

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211230Orig1s000

211230Orig2s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 107203
IND 122590

MEETING MINUTES

Jazz Pharmaceuticals, Inc.
Attention: Lily Gong
Associate Director, Regulatory Affairs
3180 Porter Drive
Palo Alto, CA 94304

Dear Ms. Gong:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for JZP-110.

We also refer to the meeting between representatives of your firm and the FDA on September 19, 2017. The purpose of the meeting was to discuss and confirm the adequacy of your data and submission plan for an NDA for JZP-110.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact CAPT Kofi Ansah, Pharm.D., Senior Regulatory Project Manager, at (301)796-4158 or email: Kofi.Ansah@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
CAPT, USPHS
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA Meeting

Meeting Date and Time: September 19, 2017; 12:00 pm EDT
Meeting Location: FDA White Oak Campus, Bldg. 22, Room #1415
10903 New Hampshire Ave, Silver Spring MD 20993

Application Number: IND 107203 & IND 122590
Product Name: JZP-110
Indication: Treatment of Excessive Sleepiness in Narcolepsy and Obstructive Sleep Apnea (OSA)
Sponsor/Applicant Name: Jazz Pharmaceuticals, Inc.

Meeting Chair: Mitchell Mathis, MD

FDA ATTENDEES:

Robert Temple, MD	Deputy Director, Office of Drug Evaluation-I (ODE-I)
Mitchell Mathis, MD	Director, Division of Psychiatry Products (DPP)
Tiffany Farchione, MD	Deputy Director, DPP
Naomi Lowy, MD	Associate Director for Regulatory Science, ODE-I
Javier A. Muniz, MD	Clinical Team Leader, DPP
Kofi Ansah, PharmD, RAC	Senior Regulatory Project Manager, DPP
Sarah Seung, PharmD	Regulatory Project Manager, DPP
Glenn Mannheim, MD	Medical Officer/Clinical Reviewer, DPP
Aisar Atrakchi, PhD	Pharmacology/Toxicology Supervisor, DPP
Amy Avila, PhD	Pharmacology/Toxicology Reviewer, DPP
James Miller, PhD	Pharmacology/Toxicology Reviewer, DPP
Hao Zhu, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Huixia Zhang, PhD	Clinical Pharmacology Reviewer, OCP
Peiling Yang, PhD	Biometrics Team Leader, DBI/OB
Yang "Kelly" Yang, PhD	Biometrics Reviewer, DBI/OB
Daniel Berger, PhD	CMC Reviewer, Office of Pharmaceutical Quality (OPQ)
Shalini Bansil, MD	Reviewer, Controlled Substance Staff
Hari Cheryl Sachs, MD	Clinical Team Leader, Division of Pediatric & Maternal Health (DPMH)
Denise Johnson-Lyles, PhD	Senior Regulatory Project Manager, DPMH
Michelle Campbell, PhD	Reviewer, Clinical Outcome Assessments (COA) Staff

Douglas Warfield, PhD	Associate Director Biomedical Informatics, DPP
Jacqueline Sheppard, PharmD	Risk Management Analyst, Division of Risk Management
Vicky Chan, PharmD, BCPS	Team Leader, Division of Pharmacovigilance-I (DPV-I)
Kelly Harbourt, PharmD, BCPS	Safety Evaluator, DPV-I
Danijela Stojanovic, PharmD, PhD	Reviewer, DEPI

Jazz Therapeutics Attendees

In person

Karen Smith, MD, PhD, MBA	Global Head of Research/Development & Chief Medical Officer
Jed Black, MD	Senior Vice President, Sleep Medicine Therapeutic Area Head
Charles LaPree,	Senior Vice President, Global Regulatory Affairs
Philip Jochelson, MD	Vice President, Global Development Lead, Sleep & CNS
Lawrence Carter, PhD	Senior Director, Clinical Development
Dan Chen, MD, PhD	Senior Director, Clinical Development
Michelle Baladi, PhD	Senior Manager, Clinical Development
Maja Miloslavsky, PhD	Executive Director, Biostatistics
Jagan Mohan Achi,	Associate Director, Statistical Programming
Katie Zomorodi, PhD	Senior Director, Early Development and Clinical Pharmacology
Jingsong Zhao, PhD, DABT	Director, Nonclinical Development
Gary Appio, PharmD	Executive Director, Benefit Risk Management
Janice Mallison	Senior Director, Global Regulatory Affairs
Lily Gong	Associate Director, Global Regulatory Affairs
Kelly Seither	Global Molecule Lead
Joanne Curley,	Exec Director, Global Promotional Regulatory Affairs & Labeling
Darshan Patel	Head of Regulatory Affairs, SK Life Science, Inc. (partner)

Via Teleconference

Joel Selcher, PhD	Executive Director, Head of Regulatory Strategy
Sonia Rodrigues, PhD	Director, Global Regulatory Lead
Eileen Connolly	Global Regulatory Affairs-CMC
Darshika Doshi	Manager, Regulatory Strategy

1.0 BACKGROUND

Jazz Pharmaceuticals, Inc (Jazz) is developing JZP-110 for the treatment of excessive sleepiness in subjects with narcolepsy (IND 107203) and obstructive sleep apnea (IND 122590) (b) (4)

JZP-110 is a phenylalanine derivative that is a selective dopamine and norepinephrine reuptake inhibitor.

Jazz has had multiple interactions with the Agency throughout this drug development program when both INDs resided in the Division of Neurology Products. These include an End-of-Phase 2 meeting on July 8, 2014, and a number of Written Response Only meetings (i.e., Written Responses dated March 19, 2015, July 19, 2016, and January 26, 2017). Some of the clinical

issues identified in the End-of-Phase 2 meeting include the need for a lower dose arm for Phase 3 Study (14-003), use of co-primary objective and subjective endpoints, need for exclusionary criteria to be limited to medically unstable subjects, need to analyze cardiovascular adverse events in detail, and need for a double-blind withdrawal period at 6 months in the long-term open label study (14-004).

(b) (4) JZP-110 (then known as ADX-N05) was previously evaluated in the treatment of Major Depressive Disorder (MDD). A total of 512 subjects received ADX-N05 at doses ranging from 200 mg to 1000 mg/day, with exposures ranging from single dose to 8 weeks. Notable adverse events in these trials include a myocardial infarction, T-wave changes, increased heart rate, and elevated liver enzymes (6.5 to 7 times normal upper range).

The current clinical development programs consist of two studies in narcolepsy (ADX-N05 202 and 14-002), two studies in OSA (14-003 and 14-004), and a common, double-blind, placebo-controlled randomized withdrawal study at 6 months within the long-term open-label safety and efficacy study (14-005). The open-label part of the study is ongoing.

The Sponsor's stated purposes for this meeting are to:

- Introduce the JZP-110 development program to the DPP, which now has responsibility for the relevant INDs and upcoming NDA review
- Gain Agency feedback on the proposed submission plan and content of the upcoming NDA for JZP-110 in narcolepsy and OSA
- Review Agency feedback from EOP2 and Type C meetings with the previous reviewing Division of Neurology Products (DNP)
- Gain agency feedback on the adequacy of the nonclinical and clinical pharmacology packages
- Gain Agency feedback on the adequate and well-controlled registration studies ADXN05 202, 14-002, 14-003, 14-004, and 14-005 providing sufficient and reproducible evidence to support the efficacy and safety of JZP-110 for the reduction of excessive sleepiness and improvement of wakefulness throughout the day in patients with sleep disorders, including narcolepsy or obstructive sleep apnea (OSA)
- Gain Agency feedback on the proposed recommended doses of JZP-110 in patients with narcolepsy and OSA based on data from the registration studies
- Obtain Agency comments on the adequacy of the planned population pharmacokinetic/ pharmacodynamics analyses to be conducted in support of this NDA submission.

