mmHg)			
Low	8/907 (0.9%)	4/360 (1.1%)	0/122
High	6/907 (0.7%)	3/360 (0.8%)	2/122 (1.6%)
DBP, standing (mmHg)			
Low	3/690 (0.4%)	2/329 (0.6%)	1/122 (0.8%)
High	8/690 (1.2%)	7/329 (2.1%)	4/122 (3.3%)
DBP, supine (mmHg)			
Low	3/396 (0.8%)	2/211 (0.9%)	NA
High	5/396 (1.3%)	2/211 (0.9%)	

Source: Table 102 (ISS)

* Pulse: Low ≤ 50 and ≥ 15 bpm decrease from baseline; High ≥ 120 and ≥ 15 bpm increase from baseline

SBP: Low ≤ 90 and ≥ 20 mmHg decrease from baseline; High ≥ 180 and ≥ 20 mmHg increase from baseline

DBP: Low ≤ 50 and ≥ 15 mmHg decrease from baseline; High ≥ 105 and ≥ 15 mmHg increase from baseline

The Sponsor did not submit data for orthostatic hypotension by vital sign assessment, though these measurements were taken in some of the clinical trials. Upon request, the Sponsor submitted these data for studies D1050196, D1050229 and D1050231 since those included vital sign assessments in standing positions (Table 116). Orthostatic hypotension was defined as: ≥ 20 mmHg decrease in SBP (sitting to standing or supine to standing) and ≥ 10 bpm increase in pulse. Studies D1050229 and D1050231 obtained vital signs in the sitting position for 5 minutes, standing for 1 minute and standing for 3 minutes. Study D1050196 obtained vital signs in the supine position for 5 minutes and after standing for 1 minute. The Sponsor did not specify whether they included the 1 minute or 3 minute standing vital signs from Studies D1050229 and D1050231. Data were provided in a pooled analysis only for all three studies.

Lurasidone does appear to have a higher incidence of orthostatic hypotension as defined by vital sign changes, 1.3%, compared to placebo, 0.9%. There also appears to be a relationship of orthostatic hypotension and lurasidone dose; the 40 mg dose is similar to placebo, and the 80 mg and 120 mg doses are associated with greater frequency of orthostatic hypotension with 1.4% and 1.7% of patients exhibiting these vital sign changes. The Sponsor noted that this trend by dose assignment was also noted at baseline, though it is unknown what prior medications these patients were on that may have impacted any baseline assessments.

Table 116. Orthostatic Hypotension by Visit and LOCF Endpoint (P2/3STC)

	Lurasidone 40 mg (N = 243)	Lurasidone 80 mg (N = 211)	Lurasidone 120 mg (N = 242)	All Lurasidone (N = 696)	Placebo (N = 333)	Olanzapine 15 mg (N = 122)
Baseline	2/243 (0.8%)	3/211 (1.4%)	6/241 (2.5%)	11/695 (1.6%)	7/333 (2.1%)	2/122 (1.6%)
Week 2	4/219 (1.8%)	3/175 (1.7%)	3/207 (1.4%)	10/601 (1.7%)	2/297 (0.7%)	2/115 (1.7%)
Week 4	5/203 (2.5%)	1/156 (0.6%)	3/181 (1.7%)	9/540 (1.7%)	2/258 (0.8%)	1/106 (0.9%)
Week 6	1/166 (0.6%)	1/141 (0.7%)	2/155 (1.3%)	4/462 (0.9%)	3/198 (1.5%)	1/89 (1.1%)
LOCF	2/240 (0.8%)	3/208 (1.4%)	4/242 (1.7%)	9/690 (1.3%)	3/329 (0.9%)	1/122 (0.8%)

Source: Table 4 in Amendment SD-28 to NDA

Weight

Phase 1 Studies

The Sponsor did not provide mean change from baseline in weight for the Phase 1 studies.

Phase 2/3 Studies

In the 6-week studies, lurasidone was associated with a 0.75 kg mean increase in weight compared to a 0.26 kg mean increase in the placebo group, this was significantly different.

Table 117. Weight (kg): Mean Change (SD) from Baseline to Endpoint (P2/3STC)

Weight (kg)	All Lurasidone (N = 1004)	Placebo (N = 455)	Olanzapine 15 mg (N = 122)	P-value
Week 2 n Mean Change (SD)	824 0.39 (1.89)	385 0.34 (1.91)	115 2.17 (2.37)	Lur vs. PC = NS Lur vs. Olanz p < 0.001
Week 4 n Mean Change (SD)	725 0.99 (2.88)	331 0.36 (2.75)	106 4.05 (3.90)	Lur vs. PC p < 0.001 Lur vs. Olanz p < 0.001
Week 6 n Mean Change (SD)	587 1.11 (3.17)	250 0.40 (3.25)	89 4.64 (4.47)	Lur vs. PC p = 0.004 Lur vs. Olanz p < 0.001
Change to LOCF Endpoint n Mean Change (SD)	999 0.75 (2.94)	450 0.26 (2.81)	122 4.15 (4.26)	Lur vs. PC p = 0.003 Lur vs. Olanz p < 0.001

Source: Table 105 (ISS)
 NS = not significant, p > 0.05

There did not appear to be a robust dose-related increase in weight for lurasidone, mean change from baseline to LOCF endpoint was -0.15 kg for the 20 mg dose, 0.67 kg for the 40 mg dose, 1.14 kg for the 80 mg dose and 0.68 kg for the 120 mg dose. A similar pattern was observed with the change from baseline to week 6 (observed cases).

Table 118. Weight (kg): Categorical Change from Baseline (P2/3STC)

Weight Change (kg)	All Lurasidone (N = 1004)	Placebo (N = 455)	Olanzapine (N = 122)
Change from Baseline			
LOCF Endpoint (n)	999	450	122
Weight Increase (kg)			
0 to 5 kg	613 (61.4%)	252 (56%)	69 (56.6%)
> 5 to 10 kg	58 (5.8%)	19 (4.2%)	26 (21.3%)
> 10 to 15 kg	2 (0.2%)	1 (0.2%)	12 (9.8%)
> 15 to 20 kg	1 (0.1%)	0	2 (1.6%)
> 20 to 25 kg	0	0	0
> 25 to 30 kg	1 (0.1%)	0	0
> 30 kg	0	0	0
≥ 7% Increase	56 (5.6%)	18 (4%)	42 (34.4%)
Weight Decrease (kg)	324 (32.4%)	178 (39.6%)	13 (10.7%)
> 7% Decrease	11 (1.1%)	9 (2%)	0

Source: Table 107 (ISS), Table 9.3.2.1 (ISS)

Similar to mean weight increase, there was no robust association of weight increase by ≥ 7% and lurasidone dose: 1.4% at 20 mg, 5.9% at 40 mg, 6.8% at 80 mg and 5.2% at 120 mg.

Table 119. Weight (kg): Mean Change from Baseline to Endpoint by Baseline Body Mass Index (P2/3STC)

BMI Category (kg/m ²)		All Lurasidone (N = 1004)	Placebo (N = 455)	Olanzapine (N = 122)
BMI < 18.5 (Underweight)	n	14	5	2
	Mean (SD) Change	0.46 (1.77)	1.08 (2.68)	3.27 (0.38)
	p-value (vs. PC)	NS		
	p-value (vs. OLZ)	NS		
18.5 - < 25 (Normal weight)	n	410	159	62
	Mean (SD) Change	0.81 (2.39)	0.44 (2.31)	3.19 (3.81)
	p-value (vs. PC)	NS		
	p-value (vs. OLZ)	p < 0.001		
25 - < 30 (Overweight)	n	255	135	27
	Mean (SD) Change	0.78 (3.09)	0.49 (2.80)	6.25 (4.97)
	p-value (vs. PC)	NS		
	p-value (vs. OLZ)	p < 0.001		
≥ 30 (Obese)	n	320	151	31
	Mean (SD) Change	0.64 (3.46)	-0.15 (3.24)	4.28 (4.04)
	p-value (vs. PC)	p = 0.014		
	p-value (vs. OLZ)	p < 0.001		

Source: Table 9.3.4.1 (ISS)

Longterm Data (P2/3ALL subset with > 24 weeks exposure)

The mean change in weight from baseline for patients receiving lurasidone was -0.60 (5.21) kg at week 24 [n = 480], -0.47 (6.12) kg at week 36 [n = 277] and -1.05 (6.23) kg at week 52 [n = 192].

At weeks 24, 36 and 52, more patients had a ≥ 7% weight decrease than a ≥ 7% increase:

Table 120. Categorical Weight Change at Weeks 24, 36 and 52 (P2/3ALL)

	All Lurasidone (N = 2094)		
	Week 24	Week 36	Week 52
n	480	277	192
Weight Decrease (kg)	244 (50.8%)	135 (48.7%)	105 (54.7%)
Weight Increase (kg)	236 (49.2%)	142 (51.3%)	87 (45.3%)
0 to 5 kg	184 (38.3%)	105 (37.9%)	60 (31.3%)
> 5 to 10 kg	41 (8.5%)	29 (10.5%)	22 (11.5%)
> 10 to 15 kg	9 (1.9%)	6 (2.2%)	4 (2.1%)
> 15 to 20 kg	2 (0.4%)	1 (0.4%)	1 (0.5%)
> 20 to 25 kg	0	0	0
> 25 to 30 kg	0	0	0
> 30 kg	0	1 (0.4%)	0
≥ 7% Increase	57 (11.9%)	41 (14.8%)	34 (17.7%)
Weight Decrease (kg)			
> 7% Decrease	77 (16.0%)	58 (20.9%)	48 (25.0%)

Source: Table 9.3.2.3 (ISS)

Table 121. Weight (kg): Mean Change from Baseline to Weeks 24, 36 and 52 by Baseline Body Mass Index (P2/3ALL)

BMI Category (kg/m ²)		Lurasidone		
		Week 24	Week 36	Week 52
BMI < 18.5 (Underweight)	n	18	11	12
	Mean (SD) Change	2.04 (3.17)	2.78 (3.08)	3.33 (3.96)
18.5 - < 25 (Normal weight)	n	228	148	108
	Mean (SD) Change	-0.20 (4.39)	-0.14 (4.96)	-0.34 (5.54)
25 - < 30 (Overweight)	n	120	70	46
	Mean (SD) Change	-1.55 (5.70)	-2.0 (6.17)	-3.64 (6.97)
≥ 30 (Obese)	n	114	48	26
	Mean (SD) Change	-0.82 (6.19)	-0.02 (8.88)	-1.40 (6.83)

Source: Table 9.3.4.3 (ISS)

7.4.4 Electrocardiograms (ECG's)

Mean Change from Baseline

Phase 1 Studies

Healthy Volunteers (P1NON)

The mean change from baseline was 1.3 (19.4) msec for QTcB and -1.6 (19.2) msec for QTcF [mean values are for the all lurasidone group]. Of note, one subject receiving lurasidone 40 mg/day had a 164 msec increase in QTcB and 166 msec increase in QTcF. The Sponsor was asked to provide more information regarding this subject. This 67 YOWM participated in the renal impairment study and had a significant cardiovascular history (ischemic heart disease, coronary bypass) along with renal insufficiency secondary to diabetic kidney disease. At screening, his QTcB and QTcF were 451 and 449 msec. On Day 1, his QTcB and QTcF were 324 and 323 msec. At the discharge visit (96 hours post dose), his QTcB and QTcF were 488 and 489 msec (~40 msec greater than the screening values). These QT assessments were based on single ECG recordings.

Table 122. ECG Parameters: Mean Change from Baseline to LOCF Endpoint (P1NON)

	Lurasidone ≤ 30 mg (n = 202)	Lurasidone 40 mg (N = 110)	Lurasidone 60 – 100 mg (N = 35)	All Lurasidone (N = 323)	Placebo (N = 73)
Heart rate (bpm)	2.0 (7.2)	4.2 (7.2)	8.5 (8.0)	3.5 (7.7)	7.0 (6.5)
RR Interval (msec)	-27.2 (108)	-58.0 (105)	-146.8 (130)	-51.4 (117)	-109.8 (105)
PR Interval (msec)	0.3 (12.1)	-3.4 (16.3)	-3.6 (7.4)	-1.6 (13.5)	-1.7 (10.7)
QRS Interval (msec)	-0.4 (5.2)	-1.4 (5.9)	-0.4 (5.0)	-1.0 (5.3)	-0.8 (4.3)
QT Interval (msec)	-4.2 (20.1)	-8.8 (29.1)	-27.4 (24.9)	-8.7 (25.6)	-18.6 (24.2)
QTcB Interval (msec)	0.4 (15.0)	3.4 (25.5)	1.3 (15.2)	1.3 (19.4)	2.8 (15.0)
QTcF Interval (msec)	-0.3 (15.2)	-0.7 (24.5)	-8.2 (14.6)	-1.6 (19.2)	-3.6 (15.1)

Source: Table 10.1.1.1 (ISS)

Schizophrenia (P1SCH)

The maximum mean change from BL for QTcB was 54 msec in the > 120 mg group; QTcF was 49 msec in the 120 mg group.

Table 123. ECG Parameters: Mean Change from Baseline to LOCF Endpoint (P1SCH)

	Lurasidone 120 mg (N = 162)	Lurasidone > 120 mg (N = 96)	All Lurasidone (N = 258)	Placebo (N = 16)	Ziprasidone 160 mg (N = 29)
Heart rate (bpm)	4.7 (9.7)	4.7 (10.8)	4.7 (10.1)	2.6 (13.1)	4.3 (9.4)
RR Interval (msec)	-51.8 (122)	-54.3 (129)	-52.8 (124)	-37.9 (149)	-51.8 (123)
PR Interval (msec)	1.2 (10.5)	0.1 (11.1)	0.8 (10.7)	1.8 (9.8)	-0.3 (12.7)
QRS Interval (msec)	-0.7 (9.0)	0.4 (6.6)	-0.3 (8.2)	0.8 (8.7)	-2.1 (5.5)
QT Interval (msec)	-7.7 (25.2)	-5.8 (25.1)	-7.0 (25.1)	-8.4 (32.1)	-2.4 (27.8)
QTcB Interval (msec)	4.4 (14.3)	6.0 (15.8)	5.0 (14.9)	-0.3 (20.3)	10.3 (14.5)
QTcF Interval (msec)	0.3 (14.2)	2.2 (13.5)	1.0 (13.9)	-3.4 (19.3)	5.8 (15.1)

Source: Table 10.1.1.2 (ISS)

Phase 2/3 Studies

Table 124. ECG Parameters: Mean Change from Baseline to LOCF Endpoint (P2/3STC)

	All Lurasidone (N = 1004)	Placebo (N = 455)	Haloperidol 10 mg (N = 72)	Olanzapine 15 mg (N = 122)
Heart rate (bpm)	0.6 (14.3)	2.1 (14.3)	4.3 (13.0)	6.3 (15.0)
RR Interval (msec)	-3.7 (151)	-20.8 (151)	-46.9 (126)	-60.0 (166)
PR Interval (msec)	-0.9 (12.8)	-1.3 (13.0)	-3.6 (13.8)	-1.5 (12.7)
QRS Interval (msec)	0.3 (9.9)	1.0 (9.3)	-1.0 (13.0)	0.9 (7.8)
QT Interval (msec)	0.7 (30.9)	-1.3 (28.2)	-9.9 (30.4)	-5.6 (28.2)
QTcB Interval (msec)	1.8 (21.6)	3.8 (21.2)	0.6 (20.4)	9.7 (21.7)
QTcF Interval (msec)	1.5 (18.9)	1.9 (17.1)	-2.8 (19.7)	4.1 (16.1)

Source: Table 10.1.1.3 (ISS)

Table 125. ECG Parameters: Mean Change from Baseline to LOCF Endpoint by Dose (P2/3STC)

	Lurasidone 20 mg (N = 71)	Lurasidone 40 mg (N = 360)	Lurasidone 80 mg (N = 282)	Lurasidone 120 mg (N = 291)
Heart rate (bpm)	0.6 (12.1)	1.0 (14.9)	1.5 (14.4)	-0.9 (13.9)
RR Interval (msec)	-0.9 (123)	-10.2 (160)	-7.7 (152)	7.9 (144)
PR Interval (msec)	-1.7 (14.0)	-0.9 (12.7)	-1.4 (12.9)	-0.2 (12.8)
QRS Interval (msec)	-0.5 (12.7)	0.2 (9.8)	-0.3 (9.1)	1.2 (10.0)
QT Interval (msec)	0.0 (33.0)	0.6 (32.6)	-1.1 (30.2)	2.8 (28.9)
QTcB Interval (msec)	0.5 (20.4)	3.2 (22.2)	1.3 (22.4)	0.9 (20.1)
QTcF Interval (msec)	0.4 (22.1)	2.3 (19.6)	0.4 (18.8)	1.7 (17.4)

Source: Table 10.1.1.3 (ISS)

Abnormal Post-Baseline Values

Phase 1 Studies

Healthy Volunteers (P1NON)

The percentage of subjects with any QTc > 450 msec in the lurasidone groups was 7.6% (QTcB) and 5.2% (QTcF) compared to 2.1% (QTcB and QTcF) for subjects receiving placebo. One subject receiving lurasidone \leq 30 mg had an increase in QTcB (only) > 500 msec. One subject in the lurasidone 40 mg group and one subject in the placebo group had an increase > 60 msec from baseline (for both corrections). There were no remarkable findings for the evaluation of abnormal ECG parameters.

Schizophrenia (P1SCH)

Definitions of abnormal ECG values are included in the table. Since lurasidone is associated with an increase in heart rate, the QTcF correction is a more accurate assessment of QT prolongation compared to the QTcB correction method (the Sponsor provided data for both correction methods).

Table 126. Incidence of Abnormal ECG Values (P1SCH)

	Lurasidone 120 mg (N = 162)	Lurasidone > 120 mg (N = 96)	All Lurasidone (N = 258)	Placebo (N = 16)	Ziprasidone 160 mg (N = 29)
Heart Rate \geq 100 bpm					
Baseline	0/162	2/96 (2.1%)	2/258 (0.8%)	0/16	0/29
LOCF Endpoint	3/161 (1.9%)	2/96 (2.1%)	5/257 (1.9%)	1/16 (6.3%)	1/29 (3.4%)
Overall Post-Baseline	7/161 (4.3%)	6/96 (6.3%)	13/257 (5.1%)	1/16 (6.3%)	4/29 (13.8%)
PR Interval \geq 210 msec					
Baseline	2/162 (1.2%)	1/96 (1%)	3/258 (1.2%)	0/16	0/29
LOCF Endpoint	2/161 (1.2%)	1/96 (1%)	3/257 (1.2%)	0/16	0/29
Overall Post-Baseline	14/161 (8.7%)	2/96 (2.1%)	16/257 (6.2%)	0/16	1/29 (3.4%)
QRS Interval \geq 120 msec					
Baseline	2/162 (1.2%)	0/96	2/258 (0.8%)	0/16	0/29
LOCF Endpoint	2/161 (1.2%)	0/96	2/257 (0.8%)	0/16	0/29
Overall Post-Baseline	5/161 (3.1%)	0/96	5/257 (1.9%)	0/16	0/29
QT Interval \geq 500 msec					
Baseline	0/162	0/96	0/258	0/16	0/29
LOCF Endpoint	1/161 (0.6%)	0/96	1/257 (0.4%)	0/16	0/29
Overall Post-Baseline	4/161 (2.5%)	0/96	4/257 (1.6%)	0/16	0/29

Source: Table 32 (ISS)

Two patients in the lurasidone 120 mg group had an increase in QTcF > 500 msec (Table 127). Patient D1050263-0001-00162, a 40 YOM, participated in study D1050263 in which triplicate ECGs were obtained at various timepoints in this bioequivalence study. The QTcF values recorded on Day 7 (predose) were 462 msec, 727 msec and 405 msec (these ECG were 2 minutes apart on Day 7). The corresponding QTcB values were 417 msec, 663 msec and 405 msec. It is possible that the > 500 msec reading was an error. The other patient (D1050247-0001-00112) had a QTcF = 503 msec on Day 17 of the study. The QTcF values during the preceding washout period ranged from 397 to 472 msec.

Table 127. Incidence of Prolonged QTc (P1SCH)

	Lurasidone 120 mg (N = 162)	Lurasidone > 120 mg (N = 96)	All Lurasidone (N = 258)	Placebo (N = 16)	Ziprasidone 160 mg (N = 29)
Male QTc > 450 msec or Female QTc > 470 msec					
QTcB	12/161 (7.5%)	4/96 (4.2%)	16/257 (6.2%)	0/16	4/29 (13.8%)
QTcF	7/161 (4.3%)	0/96	7/257 (2.7%)	1/16 (6.3%)	1/29 (3.4%)
Any QTc > 450 msec					
QTcB	19/161 (11.8%)	5/96 (5.2%)	24/257 (9.3%)	0/16	5/29 (17.2%)
QTcF	9/161 (5.6%)	0/96	9/257 (3.5%)	1/16 (6.3%)	1/29 (3.4%)
Any QTc > 500 msec					
QTcB	3/161 (1.9%)	0/96	3/257 (1.2%)	0/16	0/29
QTcF	2/161 (1.2%)	0/96	2/257 (0.8%)	0/16	0/29
Incr. from BL \geq 30					
QTcB	29/161 (18%)	18/96 (18.8%)	47/257 (18.3%)	1/16 (6.3%)	10/29 (34.5%)
QTcF	24/161 (14.9%)	7/96 (7.3%)	31/257 (12.1%)	1/16 (6.3%)	7/29 (24.1%)
Incr. from BL \geq 60					
QTcB	4/161 (2.5%)	1/96 (1.0%)	5/257 (1.9%)	0/16	1/29 (3.4%)
QTcF	3/161 (1.9%)	0/96	3/257 (1.2%)	0/16	0/29

Source: Table 31 (ISS)

Though the incidence of PR interval prolongation (overall post-baseline) was 8.7% in the lurasidone 120 mg group in the P1SCH studies, the incidence is similar to placebo in the P2/3STC studies. Heart rate \geq 100 bpm in the lurasidone and placebo groups was 13%; there was no relationship to lurasidone dose and the incidence was highest in the 80 mg group (20%).

Table 128. Incidence of Abnormal ECG Values (P2/3STC)

	All Lurasidone (N = 1004)	Placebo (N = 455)	Haloperidol 10 mg (N = 72)	Olanzapine 15 mg (N = 122)
Heart Rate \geq 100 bpm				
Baseline	56/992 (5.6%)	26/451 (5.8%)	5/67 (7.5%)	2/122 (1.6%)
LOCF Endpoint	71/973 (7.3%)	35/436 (8.0%)	6/67 (9.0%)	12/121 (9.9%)
Overall Post-Baseline	131/973 (13.5%)	57/436 (13.1%)	10/67 (14.9%)	22/121 (18.2%)
PR Interval \geq 210 msec				
Baseline	12/992 (1.2%)	5/451 (1.1%)	0/67	0/122
LOCF Endpoint	11/973 (1.1%)	6/436 (1.4%)	0/67	1/121 (0.8%)
Overall Post-Baseline	19/973 (2.0%)	10/436 (2.3%)	1/67 (1.5%)	2/121 (1.7%)
QRS Interval \geq 120 msec				
Baseline	7/992 (0.7%)	4/451 (0.9%)	1/67 (1.5%)	0/122
LOCF Endpoint	9/973 (0.9%)	4/436 (0.9%)	0/67	0/121
Overall Post-Baseline	13/973 (1.3%)	4/436 (0.9%)	1/67 (1.5%)	0/121
QT Interval \geq 500 msec				
Baseline	1/992 (0.1%)	0/451	0/67	0/122
LOCF Endpoint	0/973	0/436	0/67	0/121
Overall Post-Baseline	0/973	0/436	0/67	0/121

Source: Table 113 (ISS)

Table 129. Incidence of Abnormal ECG Values by Dose (P2/3 STC)

	Lurasidone 20 mg (N = 71)	Lurasidone 40 mg (N = 360)	Lurasidone 80 mg (N = 282)	Lurasidone 120 mg (N = 291)
Heart Rate \geq 100 bpm				
Baseline	2/66 (3.0%)	22/358 (6.1%)	20/278 (7.2%)	12/290 (4.1%)
LOCF Endpoint	4/66 (6.1%)	24/353 (6.8%)	28/274 (10.2%)	15/280 (5.4%)
Overall Post-Baseline	9/66 (13.6%)	43/353 (12.2%)	55/274 (20.1%)	24/280 (8.6%)
PR Interval \geq 210 msec				
Baseline	0/66	3/358 (0.8%)	6/278 (2.2%)	3/290 (1.0%)
LOCF Endpoint	1/66 (1.5%)	2/353 (0.6%)	3/274 (1.1%)	5/280 (1.8%)
Overall Post-Baseline	1/66 (1.5%)	5/353 (1.4%)	6/274 (2.2%)	7/280 (2.5%)
QRS Interval \geq 120 msec				
Baseline	2/66 (3.0%)	1/358 (0.3%)	2/278 (0.7%)	2/290 (0.7%)
LOCF Endpoint	3/66 (4.5%)	2/353 (0.6%)	2/274 (0.7%)	2/280 (0.7%)
Overall Post-Baseline	4/66 (6.1%)	2/353 (0.6%)	4/274 (1.5%)	3/280 (1.1%)
QT Interval \geq 500 msec				
Baseline	0/66	1/358 (0.3%)	0/278	0/290
LOCF Endpoint	0/66	0/353	0/274	0/280
Overall Post-Baseline	0/66	0/353	0/274	0/280

Source: Table 113 (ISS)

There were no incidences of QTc prolongation > 500 msec.

Table 130. Incidence of Prolonged QTc (P2/3STC)

	All Lurasidone (N = 1004)	Placebo (N = 455)	Haloperidol 10 mg (N = 72)	Olanzapine 15 mg (N = 122)
Male QTc > 450 msec or Female QTc > 470 msec				
QTcB	38/973 (3.9%)	15/436 (3.4%)	3/67 (4.5%)	7/121 (5.8%)
QTcF	12/973 (1.2%)	1/436 (0.2%)	1/67 (1.5%)	0/121
Any QTc > 450 msec				
QTcB	60/973 (6.2%)	20/436 (4.6%)	3/67 (4.5%)	11/121 (9.1%)
QTcF	14/973 (1.4%)	1/436 (0.2%)	1/67 (1.5%)	0/121
Any QTc > 500 msec				
QTcB	0/973	0/436	0/67	0/121
QTcF	0/973	0/436	0/67	0/121
Incr. from BL \geq 30				
QTcB	159/972 (16.4%)	77/436 (17.7%)	15/67 (22.4%)	33/121 (27.3%)
QTcF	88/972 (9.1%)	39/436 (8.9%)	9/67 (13.4%)	14/121 (11.6%)
Incr. from BL \geq 60				
QTcB	12/972 (1.2%)	8/436 (1.8%)	1/67 (1.5%)	3/121 (2.5%)
QTcF	5/972 (0.5%)	3/436 (0.7%)	0/67	0/121

Source: Table 10.1.1.3 (ISS)

Table 131. Incidence of Prolonged QTc by Dose (P2/3 STC)

	Lurasidone 20 mg (N = 71)	Lurasidone 40 mg (N = 360)	Lurasidone 80 mg (N = 282)	Lurasidone 120 mg (N = 291)
Male QTc > 450 msec or Female QTc > 470 msec				
QTcB	1.5%	3.1%	5.5%	3.9%
QTcF	1.5%	1.4%	1.1%	1.1%
Any QTc > 450 msec				
QTcB	1.5%	5.4%	8.0%	6.4%
QTcF	1.5%	1.7%	1.5%	1.1%
Any QTc > 500 msec	0	0	0	0
Incr. from BL ≥ 30				
QTcB	21.2%	18.8%	14.6%	13.9%
QTcF	13.6%	10.2%	7.3%	8.2%
Incr. from BL ≥ 60				
QTcB	0	0.9%	2.6%	0.7%
QTcF	0	0.3%	1.5%	0

Source: Table 10.1.1.3 (ISS)

Thorough QT Study

The Sponsor conducted a thorough QT study, D1050249 “A double-blind, double-dummy, active controlled, randomized, 3-arm parallel study to evaluate the effects of therapeutic and suprathreshold doses of MK-3756 (lurasidone) on QTc interval in male and female schizophrenic or schizoaffective patients”.

Patients were randomized to lurasidone 120 mg/day, lurasidone titrated to 600 mg/day and ziprasidone titrated to 160 mg/day.

ECG measurements for assessment of QTc were obtained on Day 0 and Day 11 at 1, 2, 4, 6, and 8 hours post-dose. Blood samples for determination of lurasidone concentrations were obtained on Day 11 at 1, 2, 3, 4, 6, 8 and 24 hours post-dose with additional trough concentrations obtained from day 2-11. Seventy-three of the 87 enrolled patients completed this study.

The QT Interdisciplinary Review Team was consulted to review these data. The QT IRT reviewer used a mixed model to analyze the Δ QTcI (individual-based correction) effect (Table 132).

Table 132. QT IRT Analysis Results of Δ QTcI for Lurasidone and Ziprasidone

Time (hr)	Δ QTcI: Lurasidone 120				Δ QTcI: Lurasidone 600				Δ QTcI: Ziprasidone			
	N	Mean	SD	90% CI	N	Mean	SD	90% CI	N	Mean	SD	90% CI
1	23	1.0	2.6	(-3.4, 5.4)	19	3.2	2.9	(-1.6, 8.0)	24	12.3	2.6	(8.0, 16.6)
2	23	7.5	2.5	(3.3, 11.7)	20	3.3	2.7	(-1.2, 7.8)	24	13.6	2.4	(9.5, 17.7)
4	23	5.4	2.7	(0.9, 9.8)	19	4.6	2.9	(-0.2, 9.5)	23	15.1	2.7	(10.6, 19.5)
6	23	2.3	2.4	(-1.7, 6.2)	19	3.9	2.6	(-0.5, 8.3)	23	16.3	2.4	(12.3, 20.3)
8	21	1.5	2.3	(-2.4, 5.3)	19	5.2	2.4	(1.1, 9.2)	22	12.2	2.3	(8.4, 15.9)

Source: QT IRT Review

The highest mean increases in $\Delta QTcI$ occurred 2 hours for lurasidone 120 mg (7.5 msec), 8 hours for lurasidone 600 mg (5.2 msec) and 6 hours for ziprasidone (16.3 msec). It should be acknowledged that the 90% Confidence Intervals are quite broad.

The overall assessment by the QT IRT reviewer was that the QT results are inconclusive since the primary endpoint was inadequately defined (should be time-matched, baseline-corrected, and placebo-adjusted QTc ($\Delta\Delta QTc$) and that assay sensitivity was not established due to the lack of the $\Delta\Delta QTc$ analysis.

This reviewer discussed these comments with the QT IRT reviewer and emphasized that thorough QT studies for antipsychotic drugs will usually be conducted in patients with schizophrenia since these drugs (especially at high/supratherapeutic doses) are not tolerated in healthy volunteers, so a placebo comparator arm is not feasible. The QT IRT reviewer also noted that drugs such as moxifloxacin are usually included as the active control in these studies. Again, due to the population studied, that is not a feasible option. Since ziprasidone showed an effect on QTc in this study, it would appear that assay sensitivity was met. It was noted, however, that the 90% confidence intervals are very large, likely due to the small sample sizes in this trial.

The 120 mg dose is the highest dose proposed by the Sponsor for the treatment of schizophrenia. The 600 mg dose was chosen as a supratherapeutic dose and is a dose 5 times the highest proposed dose. Interestingly, however, the mean C_{max} obtained with the 600 mg dose was only 3.6 times the mean C_{max} obtained with the 120 mg dose (470 ng/ml vs. 129 ng/ml). Since drug interactions have noted that ketoconazole will increase the C_{max} of lurasidone by ~7-fold and AUC by ~9-fold, the Sponsor was asked to perform some modeling to predict the effect of a potent CYP3A4 inhibitor (such as ketoconazole) on QTc for a patient receiving lurasidone 120 mg/day.

The Sponsor included a report (M1050004) which was an exposure-modeling report on effects on QT. The Sponsor predicted the following increases at various lurasidone concentrations:

Table 133. Sponsor Table. QTcI Prolongation Predictions at Various Lurasidone Concentrations

QTcI prolongation predictions and 90% CI upper limits for the 'final' model

Lurasidone Concentration (CpL) (ng/ml)	QTcI Prolongation Predictions (msec)	Lower Limit 90% CI Of Prediction	Upper Limit 90% CI Of Prediction (msec)
0	0	0	0
100	0.281	-0.522	1.09
129 ^a	0.363	-0.674	1.40
200	0.563	-1.04	2.17
300	0.844	-1.57	3.26
400	1.13	-2.09	4.34
470 ^b	1.32	-2.45	5.10
500	1.41	-2.61	5.43
600	1.69	-3.13	6.51
700	1.97	-3.66	7.6
800	2.25	-4.18	8.68
900	2.53	-4.7	9.77
1000	2.81	-5.22	10.9

Source: Table 9 CSR for M1050004

The QT IRT reviewer was asked to comment on the validity of their model in predicting the overall effect of lurasidone on QTc. The reviewer did not specifically address this paper, but did state that the data on which the model was based was problematic.

If this model is appropriate, which is outside the scope of this reviewer's expertise to determine, it is somewhat reassuring that the QTcI prolongation at 1000 ng/ml would be estimated at 2.81 msec – though the 90% confidence interval is, again, very large (-5.2, 10.9). Patients taking lurasidone 120 mg/day (mean C_{max} 129 ng/ml) may achieve concentrations in that range if taking a potent CYP3A4 inhibitor.

Additionally, the findings for ziprasidone (included for assay sensitivity) are similar to findings of Study 054, the definitive thorough QT study conducted by Pfizer for ziprasidone.³ The sample size in Study 054 was also similar to the lurasidone thorough QT study, 24-31 patients per group were evaluated in Study 054. For comparison purposes, patients in the ziprasidone 160 mg group in Study 054 had a mean increase in QTcB of 20.3 msec (95% CI 14.2, 26.4) at T_{max} (~ 6 hours) while the patients in the ziprasidone 160 mg group in the lurasidone study had a mean increase in QTcB of 28.8 msec (90% CI 22.5, 35.0) at 6 hours. Though QTcB is probably not the best correction method to use due to effects of these drugs on heart rate, it is included here for comparison

³ Briefing document for Zeldox Capsules (ziprasidone HCl), FDA Psychopharmacological Drugs Advisory Committee, July 19, 2000.

purposes only. Study 054 also used a baseline correction method for QT that was different than QTcl used in the lurasidone QT study.

It should be noted that the definitive thorough QT study conducted by Pfizer for ziprasidone (Study 054) included data for 24-31 patients per treatment group. In this study, [the mean increase in the baseline corrected QT interval was 15.9 msec (95% CI 10.6, 21.2)].

7.4.5 Special Safety Studies/Clinical Trials

Bone Mineral Density

Due to the effect of lurasidone on prolactin concentrations, the Sponsor was asked to include DEXA scans in one of their long-term studies. The Sponsor included these assessments WHERE and in D1050237, the 12-month double-blind, randomized clinical trial in which patients receive either lurasidone or risperidone (2:1). The Division of Reproductive and Urologic Products was consulted to review the data from study D1050237. At the time this clinical review was being finalized, the consult had not been completed.

Table 134 lists the adverse events coded to preferred terms related to bone fractures in P2/3ALL. A number of these fractures were associated with falls (see comments section). Of note, one patient had 3 fractures and one patient had 2 fractures (see footnotes). No further information is available in narratives for the spinal compression fractures.