Jazz Pharmaceuticals, Inc (Jazz) is developing JZP-110 for the treatment of excessive sleepiness in subjects with narcolepsy (IND 107203) and obstructive sleep apnea (IND 122590) (b) (4). JZP-110 is a phenylalanine derivative that is a selective dopamine and norepinephrine reuptake inhibitor.

FDA sent Preliminary Comments to Jazz Pharmaceuticals on September 15, 2017.

2. DISCUSSION

Following are Jazz Pharmaceuticals, Inc's specific questions and FDA/DPP's responses and the discussion at the meeting.

2.1. Nonclinical/Pharmacology-Toxicology

Question 1: Nonclinical studies have been conducted to evaluate JZP-110 in pharmacology (including safety pharmacology), drug metabolism and pharmacokinetics, and toxicology (including abuse potential) studies. These studies have been previously summarized and submitted in the forms of the IND package, Investigator Brochure, and Annual Reports. Final study reports will be included in the NDA. The nonclinical safety evaluation package for JZP-110 was shared with the DNP at the EOP2 meeting (08 July 2014; meeting minutes dated 06 August 2014) and Type C Written Response (26 January 2017) and the feedback received from the Agency was integrated into the nonclinical development plan. We have now performed and completed a pre- and postnatal (Segment III) reproductive toxicity study in rats, and 2-year carcinogenicity studies in both mice and rats to support the market registration of JZP-110. Results of these studies are described in Section 5.2.1. Lists of the nonclinical studies to be included in the NDA are in Section 7.1.

Does the DPP agree that the nonclinical safety evaluation package is adequate and complete to allow review of the NDA submission to support market approval of JZP-110?

FDA Response to Question 1: *The nonclinical package appears sufficient to support review of the NDA. However, the overall adequacy of all studies will be a matter of review. Additional studies may be needed pending the review and evaluation of the study results.*

Sponsor's Comments: Jazz thanks the Agency for the feedback. No further discussion is requested at the meeting. However, assuming time permits at the end of the meeting, Jazz would be interested in understanding what additional studies may be required.

Discussion at Meeting: *The Division indicated that there are no specific additional nonclinical studies required at this time. However, if safety concerns arise during the course of reviewing the NDA, or if any safety signals arise during the clinical trials, additional nonclinical studies may be warranted at that time.*

2.2. Clinical Pharmacology

Question 2: The pharmacokinetics of JZP-110 after single and repeat doses has been well characterized in Phase 1 clinical studies, as described in Section 5.4 and in the briefing package submitted to FDA in December 2016 (IND 107,203; SN 0107 submitted on 21 December 2016). Based on the EOP2 meeting with the FDA (08 July 2014; meeting minutes dated 06 August 2014), the clinical pharmacology package now also includes the following studies:

- Study 14-001: A Phase 1, randomized, double-blind, placebo-controlled, crossover, human abuse liability study of JZP-110 in recreational polydrug users with recent histories of stimulant use
- Study 15-001: A Phase 1, single-dose, open-label study of the pharmacokinetics and safety of JZP-110 in subjects with normal or impaired renal function and in subjects with end-stage renal disease requiring hemodialysis
- Study 15-002: A Phase 1, randomized, double-blind, placebo-and positive-controlled, four-period crossover study of the effects of 300 mg and 900 mg of JZP-110 on QT/QTc intervals in healthy subjects
- Study 15-009: A Phase 1, randomized, crossover, open-label, food effect study of the pharmacokinetics, safety, and tolerability of JZP-110 in healthy adult subjects

The clinical pharmacology studies to be included in the NDA are listed in Table 4. Jazz has also completed six in vitro studies with human biomaterials to determine whether JZP-110 is a substrate, inhibitor, or inducer of relevant metabolizing enzymes and transporter proteins. Final study reports will be included in the NDA submission. The clinical pharmacology package for JZP-110 was designed in consultation with the DNP and is in line with feedback received from the Division at the EOP2 meeting (08 July 2014; meeting minutes dated 06 August 2014), Type C Written Response (26 January 2017), and the BCS 1 designation (Appendix, Summary of EOP2 and Type C Responses).

Does the DPP agree that the clinical pharmacology package as outlined is adequate and complete to allow the review of the NDA submission to support market approval of JZP-110?

FDA Response to Question 2: *The clinical pharmacology package appears adequate. However, it is possible that review of your study results may reveal a need for other studies to better inform the label. Please confirm whether the food effect study was conducted with the final to-be-marketed formulation. If not, please provide a justification as to why your findings from Study 15-009 are relevant.*

Sponsor's Comments: Jazz confirms that the food effect study was conducted with the final to-be-marketed formulation. However, assuming time permits at the end of the meeting, Jazz would be interested in understanding what other studies may be required to better inform the label.

Discussion at Meeting: *The Division confirmed that, on face, the completed clinical pharmacology studies are sufficient to support the NDA filing. The Sponsor raised the question on what other studies might be needed after the review. The Division provided an example on a drug-drug interaction study for a concomitant use of a urinary pH modulator if JZP-110 demonstrates pH-dependent change in solubility. The Division indicated that needs for such as a study will be determined after reviewing the totality of information in the package.*

Post Meeting Comment: *Please provide a Clinical Pharmacology Summary using the template attached at the time of NDA submission.*

Question 3: Jazz is performing a population pharmacokinetic and exposure-response analysis. The overall objective is to determine whether there are patient covariates that significantly affect JZP-110 exposure. In addition, the relationship between JZP-110 exposure and key efficacy and selected safety parameters will be evaluated. These analyses may inform dose selection and whether dose adjustments are warranted in specific populations. The modeling and simulation analysis plan is described in more detail in Section 7.2 and the analysis plan for the population pharmacokinetic and exposure-response analysis is in Appendix 2.

Does the DPP agree with the modeling and simulation analysis plan for population pharmacokinetics and exposure-response? In particular, are the covariates, key efficacy and safety parameters, and the overall modeling approach acceptable to the DPP?

FDA Response to Question 3: *We agree with the modeling and simulation analysis plan for population pharmacokinetics. We agree with the exposure-response analysis plan for efficacy endpoints. However, we would like you to make changes to your exposure-response analysis plan for hemodynamic endpoints (safety) such as pulse rate, diastolic and systolic blood pressure. You plan to include data from healthy subjects and patients in this analysis. Given that patients enrolled in the Phase 3 studies could be on background medications (e.g., antihypertensives), an integrated exposure-safety analysis of Phase 1 and Phase 3 studies for hemodynamic endpoints could be confounded. Such analysis would also need to consider the background antihypertensive medications. Hence, we recommend that the exposure-response analysis for hemodynamic endpoints be conducted separately for Phase 1 and Phase 3 studies.*

Please find below recommendations for the submission of model and data files. Prior to submitting the model and data files, please ensure that the column names in model control files and datasets are in the same order.

The following are the general expectations for submitting pharmacometric data and models:

- *All datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.*
- *Model codes or control streams and output listings should be provided for all major model building steps (e.g., base structural model, covariates models, final model, and validation model). These files should be submitted as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt).*
- *A model development decision tree and/or table which gives an overview of modeling steps should be included.*
- *For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as*

THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

- *In terms of where the code and data should be submitted, the following folders can be used as one example for population PK related codes and data. The codes should be submitted under "module5/datasets/poppk/analysis/programs/" folder (such as run1.ctl.txt, run1.lst.txt, plot1.R.txt) with a define.pdf file to explain the role of each file and sometimes with a pdf file as the revieweraid.pdf to explain the flow of running the code if necessary. The datasets should be submitted under "module5/datasets/poppk/analysis/datasets/" folder (such as poppk.xpt, pkpd.xpt) with a define.pdf file to explain the variables within each data file.*

Sponsor's Comments: Jazz thanks the Agency for the comments and confirms that the exposure-response analysis for hemodynamic endpoints has been conducted separately for Phase 1 and Phase 3 studies. No further discussion is requested at the meeting.