Table 134. Incidence of Bone Fractures in Lurasidone-Treated Patients (P2/3ALL)

Demographics	Preferred term	Verbatim term	Comments	All Lurasidone (N = 2096)
31 YOM D1001001-0000-00506	Foot fracture	Right metatarsal fracture		2 (< 0.1%)
61 YOF D1050229-0180-00010	Foot fracture	Closed nondisplaced fracture of second and third metatarsus bones of the left foot		
20 YOF D1001048-0000-00060	Hand fracture	Bone fracture in 3 rd , 4 th and 5 th fingers		2 (< 0.1%)
60 YOM D1001048-0000-00102	Hand fracture	Fracture of the metacarpal bone of the 5 th finger of the right hand		
44 YOM D1050229-0001-00008	Humerus fracture	Fracture in right humerus	JMP AE file noted fall	2 (< 0.1%)
D1001001-0000-	Humerus fracture	Fracture of right		

00216		upper arm bone		
57 YOF D1001001-0000-00341	Spinal compression fracture	Compression fracture of lumbar vertebrae	Received lurasidone for 279 days, no history of osteoporosis	2 (< 0.1%)
62 YOM D1001001-0000-00166	Spinal compression fracture	Compression fracture of 8 th thoracic vertebrae	Received lurasidone for 25 days, no history of osteoporosis	
23 YOM D1050237-0018-00033	Clavicle fracture*	Fractured clavicle	See footnote	1 (< 0.1%)
	Femur fracture*	Fractured femur	See footnote	1 (< 0.1%)
	Rib fracture*	Fracture 2 ribs	See footnote	1 (< 0.1%)
25 YOM D1050049-0020-09015	Lower limb fracture**	Right tibia and fibula open fracture	See footnote	1 (< 0.1%)
	Pelvic fracture**	Pelvic fracture of inferior ramus	See footnote	1 (< 0.1%)
34 YOM D1001048-0000-00153	Lumbar vertebral fracture	Burst fracture of the 3 rd lumbar vertebrae	JMP AE file also noted spinal cord injury	1 (< 0.1%)
38 YOM D1001048-0000-00160	Radius fracture	Fracture of the left distal radius		1 (< 0.1%)
35 YOF D1050229-0126-00003	Open fracture	Compound fracture of proximal phalynx of 5 th toe of right foot	JMP AE file noted osteopenia	1 (< 0.1%)

Source: Table 13 (ISS-120 day update), JMP AE file
 *D1050237-0018-00033, patient struck by a car (SAE)
 ** D1050049-0020-09015, fractures due to jump from freeway overpass

Ophthalmologic Assessments

Since lurasidone binds to melanin, the Sponsor was asked to include slit lamp and fundoscopic examinations in their clinical development program. The Sponsor included these assessments WHERE and in D1050237, the 12-month double-blind, randomized clinical trial in which patients receive either lurasidone or risperidone (2:1). The Division of Anti-Infective and Ophthalmology Products was consulted to review the data from study D1050237. At the time this clinical review was being finalized, the consult had not been completed.

A search of the adverse events in the JMP file located three cataract-related adverse events. One of these events was a discontinuation due to adverse event, the narrative indicated that the cataract was noted at end of study visit for D1050049 when the patient was receiving haloperidol. The results of the evaluation were not received until after the patient had started open-label lurasidone and the patient was subsequently discontinued from study.

Two other cases were identified, “cataract OS-abnormal coded to preferred term “cataract” (D1050049-0010-09011) in a patient receiving lurasidone 40 mg and “mild nucleosclerosis” coded to the preferred term “cataract nuclear” (D1050237-0032-00001) in a patient receiving flexible dose lurasidone. Narratives for these cases were not included in the NDA.

Fundoscopy and slit lamp examinations were also performed in studies D1050006 and D1050049. Sponsor noted that “no clinically significant findings were noted from funduscopy and slit lamp examinations”. However, contrary to this comment, one patient randomized to the haloperidol group in study D1050049 did develop cataracts noted at the end of study visit. In the CSR for both studies, results are categorized as n (%) of patients with normal or abnormal readings at screening and at endpoint, no other details were included in the CSR. For study D1050049, abnormal funduscopy examinations at screening were noted in 7-18% of patients and abnormal slit lamp examinations were noted in 11 – 27% of patients. The data summarized included all patients with data at screening (n = 349) and all patients with data at endpoint (n = 149), but did not include a summary for only those patients with both screening and endpoint examinations. Therefore, these data are limited with respect to evaluating the effect of lurasidone on these parameters in this study (no further analysis was requested from the Sponsor).

7.4.6 Immunogenicity

A number of adverse events occurred in the clinical trials program that could be related to hypersensitivity reactions. Though there were some cases of rash and pruritis, this reviewer was more concerned regarding cases related to swelling and edema.

One SAE of angioedema was noted (see Section 7.3.4 and Narrative in Appendix 9.6.2) which appeared to progress to respiratory failure (which was not identified by the Sponsor). In reviewing the adverse event summaries and JMP files for adverse events, a number of potential hypersensitivity reactions were identified. In the P2/3ALL database, the following adverse events were noted: swelling face (n = 4), eyelid edema (n = 1), swollen tongue (n = 2), lip swelling (n = 1), peripheral edema (n = 12) and edema (n = 3).

In addition, some of these events may have been “subsumed” in other AE categories. For example, there were 5 cases of “tongue disorder” which were described as “tongue thickening” or “nondystonic tongue thickening”, which could also potentially be described as tongue swelling.

In another case classified as EPS disorder due to the constellation of adverse events, one event was “swollen tongue”. It is not known whether this adverse event was captured separately from the EPS disorder adverse event.

Additionally, one case of a “dystonic reaction” included a description “tongue was swelling”.

The Sponsor should more fully characterize the adverse events related to “swelling”. It is assumed that many of these adverse events were either mild or resolved with continued therapy since few were identified as adverse events leading to discontinuation (as such, no narratives for these cases were provided with the NDA). At least three of these cases led to discontinuation from clinical trials (angioedema, swollen tongue, dystonic reaction [tongue swelling]).

7.4.7 Select Safety Integrations and Summaries

This reviewer wanted to summarize some relevant safety signals as they cut across different domains – e.g. extrapyramidal side effects measured as adverse events, scores on rating scales (SAS) and concomitant medication use; prolactin elevations measured as prolactin concentration elevation in labs but also as noted in related adverse events (galactorrhea). A section specific to this type of integration appears lacking in the review template (other than the overall summary section).

Extrapyramidal Side Effects

Akathisia

Extrapyramidal side effects were significant for lurasidone in the clinical trials. In the P2/3STC, akathisia was reported in 15% of lurasidone-treated patients, 3.3% of placebo patients and 19.4% of haloperidol-treated patients (10 mg). There did appear to be a dose-related effect with 5.6% (20 mg), 11.4% (40 mg), 14.9% (80 mg) and 22% (120 mg) experiencing akathisia in the lurasidone groups. Of note, the frequency of akathisia in the lurasidone 120 mg/day group was similar to the haloperidol 10 mg/day group. In this analysis, “restlessness” was not added to the term “akathisia”, though there is likely some overlap in these terms. The percentage of patients discontinuing the clinical trials due to akathisia was 1.7% in the lurasidone groups (2.4% in the 120 mg group), 4.2% in the haloperidol group and 0 in the placebo group.

The mean change in the Barnes Akathisia Scale (BAS) was 0.3 in the lurasidone groups, -0.0 in the placebo group and 0.9 in the haloperidol 10 mg group (Table 136). Sixteen percent of patients in the lurasidone groups worsened on the BAS compared to 7.6% in the placebo group and 33% in the haloperidol 10 mg group. As with the incidence of akathisia, the mean change and % of patients who worsened on the BAS appeared dose-related (Table 137).

It is difficult to assess concomitant medication use for akathisia since many different medications can be administered (e.g. beta blockers, anticholinergics, benzodiazepines) – though anticholinergics are not usually the treatment of choice for akathisia. Since the use of beta blockers is less likely to be confounded by other treatment indications (other than cardiac-related), the use of this concomitant medication was reviewed for D1050229, D1050231 and D1050049 (haloperidol as comparator). In study D1050229, ~5-7% of patients

received beta blockers in the lurasidone groups compared to ~3% in the placebo group. In study D1050231, beta blockers were administered in 6% of patients in the lurasidone 40 mg group, 11% of patients in the lurasidone 120 mg group and ~4% of patients in the placebo group. In study D1050049, beta blockers were administered in 1.4% of patients in the lurasidone 20 mg group, 0 patients in the lurasidone 40 mg group, 3% of patients in the lurasidone 80 mg group and 3% of patients in the haloperidol 10 mg group.

Parkinsonism

As previously stated, it is difficult to ascertain the incidence of parkinsonian symptoms in these clinical trials due to lumping and splitting of terms. Some terms seems to be lumping – e.g. parkinsonism, extrapyramidal disorder, while others seemed to split – e.g. tremor, bradykinesia, drooling. The Sponsor did not capture “salivary hypersecretion” as an EPS-related term, though this seems similar to “drooling” to this reviewer and the latter term was captured as an EPS-related term. Gait disturbance was also not necessarily captured adequately when mapping from verbatim terms – some cases where the gait was parkinsonian-like (e.g. “decrease arm swing during walk” mapped to preferred term “gait disturbance” with other adverse events consistent with EPS, “shuffling gait”). In the Parkinsonism-related terms, the most frequently reported adverse events were “parkinsonism”, “tremor”, “salivary hypersecretion” and “extrapyramidal disorder” (Table 135). Lurasidone was associated with parkinsonian adverse events. Interestingly, “parkinsonism” was noted in 4.9% of patients in the lurasidone groups compared to 0 in the haloperidol group while “extrapyramidal disorder” was noted in only 2% of patients in the lurasidone groups compared to 18% of patients in the haloperidol group – again, issues with lumping and splitting likely evident as well as differences in overall coding of verbatim terms. The dose-relationship of lurasidone and parkinsonian adverse events is not as clear, perhaps due to some of the coding issues described. “Parkinsonism” was present in 0 patients in the 20 mg group, 5.3% in the 40 mg group, 1.8% in the 80 mg group and 8.6% in the 120 mg group. In nearly all parkinsonism-related categories, the highest frequencies were in the lurasidone 120 mg group. There were very few discontinuations due to parkinsonian adverse events.

Table 135. Frequencies for Parkinsonian-related Adverse Events “Parkinsonism”, “Tremor”, “Salivary Hypersecretion” and “Extrapyramidal Disorder”.

	All Lurasidone (N = 1004)	Placebo (N = 455)	Haloperidol 10 mg (N = 72)	Olanzapine 15 mg (N = 122)
<i>Parkinsonian-related</i>				
Parkinsonism	49 (4.9%)	2 (0.4%)	0	7 (5.7%)
Tremor	30 (3.0%)	10 (2.2%)	5 (6.9%)	7 (5.7%)
Salivary Hypersecretion	21 (2.1%)	2 (0.4%)	3 (4.2%)	0
Extrapyramidal disorder	20 (2.0%)	7 (1.5%)	13 (18.1%)	0

The mean change in the Simpson Angus Scale (SAS) was 0.03 in the lurasidone groups, -0.0 in the placebo group and 0.13 in the haloperidol 10 mg group (Table 136). Five percent of patients in the lurasidone groups had a normal to abnormal shift on the SAS compared to 2.5% in the placebo group and 11% in the haloperidol 10 mg group. There was not a clear dose relationship to mean change on the SAS, but it is noteworthy that ~4% of patients had a shift from normal to abnormal on the SAS for lurasidone 20, 40 and 80 mg and this increased to 8% in the lurasidone 120 mg group.

In study D1050229, anticholinergic medications were administered to 14% of patients in the lurasidone 40 mg group, 23% of patients in the lurasidone 80 mg group and 29% of patients in the 120 mg group compared to 8% of patients in the placebo group. In study D1050231, anticholinergic medications were administered to 20% of patients in the lurasidone 40 mg group, 41% of patients in the lurasidone 120 mg group, 18% of patients in the olanzapine 15 mg group and 9% of patients in the placebo group. In study D1050049, anticholinergics were administered to 10% of patients in the lurasidone 20 mg group, 15% of patients in the lurasidone 40 mg group, 25% of patients in the lurasidone 80 mg group, 43% of patients in the haloperidol group and 14% of patients in the placebo group.

Table 136. Barnes Akathisia Scale and Simpson-Angus Rating Scale: Mean Change (SD) and Shift Change from Baseline to Endpoint (P2/3STC)

	All Lurasidone (N = 1004)	Placebo (N = 455)	Haloperidol 10 mg (N = 72)	Olanzapine 15 mg (N = 122)
BAS				
Mean change (SD)	0.3 (1.5)	-0.0 (1.1)	0.9 (2.4)	0.0 (1.3)
Worsened	16%	7.6%	33.3%	9%
SAS				
Mean change (SD)	0.03 (0.20)	-0.0 (0.13)	0.13 (0.33)	-0.01 (0.21)
Normal to Abnormal*	5.3%	2.5%	11.1%	4.9%

Source: Tables 117 – 122 (ISS)

*Shift from normal baseline to abnormal endpoint classification

Table 137. BAS and SAS: Mean Change and Shift Change from Baseline to Endpoint *by Dose* (P2/3STC)

	Lurasidone 20 mg (N = 71)	Lurasidone 40 mg (N = 360)	Lurasidone 80 mg (N = 282)	Lurasidone 120 mg (N = 291)
BAS				
Mean change (SD)	-0.0 (1.4)	0.1 (1.5)	0.2 (1.4)	0.5 (1.7)
Worsened	11.3%	13%	16.2%	20.7%
SAS				
Mean change (SD)	0.05 (0.20)	0.00 (0.21)	0.02 (0.15)	0.07 (0.23)
Normal to Abnormal*	4.2%	4%	4%	8.4%

Source: Tables 117 – 122 (ISS)

*Shift from normal baseline to abnormal endpoint classification

Dystonias

Similar to categorization of parkinsonian-related adverse events, there were some problems with categorizations of dystonic events. Dystonic events can be lumped (dystonia) or split (oculogyric crisis, torticollis) and it is difficult to determine a frequency given those coding issues. Additionally, oromandibular dystonia is a different preferred term from dystonia. This reviewer also noted some coding problems where verbatim terms such as “eye rolling (EPS)” were coded to the preferred term “eye rolling” which would not be captured as a dystonic event. This reviewer is still not clear what types of events were mapped to the preferred term “tongue disorder”, some of these included tongue thickening that was sometimes described as “nondystonic” and sometimes did not have a qualifier. Given those limitations, frequencies for dystonia, oculogyric crisis, oromandibular dystonia and torticollis are provided in Table 138. There were a significant number of dystonic events in the lurasidone group and, not unexpectedly, more in the haloperidol 10 mg group. There was no obvious relationship to lurasidone dose though all 4 of the torticollis cases occurred in the lurasidone 120 mg group. The percentage of patients discontinuing the clinical trials due to “dystonia” was 0.7% in the lurasidone groups (all in the 80 and 120 mg groups), 4.2% in the haloperidol group and 0 in the placebo group.

Table 138. Frequencies for Dystonia-Related Preferred Terms (P2/3STC)

	All Lurasidone (N = 1004)	Placebo (N = 455)	Haloperidol 10 mg (N = 72)	Olanzapine 15 mg (N = 122)
<i>Dystonia-related</i>				
Dystonia	35 (3.5%)	3 (0.7%)	9 (12.5%)	1 (0.8%)
Oculogyric Crisis	2 (0.2%)	0	1 (1.4%)	1 (0.8%)
Oromandibular dystonia	5 (0.5%)	0	3 (4.2%)	1 (0.8%)
Torticollis	4 (0.4%)	0	0	0

In the P2/3ALL database, there were ~21 cases of dystonia as an SAE and/or discontinuation due to AE. In ~9 of these cases, patients received parenteral administration of either an anticholinergic, antihistamine or benzodiazepine.

Prolactin

Lurasidone was associated with an increase in prolactin in the clinical trials. The mean change from normal baseline was 9 ng/ml for lurasidone groups, 0.6 ng/ml for the placebo group and 17 ng/ml for the haloperidol 10 mg group. Females exhibited a more pronounced mean elevation from normal baseline: 20 ng/ml for lurasidone groups, 2 ng/ml for placebo group and 41 ng/ml for the haloperidol group. There was a relationship to lurasidone dose, mean change from normal baseline was 4.5 ng/ml in the lurasidone 20 mg group, 5.9 ng/ml in the lurasidone 40 mg group, 9.8 ng/ml in the lurasidone 80 mg group and 12.9 ng/ml in the lurasidone 120 mg group (this relationship was present for both males and females). The percent of patients with elevations > 5x ULN were 3.6% for the lurasidone groups and 0.7% for the placebo group. For female patients, 8.3% in the lurasidone groups had elevations > 5x ULN compared to 1% in the placebo group.

Many adverse events potentially related to increased prolactin are not specific to elevated prolactin (e.g. sexual dysfunction, changes in menses). Galactorrhea, however, is fairly specific to elevated prolactin and, in the absence of breastfeeding, is likely to be related to the ingested medication. Galactorrhea was not reported in the P2/3STC database, but was reported in 2 patients in the P2/3ALL database and 2 patients in study D1050237. In one of the P2/3ALL cases, prolactin was not elevated per review of the JMP lab data; in the other case, prolactin concentrations were increased to 108 ng/ml.

The Sponsor was asked to provide line listings for the patients with prolactin > 5x ULN (see Section 7.4.2). Though this reviewer questions the sensitivity of the assay (see Section 7.4.2), significant prolactin elevations occurred in 34 patients in the P2/3STC database and fairly equally between the 40, 80 and 120 mg lurasidone doses. Of the 34 cases, 22 patients had a maximum prolactin concentration ≥ 100 and < 199 ng/ml, 5 patients had a maximum prolactin concentration ≥ 200 and < 299 ng/ml and 2 patients had a maximum prolactin concentration > 300 ng/ml (315.7 and 393.3 ng/ml). Sixty-two percent of patients with prolactin > 5x ULN were female.

There is insufficient data available from the open-label extension studies to determine whether prolactin concentrations remain elevated or normalize with continued administration of lurasidone. The Sponsor did submit prolactin data for change from baseline at weeks 24, 36 and 52 (Table 87); but they were not matched to timepoint and are more difficult to interpret. On face, those data indicate that there may not be a sustained prolactin elevation, but more data would need to be submitted to more fully evaluate this signal. Study D1050237 gives some comparisons to risperidone (mean doses not available), but attrition was high in both groups over the course of this 52 week study (Table 139).

Table 139. Mean Change in Prolactin Over Time: Study D1050237

Prolactin	Lurasidone (N = 190)	Risperidone (N = 85)
Baseline		
n	190	85
Mean (SD)	11.2 (12.8)	13.7 (19.7)
Week 6		
n	106	45
Mean Change (SD)	6.8 (42.1)	18.1 (27.6)
Median Change	0.9	10.7
Min, Max	-68, 386	-19, 116
Week 12		
n	66	27
Mean Change (SD)	0.4 (14.2)	12 (21.7)
Median Change	1.1	7.1
Min, Max	-72, 33	-21, 63
Week 24		
n	33	20
Mean Change (SD)	3.3 (21.4)	23.3 (31.7)
Median Change	0.9	17.5
Min, Max	-72, 51	-17, 92
Week 52		
n	17	10
Mean Change (SD)	-3.0 (20.1)	17.8 (15.9)
Median Change	-2.6	19.9
Min, Max	-70, 26	-5, 38
Change from Baseline to Endpoint (LOCF)		
n	156	65
Mean Change (SD)	3.9 (23.1)	18.4 (44.0)
Median Change	0.4	6.4
Min, Max	-70, 169	-21, 302

Source: Table 7.1.1.4 (ISS)

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose dependency is evaluated in those respective adverse event sections.