Discussion at Meeting: *There was no further discussion.*

2.3. Clinical

Question 4: The clinical development program for JZP-110 was designed in consultation with the DNP. Feedback received from the Agency at the EOP2 meeting (08 July 2014; meeting minutes dated 06 August 2014) and in the Type C Written Response (26 January 2017) was integrated into the program. The clinical development program includes 5 adequate and well-controlled registration studies: 2 studies in patients with narcolepsy (ADX-N05 202 and 14-002), 2 studies in patients with OSA (14-003 and 14-004), and a double-blind, placebo-controlled randomized withdrawal (maintenance of efficacy) study at 6 months within the long-term open-label safety and efficacy study of JZP-110 in both OSA and narcolepsy patients (14-005). The open-label part of the study is currently ongoing; however, an interim data cut of the open-label safety and efficacy data and a complete analysis of the double-blind, placebo-controlled randomized withdrawal data will be submitted with the NDA. Studies 14-002 and 14-003 had nearly the same trial design (except for inclusion of a 37.5 mg dose arm in 14-003), with the same co-primary endpoints and safety assessments. Collectively, the registration studies have shown consistent and reproducible favorable effects on both subjective and objective efficacy measures, as well as consistent and reproducible safety and tolerability profiles, as described in Section 5 (Appendix). The clinical studies to be included in the NDA are shown in Table 4 and Table 5. Jazz believes that the clinical development program provides adequate and well controlled evidence of efficacy and safety of JZP-110.

Does the DPP agree the clinical development program as outlined is adequate and complete to allow the review of the NDA submission to support market approval of JZP-110 in the proposed indication?

FDA Response to Question 4: *On face, these studies appear to be adequate for purposes of NDA submission. Whether they will support a labeling claim or claims will be a matter of review. As stated in the Information Request dated, September 11, 2017, provide in your NDA*

submission exact copies of the MWT, ESS, PGIc, CGIc, scoring algorithms, user manuals and any training materials.

Need for a Pediatric Development Program for Narcolepsy

We note your agreed initial Pediatric Study Plan (iPSP) providing for a full waiver of pediatric studies in the treatment of excessive sleepiness in OSA. DPP agrees that a plan for a full pediatric waiver for the OSA indication is appropriate because primary treatment of OSA in pediatric patients is surgical management and professional guidelines do not recommend pharmaceutical therapy.

However, a full pediatric waiver of required studies under PREA may not be acceptable for the narcolepsy indication given that other products have been successfully developed in pediatric patients 7 years of age and older. Therefore, barring a specific safety concern for JZP-110 that precludes pediatric studies for narcolepsy, the lack of an agreed upon iPSP could be a filing issue. If you plan to submit a single NDA for both indications, we recommend the NDA include a pediatric study plan (PSP) detailing how you plan to study the safety and efficacy of this product in pediatric patients for the narcolepsy indication. The PSP should include any requests for partial waivers along with a scientific rationale to justify any waiver request(s) (e.g., for patients less than 6 years of age). A full waiver could be considered if there is a product- or class-specific safety concern which has been well-established. Describe the deferred studies you plan to conduct, including any juvenile toxicology studies and age-appropriate formulation development (if needed). Because the PSP would not be an Agreed iPSP, the pediatric study requirements for the narcolepsy indication will not be negotiated prior to the NDA submission. The need for PMRs under PREA will be determined by FDA during the NDA review.

Sponsor's Comments: An iPSP was not submitted for the narcolepsy indication as Jazz was considered exempt from the PREA requirement since JZP-110 has an orphan drug designation for this indication (EOP2 meeting minutes dated 06 August 2014). However, Jazz recognizes the Agency's concern about safety and efficacy of this product in pediatric patients. Therefore, Jazz requests further discussion on this topic at the pre-NDA meeting.

Discussion at Meeting: *The Division confirmed the orphan drug designation for JZP-110 (granted under the name “(b) (4) phenylalanine derivative”) for this indication and, as such, agreed that PREA requirements do not apply. However, the Division encouraged the Sponsor to consider developing a pediatric program in children with narcolepsy provided that no safety concerns preclude it. The Sponsor could consider submitting a Proposed Pediatric Study Request (PPSR) to address any other potentially useful indication for pediatric patients for the proposed product.*

Question 5: In subjects with narcolepsy, the efficacy of JZP-110 (at doses of 150 mg and 300 mg) for excessive sleepiness had previously been shown in 12-week Study ADX-N05 202 on the endpoints of MWT, ESS, and PGIc. Consistent with those results, in the recently conducted 12-week Study 14-002, JZP-110 demonstrated clinically and statistically significant improvement in the co-primary endpoints of the MWT (an objective measure) and the ESS (a subjective measure) and on the key secondary endpoint of the Patient Global Impression of

Change (PGIc) scale at the 300 mg and 150 mg doses compared to placebo, with a more pronounced effect at the 300 mg dose. The 75 mg dose reached statistical significance on the coprimary endpoint of ESS but not on the co-primary endpoint of MWT, with a nominal p-value of 0.0023 on the PGIc. In subjects with OSA, JZP-110 demonstrated clinically and statistically significant differences compared to placebo on the co-primary efficacy endpoints of sleep latency on the MWT and the ESS, and on the key secondary endpoint (PGIc). In Study 14-003, which was designed to evaluate dose-response, statistically significant effects were shown at all doses (37.5, 75, 150, 300 mg) on the co-primary endpoints in a general dose-dependent manner. In that study, key secondary endpoint comparisons to placebo were statistically significant for all JZP-110 doses except 37.5 mg. At the 37.5 mg dose, ratings of improvement on the PGIc were not statistically different from placebo, and MWT sleep latency on individual MWT trials was inconsistent and only statistically different from placebo on the second MWT trial at week 12 according to the pre-specified approach to this analysis.

The safety profile of JZP-110 observed in subjects in the Phase 3 studies was comparable to that observed in earlier studies with JZP-110 in terms of the overall tolerability profile as well as the most frequent adverse events and effects on blood pressure and heart rate. In most subjects, JZP-110 was well tolerated, with acceptable tolerability at the highest proposed clinical dose, 300 mg. In general, a dose-response relationship with JZP-110 was apparent with greater frequencies of adverse events, overall discontinuations and other safety parameters evidenced in higher dose groups compared to lower dose groups and placebo. JZP-110 at 75 mg was not associated with important adverse effects or changes in cardiovascular or other safety measures. Rates of adverse events and discontinuations at the 37.5 mg dose were not meaningfully lower than those at the 75 mg dose.

Based on the clinical data, Jazz recommends a therapeutic dose range of (b) (4) mg of JZP-110 (b) (4). In the OSA Phase 3 trial 14-003, (b) (4)

Therefore, Jazz proposes to make a 37.5 mg dose available by scoring the 75 mg JZP-110 tablet

(a) Jazz is proposing a starting dose of 75 mg for narcolepsy, with a therapeutic dose range of 75-(b) (4) mg. Does the DPP agree that the efficacy and safety profile supports the proposed dose range and the recommended starting dose of 75 mg for patients with narcolepsy?

FDA Response to Question 5(a): We will need to review all the safety and efficacy data prior to determining the acceptability of the (b) (4) dose and the entire (b) (4) mg dose range, (b) (4)

Sponsor's Comments: Jazz believes this response relates to Question 5b for the OSA population. Could the Agency please confirm? Jazz requests additional discussion to better

understand [REDACTED] (b) (4) in the OSA population.

Discussion at Meeting: See discussion under Question 5(b)

(b) Jazz is proposing a starting dose of [REDACTED] (b) (4) for OSA, with a therapeutic dose range of [REDACTED] (b) (4) mg. Does the DPP agree that the efficacy and safety profile supports the proposed dose range and the recommended starting dose of [REDACTED] (b) (4) for patients with OSA??

FDA Response to Question 5(b): The acceptability of the proposed dosage range will be a matter of review. We must consider the totality of efficacy and safety data in order to determine which dosages to recommend in labeling. Based on our preliminary review, the lack of statistical significance on one of the co-primary measures in the [REDACTED] (b) (4) dosage group and [REDACTED] (b) (4) will be areas of focus during the NDA review.