7.5.2 Time Dependency for Adverse Events

This reviewer was unable to locate an analysis for time dependency of adverse events.

7.5.3 Drug-Demographic Interactions

Prolactin concentrations were more elevated in females compared to males (see Section 7.4.2). CPK increased (as captured as adverse event in SOC Investigations) were reported only in males (2.2% lurasidone vs. 1.7% placebo).. Female patients experienced more nausea, vomiting, and dyskinesias compared to male patients.

Table 140. Select Adverse Events by Gender (P2/3STC)

	Males		Females	
	All Lurasidone (N = 728)	Placebo (N = 350)	All Lurasidone (N = 276)	Placebo (N = 105)
Dyspepsia	8.9%	6.3%	4%	4.8%
Nausea	8.7%	6.6%	20.7%	3.8%
Vomiting			12.3%	7.6%
Musculoskeletal stiffness	2.3%	3.7%	2.2%	3.8%
Muscle rigidity	0.7%	0.6%	0.7%	0
Torticollis	0.4%	0	0.4%	0
Akathisia	15.5%	2.0%	13.8%	7.6%
Sedation	12%	6.9%	11.6%	1%
Somnolence	10.6%	5.1%	10.9%	2.9%
Parkinsonism	4.7%	0.6%	5.4%	0
Dystonia	3.4%	0.6%	3.6%	1%
Tremor	3.0%	2.6%	2.9%	1%
EPS disorder	1.9%	1.7%	2.2%	1%
Dyskinesia	1%	2%	4%	1.9%
Drooling	0.7%	0.6%	0.7%	0
Salivary hypersecretion	1.9%	0.6%	2.5%	0
Oromandibular dystonia	0.4%	0	0.7%	0
Bradykinesia	0.3%	0		
Cogwheel rigidity	0.3%	0	1.1%	0
Insomnia	7.6%	6.9%	10.5%	5.7%
Anxiety	7%	3.4%	4.3%	2.9%
Bruxism	0.3%	0.3%	0.7%	1%
Eye rolling	0	0.3%	0.7%	0
Oculogyric crisis	0.1%	0	0.4%	0

Source: Table 6.1.4.1 (ISS)

Table 141 includes adverse event frequencies by race, the Sponsor included all races, but only two are included here since those categories contained the majority of patients in the clinical trials. This table includes only those adverse events that appeared to have different frequencies between the two races.

Table 141. Adverse Events by Race (P2/3STC)*

	White		Black/African American	
	All Lurasidone (N = 433)	Placebo (N = 187)	All Lurasidone (N = 403)	Placebo (N = 188)
Akathisia	17.6%	3.7%	11.9%	3.7%
Sedation	11.3%	4.3%	15.4%	7.4%
Somnolence	8.3%	4.3%	12.7%	6.4%
Dystonia	2.8%	1.1%	4.7%	0.5%

Source: Table 57 (ISS)

*Table lists only those adverse events with frequencies that appeared to differ between the two races.

Table 142 provides the most frequent (> 2%) adverse events in the US population and compares those adverse events to the Europe and Asia regions.

The most frequent (> 2%) adverse events in Asia were: salivary hypersecretion (7.2%), gastritis (3.6%), pain in extremity (5.4%), muscle rigidity (2.7%), torticollis (2.7%), parkinsonism (20.7%), and cogwheel rigidity (2.7%). The most frequent (> 2%) adverse events in Europe were: headache (7.3%), parkinsonism (7.3%) Data for South America not shown since few patients enrolled in that region (N = 24 for all lurasidone).

Table 142. Adverse Events by Geographic Region
 [> 2% in lurasidone group and > PC in U.S. compared to other regions]
 [in order by SOC] (P2/3STC)

	All Lurasidone		
	USA (N = 746)	Asia (N = 111)	Europe (N = 123)
Vision blurred	2.3%	0	0
Nausea	12.9%	10.8%*	8.1%
Dyspepsia	10.1%	0.9%*	0
Vomiting	8.6%	9%*	3.3%
Abdominal pain, upper	2.3%	0.9%	0.8%
Fatigue	4.4%	1.8%	0.8%
Weight increased	2.9%	0	0.8%
Back pain	4.6%	1.8%*	0
Musculoskeletal stiffness	4.2%	1.8%*	0
Akathisia	14.7%	14.4%	13.8%
Sedation	14.5%	3.6%	5.7%
Somnolence	10.3%	11.7%	5.7%
Dizziness	5%	3.6%	1.6%*
Dystonia	3.9%	1.8%	1.6%
Tremor	3.6%	1.8%*	0.8%
EPS disorder	2.7%	0	0
Anxiety	6.8%	2.7%	4.1%
Insomnia	6.7%	13.5%*	11.4%
Agitation	6.6%	6.3%*	6.5%
Restlessness	3.2%	1.8%	0

Source: Table 6.1.4.3 (ISS)

*Incidence in placebo group > lurasidone group

7.5.4 Drug-Disease Interactions

Hepatic Impairment

Data from the clinical trial (Study D1050264) are being reviewed by Clinical Pharmacology. The Sponsor indicates that hepatic impairment resulted in minor impact on the C_{max} of lurasidone, with ratios of geometric mean in mild, moderate and severe hepatic impairment groups ranging from 120 to 160% relative to healthy matched controls. However, hepatic impairment resulted in larger effects on AUC_{0-last} of lurasidone, with ratios of geometric mean in mild,

moderate and severe hepatic impairment of 140, 166 and 299% relative to healthy matched controls.

(b) (4)

Clinical Pharmacology to evaluate.

Renal Impairment

Data from the clinical trial (Study D1050265) are being reviewed by Clinical Pharmacology. The Sponsor indicates that renal impairment resulted in minor impact on the C_{max} of lurasidone, with ratios of geometric mean in mild, moderate and severe renal impairment groups ranging from 140 to 192% relative to healthy matched controls. A similar effect on AUC_{0-last} was noted with ratios of geometric mean in mild, moderate and severe renal impairment groups 151, 186 and 181% relative to healthy matched controls.

(b) (4)

Clinical Pharmacology to evaluate.

7.5.5 Drug-Drug Interactions

The review completed by clinical pharmacology and provides a more comprehensive review of drug-drug interactions.

The most significant drug interactions involved CYP3A4 inhibitors and CYP3A4 inducers. Ketoconazole (potent CYP3A4 inhibitor) increased the AUC_{0-last} of lurasidone by 9.3 fold (201.8 ng*hr/ml vs. 21.7 ng*hr/ml) and the C_{max} by 6.8 fold (44.0 ng/ml vs. 6.5 ng/ml). The active metabolite, ID-14283, also increased but to a lesser extent. Diltiazem (a moderate CYP3A4 inhibitor) increased the AUC_{0-inf} of lurasidone 2.2-fold and the C_{max} 2.1-fold. Similar increases were found for ID-14283.

Co-administration of lurasidone and rifampin resulted in a 5.5-fold decrease in lurasidone AUC (0-inf) and a 6.8-fold decrease in lurasidone C_{max}.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The overall incidence of adverse events in the SOC “Neoplasms benign, malignant and unspecified” was reviewed to determine whether there may be a potential signal of human carcinogenicity in the lurasidone development program.

There was one death due to lung neoplasm, malignant and metastatic neoplasm occurring in a 58 YOM.

In the P2/3STC studies, there was one case of uterine leiomyoma occurring in a patient taking lurasidone 20 mg. One case of acrochordon (cutaneous skin tag) in a patient taking lurasidone 120 mg and one case of prostatic adenoma in a patient taking lurasidone 20 mg. One additional case of “mass” was noted under SOC hepatobiliary disorders in a patient taking lurasidone 80 mg.

In the P2/3ALL studies, there was one case of gastric cancer and one case of hepatic cancer, metastatic. Both were classified as SAEs.

In P2/3ALL, 4 cases of uterine leiomyoma (including the 1 above), one case of lipoma, one case of skin papilloma.

7.6.2 Human Reproduction and Pregnancy Data

Pregnancy

The source for information on pregnancies is from the Pregnancy Report Forms submitted to the Sponsor and entered into the ARISg database. Three confirmed pregnancies were reported as of the September 1, 2009 cut-off, two of these cases were known to have been treated with lurasidone. Two additional cases were included in the 120-day safety update (December 1, 2009 cut-off); both cases are blinded to medication assignment.

Subject D1050229-22918002: A 33 YOF received open label lurasidone 80 mg from September 8, 2008 – February 14, 2009, when medication was discontinued. Pregnancy was confirmed on February 16, 2009; total exposure at the time that pregnancy was detected was 163 days with an estimated due date of October 18, 2009. On September 1, 2009, the subject developed severe pre-eclampsia and was admitted to the hospital. On (b) (6) the subject underwent a cesarean section and delivered a premature female infant weighing 1700 grams (3.75 pounds) with a gestational age of (b) (6). No congenital anomalies were noted.

Subject D1050237-23703020: A 31 YOF received her first dose of lurasidone on October 11, 2008. On October 28, the subject was noted to be pregnant and medication was discontinued. Total exposure at the time of pregnancy was detected was 18 days. The subject elected to have an abortion.

Subject D1050237-23751503: A 32 YOF received her first dose of lurasidone on December 2, 2008. On May 21, 2009, during a clinic visit, a urine HCG assay was performed and detected a borderline result which was confirmed as positive by a blood HCG assay. The subject discontinued from the study and the last day of study medication was May 20, 2009. Total exposure at the time that pregnancy was detected was 161 days (23 weeks). The outcome of the pregnancy was spontaneous abortion.

Subject D1050236-23610902: A 24 YOF received blinded study medication from November 18, 2009 to November 24, 2009, when study medication was discontinued. Total exposure to study medication at the time pregnancy was detected was 7 days. The pregnancy was continuing with a estimated due date of August 2010.

Subject D1050237-23702318: A 26 YOF received blinded study medication from January 28, 2009 to November 16, 2009. Total exposure to study medication at

the time pregnancy was detected was approximately 293 days. The pregnancy was continuing with an estimated due date of August 16, 2010.

Lactation

Lurasidone is excreted in the milk of rats during lactation. Lurasidone has not been studied in lactating women, so it is not known whether lurasidone is excreted in human breast milk.

7.6.3 Pediatrics and Assessment of Effects on Growth

No clinical trials have been conducted in the pediatric population.

7.6.4 Overdose, “Supratherapeutic” Dose, Drug Abuse Potential, Withdrawal and Rebound

Overdose

One case of lurasidone overdose was noted in the ISS:

Subject D1001036-0041-00002, a 35 YOF ingested an estimated 560 mg of lurasidone. There were no associated adverse events or SAEs reported. Lurasidone was temporarily interrupted for 4 days. The subject recovered without sequelae and continued in the study.

Supratherapeutic Dose

A “supratherapeutic” dose of lurasidone was administered to patients with schizophrenia in the thorough QT study D1050249. Lurasidone was titrated to 600 mg over 6 days and this dose was then administered for 5 days (n = 29). Lurasidone 120 mg was also administered in this study (n = 29). In general, the frequency of specific adverse events was higher in the 120 mg group compared to the 600 mg group. Adverse events that occurred more frequently in the 600 mg group included dystonia (13.8% vs. 10.3%), extrapyramidal disorder (10.3% vs. 3.4%), anxiety (17.2% vs. 13.8%) and diarrhea (10.3% vs. 6.9%). Slightly more patients discontinued the study in the 600 mg group – 24.1% vs. 13.8%. The most common reason for discontinuation was “subject withdrew consent”. There were no deaths or SAEs in this study.

Drug Abuse Potential

No clinical studies of abuse potential with lurasidone were conducted. In the ISS, the Sponsor stated “in the studies supporting this submission, there were no reports of AEs suggesting drug abuse”.

Withdrawal and Rebound

In the ISS, the Sponsor stated that “no safety signal has been identified following abrupt discontinuation of lurasidone treatment, nor has a withdrawal syndrome associated with lurasidone treatment cessation been observed. Further, there have been no treatment-emergent adverse events of ‘withdrawal syndrome’ or

'drug withdrawal syndrome' (preferred terms) reported to date in the short and long-term study Phase 2/3 clinical database (P23ALL)."

The clinical studies were not designed to specifically address this issue. However, if measured, adverse event rates at various timepoints in clinical trials could have been assessed. For example, in Study D1050231, lurasidone-treated patients were randomized to lurasidone 40 mg or lurasidone 120 mg. After completion of this 6-week clinical trial, patients had the option of continuing in a 6-month open-label study. At the end of D1050231, all patients who were to enter the open-label extension study were to receive 3 days of treatment with placebo (single-blind, 3-day washout). Adverse events could have been assessed at this juncture to evaluate abrupt discontinuation of lurasidone – though only for that 3-day period. There was no similar gap in study drug administration in study D1050229.

The JMP files for adverse events were reviewed and 3 withdrawal terms for 3 different subjects were noted in the verbatim term column: Withdrawal akathisia (mapped to preferred term, akathisia), withdrawal syndrome, withdrawal dyskinesia (mapped to preferred term, dyskinesia). This reviewer would assume, given the extensive extrapyramidal adverse events associated with lurasidone, that withdrawal dyskinesias would be expected with this compound.

7.7 Additional Submissions/Safety Issues

None identified.

8 POSTMARKET EXPERIENCE

Lurasidone is not marketed an any country.

9 APPENDICES

9.1 Literature Review/References

The Sponsor conducted a comprehensive search of the worldwide published literature on 3/6/2009 and 8/26/2009 using the following databases: Biosis Previews, EMBASE, MEDLINE, and ToxFile. Searches were conducted for terms lurasidone and SM13496. Searches were performed by "a trained research associate". A total of 35 unique citations were identified. One article (Enomoto T, Ishibashi T, Tokuda K, Ishiyama T, Toma S, Ito A. Lurasidone reverses MK-801-induced impairment of learning and memory in the Morris water maze and radial-arm maze tests in rats. *Behavioural Brain Research* 2008;186:197-207) was retrieved, reviewed, and summarized in the Pharmacology Written Summary and the majority of the citations were posters presented at meetings or publications of study reports that are summarized in the original NDA submission. The Sponsor states "we warrant that the citations were systematically reviewed in detail and no finding was discovered that adversely

affects the conclusions regarding the safety of lurasidone”. The Sponsor did include copies of the articles, due to time constraints, this reviewer did not review these articles.

9.2 Labeling Recommendations

Recommendations for labeling are not included in this clinical review but will be provided as an addendum to this review.

This reviewer is recommending a Complete Response action and did not wish to devote significant review time to labeling issues at this time.

9.3 Advisory Committee Meeting

The Division did not take this NDA to the Psychopharmacological Drugs Advisory Committee.

9.4 Requests for Information to Sponsor

The following requests for information were sent to the Sponsor during the course of the review. The Sponsor has submitted data in response to these requests as amendments to the NDA:

Please include a more detailed description of “abnormal” findings on ophthalmologic examinations. State what the abnormalities were and, for subjects with abnormal baseline and abnormal end-of-study examinations, if those abnormalities were unchanged. Since the majority of the ophthalmologic examination data will be provided in the 120-day safety update, it is acceptable to include this information for all data at that time (e.g. you do not need to provide these data at this time for the few subjects for which data have already been submitted). [Filing letter]

For all deaths, please provide comprehensive narratives that include relevant clinical details including laboratory assessments, ECG data and vital signs. [Filing letter]

Please provide the autopsy report and any other relevant clinical details for patient #23701730. The event “sudden death-hypertensive heart disease” is noted, however, the information provided in the narrative does not indicate a prior history of hypertension. Please clarify. [Filing letter]

Please provide an updated narrative for patient D1050231-0011-00001 who died due to “accidental (heroin) overdose”. The current narrative only provides information relevant to ALT changes (the AE that led to discontinuation from study). [Filing letter]

Please indicate whether an application for lurasidone for any indication has been submitted to any foreign country. [Filing letter]

On page 410 of the ISS, it appears that a literature search was performed, but there is little information regarding the clinical findings of this search. Please provide a summary of worldwide experience on the safety of this drug. We will need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of lurasidone. The report should also detail whether it relied on abstracts or full texts (including translations) of articles. The report should emphasize clinical data, but new findings in preclinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.
[Filing letter]

Please provide more information regarding concomitant medications for the 4 pivotal clinical trials (D1050006, D1050196, D1050229, D1050231). Specifically, provide a table similar to Table 10.2.1 in the CSR for study D1050196 (patient number, treatment allocation, concomitant med, dose, days received relative to study days, etc.) for all concomitant antipsychotics received during the double-blind phase of these studies. Though this table was provided for study D1050196, it does not appear to be complete for this study (e.g. in the lurasidone group, only one subject is listed for concomitant quetiapine use while Table 30 indicates that as many as 4 subjects may have taken concomitant quetiapine).

For each treatment group in all 4 pivotal studies, please provide the mean daily dose/week in the double-blind phases for all benzodiazepines received concomitantly.

In Table 2.1 (Major Protocol Deviations/Violations) of the CSR for study D1050196, it is noted that 3 patients had previous exposure to lurasidone and 2 patients had "non-zero serum concentrations" of lurasidone at baseline. Please describe in more detail what the previous exposures were - e.g. did these patients complete a prior trial and, if so, please provide the protocol number and patient number for the other clinical trial. Please provide more information for the "non-zero" concentrations of lurasidone. Had these patients been in prior clinical trials? What were the values for the non-zero serum concentrations for lurasidone?

Please perform an analysis of patient cases that met criteria for Hy's Law for all clinical trials - Phase 1, Phase 2/3 controlled short term and Phase 2/3ALL for all treatment groups (placebo, lurasidone, active comparators). If this analysis is included in the NDA submission, please indicate the location.

Was an autopsy performed on patient 23702036 (sudden death) who was receiving blinded study medication? If so, please provide results and a copy of the report. Is any additional clinical information available for this patient case?

Please provide a copy of the autopsy report for patient 23305802 (MI).