Sponsor's Comments: We believe this response relates to Question 5a for the narcolepsy population. Could the Agency please confirm? Jazz requests additional discussion to better understand Agency's concern regarding the lack of statistical significance on one of the co-primary measures in the [REDACTED] (b) (4) dosage group and [REDACTED] (b) (4).

Discussion at Meeting: The Division acknowledged that there was an unintended transposition in the Division's preliminary comments for questions 5(a) and 5(b) regarding the 75mg dosage efficacy results in the narcolepsy trial. [REDACTED] (b) (4)

[REDACTED] The Division expressed interest in determining if there is a clinically meaningful difference in the dose-response profile of these doses. The Sponsor indicated that in the most severe patient population, a clear dose response was seen going from [REDACTED] (b) (4) mg and stated that they would provide this analysis with the NDA submission. Additionally, PK/PD data may help further inform dose selection.

The Sponsor indicated that there seemed to be a "condition-independent response" where baseline severity determined response, and that the simplest thing to do would be to have uniform dosing across all patients. However, the Division indicated that different doses may be recommended for OSA and narcolepsy, as each condition may have a different benefit/risk profile. For example, OSA patients may be at a higher risk of adverse cardiovascular events than patients with narcolepsy.

(c) Does the DPP agree with the proposal to make a scored 75 mg tablet available to allow a dose of 37.5 mg [REDACTED] (b) (4) ?

FDA Response to Question 5(c): [REDACTED] (b) (4)

Refer to '[Guidance for Industry Tablet](#)

Scoring: Nomenclature, Labeling, and Data for Evaluation for product quality expectations of scored tablets.

Sponsor's Comments: Jazz proposes to make the 37.5 mg dose available for patients with severe renal impairment. [REDACTED] (b) (4)

Discussion at Meeting: [REDACTED] (b) (4)
[REDACTED] (b) (4)
They also clarified [REDACTED] (b) (4)
scoring is not expected to affect the stability of the formulation. The Division suggested that the Sponsor include the relevant rationale supporting the use of a scored tablet in the NDA submission.

Question 6: Since the feedback received from the DNP at the EOP2 meeting (08 July 2014; meeting minutes dated 06 August 2014), Jazz has revised the wording of the proposed indication for JZP-110 as follows:

JZP-110 is indicated [REDACTED] (b) (4)

Does the DPP have any feedback on the wording of the proposed indication as supported by the clinical development program?

FDA Response to Question 6: *The precise wording of the indication statement will be a matter of review.*

Sponsor's Comments: Jazz appreciates that the indication statement is a review matter, however, Jazz requests some further discussion at the pre-NDA meeting to get Agency's feedback [REDACTED] (b) (4)

Discussion at Meeting: *The Sponsor stated that they have only studied JZP-110 in two specific populations (narcolepsy and OSA)* [REDACTED] (b) (4)

Question 7: Jazz believes that the cardiovascular safety profile of JZP-110, including changes in blood pressure and heart rate and the incidence of cardiovascular adverse events, at the proposed therapeutic dose range of (b) (4) mg of JZP-110 has been sufficiently characterized to permit NDA review for the narcolepsy and OSA indications. The safety profile of JZP-110 in subjects with narcolepsy or OSA observed in the clinical studies is consistent with the expected pharmacology of JZP-110 and with that of other wake-promoting agents that act as reuptake inhibitors such as modafinil and armodafinil. However, given the comorbidities in the population with OSA and based on feedback from the Agency at the EOP2 meeting, cardiovascular effects have been extensively evaluated in the clinical program:

- a thorough QT study has been conducted (15-002)
- the 12-week Phase 3 studies included extensive monitoring of vital signs:
 - taking regular clinic vital signs at all visits
 - taking vital signs throughout the day relative to dosing at all visits at which the MWT was performed to characterize hemodynamic effects at expected peak (1 to 4 hours after dosing) and trough (pre-dose) serum concentration
 - conducting 24-hour ambulatory blood pressure monitoring to assess hemodynamic effects across the entire 24 hour period
 - taking ECG readings at every visit
- analyses of cardiovascular adverse events in individual studies and integrated analyses
- collection of long-term safety data in Study 14-005
- Concentration-response analyses on heart rate and blood pressure
- Blinded adjudication of cardiovascular and potential cardiovascular events

Safety results from Studies 14-002, 14-003, and 14-004 are described in Section 5. The statistical analysis plan (SAP) for the ISS is briefly described in Section 7.3.3.2 and attached in Appendix 3.

Does the DPP have any feedback on the cardiovascular safety data and profile as outlined in the briefing package?

FDA Response to Question 7: *We have no objections to including the above information in your NDA submission.*

In addition to data generated under IND 107203 (narcolepsy) and IND 122590 (OSA), the total cardiovascular safety data base should also include the complete safety experiences (b) (4) relating to the previous valuation of JZP-110 (ADX-N05) in the treatment of Major Depressive Disorder (MDD). Changes in blood pressure, heart rate, electrocardiogram, cardiovascular and vascular events (e.g., stroke, retinal vessel occlusion, Raynauds or other vascular changes in other body parts, etc.) should be included and assessed against dose, identified patient co-morbidities and concurrent medications.

In order to assess the potential for JZP-110 to cause cardiovascular adverse events, please combine the following groups of preferred terms and compare frequencies of adverse events between drug and placebo:

Hypertension: accelerated hypertension, blood pressure diastolic increased, blood pressure inadequately controlled, blood pressure increased, blood pressure systolic increased, diastolic hypertension, essential hypertension, hypertension, hypertensive angiopathy, hypertensive crisis, hypertensive emergency, hypertensive encephalopathy, labile blood pressure, labile hypertension, malignant hypertension, procedural hypertension, renal hypertension, renovascular hypertension, systolic hypertension, withdrawal hypertension

Arrhythmia: atrial bigeminy, supraventricular extrasystoles, arrhythmia supraventricular, atrial fibrillation, atrial flutter, atrial tachycardia, sinus arrhythmia, sinus bradycardia, supraventricular tachyarrhythmia, supraventricular tachycardia, wandering pacemaker, accelerated idioventricular rhythm, arrhythmia, bradyarrhythmia, bradycardia, cardiac flutter, extrasystoles, heart rate decreased, heart rate increased, heart rate irregular, nodal arrhythmia, nodal rhythm, parasystole, paroxysmal arrhythmia, rhythm idioventricular, sick sinus syndrome, sinus tachycardia, tachyarrhythmia, tachycardia, tachycardia paroxysmal, torsade de pointes, ventricular arrhythmia, ventricular bigeminy, ventricular extrasystoles, ventricular fibrillation, ventricular flutter, ventricular parasystole, ventricular tachyarrhythmia, ventricular tachycardia, ventricular trigeminy.

Tachycardia: atrial flutter, atrial tachycardia, supraventricular tachyarrhythmia, supraventricular tachycardia, heart rate increased, sinus tachycardia, tachyarrhythmia, tachycardia, tachycardia paroxysmal, ventricular flutter.

Sponsor's Comments: *Jazz thanks the Agency for the feedback. No further discussion is requested at the meeting.*

Discussion at Meeting: *There was no further discussion.*

Question 8: At the EOP2 meeting, it was agreed that the proposed size and make-up of the safety database, as described in the briefing package, including total exposures and exposures of 6 months and 1 year duration, would support the registration of JZP-110, barring any unexpected safety findings that require additional characterization before approval. The JZP-110 NDA submission will include data from 1690 subjects—approximately 485 subjects with ≥ 6 months and 174 with ≥ 11 months (≥ 330 days) of exposure to JZP-110— to characterize the safety of JZP-110 in a population of subjects with excessive sleepiness due to OSA or narcolepsy that is representative of the target patient population. With the additional long-term safety data that will be included in the 120-day Safety Update, the program is projected to include 246 exposures of ≥ 12 months (≥ 360 days).