Perform an analysis for prolactin change from baseline to LOCF endpoint for P2/3STC studies (e.g. Table 85 in ISS), but include only those patients with a baseline prolactin within the normal range.

Provide a line listing of all subjects with prolactin levels meeting criteria for MAPLV and list all prolactin levels for these patients by visit.

Provide details regarding the patient receiving lurasidone who gained > 25 to 30 kg in the P2/3STC group (Table 107, ISS).

Please provide details for the P1NON subjects receiving lurasidone 40 mg/day who experienced an increase in QTcB of 164 msec and QTcF of 166 msec (same or different subjects?) [Table 10.1.1.1 in ISS].

The urinalysis laboratory data for the P2/3STC population [Table 7.5.1.3 in the ISS] show that 4.2% of patients receiving placebo had ketones present at LOCF endpoint compared to 2 - 2.2% of patients receiving lurasidone. Is there an explanation for the increase in ketones in the placebo group?

Please verify the number (%) of patients with $\geq 7\%$ weight gain in the P2/3STC studies. Table 7.5.1.3 (ISS) and Table 9.2.1.3 (ISS) have different numbers. For example, in the All Lurasidone group, Table 9.2.1.3 indicates that 65/999 (6.5%) of patients had this weight change whereas Table 9.3.2.1 indicates that 56/999 (5.6%) of patients had this weight change. It appears to be more than a transcription error (56/65) since the numbers in the olanzapine group are also different between the two tables.

For P2/3STC and P1SCH populations, perform an analysis for patients meeting criteria for changes in vital signs consistent with orthostatic hypotension - e.g. ≥ 20 mmHg decrease in SBP (sitting to standing or supine to standing) and ≥ 10 bpm increase in pulse (same positions).

We had previously asked that you provide a listing of patients who received concomitant antipsychotics during the four pivotal clinical trials. You provided these data in an amendment submitted 5/10/2010. Upon review of these data, we are unable to reconcile disparities between the submitted line listing and the data from the clinical study reports. For example, for study D1050006, Table 26 indicates that 9 (18%) patients in the lurasidone 40 mg group and 7 (14.3%) of patients in the lurasidone 120 mg group received concomitant olanzapine. However, the line listing (Listing 1.1.1.3) submitted in the amendment indicates that only one patient in each of the lurasidone groups received concomitant olanzapine. Please clarify.

Please review all data submitted in the amendment, reconcile with data from the respective clinical study reports and resubmit. At the current time, this request pertains only to the concomitant antipsychotic data.

We recently received the NDA amendment dated 7/30/2010 which included laboratory data that was inadvertently not included in the NDA for study D1050006. Though you included these data as line listings and as summary tables for the CSR, we need these data also included in the ISS. Please make sure that all other safety data for these 27 patients have been incorporated into the NDA - e.g. adverse events, vital signs, etc. If not, please include in the revised ISS. With the inclusion of these additional data, have any safety conclusions been altered?

Since laboratory data for Dr. Plopper's site was omitted from the NDA, please verify that data from his site for study D1050229 is included in the NDA.

Please submit a revised ISS that includes safety data from these additional 27 patients by Monday, August 9, 2010.

Additionally, please ascertain how many patients in studies D1050196, D1050229 and D1050231 had a prn dose of lorazepam within 8 hours of efficacy assessments (specifically the primary efficacy variable). Please submit these data within 2 weeks.

In protocol 1050006, the CSR states that 16 protocol waivers were granted for deviations in inclusion/exclusion criterion. Please provide these specific protocol deviations that were granted waivers. If this information is already in this submission, please specify location.

Perform an analysis for prolactin change from baseline to LOCF endpoint for P2/3STC studies (e.g. Table 85 in ISS), but include only those patients with a baseline prolactin within the normal range.

Provide a line listing of all subjects with prolactin levels meeting criteria for MAPLV and list all prolactin levels for these patients by visit.

Provide details regarding the patient receiving lurasidone who gained > 25 to 30 kg in the P2/3STC group (Table 107, ISS).

Please provide details for the P1NON subjects receiving lurasidone 40 mg/day who experienced an increase in QTcB of 164 msec and QTcF of 166 msec (same or different subjects?) [Table 10.1.1.1 in ISS].

The urinalysis laboratory data for the P2/3STC population [Table 7.5.1.3 in the ISS] show that 4.2% of patients receiving placebo had ketones present at LOCF endpoint compared to 2 - 2.2% of patients receiving lurasidone. Is there an explanation for the increase in ketones in the placebo group?

Please verify the number (%) of patients with $\geq 7\%$ weight gain in the P2/3STC studies. Table 7.5.1.3 (ISS) and Table 9.2.1.3 (ISS) have different numbers. For example, in the All Lurasidone group, Table 9.2.1.3 indicates that 65/999 (6.5%) of patients had this weight change whereas Table 9.3.2.1 indicates that 56/999 (5.6%) of patients had this weight change. It appears to be more than a transcription error (56/65) since the numbers in the olanzapine group are also different between the two tables.

For P2/3STC and P1SCH populations, perform an analysis for patients meeting criteria for changes in vital signs consistent with orthostatic hypotension - e.g. ≥ 20 mmHg decrease in SBP (sitting to standing or supine to standing) and ≥ 10 bpm increase in pulse (same positions).

9.5 Inclusion and Exclusion Criteria for Pivotal Efficacy Trials

D1050006

Inclusion

1. Provided written informed consent (subject or legal guardian)
2. DSM-IV criteria for a primary diagnosis of schizophrenia as established by the Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician's Version (SCID-CV). This includes disorganized, paranoid, and undifferentiated subtypes of schizophrenia. The patient must have an acute exacerbation of symptoms to be eligible for inclusion.
3. The patient has a minimum duration of illness of at least 1 year.
4. The patient is either male or female, aged 18 to 64 years inclusive. Females who are not at least 1 year postmenopausal or irreversibly surgically sterilized (by hysterectomy, oophorectomy, or bilateral tubal ligation with resection) must have a negative urine pregnancy test at screening, must be non-lactating, and using adequate and reliable contraception throughout the trial. Adequate contraception is defined as continuous use of one of the following: Norplant (inserted at least 3 months prior to washout), medroxyprogesterone acetate injection (given at least 14 days prior to washout), oral contraception (taken as directed for at least 1 month prior to washout), double-barrier method (e.g. condom and spermicide).
5. The patient has a total rating at screening of ≥ 42 on the BPRS (as extracted from the PANSS by adding items 2-9 and 15-24 on a 1 to 7 point scale per item). A score of at least 4 in two or more items of the positive symptom subcluster on the PANSS (items P1 through P7) is required.
6. The patient has a rating at screening of at least moderate or greater (≥ 4) on the CGI-S.
7. The patient has ratings at screening of normal to minimal symptoms on individual items of the Simpson-Angus Scale (< 2 acceptable) and the AIMS (< 3 acceptable).
8. The patient is able to remain off antipsychotic medication for a minimum of 3 days.

Exclusion

1. The patient is incapable of understanding or following the instructions given in the study, or cannot read and understand English. In the opinion of the investigator, the patient is unlikely to be compliant with study procedures and medication. If assistance is required

- for reliable compliance, then the same level and type of assistance must be consistently available throughout the trial.
2. The patient has a DSM-IV diagnosis of schizophreniform disorder, schizoaffective disorder, or schizophrenia, residual subtype or catatonic subtype.
 3. Other than current hospitalization, patients must not have had any psychiatric hospitalizations within the 3 months prior to screening. The duration of the present hospitalization may not be greater than 3 weeks prior to screening.
 4. The patient is resistant to neuroleptic treatment, defined as failure to respond to 2 or more antipsychotic agents from 2 chemical classes or clozapine, given at an adequate dose for sufficient time.
 5. The patient has evidence of any chronic organic disease of the CNS (other than schizophrenia) such as tumors, inflammation, epilepsy currently requiring treatment, vascular disorder, Parkinson's disease, myasthenia gravis, or other degenerative processes.
 6. The patient has a history of gastrointestinal, liver, or kidney disease, or other condition that would interfere with the absorption, distribution, metabolism or excretion of medications.
 7. The patient is known by history to be seropositive for HIV or has a history of diagnosed symptomatic HIV disease (AIDS).
 8. The patient has a positive test for Hepatitis A antibody IgM fraction or positive test for Hepatitis C antibody with concurrent evidence of active liver disease (increased liver function tests (AST or ALT) > 2 times ULN). A positive test for Hepatitis B surface antigen is exclusionary.
 9. The patient has a current clinically significant cardiovascular disease, including any of the following: cardiac surgery or myocardial infarction within the past 6 months; unstable angina (e.g. has not achieved a constant or reproducible pattern in 60 days); medication change for coronary artery disease in the past 3 months; decompensated congestive heart failure; significant cardiac arrhythmia or conduction disturbance, particularly those resulting in atrial or ventricular fibrillation, or causing syncope, near syncope, or other alterations in mental status; severe mitral or aortic valvular disease; uncontrolled high blood pressure or congenital heart disease.
 10. The patient is considered by the investigator to be at imminent risk of suicide, injury to self or others, or causing significant damage to property.
 11. The patient has been treated with depot neuroleptics within one standard treatment cycle.
 12. The patient has a history of substance abuse (including alcohol), or organic mental disorder within 3 months of study entry. A history of tobacco dependence is not exclusionary.
 13. The patient demonstrates a total $\geq 25\%$ decrease in score in the BPRS as extracted from the PANSS between the washout and the baseline visits.
 14. The patient has been exposed to antidepressants or reversible MAO-inhibitors within 1 week of entry into the washout period (within 1 month for fluoxetine or irreversible MAO-I).
 15. The patient has had ECT within 3 months of entry into the washout period of the study.
 16. The patient has used an investigational drug within the past 30 days.
 17. The patient has narrow-angle glaucoma, cataracts, or retinal disease.
 18. The patient has a history of an allergic reaction or intolerance to lurasidone or to any of its components.
 19. The patient was screened or washout out more than 1 time previously for this study.

D1050196

Inclusion

1. The patient and/or guardian have provided written informed consent.
2. The patient is aged 18 to 64 years, inclusive

3. The patient meets DSM-IV criteria for a primary diagnosis of schizophrenia as established by SCID-CV. This includes disorganized, paranoid, and undifferentiated subtypes of schizophrenia. The patient must have an acute exacerbation of symptoms to be eligible for inclusion.
4. The duration of the patient's illness, whether treated or untreated, must be ≥ 1 year.
5. The patient has a BPRS score at screening and baseline of ≥ 42 . A score of at least 4 on 2 or more items of the positive symptom subcluster on the PANSS (items P1 through P7) is required.
6. The patient has a rating at baseline of at least moderate or greater (≥ 4) on the CGI-S.

Exclusion

1. The patient is incapable of understanding or following the instructions given in the study, cannot read and understand English, or, in the opinion of the investigator, is unlikely to be compliant with study procedures and medication. If assistance is required for reliable compliance, then the same level and type of assistance must be consistently available throughout the trial.
2. The patient has a DSM-IV diagnosis of schizophreniform disorder, schizoaffective disorder, or schizophrenia, residual subtype or catatonic subtype.
3. Other than the current hospitalization, patients must not have had any psychiatric hospitalizations within 1 month prior to screening. In addition, the present hospitalization may not have begun more than 3 weeks prior to date of the screening visit. This exclusion criterion does not include administrative hospitalization.
4. The patient is resistant to antipsychotic drug treatment, defined as failure to respond to 2 or more antipsychotic agents from 2 chemical classes or clozapine, given at an adequate dose for sufficient time. That is, the patient must fail to show at least minimal clinical response to treatment with either 1) 2 neuroleptics in 2 chemical classes dosed at 800 chlorpromazine equivalents per day for at least 6 weeks, or 2) clozapine dosed at 400 mg/day for at least 6 weeks.
5. The patient has evidence of any chronic organic disease of the CNS (other than schizophrenia), such as neoplasm, inflammation, epilepsy currently requiring treatment, vascular disorder, Parkinson's disease, myasthenia gravis, or other degenerative diseases.
6. The patient has a history of gastrointestinal, liver, or kidney disease, or other condition that would interfere with the absorption, distribution, metabolism, or excretion of SM-13496 to a clinically meaningful extent. Patients with impaired hepatic function as shown by AST or ALT greater than 2 times ULN must be excluded.
7. The patient is known by history to be seropositive for HIV or has a history of diagnosed symptomatic HIV disease (AIDS).
8. The patient has a positive test for hepatitis C antibody with concurrent evidence of impaired hepatic function (increased AST or ALT > 2 times ULN). A positive test for hepatitis B surface antigen, irrespective of the AST or ALT values, is also exclusionary.
9. The patient has a prolactin level ≥ 200 ng/ml at screening or baseline. The patient can be enrolled pending the results of the final laboratory result.
10. Females who are not at least 1 year postmenopausal or irreversibly surgically sterilized (by hysterectomy, oophorectomy, or bilateral tubal ligation with resection) must have a negative urine pregnancy test at screening, must use adequate and reliable contraception throughout the trial. Adequate and reliable contraception is defined as continuous use of 1 of the following: Norplant (inserted at least 3 months prior to washout), medroxyprogesterone acetate injection (given at least 14 days prior to washout), oral contraception (taken as directed for at least 1 month prior to washout), double-barrier method (e.g. condom plus spermicide).
11. The patient has a current clinically significant cardiovascular disease, including any of the following:
 - a. Cardiac surgery or myocardial infarction within the past 6 months

- b. Unstable angina (e.g. has not achieved a constant or reproducible pattern in 60 days)
 - c. Decompensated congestive heart failure
 - d. Clinically significant cardiac arrhythmia or conduction disturbance, particularly those involving atrial or ventricular fibrillation, or causing syncope, near syncope, or other alterations in mental status
 - e. Severe mitral or aortic valvular disease
 - f. Uncontrolled high blood pressure or > 160/100 mmHg, with case-by-case discussion between the investigator and medical monitor required prior to any exceptions
 - g. Congenital heart disease
12. The patient is considered by the investigator to be at imminent risk of suicide, injury to self or others, or causing significant damage to property.
 13. The patient has been treated with depot neuroleptics within 1 standard treatment cycle (e.g. if a patient has been receiving haloperidol decanoate every 3 weeks, a 3-week period must elapse from the last injection to the beginning of washout for the patient to be eligible).
 14. The patient tests positive on urine drug screen conducted at the screening or baseline visit for any of the following substances not taken by prescription: cocaine, barbiturates, amphetamines, benzodiazepines, or opiates. A positive drug screen for alcohol, cannabinoids, or substances taken by prescription is not necessarily exclusionary and should be discussed with the medical monitor.
 15. The patient has a history of substance abuse (including alcohol) or substance-induced mental disorder as defined by the DSM-IV criteria within 3 months of study entry. A history of tobacco dependence is not exclusionary.
 16. The patient has individual item scores of ≥ 2 on any of the SAS items or ≥ 3 on any items of the AIMS.
 17. The patient demonstrates a decrease (improvement) of $\geq 20\%$ in the BPRS score between the screening and baseline visits, or the BPRS score falls below 42 at baseline.
 18. The patient has been exposed to antidepressants or reversible MAOIs within 1 week of entry into the washout period (within 1 month for fluoxetine or irreversible MAOIs, e.g. L-deprenyl).
 19. The patient has had ECT within 3 months of entry into the washout period of the study.
 20. The patient has used an investigational drug within the past 30 days.
 21. The patient has participated in a previous SM-13496.
 22. The patient was screened or washed out previously more than 1 time for this study (i.e. altogether, a patient may undergo no more than 2 screening and washout periods for this study).

D1050229

Inclusion

1. Subject agrees to participate by providing written informed consent.
2. Subject is between 18 and 75 years of age, inclusive, on the day of signing informed consent.
3. Subject meets DSM-IV criteria for a primary diagnosis of schizophrenia (including disorganized, paranoid, undifferentiated subtypes) as established by clinical interview using the MINI Plus diagnostic interview. The duration of the subject's illness, whether treated or untreated, must have been > 1 year.
4. Subject had an acute exacerbation of psychotic symptoms (no longer than 2 months) and marked deterioration of function from baseline (by history) or subject had been hospitalized for the purpose of treating an acute psychotic exacerbation for 2 consecutive weeks or less immediately before screening. Subjects who had been hospitalized for > 2 weeks for reasons unrelated to acute exacerbation could have been included with

concurrency from the Medical Monitor that such hospitalization was for a reason other than acute relapse.

5. Subject has a PANSS total score ≥ 80 at screening and baseline, with a score ≥ 4 on 2 or more PANSS items: delusions, conceptual disorganization, hallucinations, unusual thought content, and suspiciousness.
6. Subject has a score ≥ 4 on the CGI-S at screening and baseline.
7. Subject tests negative for selected drugs of abuse at screening and baseline. In the event a subject tests positive for cannabinoids or alcohol, the investigator will evaluate the subject's ability to abstain from prohibited substances during the study. If in the investigator's clinical judgment the subject will abstain, the subject may be enrolled after consultation with the Medical Monitor.
8. Subject is not pregnant (must have a negative serum pregnancy test at screening) or nursing (must not be lactating) and is not planning pregnancy within the projected duration of the study.
9. A subject who is of reproductive potential (i.e. not surgically sterile or postmenopausal defined as at least 12 months of spontaneous amenorrhea or between 6 and 12 months spontaneous amenorrhea with FSH concentrations within postmenopausal range as determined by laboratory analysis) agrees to remain abstinent or use adequate and reliable contraception throughout the study, and in the investigator's judgment, the subject will adhere to this requirement.

Adequate contraception is defined as continuous use of either 2 barrier methods (e.g. condom and spermicide or diaphragm with spermicide) or hormonal contraceptives in combination with at least 1 barrier method. Acceptable hormonal contraceptives include the following: contraceptive implant (such as Norplant) inserted at least 3 months prior to washout; injectable contraceptive (such as medroxyprogesterone acetate injection) given at least 14 days prior to washout; or oral contraception taken as directed for at least 1 month prior to washout.

10. Subject is able and agrees to remain off prior antipsychotic medication for the duration of the study.
11. Subject has had a stable living arrangement for at least 3 months prior to randomization and agrees to return to a similar living arrangement after discharge. Chronically homeless subjects should not be enrolled.
12. Subject is in good physical health on the basis of medical history, physical examination, and laboratory screening.
13. Subject is willing and able to comply with the protocol, including the inpatient requirements and outpatient visits, in the opinion of the study nurse/coordinator and the investigator.
14. Subjects who require concomitant medication treatment with the following agents may be included if they had been on stable doses for the specified times: oral hypoglycemics (30 days), thyroid replacement (3 months), antihypertensive medication (30 days).

Exclusion

1. Subject currently has a clinically significant neurological, metabolic (including type 1 diabetes), hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, and/or urologic disorder such as unstable angina, CHF (uncontrolled), or CNS infection that would pose a risk to the subject if they were to participate in the study or that might confound the results of the study. Subjects with HIV seropositivity (or history of seropositivity) will be excluded.

(Active medical conditions that are minor or well-controlled are not exclusionary if they do not affect risk to the subject or the study results. In cases in which the impact of the condition upon risk to the subject or study results is unclear, the Medical Monitor should

- be consulted. Any subject with known cardiovascular disease or condition (even if under control) must be discussed with the Medical Monitor before being randomized in the study.
2. The subject has evidence of acute hepatitis, clinically significant chronic hepatitis, or evidence of clinically significant impaired hepatic function through clinical and laboratory evaluation.
(Subjects with ALT or AST > 3 times the upper limit of the reference ranges provided by the central laboratory require retesting. If on retesting, the laboratory value remains > 3 times the upper limit, such subjects must be discussed with the Medical Monitor for enrollment consideration.)
 3. Subject's estimated creatinine clearance is < 60 ml/min.
 4. Subject has a history of stomach or intestinal surgery or any other condition that could interfere with absorption, distribution, metabolism, or excretion of medications.
 5. Subject has a history of malignancy < 5 years prior to signing the informed consent, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. Subjects with pituitary tumors of any duration are excluded.
 6. The subject has evidence of any chronic organic disease of the CNS (other than schizophrenia) such as tumors, inflammation, active seizure disorder, vascular disorder, Parkinson's disease, Alzheimer's disease or other forms of dementia, myasthenia gravis, or other degenerative processes. In addition, subjects must not have a history of mental retardation or persistent neurological symptoms attributable to serious head injury. Past history of febrile seizure, drug-induced seizure, or alcohol withdrawal seizure is not exclusionary.
 7. Subject has a history of neuroleptic malignant syndrome.
 8. Subject exhibits evidence of severe tardive dyskinesia, severe chronic tardive dystonia, or any other severe movement disorder. Severity is to be determined by the investigator.
 9. Subject is considered by the investigator to be at imminent risk of suicide or injury to self, others, or property.
 10. Subject has current clinically significant or history of alcohol abuse/alcoholism or drug abuse/dependence within the last 6 months. Exceptions include caffeine or nicotine abuse/dependence.
 11. Subject has a history of macular or retinal pigmentary disease.
 12. Subject has any abnormal laboratory parameter (with the exception of glucose or HbA1c) that indicates a clinically significant medical condition as determined by the investigator. Elevated glucose or HbA1c are exclusionary only in cases where, in the opinion of the investigator, participation in the protocol poses a significant risk to the subject.
 13. Subject has a prolactin concentration > 100 ng/ml at screening or has a history of pituitary adenoma.
 14. Subject has a history or presence of abnormal ECG which, in the investigator's opinion, is clinically significant.
 15. Subject has a BMI > 40 or < 18.5 kg/m².
 16. Subject has, in the opinion of the study site staff, poor peripheral venous access.
 17. Subject has a history of hypersensitivity to more than 2 distinct chemical classes of drug.
 18. Subject is resistant to neuroleptic treatment, defined as failure to respond to 2 or more marketed antipsychotic agents from 2 different classes, given at an adequate dose for at least 8 weeks over the last 1 year.
 19. Subject has received depot neuroleptics unless the last injection was at least 1 treatment cycle before randomization.
 20. Subject has a history of treatment with clozapine for refractory psychosis and/or subject has been treated with clozapine within 4 months of randomization.

21. Subject has received treatment with mood stabilizers or antidepressants within 1 week, fluoxetine hydrochloride at any time within 1 month, or an MAOI within 3 weeks of randomization.
22. Subject will require treatment with any potent CYP3A4 inhibitors or inducers during the study. Subject requires treatment with a drug that prolongs the QTc.
23. Subject has received ECT treatment within the 3 months prior to randomization.
24. The subject demonstrates a decrease (improvement) of $\geq 20\%$ in the PANSS score between the screening and baseline visits, or the PANSS score falls below 80 at baseline.
25. The subject has participated in a prior trial of lurasidone HCl.
26. The subject was screened or washed out previously more than twice for this study (altogether, a subject may undergo no more than 3 screening and washout periods for this study).
27. Subject is currently participating or has participated in a study with an investigational compound or device within 30 days prior to signing the informed consent. This includes studies using marketed compounds or devices.
28. In the opinion of the investigator, subject is unable to cooperate with any study procedures, unlikely to adhere to the study procedures, keep appointments, or is planning to relocate during the study.

D1050231

Inclusion

1. Subject agrees to participate by providing written informed consent.
2. Subject is between 18 to 75 years of age inclusive on the day of signing informed consent.
3. Subject meets DSM-IV criteria for a primary diagnosis of schizophrenia (including disorganized, paranoid, or undifferentiated subtypes as established by clinical interview [using the Mini-International Neuropsychiatric Interview]). The duration of the subject's illness whether treated or untreated must be > 1 year.
4. Subject has an acute exacerbation of psychotic symptoms (no longer than 2 months) and marked deterioration of function from baseline (by history) or subject has been hospitalized for the purpose of treating an acute psychotic exacerbation for 2 consecutive weeks or less immediately before screening. Subjects who have been hospitalized for more than 2 weeks for reasons unrelated to acute exacerbation can be included with concurrence from the Medical Monitor that such hospitalization was for a reason other than acute relapse. For example, subjects in long-term hospitals (e.g. for years) who have a clear acute exacerbation and are transferred to an acute unit (for 2 weeks or less) are suitable for this protocol.
5. Subject has a PANSS total score ≥ 80 at screening and baseline, with a score ≥ 4 (moderate) on 2 or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, unusual thought content, and suspiciousness. Subject has a score ≥ 4 on the CGI-S at screening and baseline.
6. Subject tests negative for selected drugs of abuse at screening and baseline. In the event a subject tests positive for cannabinoids (THC) or alcohol, the investigator will evaluate the subject's ability to abstain from prohibited substances during the study. If in the investigator's clinical judgment the subject will abstain, the subject may be enrolled after consultation with the Medical Monitor.
7. Subject is not pregnant (must have a negative serum pregnancy test at screening) or nursing (must not be lactating) and is not planning pregnancy within the projected duration of the study.
8. A subject who is of reproductive potential (i.e. not surgically sterile or postmenopausal defined as at least 12 months of spontaneous amenorrhea or between 6 and 12 months spontaneous amenorrhea with FSH concentrations within postmenopausal range as determined by laboratory analysis) agrees to remain abstinent or use adequate and

reliable contraception throughout the study, and in the investigator's judgment, the subject will adhere to this requirement.

Adequate contraception is defined as continuous use of either 2 barrier methods (e.g. condom and spermicide or diaphragm with spermicide) or hormonal contraceptives in combination with at least 1 barrier method. Acceptable hormonal contraceptives include the following: contraceptive implant (such as Norplant) inserted at least 3 months prior to washout, injectable contraception (such as medroxyprogesterone acetate injection) given at least 14 days prior to washout, or oral contraception taken as directed for at least 1 month prior to washout.

9. Subject is able and agrees to remain off prior antipsychotic medication for the duration of the study.
10. Subject has had a stable living arrangement for at least 3 months prior to randomization and agrees to return to a similar living arrangement after discharge. This criterion is not meant to exclude subjects who have temporarily left a stable living arrangement (e.g. due to psychosis). Such subjects remain eligible to participate in this protocol. Chronically homeless subjects should not be enrolled. The Medical Monitor should be consulted for individual cases as needed.
11. Subject is in good physical health on the basis of medical history, physical examination, and laboratory screening.
12. Subject is willing and able to comply with the protocol, including the inpatient requirements and outpatient visits, in the opinion of the study nurse/coordinator and the investigator.
13. Subjects who require concomitant medication treatment with the following agents may be included if they have been on stable doses for the prespecified times: 1) oral hypoglycemics must be stabilized for at least 30 days prior to randomization, 2) thyroid replacement must be stable for at least 3 months prior to randomization, 3) anti-hypertensive agents must be stable for at least 30 days prior to randomization. The subject's medical condition should be deemed essentially stable following consultation with the Medical Monitor as needed.

Exclusion

1. Subject currently has a clinically significant neurological, metabolic (including type 1 diabetes), hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, and/or urological disorder such as unstable angina, congestive heart failure (uncontrolled), or central nervous system infection that would pose a risk to the subject if they were to participate in the study or that might confound the results of the study. Subjects with human HIV seropositivity (or history of seropositivity) will be excluded. Active medical conditions that are minor or well-controlled are not exclusionary if they do not affect risk to the subject or study results is unclear, the Medical Monitor should be consulted. Any subject with a known cardiovascular disease or condition (even if under control) must be discussed with the Medical Monitor before being randomized in the study.
2. The subject has evidence of acute hepatitis, clinically significant chronic hepatitis, or evidence of clinically significant impaired hepatic function through clinical and laboratory evaluation. Subjects with ALT or AST \geq 3 times ULN require re-testing. If on re-testing, the laboratory value remains \geq 3 times ULN, such subjects must be discussed with the Medical Monitor for enrollment consideration.
3. Subject's estimated creatinine clearance is $<$ 60 ml/min.
4. Subject has a history of stomach or intestinal surgery or any other condition that could interfere with absorption, distribution, metabolism or excretion of medications.
5. Subject has a history of malignancy $<$ 5 years prior to signing the informed consent, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. Subjects with pituitary tumors of any duration are excluded.

6. The subject has evidence of any chronic organic disease of the CNS (other than schizophrenia) such as tumors, inflammation, active seizure disorder, vascular disorder, Parkinson's disease, Alzheimer's disease or other forms of dementia, myasthenia gravis, or other degenerative processes. In addition, subjects must not have a history of mental retardation or persistent neurological symptoms attributable to serious head injury. Past history of febrile seizure, drug-induced seizure, or alcohol withdrawal seizure is not exclusionary.
7. Subject has a history of NMS.
8. Subject exhibits evidence of severe tardive dyskinesia, severe dystonia, or any other severe movement disorder. Severity is to be determined by the investigator.
9. Subject is considered by the investigator to be at imminent risk of suicide or injury to self, others or property.
10. Subject has current clinically significant or history of alcohol abuse/alcoholism or drug abuse/dependence within the last 6 months. Exceptions include caffeine or nicotine abuse/dependence.
11. Subject has a history of macular or retinal pigmentary disease.
12. Subject has any abnormal laboratory parameter (with the exception of glucose or HbA1c) that indicates a clinically significant medical condition as determined by the investigator. Elevated glucose or HbA1c are exclusionary only in cases where, in the opinion of the investigator, participation in the protocol poses a significant risk to the subject (with Medical Monitor approval).
13. Subject has a prolactin concentration of > 100 ng/ml at screening or has a history of pituitary adenoma.
14. Subject has a history or presence of abnormal ECG, which in the investigator's opinion, is clinically significant.
15. Subject has a BMI greater than 40 or less than 18.5 kg/m².
16. Subject has, in the opinion of the study site staff, poor peripheral venous access.
17. Subject has a history of hypersensitivity to more than 2 distinct chemical classes of drug.
18. Subject has a history of hypersensitivity to olanzapine.
19. Subject has used olanzapine within 30 days prior to screening and/or has had an inadequate response or intolerability due to olanzapine treatment.
20. Subject is resistant to neuroleptic treatment, defined as failure to respond to 2 or more marketed antipsychotic agents from 2 different classes, given at an adequate dose for at least 8 weeks over the last year.
21. Subject has received depot neuroleptics unless the last injection was at least 1 treatment cycle before randomization.
22. Subject has a history of treatment with clozapine for refractory psychosis and/or subject has been treated with clozapine within 4 months of randomization.
23. Subject has received treatment with mood stabilizers or antidepressants within 1 week, fluoxetine hydrochloride at any time within 1 month, or a MAOI within 3 weeks of randomization.
24. Subject will require treatment with any CYP3A4 inhibitors or inducers during the study. Subject requires treatment with a drug that prolongs the QTc interval.
25. Subject has received ECT treatment within the 3 months prior to randomization.
26. The subject demonstrates a decrease (improvement) of $\geq 20\%$ in the PANSS score between the screening and baseline visits, or the PANSS score falls below 80 at baseline.
27. Subject has participated in a prior trial of lurasidone HCl.
28. Subject was screened or washed out previously more than twice for this study (altogether, a subject may undergo no more than 3 screening and washout periods for this study).
29. Subject is currently participating or has participated in a study with an investigational compound or device within 30 days prior to signing the informed consent. This includes studies using marketed compounds or devices.

30. In the opinion of the investigator, subject is unable to cooperate with any study procedures, unlikely to adhere to the study procedures, keep appointments, or is planning to relocate during the study.

9.6 Patient Narratives

9.6.1 Narratives for Sudden Death (and Related) Cases

D1001048-0000-00039; 59 YO Asian male [Sudden Death]

The subject started treatment with open-label, flexible dose study medication (lurasidone) on 22 May 2007 at 40 mg/day. The dose was increased to 60 mg/day on 29 May 2007 since the subject's condition did not improve. On 9 Jun 2007, he developed peripheral circulatory failure in the lower extremities and complained of pain and edema between the region of the lower thighs and feet. Week 4 examination was done on the subject on 19 Jun 2007 and although his ECG showed premature ventricular contractions and flattening of the T wave in lead aVL, these were not considered problematic. Pain and edema of the lower extremities did not resolve and on 8 Aug 2007, the subject consulted the trauma department and Vitamedin (benfotiamine), Carnaculin (kallidinogenase), and Loxonin (loxoprofen sodium hydrate) were started. Week 16 examination/assessment was performed on the subject on 11 Sep 2007 and although his ECG showed premature ventricular contractions and sinus bradycardia, these were not considered problematic. On 19 Sep 2007, symptoms of peripheral circulatory failure in the lower extremities resolved. On 08 Jan 2008, the subject experienced auditory hallucinations with disinhibition and delusions considered to be an aggravation of his schizophrenia and he was started on Cercine (diazepam) 5 mg/day the following day. On 15 Jan 2008, delusional and disinhibitional behaviors became frequent and the dose of the study medication was increased to 80 mg/day. An ECG done on the subject on 28 Jan 2008 showed axis deviation and another ECG done the following day on his Week 36 examination showed flattening of the T wave in aVL, both of which were judged to be not problematic. Since symptoms of aggravated schizophrenia were still present, the dose of the study medication was increased to 100 mg/day. On 05 Feb 2008, although the patient denied that he was experiencing auditory hallucination, persecutory delusion and disorganized behavior persisted and dose of the study medication was increased to 120 mg/day. On 22 Apr 2008, the subject thought that his food looked like a human being, did not eat, and from then on his food intake decreased. On 13 May 2008, improper thinking pattern was observed during consultation, the subject was in an aggressive mood, and although he took the prescribed drugs including the study medication, after supper, he vomited all of these. On that day his laboratory results were unremarkable; Na was 138 meq/dL, K was 5.0 meq/dL, Cl 102 meq/dL and glucose 107 mg/dL and his ECG was normal with normal vital signs of BP 134/62 mmHg and heart rate of 84/min. He refused the administration of Cercine [diazepam] to control his unrest. Since there was significant hallucination, delusion, and psychomotor excitability, Serenace 1A (haloperidol) was injected intramuscularly. Vital signs taken the following day were normal but the subject

had persecutory delusion, took only staple food for lunch and refused supper. The subject, however, took the study medication. On 15 May 2008, the subject's vital signs were normal. In the afternoon, he claimed that he "collapsed but didn't hit anything." He refused to take Cercine [diazepam] and was instead given an intramuscular injection of Serenace 1A. The last dose (b) (6) of the study medication was taken on the evening of (b) (6). Five minutes after midnight, on (b) (6), a nurse noted that the subject was not breathing and was incontinent. There was cyanosis of the lips, he was pulseless, and his pupils were dilated with negative pupillary light reflex. CPR was initiated with ECG monitoring, Veen-D injection was given, and oxygen at 4L/min was administered. No substances were found upon suctioning of the mouth. The subject did not respond to the CPR and was subsequently declared dead. An autopsy was not performed.

The investigator reported the event of sudden death to be serious and possibly related to treatment with the study medication. The investigator also reported the event of sudden death to be probably related to Serenace [haloperidol].

D1050237-0410-00001; 73 YOWF [Sudden Death]

On (b) (6) of treatment with lurasidone 80 mg daily, the subject died very suddenly. The subject was last seen at Visit 12 (month 7) of the study. Her prior laboratory results from 05 Dec 2009 were unremarkable except for high cholesterol and LDL, which had been present throughout the study. Her ECG showed a HR of 63/min, PR of 161 msec, QRS of 85 msec, and QTcF of 419 msec. There was also possible left lateral ischemia that on further evaluation was likely only non-specific ST-T wave changes. She had a prior myocardial infarction in the distant past, but was never on medication nor was she followed and has been stable since. Her vital signs performed on 19 Dec 2009 were HR of 68/min sitting and 92/min standing, BP of 100/60 mmHg sitting and 120/90 mmHg standing,; RR was 26/min and temperature 36.4° Celsius. The staff at the retirement village reported that the subject was physically very well and active prior to her death. The staff did not notice any physical signs or symptoms of any illness during the week before her death. The investigator also confirmed that the subject was very stable the week before the event. She had gone to the hairdresser and presented with no symptoms of any illness whatsoever. Furthermore during the site's weekly phone call, the subject did not have any complaints. In contrast to the site's assessment of her condition, the subject reported some mild shortness of breath to her son during the week prior to her death. Her son only mentioned this to the staff after the subject's death. He was not too concerned, but made an appointment for her to see a physician on a non-urgent basis.

On the day of the event, the subject's son confirmed that she was seen approximately 20 minutes prior to her death with no complaints. The subject was found in her bathroom sitting in a chair after telling staff that she was going for a bath. The subject's cause of death was not known. The subject's family was not

interested in having an autopsy performed. The investigator confirmed that an autopsy was definitely not performed.