Therefore, Jazz believes that the clinical development program adequately characterizes the safety of JZP-110 and will be adequate to enable the filing of the NDA for JZP-110. The size and make-up of the safety database, and projected additional exposures, are described in Section 7.3.3.1.

In the context of the proposed therapeutic doses for narcolepsy and OSA, does the DPP agree that the size and make-up of the safety database is adequate to enable the filing and review of an NDA for JZP-110?

FDA Response to Question 8: *The number of subjects exposed at 37.7 mg and 75 mg appears small. However, the overall safety set appears, on face, to be adequate.*

Sponsor's Comments: Jazz would like to note that the propose dosage is 37.5 mg and not 37.7 mg. Jazz requests further discussion at the Pre-NDA meeting to understand Agency's comment regarding the number of subjects exposed at 37.5 mg and 75 mg.

Discussion at Meeting: *The Division noted that this comment referred to the 6 % of subjects exposed to 37.5 mg in OSA, and that 13 to 15 % exposed to 75 mg in OSA and narcolepsy, respectively. As stated in the preliminary comments, the overall safety set appears adequate.*

Question 9: In the Type C Written response (26 January 2017), the Agency asked Jazz to "...submit case narratives of abuse-related adverse events with any future NDA." The Agency also instructed Jazz that "...for all Phase 1, 2 and 3 studies, case narratives of adverse events (AE) associated with potential abuse or overdose should be provided, especially for any patient with serious AEs (SAEs). These should include cases involving lack of compliance or patients who discontinue participation without returning the study medication."

In Section 7.3.1, we have detailed the proposal for identifying and providing case narratives of abuse-related AEs and potential cases of study drug abuse, misuse, and diversion.

Does the Agency agree that Jazz' proposal for providing narratives for abuse related AEs is consistent with the Agency's feedback in the Type C meeting written response and adequate for Controlled Substance Staff review of abuse potential and preparation of an 8-Factor Analysis and scheduling recommendation?

FDA Response to Question 9: *The proposal for identifying and providing case narratives of abuse related AEs appears adequate for evaluating the abuse potential of JZP-110 in conjunction with other data (human abuse potential study, preclinical studies) that should be submitted in the NDA.*

We remind you that, although we support the assessment of withdrawal symptoms at the conclusion of a clinical study, it is important that this evaluation be conducted systematically. Therefore, you should propose a structured assessment in which validated withdrawal scales are used both before and after abrupt drug discontinuation. The observation period should last at least 2 weeks with daily use of the scales, in addition to spontaneously reported AEs. The scales should be validated on the basis of measuring withdrawal associated with stimulants. You may reference Section V.E in the [Guidance for Industry: Assessment of Abuse Potential of Drugs](#) for additional details concerning the assessment of physical dependence.

Sponsor's Comments: Jazz thanks the Agency for their agreement with the proposed approach for identifying and providing case narratives of abuse-related AEs.

Consistent with the Type C interaction (Jan 27, 2017) and response to Question 6 that no further studies or analyses other than those proposed are recommended, Jazz does not plan to conduct

additional studies or analyses to characterize withdrawal symptoms. Does the agency agree with this approach?

With regard to the systematic assessment of withdrawal symptoms, we have taken an approach in the Phase 3 program that involved weekly collection of AEs and use of validated scales after abrupt discontinuation during 2 randomized withdrawal periods (one after 4 weeks of exposure in study 14-004 and one after at least 6 months of exposure in study 14-005) of two weeks duration, in addition to during the two-week safety follow up periods in each of the Phase 3 studies and after discontinuation in all other studies. Jazz adopted this approach in response to feedback received at the EOP2 meeting in which the agency commented that it was not clear that use of the proposed Amphetamine Cessation Symptom Assessment scale included all potential AEs or whether it represented an efficient way to look for such effects. As a result of this feedback, we have taken an approach that focuses primarily on the day-to-day emergence of all AEs after the last dose in the two placebo-controlled, randomized withdrawal studies described above, with supportive evidence from validated and structured assessments such as the Epworth Sleepiness Scale and the Columbia-Suicide Severity Rating Scale. In addition, we will report on all AEs that occur in the safety follow up periods of all other clinical studies. Of the AEs that are identified with this approach, we will focus on a list of AEs of special interest that we have compiled based on validated instruments such as the Amphetamine Cessation Symptom Assessment scale, Amphetamine Withdrawal Questionnaire, Cocaine Selective Severity Assessment, and symptoms of stimulant withdrawal from the DSM-5. Our intent of taking this approach is to provide a rigorous and systematic analysis of clinical withdrawal symptoms in an efficient manner while avoiding the potential confounds associated with underlying narcolepsy and OSA pathology and asking sleep physicians to administer abuse-related questionnaires.

Discussion at Meeting: *The Sponsor submitted a handout which describes their approach to assessing withdrawal symptoms (see Attachment). In general, the Division agrees with the Sponsor's approach to assess withdrawal symptoms and no new structured withdrawal assessments are needed. The Sponsor plans to abruptly withdraw the JZP-110 during their 4-week and 6-month studies and use scales to assess for symptoms of withdrawal. In addition, the Sponsor will analyze all the available safety data for AEs of interest. The Division pointed out that patients should be assessed for these AEs while on the drug in order to better differentiate what is related to the drug vs. withdrawal.*

Question 10: Per the Agency's feedback at the EOP2 meeting, Jazz is planning to submit a single NDA for both OSA and narcolepsy indications. Summary modules (2.7.3 and 2.7.4), ISS, and Integrated Summary of Efficacy (ISE) will be presented for both indications jointly including relevant indication-specific analyses. The proposed presentation of the data (analysis, datasets, narratives, safety topics of special interest and the pooling and analysis strategy) is described in Section 6 and Section 7. The ISS and ISE statistical analysis plans (SAPs) are in Appendix 3 and Appendix 4, respectively.

(a) Does the DPP agree with the proposed presentation of the safety and efficacy data as described in Section 6 and Section 7 of the briefing package?

FDA Response to Question 10(a): *In addition to ISE and ISS, separate efficacy and safety tables should be submitted for each indication. Please include individual patient listings with the Clinical Study Reports. Include with your safety data, all safety from (b)(4) (MDD). Safety information should also be provided by dose and treatment duration, and relevant co-morbidities should be highlighted.*

Sponsor's Comments: Jazz thanks the Agency for the feedback. No further discussion is requested at the meeting.

Discussion at Meeting: *There was no further discussion.*

(b) Does the DPP agree with the proposed pooling and analysis strategy for the ISS and ISE that will be included in the JZP-110 NDA?

FDA Response to Question 10(b): *Because of the exploratory nature of the ISE, we have no objection to your proposal. However, the efficacy data should also be integrated separately by narcolepsy and by OSA. We may request for more analyses during the NDA review.*

Sponsor's Comments: Jazz thanks the Agency for the feedback. No further discussion is requested at the meeting.

Discussion at Meeting: *There was no further discussion.*

Question 11: Jazz intends to submit summary level clinical site datasets for the JZP-110 studies for Studies 14-002, 14-003, and 14-004 in the format described in the "Guidance for Industry – Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning."

Does the DPP agree that the proposal for clinical site datasets for Studies 14-002, 14-003, and 14-004 will satisfy OSI requirements?

FDA Response to Question 11: *Please refer to Office of Scientific Investigations (OSI) Requests below (under Section 3).*

Sponsor's Comments: Jazz thanks the Agency for the feedback and asks the Agency to confirm that the studies listed above are sufficient.

Discussion at Meeting: *OSI was not present at the meeting. The Division agreed to confer with OSI and provide their response as a post-meeting comment.*

Post-Meeting Comment: *The data for the clinical studies should consist of all pivotal studies. In addition to pivotal Studies 14-002, 14-003, and 14-004, which you have identified above, also include pivotal Study ADX-N05 202.*

2.4. Risk Management

Question 12: Feedback from the Agency regarding safety assessments received at the EOP2 meeting and in subsequent interactions was incorporated into the most recent studies in the clinical development program. The safety profile in the Phase 3 studies has been consistent with the pharmacology of the drug, and is comparable to that observed in earlier studies with JZP-110. Based on the safety profile and risks, Jazz proposes to manage product safety issues through labeling and routine pharmacovigilance and reporting requirements. These risk management activities will be detailed in the NDA.