The investigator reported the serious adverse event, (sudden death) pulmonary embolism, to be serious because it was fatal and was considered unlikely related to the study medication. Possible causes of death included pulmonary embolus and myocardial infarction. The investigator stated the following: "It would be unusual for the study medication to cause this serious adverse event as the subject was on the study medication for 6 months without any problems. The family has refused an autopsy and therefore causality cannot be ruled out with certainty. The subject had a myocardial infarction years ago and has never been on any cardiac medication and was quite stable from a cardiac point of view." There was no known prior history of thrombosis or emboli.

D1001002-0107-0004; 49 YO Asian female [Sudden Death]

Screening laboratory tests and electrocardiogram (EKG) were unremarkable on 19 Jan 2009. On 02 Feb 2009 (baseline) the subject's laboratory results were also unremarkable: sodium = 142 meq/dL, potassium = 3.5 meq/dL, chlorine = 108 meq/dL, and glucose 93 mg/dL; platelets, hematocrit and white blood cells were all normal as was her EKG (QTcF 397 msec). On 13 Feb 2009, 18 days from the start of treatment with double-blind study medication (lurasidone 80 mg), the subject was noted to be anorexic. No treatment was given for the event and treatment with the study medication was continued. An ECG was done on 17 Feb 2009 and the result was normal (QTcF 385 msec). On 21 Feb 2009, she complained of giddiness, flatulence, queasiness, and headache. Vital signs revealed a blood pressure (BP) of 139/96 mmHg and a pulse rate (PR) of 84/min; bed rest was advised. There were no appreciable findings thereafter until 25 Feb 2009 at 10:20 AM, when she again complained of giddiness and was clutching her head with her hands. BP was 127/94 mmHg and pulse rate was 92/min; bed rest was advised. Twenty minutes thereafter, her roommate reported that she was giddy in the upright position. BP was 158/83 mmHg and pulse rate was 87/min. At 12:30 PM of the same day, she complained of chilliness. Her temperature was 36.8 degrees Celsius. She was placed on bed rest and clinical observation. On 26 Feb 2009, she developed excoriation of the upper extremities, which was noted to be bleeding. A physician examined her and Eurax (crotamiton) and gentamicin ointments were applied on the excoriation. She took only a bite for dinner and went to bed early. On 27 Feb 2009 at 3:15 PM, she was noted to have a stone-like facial expression and was sweating. Temperature was 36.3 degrees Celsius and pulse rate was 96/min. Communication level and mental condition remained the same. Marked excoriation on her upper extremities was again noted. Progression of anorexia was also observed and treatment with the study medication was discontinued after that evening's dose. Treatment with other antipsychotic drugs was to be resumed the (b) (6), she was found in the supine position, rigid and cyanotic with no palpable pulse. There was no appreciable blood pressure and she had urinary incontinence. She was brought

to the treatment room at 3:20 AM and an ECG showed asystolic cardiac arrest. Her ECG results at screening, baseline, and visit 4 were normal and her laboratory test results at screening and baseline had been normal as previously noted. Post-mortem CT scans of the head and chest revealed venous bleeding in the brainstem and pericardial bleeding, but no specific cause of death was listed. An autopsy was suggested for further investigation but her family declined. On 16 Mar 2009, the study code was broken by the Principal Investigator; the subject was found to be receiving lurasidone 80 mg daily. The investigator judged the event of sudden death to be serious (fatal) and possibly related to treatment with study medication. The investigator judged the events of anorexia (appetite loss) and excoriation (scratch) to be moderate and possibly related to treatment with study medication. The event of giddiness (dizziness) was judged by the investigator to be mild and possibly related to treatment with study medication.

D1050237-0017-00030; 52 YOWM [Sudden Death reclassified to Hypertensive Heart Disease based on autopsy findings]

On (b) (6) of treatment with lurasidone 80 mg daily, the subject was found dead in bed as if he was asleep. No prior hypertensive heart disease or history of hypertension had been reported. He did have a history of hypokalemia for which he was receiving potassium supplementation; he also had a history of cocaine use. Prior laboratory results on 30 Jan 2009 showed Hct of 36.5% with normal MCV and MCHC and a WBC of 4,100 μ L; on 05 Feb 2009 electrolytes were Na = 138 meq/L, K = 3.1 meq/L, Cl = 96 meq/L and HCO₃ 33 meq/L. A prior ECG done on 30 Jan 2009 showed a HR of 63/min, PR of 203 msec (present at baseline as well), QRS of 85 msec, and QTcF of 464 msec (range 437 to 473 msec at prior visits). Vital signs on 20 Feb 2009 were HR 66/min sitting and 90/min standing, BP 126/84 mmHg sitting and 100/70 mmHg standing, and RR 18/min.

Maintenance personnel contacted the subject's sister who in turn contacted the site to inform the investigator about the subject's sudden death. An autopsy then cremation was performed. The autopsy revealed the internal examination for the cardiovascular system reported heart weighed 310 grams with advanced autolysis. The left ventricle was of normal thickness with a ventricular wall thickness measuring 1.2 cm. The red-brown myocardium is soft and free of discrete lesions. Histopathology revealed diffuse ventricular interstitial fibrosis and atherosclerotic coronary artery disease with 70% occlusion of the left anterior descending coronary artery. The coronary arteries are normally distributed with a right dominant pattern and display mild atherosclerosis. The epicardium, valve leaflets, chordae tendineae, and endocardium appear normally formed. The thoracoabdominal aorta and its major branches are normally distributed and display mid atherosclerosis. Mild arteriolonephrosclerosis was also noted. The cause of death was recorded as hypertensive cardiovascular disease, specifically diffuse ventricular interstitial

fibrosis and mild arteriolonephrosclerosis. The medical examiner noted to manner of death was natural.

The investigator reported the serious adverse event, hypertensive heart disease, to be serious because it was fatal and considered unrelated to the study medication. On follow-up after receipt of the autopsy report, the investigator reported the sudden death was due to hypertensive cardiovascular disease.

D1050237-0020-00036; 44 YOWM [Sudden Death reclassified to Massive GI Hemorrhage based on autopsy findings] (blinded study med)

On (b) (6) Day 178 of treatment with double-blind study medication, the subject was found dead. On (b) (6), the subject was due for Study Visit 11 at the site. The site was notified by the subject's apartment manager that the subject was found dead the previous evening. The subject completed Visit 10 where his vital signs were obtained and revealed normal findings. An ECG was performed on 05 May 2009 (Week 6) with normal results. The last known date of study medication administration was 18 Aug 2009. At the time of this report, no other relevant information was available.

The investigator reported the event, sudden death, as serious (fatal). The event was considered possibly related to the study medication.

(No prior medical history of heart disease).

D1050233-0058-00002; 46 YOBF [Myocardial Infarction] (blinded study medication)

On (b) (6), 30 days after the start of treatment with blinded study medication, the subject experienced a myocardial infarction and died in her sleep. The event was reported to the investigator by the subject's father only on 12 May 2009, after several attempts by the site coordinator to contact the subject for follow-up visits from (b) (6) failed and after a letter was sent to the subject on 30 Mar 2009. An autopsy was performed on 09 Mar 2009 and indicated that there were no injuries which could be considered a contributing cause of death. Her death is attributed to probable cardiac arrhythmia due to a congenital coronary artery anomaly (hypoplasia of the right coronary artery). A contributing factor is considered to be cardiomegaly (heart weight 530 grams). Toxicologic analyses of body fluids obtained at the time of autopsy were remarkable for presence of her prescription medications which were essentially within the therapeutic range. In view of the scene and circumstances surrounding the death and autopsy findings, the manner of death is classified as natural. Her prior laboratory results (on 05 Feb 2009) were CRP of 2.63 mg/dL and electrolytes normal (Na was 139 meq/dL, K was 3.5 meq/L, Cl was 106 meq/L, and HCO₃ was 21 meq/L). An ECG on 19 Feb 2009 was normal (PR was 157 msec, QRS was 80 msec, and QTcF was 426 msec) and vital signs on 26 Feb 2009 were HR of 79/min, RR of 18/min, and BP of 100/69 mmHg sitting and 102/74 mmHg standing.

The investigator judged the event of severe myocardial infarction to be serious (fatal) and unlikely related to study medication. The subject was no longer taking the study medication at time of the event.

9.6.2 Respiratory Failure

D1001001-00484; 56 YOAF

Time from first dose to event = 47 days

On Study Day 1, after starting treatment with double-blind study medication (lurasidone 20 mg), the subject complained of symptoms such as fatigue, insomnia, headache, and nausea. She was monitored closely. The subject has a history of hypochondriacal complaints prior to the start of the study. On 01 February 2006, she started to take Bufferin (aspirin) as needed for her headache. Complaint of headache persisted (considered a hypochondriacal symptom) and on 14 February 2006, Goodmin [sic] [Godmin – brotizolam] and Halrack [triazolam] were added as treatment. On 21 February 2006, the subject was noted to have a tendency to lie down and complained of sleepiness in the morning. On 22 February 2006, a nurse found the subject unconscious with glossoptosis and a blood pressure of 122/84 mmHg. Her physician injected Theraptique (dimorpholamine) intramuscularly but she was only responsive to pain. She exhibited open-mouth breathing, cyanosis, muscle reflex was present, weak pupillary reflex, and normal cardiac rhythm. Her oxygen saturation was 20% and she was given oxygen at 5L via nasal cannula. Her oxygen saturation improved to 95% and cyanosis was resolved. Later in the morning however, oxygen saturation started to decrease requiring the administration of higher levels of oxygen and blood pressure ranged from 152-180/112-120 mmHg. Thereafter, at around noon of the same day, the subject was noted to be tachycardic with a heart rate of 116, cyanotic with an oxygen saturation of 35%, unresponsive to pain or name calling, and her urine output was 300 mL. The subject was transferred to another hospital with a diagnosis of encephalopathy of unknown etiology where supplemental oxygen was given by mask at 10 L/min. Blood concentration tests for the study medication and for benzodiazepines were done. Determination of blood gases revealed a PaO₂ and PaCO₂ of 229 and 159, respectively. Due to respiratory acidosis, the subject underwent endotracheal intubation and was supported by an artificial respirator on SIMV mode. The subject's breathing was faint and her brainstem and oculomotor responses were negative. On 23 February 2006, the subject became conscious with recovered brainstem response. She was treated with antibiotics for a mild pulmonary complication. On 01 March 2006, she was on CPAP mode on the artificial respirator, and had recovered to be able to communicate with simple gestures, and was projected to be able to speak after extubation. Findings from imaging and spinal fluid tests and other investigations suggested that the possibility of brain damage and cerebrovascular lesions were low and that there was a possibility of drug toxicity, misuse of drugs or an inadvertent overdose of drugs. The subject's condition stabilized and on 11 March 2006, she was

transferred back to the hospital where she had been admitted during the study. On 05 April 2006, the subject was considered to have recovered from the event of respiratory failure.

The principal investigator and sub-investigator reported the event, respiratory failure, to be probably related to the study medication. Based on the subsequent results of blood concentration tests done on 22 February 2006 which revealed that the blood concentration of the study medication was within a steady state range and the serum concentration of nitrazepam was high, the principal investigator provided an opinion that the event was highly likely to have been a benzodiazepine-related respiratory depression and not related to the study medication. Therefore, the principal investigator reconsidered, and judged that there was no causal relationship with the investigational product.

D1001048-0072; 41 YOAF (death secondary to septic shock, associated respiratory failure)

Time from first dose to event = (b) (6)

The subject started treatment with open-label, flexible dose study medication (lurasidone) on 13 July 2007 at 40 mg/day. Psychiatric symptoms did not improve and the dose of the study medication was increased to 60 mg/day on 20 July 2007. The dose was further increased to 80 mg/day on 07 September 2007 and administration of Akineton (biperiden hydrochloride) 2 mg daily was re-started due to akathisia. On 21 September 2007, akathisia resolved; however, the subject developed urinary incontinence and the dose of the study medication was reduced to 60 mg/day. On 05 October 2007, since psychiatric symptoms have not improved and urinary incontinence had resolved, the dose of the study medication was increased to 80 mg/day. An electrocardiogram done on the subject on 02 November 2007 revealed sinus arrhythmia, sinus bradycardia, and right ventricular conduction delay which were not considered to be a problem and treatment with the study medication was continued. The subject developed common cold and constipation on 06 November 2007 and PL granules were given as treatment. On 09 November 2007, the subject experienced sleeplessness and aggravation of schizophrenia after learning that her nephew was being bullied at school. On 11 November 2007, she was noted to be confused, went up and down the stairs at night, wandered in the room, and suddenly took off her clothes. Sleeplessness persisted and on 12 November 2007, she was noted to be stuporous. The subject's mother called for an ambulance; however, the subject refused hospital admission and the paramedics notified the investigator. The study medication, Rohypnol (flunitrazepam) 1 mg, and Halcion (triazolam) 0.25 mg were administered orally which improved the subject's condition. The subject was given Risperdal (risperidone) 1 mL. The subject was again noted to be restless early morning of (b) (6) and another 1 mL of Risperdal was given. Three hours after, the subject was given Doral 15 mg. The subject's mother found her lying on the floor early afternoon of the same day, called for an ambulance, and when the paramedics arrived, the subject was in respiratory arrest with a systolic blood pressure of 40-50 mmHg

and a pulse rate of 60/min. On the evening of the same day, the investigator was informed by the subject's mother that the subject was brain dead. On the evening of (b) (6), the subject's blood pressure was 58/45 mmHg, and she had no spontaneous respiration. Tracheostomy was performed and the subject was given artificial respiration. Dyspnea caused by aspiration was ruled out and renal function was normal with a urine volume of 100 mL/hr. There were no abnormalities with the blood test results. On (b) (6), the subject expired. The remaining amount of study medication and other drugs prescribed were retrieved on 05 December 2007 and it was established that there was no overdose or misuse. The investigator reported the event of acute respiratory failure to be serious with an unknown relationship to treatment with the study medication. And the investigator also considered that the causal relationships with the other concomitant drugs were unknown.

The autopsy report stated the following findings: The cause of death was septic shock. Grampositive cocci infiltration shown in organs throughout the body (skeletal muscle, cardiac muscle and lung), evidence of muscle dissolution, relatively high body temperature, remarkable changes after death compared to postmortem time, generalized skin edema, and subepidermal blistering. Based on the autopsy results, the investigator reported the event of septic shock to be serious and not related to treatment with the study medication. The investigator further reported that the onset date of septic shock was (b) (6) based on the results of the CRP exam which revealed a markedly elevated level of 0.78 mg/mL and the blood coagulation test which revealed DIC.

D1050237-0027-00046; 50 YO BM

Time from first dose to event = 1 day (angioedema), 2 days (respiratory failure)

Note: this case was not identified by the Sponsor as a case of respiratory failure – only as an SAE of angioedema

On (b) (6) Day 2 of treatment with double-blind study medication (lurasidone 80 mg) the subject developed severe angioedema and was admitted to the hospital. As reported by the nursing staff, the subject complained of a pulling sensation on the left side of his neck, became anxious, and requested Ativan (lorazepam). He was given 1 mg oral Ativan; however, symptoms persisted and the subject requested to be taken to the emergency room. After the emergency room evaluation, he was hospitalized for further treatment. The subject recovered from the event on 16 June 2009.

The investigator reported the serious adverse event, angioedema, to be serious because it required inpatient hospitalization and was considered unlikely related to the study medication.

Comments from reviewer: This patient was receiving a number of concomitant medications (including amlodipine for hypertension), but had been receiving these medications since 2005 – this event occurred in 2009. Interestingly, the

narrative lists “drug hypersensitivity” as a concomitant illness with no other clinical information (preexisting?).

The CRF noted that the following medications were administered due to “respiratory failure”: prednisone (oral), levofloxacin (IV), propofol (oral), etomidate (IV), vecuronium (IV) [these were also noted as concomitant medications in a section of the narrative, but the clinical information was not adequately incorporated into the description of the clinical event itself and there was no mention of respiratory failure]. Succinylcholine (IV) was administered on (b) (6) to intubate subject secondary to angioedema.

Thus, it would appear that the respiratory failure may have been related to a severe hypersensitivity reaction that first manifest as angioedema. The angioedema was noted 1 day after lurasidone administration shortly followed by respiratory failure occurring on day 2. The lack of adequate characterization of this serious adverse event is of concern to this reviewer. The term “angioedema” does not adequately characterize this event.

9.6.3 Convulsions

D1050229-0019-00004; 21 YO BM [Complex partial seizures]

Time from first dose until event = 17 days

SAE and discontinuation due to adverse event

No history of seizures noted in narrative.

On (b) (6), 1 day after stopping double-blind study medication (following 16 days of treatment with double-blind study medication [lurasidone 40 mg], from (b) (6) at 12:15 A.M., the subject was observed to have

experienced a complex partial seizure that was considered severe in intensity. He was minimally responsive and repeated the words spoken to him. Vital signs included a thready pulse of 106, blood pressure of 100/72, and an oxygen saturation of 98. The seizure lasted for approximately 5 minutes. The site’s progress notes described the subject appeared “post-ictal – no incontinence observed.” The subject complained of nausea. He was transported to the emergency room. The emergency room records noted the investigator site nurses witnessed the seizure and described the subject as having lost consciousness and was unresponsive. Emergency room records described the subject experienced his first seizure episode. Lab results from the emergency room were normal: negative urine toxicology screen, normal electrolytes, normal blood chemistry, and normal urinalysis results. A head computerized tomography (CT) scan was performed and revealed “no acute intracranial abnormality.” An electroencephalogram was not performed. No other seizure episodes were observed while the subject was in the emergency room. A script for Keppra (levetiracetam) was written and he was subsequently returned to the facility that same day. No other seizure activities were observed. The subject was

considered to have recovered from the event, complex partial seizure, (b) (6)
(b) (6).

The investigator reported the event, complex partial seizure, to be serious because it was considered medically significant and possibly related to the study medication. The investigator comments, "Complex partial seizure was diagnosed based on the patient's report and the nurses' observations of the seizure." As per the emergency room report, labs and CT scan of the head were normal, and the subject had no additional seizure activity while in the emergency room. Per subject, "no family history and no history for self" of seizures. The company considered the event, complex partial seizure, to be serious, unexpected based on the Investigator's Brochure, and possibly related to the study medication. At the time of reporting, there had been 3 cases of convulsive seizures reported from the clinical trials from lurasidone (also based on the current Investigator's Brochure), but no cases of complex partial seizure.