Does the DPP have any preliminary comments on the Sponsor's proposed risk management activities?

FDA Response to Question 12: *At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks or, if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.*

Sponsor's Comments: Jazz thanks the Agency for the feedback. No further discussion is requested at the meeting.

Discussion at Meeting: *There was no further discussion.*

2.5. Regulatory

Question 13: Jazz proposes to provide financial disclosure information of all clinical investigators who were part of the Phase 3 studies (14-002, 14-003, and 14-004, and 14-005) in accordance with the *Guidance for Clinical Investigators, Industry, and FDA Staff – Financial Disclosure by Clinical Investigators*.

Does the DPP agree with Jazz's proposal for submission of financial disclosure certification in the NDA?

FDA Response to Question 13: *There are no objections. Please also include the same for your Phase 2a study, ADX-N05 202 in narcolepsy.*

Sponsor's Comments: Jazz thanks the Agency for the feedback. No further discussion is requested at the meeting.

Discussion at Meeting: *There was no further discussion.*

Additional Biostatistics Comments

Please include the following in your future NDA submissions:

- a) all raw as well as derived variables in .xpt format;
- b) raw data in legacy format if data were not collected in CDISC;
- c) SAS programs that produced all efficacy results;
- d) SAS programs used to generate derived variables from the original clinical database, and detailed descriptions of mappings from the clinical database to derived variables, together with a document of derived variable definitions ('define' file);
- e) A list of IND number with serial numbers and submission dates of the protocols, SAPs, amendments, and any relevant meetings.

Sponsor's Comments: Jazz would like to clarify that all clinical studies, including legacy studies, will be submitted in SDTM format as raw data. SAS programs for all efficacy results and generation of analysis files will be provided for studies 14-002, 14-003, 14-004, and 14-005.

Discussion at Meeting: *We have no objection to the Sponsor's proposal (in their response to our comments). In general, the Sponsor needs to submit those items for all efficacy trials intended to be used to support an efficacy claim.*

3.0 OTHER

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our July 10, 2017 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on PDUFA V and the Program is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.
All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30,

2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [*PLR Requirements for Prescribing Information*](#) and [*Pregnancy and Lactation Labeling Final Rule*](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. As of **May 5, 2017**, the following submission types: **NDA**, **ANDA**, and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission

[21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the Guidance for Industry, *Assessment of Abuse Potential of Drugs*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

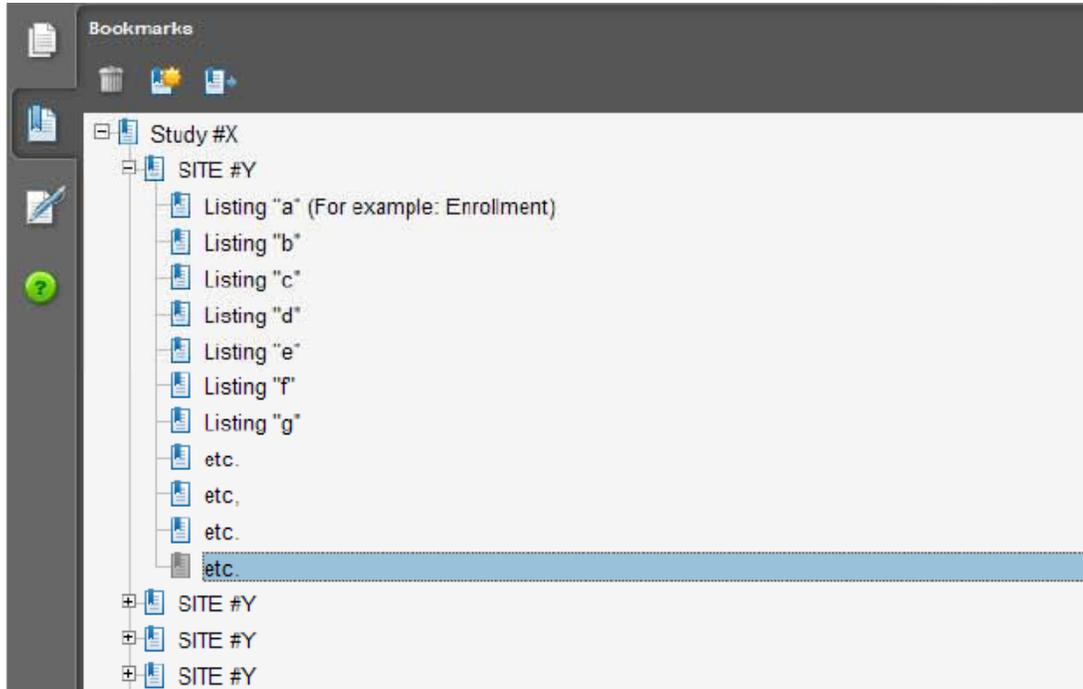
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records,

IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection

- b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
 5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

- Sponsor's handout/slide for Question 9-Discussion
- Clinical Pharmacology Summary Aid Template that goes with our post-meeting comment in Question 2

FDA Guidance (Section V.E.)

- *Physical dependence is usually assessed at the conclusion of a phase 2/3 clinical efficacy study*
- *Use of abrupt drug discontinuation is generally preferable*
- *A human physical dependence evaluation may include:*
 - *Use of drug class-specific withdrawal scales*
 - *Use of disease-specific scales for evaluation of potential symptom rebound*

Approach Taken

- All AEs related to withdrawal symptoms were systematically collected by day of onset:
 1. After abrupt discontinuation (last dose date) in all studies
 2. After abrupt discontinuation of JZP-110 under double-blind, placebo-controlled 2-week randomized withdrawal periods in the Phase 3 clinical studies:
 - After 4 weeks of active treatment
 - After 6+ months of active treatment
- AEs related to dependence and withdrawal were systematically selected based on the FDA guidance, the Amphetamine Withdrawal Questionnaire, the Cocaine Selective Severity Assessment, and the DSM-5 diagnostic criteria for stimulant withdrawal
 - Included use of the Epworth Sleepiness Scale to evaluate potential symptom rebound and use of the Columbia-Suicide Severity Rating Scale

CLINICAL PHARMACOLOGY SUMMARY AID

1. Goal

The goal of this Aid is to facilitate the creation of an optimal Clinical Pharmacology Summary that summarizes the relevant Clinical Pharmacology findings and focuses sponsor and reviewer on the critical review issues of a submission. To guide sponsors in creating the Clinical Pharmacology Summary in NDA and BLA submissions the Aid provides a generic questionnaire that covers the entire Clinical Pharmacology realm. The aggregate answers provided by sponsors generate the desired Clinical Pharmacology Summary in NDA and BLA submissions. Where needed instructions are added to the questions to clarify what the answers should address. The questions and instructions included in this guide are not intended to be either inclusive of all or exclusive of any questions that specific reviews will address.

The Clinical Pharmacology Summary generated by sponsors is a **stand-alone document**, i.e. the answers to the questions including supporting evidence should be self-sufficient. Appropriate use of complementary tables and figures should be made. The sponsors' answers to the questions should be annotated with links to the detailed information in the study reports and the raw data located in SAS transport files.

2. Question Based Review

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

All performed Clinical Pharmacology studies (*in vitro* studies with human biomaterials and *in vivo* studies) and clinical studies with PK and/or PD information along with report numbers should be tabulated. Study titles, objectives, treatments (single or multiple doses, size of the dose/interval), demographics (sex, age, race/ethnicity, body weight, creatinine clearance) and numbers of study participants should be listed. Studies whose results support the label should be marked.

2.2 General Attributes of the Drug

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

Provide background information on the drug substance (description, chemical name, molecular formula, molecular weight, structure), physical characteristics (Log D, solubility, pKa if applicable). Provide tabular information on the drug

products, strengths, quantitative composition of ingredients and lot numbers for all formulations used in all *in vivo* studies and indicate corresponding study report numbers.

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

2.2.3 What are the proposed dosages and routes of administration?

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

2.3 General Clinical Pharmacology

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

Provide a tabular description of the designs, methodology and salient findings of the clinical pharmacology-, dose-ranging-, and pivotal studies and other clinical studies with PK and/or PD information in brief for each indication. Indicate duration of study, subjects' demographics, dose regimens, endpoints (clinical/biomarkers) and study report numbers.

2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Provide a rationale for the selected clinical endpoints and biomarkers. For biomarkers indicate relationship to effectiveness and safety endpoints.

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

Indicate circulating active moieties and their plasma and-tissue concentration range after therapeutic doses of the drug of interest. Provide evidence that sensitivity of the assay method(s) used is (are) sufficient to determine apparent terminal $t_{1/2}$ and AUC.

2.4 Exposure-Response

2.4.1 Does the exposure-response relationship support evidence of effectiveness?

Describe briefly the method(s) used to determine the exposure-effectiveness relationship from randomized and well controlled trials (RCT) and other appropriate studies. Provide evidence that the exposure-response analysis supports evidence of effectiveness: e.g. a significant slope in the E-R relationship or a clear separation in effectiveness at different drug levels and placebo.

Indicate whether the selected effectiveness endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-effectiveness relationship. Indicate major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status see also 2.6/2.7) impacting the exposure-effectiveness relationship. If not identifiable by commonly known covariates, evaluate different strategies, for example therapeutic drug monitoring, to maximize effectiveness for patients with a sub-therapeutic exposure.

Provide point estimate as well as a measure of the inter-subject variability for applicable. Indicate minimum and maximum effective dose- and concentration levels (major active moieties). Provide evidence that with the proposed regimens clinically meaningful effectiveness is maintained throughout the entire dose interval or alternatively provide evidence that maintenance of effectiveness during the entire dose interval is not important. Indicate the magnitude of the effect at peak and trough concentrations with the tested dose regimens. Indicate steady-state trough and peak plasma concentrations of the major active moieties with the proposed dose regimens. Indicate whether AUC, C_{max} or C_{min} is more correlated with effectiveness. Show the distribution of the effect size for each dose/concentration level tested.

Justify if an analysis of the exposure-effectiveness relationship was not done.

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

Describe briefly the method(s) used to determine the exposure-safety relationship. The analysis should focus on adverse events responsible for discontinuations and other drug related toxicities. Indicate whether the safety endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-safety relationship. Indicate the major covariates (e.g. age, body weight, sex,

race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-safety relationship. Provide point estimate as well as a measure of the inter-subject variability for relevant safety endpoints. Indicate magnitude and/or frequency of relevant adverse events at the tested dose/concentration levels. Indicate proportion of subjects with an excessive adverse response. Indicate whether AUC, C_{max} or C_{min} is more related to clinically relevant adverse effects. Add information on the maximum tolerated single and multiple dose regimens and the corresponding plasma levels [mean (SD) C_{max} and AUC] of the circulating major active moieties.

Justify if an analysis of the exposure-safety relationship was not done.

2.4.3 Does this drug prolong QT/QTc Interval?

Provide a brief description of the study design, regimens, population and data analysis used. Indicate whether plasma concentrations of the drug and the relevant metabolites and the positive control were measured. Give a rationale for the chosen supra-therapeutic dose regimen. Report the findings on the relationship between dose/concentration and QTc interval. Indicate point estimate and 95% confidence interval for the increase of the QTc- interval at the supra-therapeutic dose level. Discuss the relevance of the findings for safety. Provide support for the appropriateness of the selected supra-therapeutic dose, if applicable. Indicate whether the pharmacokinetics of the drug of interest at supra-therapeutic levels is different from that at therapeutic levels.

2.4.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?

Provide information on the criteria used to select the dose regimen (doses, dose intervals) used in the RCTs. Indicate the therapeutic dose and/or concentration range for the drug and provide evidence that the proposed dose regimens are optimal given the effectiveness/safety profile of the drug.

2.5 What are the PK characteristics of the drug?

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

Briefly describe methods (two-stage and/or population approaches, compartment model dependent or-independent methods) in healthy subjects and in patients with the target disease used to determine the pharmacokinetic parameters of parent drug and relevant metabolites (pharmacologically active or impacting the exposure to parent drug or co-administered drugs). Provide mean, median (SD, CV%) pharmacokinetic parameters of parent drug and relevant metabolites after single doses and multiple doses at steady-state [C_{max}, t_{max}, AUC, C_{max,ss}, C_{min,ss}, C_{max,ss}/C_{min,ss}, t_{max,ss}, AUC_{0-τ}, CL/F, V/F and t_{1/2} (half-life determining accumulation factor), accumulation factor,

fluctuation, time to steady-state]. Indicate how attainment of steady-state is determined. Provide evidence for attainment of steady-state.

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

Compare the pharmacokinetic parameters of the drug of interest and relevant metabolites in healthy subjects and patients with the target disease. Provide a rationale for observed significant differences between healthy subjects and patients with the target disease.

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

Provide mean/median (SD, coefficient of variation, range within 5% to 95% confidence interval bracket for concentrations) about mean AUC, C_{max}, C_{min}, CL/F and t_{1/2} of the parent drug and relevant metabolites after single doses and at steady-state.

2.5.4 What are the characteristics of drug absorption?

Indicate absolute and relative bioavailability, lag time, t_{max}, t_{max,ss}, C_{max}, C_{max,ss} and extent of systemic absorption of parent drug and relevant metabolites in healthy subjects and patients with the target disease. Indicate mean (SD) for these parameters.

2.5.5 What are the characteristics of drug distribution?

Indicate mean (SD) V/F for the drug of interest in healthy subjects and patients with target disease. Provide mean (SD) blood/ plasma ratio for parent drug in healthy subjects. Briefly describe method and pH- and temperature conditions used for determining plasma protein binding for parent drug and relevant metabolites. Provide mean (SD) values of the plasma protein binding of the drug of interest and relevant metabolites measured over the therapeutic range in healthy subjects and patients with target disease and special populations.

2.5.6 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Present total, renal and fecal recoveries as percent of the administered total radioactivity. Indicate the percentage of radioactivity excreted as unchanged parent drug in urine and feces and the percent of radioactivity excreted as metabolites in urine and feces.

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

Provide identification for $\geq 90\%$ of the circulating total radioactivity (AUC). If multiple small peaks are present whose individual radioactivity is too small to

be assignable to individual metabolites provide an estimate for their contribution to circulating total radioactivity.

2.5.8 What are the characteristics of drug metabolism?

Present the metabolic scheme for the drug. Provide an estimate for the contribution of metabolism to the overall elimination of the drug of interest. Indicate mean (SD) values for the non-renal clearance in healthy subjects and patients with the target disease. Indicate whether active metabolites constitute major circulating moieties and if so how much they contribute to effectiveness and/or whether they affect safety.

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

If appropriate provide *in vitro* and/or *in vivo* evidence suggesting that parent drug and/or metabolites are excreted into bile (*in vitro*: parent drug and/or metabolites are substrates of BCRP, *in vivo*: recovery of unchanged parent drug in mass balance- and absolute bioavailability studies suggest excretion into bile)

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

Indicate whether there are secondary peaks and humps in the plasma concentration profile correlating with food intake.

2.5.11 What are the characteristics of drug excretion in urine?

Provide an estimate of the contribution of renal excretion to the overall elimination of parent drug in healthy volunteers. Present mean values (SD) for the renal clearance (mL/min or mL/min/1.73m²) in healthy subjects and in the target population. Using mean plasma protein binding and renal clearance values in healthy subjects estimate the respective contributions of glomerular filtration and net tubular secretion or re-absorption to renal clearance.