D1001048-00133; 37 YOAF [Convulsion]

Time from first dose until event = 310 days
SAE and discontinuation due to adverse event
No history of seizures noted in narrative.

The subject started treatment with open-label, flexible dose study medication (lurasidone) on 18 January 2008 at 40 mg/day. The dose of the study medication was increased to 60 mg/day on 01 February 2008, 80 mg/day on 15 February 2008, 100 mg/day on 29 February 2008, and 120 mg/day on 14 March 2008. On 15 November 2008, laxoselin 15 drops were administered on each day for control of bowel movement. On 16 November 2008, the subject experienced abdominal pain with slight diarrhea. She had difficulty falling asleep and was given Cysvon (nitrazepam) 1 tablet twice that day. On 17 November 2008, the subject was afebrile with body temperature of 37.4 degrees C but had diarrhea, nausea, abdominal pain, and pharyngeal pain. She was prescribed Kakkontou (reviewer could not find), Astomin (dimemorfan, cough suppressant), and SP Troches and was given Cysvon 1 tablet since she could not sleep from coughing hard. In the evening of 22 November 2008, after supper, she informed the nurse that she had diarrhea and 30 minutes after, she vomited and was found lying on the floor in her room, consciousness level was JCS 100, vital signs were normal, and SpO2 was 96%. She regained consciousness and vomited again. Thereafter, she as noted to have a silly smile on her face and laughed wildly and stated that she was having a lot of fun. This was followed by a sudden onset of tonic-clonic seizure. Horizon 10 mg (diazepam) was administered intramuscularly. She had a second episode of convulsive seizure several minutes after followed by two episodes of vomiting. The last dose of the study medication was taken after supper on 22 November 2008 at which time the investigator discontinued the patient from the study. She was to start treatment with valproic acid for convulsion, Depakene 600 mg, Risperdal 3 mg, and Horizon 15 mg (diazepam) after every meal. In the early morning of 23 November 2008,

however, she was laughing wildly and had an auditory hallucination which was followed by a convulsive seizure. Horizon 10 mg (diazepam) and Phenobarbital 100 mg were given intramuscularly. She had two more episodes of convulsion that morning. She later complained of headache and arthralgia. After lunch, her temperature was 38.2 degrees C and Voltaren 25 mg suppository was administered. In the afternoon, she had another episode of convulsion associated with urinary incontinence. She ate supper with assistance and urinary incontinence persisted. Her body temperature taken at 18:30 was 38.1 degrees C and she was given Calonal (acetaminophen) 1 tablet. She was later given Silece (flunitrazepam) and Alosetron (reviewer: laxative composed of senna leaves and other vegetables) before sleeping. The subject was released from isolation on 26 November 2008 and brain wave and head CT scan examinations done on her did not reveal any abnormal finding. The event of convulsion was considered resolved on 24 November 2008.

There was no organic lesion in the head CT scan and a viral encephalitis was less likely. The investigator reported the event of convulsion to be serious with an unknown relationship to treatment with the study medication.

D1001001-00041; 38 YOAF [Convulsion]

Time from first dose until event = 16 days

SAE

No history of seizures noted in narrative.

On 17 March 2006, after starting treatment with double-blind study medication (lurasidone 20 mg), the subject complained of insomnia and took Benzalim (nitrazepam). On 30 Mar 2006, she experienced thanatophobia (fear of death) and made many calls to her home. The following day, 31 March 2006, the subject refused blood collection for the second week of dosing, thanatophobia was aggravated further, and she was withdrawn from the study by the investigator. The last dose of study medication was on 30 March 2006. On 01 April 2006, two days after the last dose of treatment prior to dinner the subject suddenly fell and experienced epileptiform fits in the form of generalized rigidity, eyeballs raised upward, and foaming of the mouth which continued for about thirty seconds followed by cyanosis of the lips. The subject did not initially respond to her name but became conscious after five minutes and recovered on the same day. Vital signs remained stable. Although she complained of hip and thigh pain, there was no discoloration or swelling noted. However, left occipital swelling (contusion) was observed and she also experienced soft stool and vomiting. She complained later of occipital headache without nausea. The subject was advised to consult a neurosurgeon but refused. The occipital headache continued until the following day, 02 April 2006. She was treated with Benzalim (nitrazepam) on 02 April 2006 for insomnia and was started treatment on Zyprexa on 03 April 2006. Thanatophobia was ongoing at the time of reporting. The investigator reported the relationship of the event, convulsive seizure, to the study medication to be unknown.

D1001016-00066; 49 YOAM [Convulsion]

Time from first dose until event = 10 days
SAE and discontinuation due to adverse event
No history of seizures noted in narrative.

The subject started treatment with dose-flexible study medication (lurasidone) at 20 mg on 30 March 2004. The dose was increased to 40 mg on 31 March 2004 and 60 mg on 01 April 2004. On 08 April 2004, the subject slipped off his chair. At that time, the subject's blood pressure was 150/100 mmHg, pulse rate 84 beats/minute, and body temperature was 36.4 degrees centigrade. He was conscious but speechless. No head trauma was present. Automatism-like movement was present, mainly in the upper right extremity. Subsequently, the subject developed generalized convulsive seizure for 2 to 3 minutes. To prevent further seizures, 10% Phenobarbital 1A (phenobarbital) IM was administered. Treatment with the study medication was discontinued. Later on the same day, head CT and EEG were performed. Head CT revealed no abnormalities while EEG showed electromyogram artifacts but negative epileptic discharge. Although the subject was now verbally responsive and his vital signs continued to stabilize, some facial sweating was noted with mild hot flashes of the body. Three point iced pillow cooling was done which eventually resolved the hot flashes of the body. There were no tremors observed. The subject was considered as recovered from the event of convulsion. On 09 April 2004, fasting blood tests were performed which revealed an increased CPK level at 868 IU/L. Vital signs were noted to be normal and the subject had no physical complaints. ECG, EEG, and urinalysis were done on the same day and the results were within normal limits. Pyrexia, which started on the night of 08 April 2004, and increased CPK (868 IU/L) on 09 April 2004 were considered to be a series of events associated with convulsive seizure. Valproic acid was used from 09 April 2004 as prophylactic measure. The investigator reported the event, convulsion, to be a serious important medical event that required medical intervention and was considered to be probably related to the study medication.

D1050237-0021-00010; 44 YOWF [Convulsion]

Time from first dose until event = 60 days
Discontinuation due to adverse event
No history of seizures noted in narrative.

On 17 July 2009, 60 days after the subject started the open-label extension phase with study medication (lurasidone 80 mg), the subject experienced a possible seizure (verbatim term). No treatment was administered. She recovered from the event on 17 July 2009 and discontinued study medication on 20 July 2009.

The investigator judged the event, possible seizure, to be possibly related to the study medication.

9.6.4 Cerebrovascular accidents

D1050231E-0037-00004; 50 YOWF [Possible cerebrovascular accident]

Time from first dose until event = 88 days

On (b) (6), Day 14 of treatment with open label lurasidone 40 mg (following 43 days of double-blind study medication [lurasidone 40 mg] from 04 Mar 2008 to 15 April 2008, and 31 days of open-label lurasidone 80 mg from 19 (b) (6), the subject was admitted to the emergency room with right-sided weakness. She was diagnosed with moderate possible cerebrovascular accident (CVA) with minimal residual right lower extremity weakness with decreased sensation to light touch in her right upper and lower extremities. The study medication therapy was discontinued upon hospitalization. On (b) (6), a computerized tomography (CT) scan of the brain revealed mild diffuse atrophy and microangiopathic ischemic changes, and a magnetic resonance imaging (MRI) of the brain showed atrophy and microvascular disease. Both the CT scan and MRI did not reflect an acute CVA. The hospital records revealed that the subject had previously experienced a CVA in 2003. History of a CVA was not reported by the subject or noted during the initial medical history exam for this study, and no known history of CVA was noted in the previous records on file for the subject. Due to a history of psychiatric problems, the subject was evaluated by a psychiatrist. She lived alone and needed to be at a modified independent level to return to independent living. It was felt that she would benefit from comprehensive rehabilitation, and some adjustments were made to her medications. The subject showed no evidence of auditory hallucinations, delusional thoughts, or behavioral problems. She was cooperative and made nice progress in therapy. She refrained from smoking by using the Nico Derm (nicotine) patch. She remained without complaints of chest pain, breathing difficulties, or lower extremity edema, and had no complaints of pain. The subject essentially achieved a modified independent level for simple self-care, as well as gait using a front wheel walker. On (b) (6), she was discharged with ongoing residual sequelae due to the event. A home evaluation was provided on the day of discharge. The discharge diagnoses included right hemiparesis, status post cerebrovascular accident, schizoaffective disorder, history of deep vein thrombosis, previous history of stroke, congestive heart failure, tobacco dependency, and chronic obstructive pulmonary disease. The discharge medications included Aspirin (acetylsalicylic acid), NicoDerm (nicotine) patch, Protonix (pantoprazole), Seroquel (quetiapine), Depakote (divalproex), and Ambien (zolpidem).

The investigator reported the event, possible cerebrovascular accident, to be serious because it required hospitalization, and was unlikely related to the study medication. Investigator's comment: The MRI results did not show an acute CVA;

however, the symptoms experienced by the subject were consistent with a CVA. Given the subject's high risk factors for CVA: history of a CVA in 2003, obesity, prior episode of deep vein thrombosis, congestive heart, failure and hyperlipidemia, the event of possible cerebrovascular accident was considered unlikely related to the study medication.

D1050237-0014-00013; 50 YOBM [Left-sided CVA]

Time from first dose until event = 143 days

SAE and discontinuation due to adverse event

On 12 January 2009, Day 143 of treatment with double-blind study medication (lurasidone 80 mg), the subject complained of moderate difficulty ambulating and bearing weight on his right leg with weakness in his right arm and was hospitalized due to left-sided CVA (cerebrovascular accident). Myocardial infarction was ruled out. A CT scan of the brain showed findings consistent with sub-acute infarct of left parasagittal area, carotid ultrasound was normal. A brain MRI showed no evidence of acute infarction. On (b) (6), the subject showed up at the clinic for a study visit that he missed and reported that he developed a left-sided CVA and was hospitalized. After he felt dizzy, he was taken to the emergency room by ambulance and was told he may have had a "mild stroke." On (b) (6), the subject recovered from the event with sequelae of residual right-sided weakness and was discharged from the hospital. It wasn't until the investigator received the hospital medical records that it was discovered the subject had a previous medical history of left-sided CVA; had this information been conveyed at the time of enrollment, the subject would not have been enrolled into the clinical trial. The investigator reported the serious adverse event, left-sided CVA, to be serious because it required inpatient hospitalization and was considered medically significant and unlikely related to the study medication.

D1050199-0006-09011; 50 YOM [Stroke]

Time from first dose until event = 45 days

SAE and discontinuation due to adverse event

A 50 YOM with a 40-year history of smoking (1-3 packs of cigarettes daily) and hypertension, was enrolled into the blinded study D1050196 followed by this open-label study of D1050199 for the treatment of schizophrenia. He received the first dose of blinded study medication, (SM-13496) on 11-Oct-2004 and the last dose on 21-Nov-2004 followed by the open-label study medication, SM-13496 80 mg, once daily, on 23-Nov-2004 and the last dose on 25-Nov-2004. Concomitant medications included cetirizine hydrochloride, propranolol hydrochloride, Flonase NS, and temazepam. On (b) (6), the subject presented to the emergency room (ER) with symptoms of left-sided numbness and decreased vision in his left eye. He was subsequently admitted to the hospital with a stroke and study medication was discontinued due to the event. A

magnetic resonance imaging (MRI) of the brain, with and without contrast, showed multifocal ischemic lesions (acute to subacute) in the distribution of the posterior circulation of both cerebral hemispheres. The findings involved the right parahippocampus, the posterior right thalamus as well as punctate lesions of the left posterior occipitoparietal regions. The multifocal distribution of the lesions suggested possible embolic disease to the posterior circulation without evidence of hemorrhage. Incidentally noted was a left maxillary sinusitis. An electrocardiogram (ECG) was found to be normal. Laboratory studies revealed the troponin I was negative, electrolytes, BUN, creatinine, activated partial thromboplastin time (aPTT), glucose, creatine kinase MB fraction (CK-MB), creatine kinase (CK), hematocrit (HCT), white blood cell (WBC) count, platelet (PLT) count, prothrombin time (PT), and an international normalized ratio (INR) were all normal. On (b) (6), an arterial Doppler scan revealed a minimally abnormal study due to the presence of some smooth plaque in the right carotid system. There was no significant focal stenosis identified. No abnormality in the left carotid system was identified. Both vertebral arteries were identified and found to have antegrade flow. On (b) (6), an echocardiogram identified no cardiac source of embolus. There was no 2-D or color Doppler evidence of PFO (patent foramen ovale) or ASD (atrial septal defect), but no bubbles were given. A structurally normal heart, with mild bradycardia (heart rate between 52 and 64) was noted throughout the study. On (b) (6), the subject was discharged from the hospital and placed on treatment with warfarin sodium 7 mg daily. On 06-Dec-2004, the subject was seen in follow-up by his Family Practice Physician and reported slight numbness of the left side of his abdomen and left thigh. On 07-Dec-2004, he was seen by his primary care physician, and treatment with warfarin was stopped. On (b) (6), the subject developed confusion and delirium secondary to another stroke which was considered persistently/significantly disabling or incapacitating, and subsequently was admitted to the hospital. The subject was transferred to a retirement center on 27-Dec-2004 with the 2 serious events of stroke resolved with sequelae, which included numbness and tingling on his left side and poor short-term memory. His disposition and mood were excellent. The first stroke was considered serious and possibly related to the study medication SM-13496 by the investigator. The second stroke was considered serious. Since no etiology could be identified for the strokes, the investigator decided that they may be possibly related to study medication. In a follow-up report received on 26-Apr-2005, a neurology consultation done on (b) (6) found a deficit of impaired attention/concentration and acquisition abilities, limiting the subject's ability to learn new information. It was determined these findings were consistent with the acute nature of the cerebrovascular events but could also be attributed to the long-term impact of his mental illness or medication side-effects and could be better differentiated over time.

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

/s/

CARA L ALFARO
09/10/2010

NI A KHIN
09/22/2010
See CDTL review memo for additional comments and my recommendations.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number: 200603 O-1 Applicant: Dainippon
Sumitomo Pharma**

Stamp Date: 12/30/2009

Drug Name: Lurasidone NDA/BLA Type: NME

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			Ten studies were conducted in Japan.
6.	Is the clinical section legible so that substantive review can begin?			X	
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: D105006 Study Title: A double-blind, randomized, fixed dose, placebo-controlled, parallel-group, 6-week, efficacy, safety, and tolerability study of two dose levels of SM-13496 (lurasidone) in patients with schizophrenia by DMS-IV criteria who are experiencing an acute exacerbation of symptoms Sample Size: 149 Arms: lurasidone 40 mg/d, lurasidone 120 mg/d, placebo Location in submission: Module 5.3.5.1.	X			Based on input from Division in EOP2 meeting.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	<p><i>Study Number: D1050196</i> Study Title: A double-blind, fixed dose study of SM-13496 (lurasidone) and placebo in the treatment of schizophrenia Sample Size: 180 Arms: lurasidone 80 mg/d, placebo Location in submission: Module 5.3.5.1.</p> <p><i>Study Number: D1050229</i> Study Title: A Phase 3, randomized, placebo-controlled, clinical trial to study the safety and efficacy of three doses of lurasidone HCl in acutely psychotic patients with schizophrenia Sample Size: 500 Arms: lurasidone 40 mg/d, lurasidone 80 mg/d, lurasidone 120 mg/d, placebo Location in submission: Module 5.3.5.1.</p> <p><i>Study Number: D1050231</i> Study Title: A Phase III randomized, placebo- and active comparator-controlled clinical trial to study the safety and efficacy of two doses of lurasidone HCl in acutely psychotic patients with schizophrenia Sample Size: 478 Arms: lurasidone 40 mg/d, lurasidone 120 mg/d, placebo Location in submission: Module 5.3.5.1.</p>				
EFFICACY					
14.	<p>Do there appear to be the requisite number of adequate and well-controlled studies in the application?</p> <p>There are 4 pivotal studies in this submission (as outlined in #13) to support one indication</p> <p>Indication: Treatment of schizophrenia</p>	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		Two studies were US studies, two studies were US + foreign sites. The Division accepts foreign data.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	studies, if needed)?				
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	Not currently marketed in any country. Literature search conducted on 3/6/09 and 8/26/09.
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			Phase 2/3 studies Doses \geq 40 mg/day: N = 1898 exposed n = 458 \geq 24 weeks n = 161 \geq 52 weeks
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Most of the data for BMD (DEXA) and ophthalmologic exams will be submitted at the 120 day update. Division had previously agreed with this proposal.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	Waiver for children 0 – 9 years and deferral for children/adolescents 10 – 17 previously granted.
ABUSE LIABILITY					

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	Two studies were US studies, two studies were US + foreign sites. The Division accepts foreign data.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?				Evaluated by statistics
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				Evaluated by statistics
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical 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.

Please include a more detailed description of “abnormal” findings on ophthalmologic examinations. State what the abnormalities were and, for subjects with abnormal baseline and abnormal end-of-study examinations, if those abnormalities were unchanged. Since the majority of the ophthalmologic examination data will be provided in the 120-day update, it is acceptable to include this information for all data at that time (e.g. you do not need to provide these data at this time for the few subjects for which data have already been submitted).

Please provide an updated narrative for patient D1050231-0011-00001 who died due to “accidental (heroin) overdose”. The current narrative only provides information relevant to ALT changes (the AE that led to discontinuation from study).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please provide the autopsy report and any other relevant clinical details for patient #23701730. The event “sudden death – hypertensive heart disease” is noted, however, the information provided in the narrative does not indicate a prior history of hypertension. Please clarify.

For all deaths, please provide comprehensive narratives that include relevant clinical details including laboratory assessments, ECG data and vital signs.

Please indicate whether an application for lurasidone for any indication has been submitted to any foreign country.

Cara Alfaro, Pharm.D.

2/25/2010

Reviewing Clinical Analyst

Date

Clinical Team Leader

Date

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200603

ORIG-1

DAINIPPON
SUMITOMO
PHARMA AMERICA
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/

CARA L ALFARO
02/25/2010

NI A KHIN
03/01/2010