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

Briefly describe the statistical methods used to determine the type of pharmacokinetics of the drug and its relevant metabolites (linearity, dose proportionality, non-linearity, time dependency) in healthy subjects and patients with the target disease. Identify the doses tested after single and multiple dose administrations of the drug of interest and the respective dose normalized mean (SD) C_{max} and AUC values in healthy subjects and patients with the target

disease. Indicate whether the kinetics of the drug is linear, dose proportionate or nonlinear within the therapeutic range. In case of nonlinear or time dependent pharmacokinetics provide information on the suspected mechanisms involved.

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

Indicate whether the mean ratio of AUC_{0-τ} at steady-state to AUC after the first dose for the circulating major active moieties deviates statistically significantly from 1.0 in healthy subjects and patients with the target disease. Discuss the relevance of the findings and indicate whether an adjustment of the dose regimen is required. If the pharmacokinetics of the drug of interest changes with time provide a rationale for the underlying mechanism.

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

Indicate whether C_{max} and C_{min} of the parent drug after the morning and evening dose differ significantly. Discuss the relevance of the findings and whether an adjustment of the dose regimen is required for the drug of interest. Provide a rationale for the underlying mechanism for the observed circadian rhythm of the pharmacokinetics of the drug of interest. Indicate whether the dose regimens in the pivotal studies were adjusted for circadian rhythm.

2.6 Intrinsic Factors

2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, C_{max}, C_{min}) in patients with the target disease and how much of the variability is explained by the identified covariates?

Provide for all studies investigating the impact of the intrinsic factors (age, sex, body weight, ethnicity/race, renal and hepatic impairment) demographics and number of study subjects, and dose regimens. Provide summaries of the results and indicate intrinsic factors that impact significantly exposure and/or efficacy and safety of the drug of interest. Provide for each major identified covariate an estimate for its contribution to the inter-subject variability and indicate how much of the inter-subject variability is explained by the identified covariates.

Provide mean (SD) parameters for AUC, C_{max}, clearance, volume of distribution and t_{1/2} for pairs studied (e.g. elderly vs. young, male vs. female, normal body weight vs. obese, race/ethnicity(x) vs. race/ethnicity (y), mild vs. severe target disease)

2.6.2 Based upon what is known about E-R relationships in the target

population and their variability, what dosage regimen adjustments are recommended for each group?

Characterize the populations (age, sex, body weight, ethnicity/race) used to determine the impact of each intrinsic factor on variability in exposure and exposure-response. Indicate for each intrinsic factor whether a dose adjustment (change of dose or dose interval or both) is required or not and provide a rationale for either scenario.

2.6.2.1 Severity of Disease State

2.6.2.2 Sex

2.6.2.3 Body Weight

2.6.2.4 Elderly

2.6.2.5 Pediatric Patients

If available provide mean (SD, range) pharmacokinetic parameters, biomarker activity, effectiveness and safety in the pediatric sub-populations (neonates (birth-1 month), infants (1 month- 2 years), children (2-12 years) and adolescents (12- < 16 years) and define the target disease. If no information is available in the pediatric population indicate age groups to be investigated in future studies. Provide a summary stating the rationale for the studies proposed and the endpoints and age groups selected. Include a hyperlink to the development plan of the drug of interest in children.

2.6.2.6 Race/Ethnicity

2.6.2.7 Renal Impairment

Characterize the demographics for each subgroup (normal renal function, mild, moderate and severe renal impairment, on and off dialysis). Indicate mean (SD, range) for creatinine clearance estimated by the Cockcroft-Gaul- and MDRD equations for the stages of renal impairment investigated. Provide arithmetic mean (SD) AUC, C_{max} and t_{1/2} of parent drug and relevant metabolites in the different sub-groups assessed by 2-stage or population PK approaches. Show regressions including 90% confidence intervals of AUC, C_{max} and CL/F on Cl_r for parent drug and relevant metabolites. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of creatinine clearance.

Indicate mean (SD) for total and renal clearance of the drug in the different sub-groups and provide estimates of the contribution of glomerular filtration and net tubular secretion or re-absorption to the renal excretion of the drug of interest. Indicate whether plasma protein binding of the active moieties is significantly

altered in renal impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment (dose or dose interval, or both) is required or not for each of the sub-groups of patients with impaired renal function and provide a rationale for either scenario.

2.6.2.8 Hepatic Impairment

Characterize the demographics for each subgroup (normal hepatic function, mild, moderate and severe hepatic impairment based on Child-Pugh scores). Provide information on arithmetic mean (SD) AUC, C_{max}, t_{max} and t_{1/2} of parent drug and relevant metabolites in the different hepatic function sub-groups assessed by two-stage or population PK approaches. Show regressions including 90% confidence intervals of C_{max}, AUC or CL/F on the Child-Pugh score for parent drug and relevant metabolites. Indicate whether plasma protein binding of the active moieties is significantly altered in hepatic impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the subgroups of patients with impaired hepatic function and provide a rationale for either scenario. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of Child-Pugh score.

2.6.2.9 What pregnancy and lactation use information is available?

2.6.3 Does genetic variation impact exposure and/or response?

Describe the studies in which DNA samples have been collected. If no DNA samples were collected state so. Include a table with links to the studies in which DNA was analyzed and genomic/genetic information is reported. In the description of these studies include demographics, purpose of DNA analysis (effectiveness, safety, drug metabolism, rule in-out of patients, etc.), rationale for the analysis, procedures for bio-specimen sample collection and DNA isolation, genotyping methods, genotyping results in individual subjects, statistical procedures, genotype-phenotype association analysis and results, interpretation of results, conclusions. If genomic polymorphism impacts either exposure and/or response indicate the measures to be taken to safeguard efficacy and safety of the drug in subjects with varying genotypes. Indicate the contribution of genetic factors to inter-subject variability.

2.6.4 Immunogenicity (NOT applicable to small molecule drugs)

2.6.4.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the

rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

2.6.4.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

2.6.4.3 Do the anti-product antibodies have neutralizing activity?

2.6.4.4 What is the impact of anti-product antibodies on clinical efficacy?

2.6.4.5 What is the impact of anti-product antibodies on clinical safety?

Provide information on the incidence of infusion-related reactions, hypersensitivity reactions, and cross-reactivity to endogenous counterparts.

2.7 Extrinsic Factors

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

Summarize the results of the *in vitro* studies performed with the drug of interest as substrate, inhibitor or inducer of relevant CYP and non-CYP enzymes and transporters. Give rationale for why based on the *in vitro* results an interaction study in humans is required or is not required

2.7.2 Is the drug a substrate of CYP enzymes?

Briefly describe the methods used (specific chemicals/antibodies, human recombinant CYP enzymes, human microsomes). Indicate incubate, initial rate conditions, concentration range tested relative to K_m , controls etc. Provide a summary of the results of the *in vitro* studies investigating the drug of interest as a substrate of CYP 450 and non-CYP 450 enzymes. Provide for each of the relevant enzymes a mean estimate for the % contribution to the metabolism of the drug of interest. Discuss the relevance of the *in vitro* findings for the drug of interest as a substrate for deciding which drug-drug interactions should be or need not be performed in humans. For each situation provide supporting evidence.

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

Briefly describe the methods used (type and source of liver tissue, concentration range tested for the drug of interest as substrate, inhibitor and inducer, experimental conditions, pre-incubation, probe substrates, positive/negative controls. Provide summary results of the *in vitro* studies with human liver tissues for the drug of interest as a potential inhibitor or inducer of enzymes. Indicate whether the drug is a reversible inhibitor (competitive, non-competitive or un-competitive) or an irreversible inhibitor (mechanism based) and supportive evidence. Provide mean (SD) values for K_i , IC_{50} and V_{max} for each

relevant enzyme and probe substrate. Indicate the anticipated maximum total and unbound concentration of the drug of interest as inhibitor ([I]). Provide the mean (SD) % activity relative to the positive control for the drug of interest as inducer. Discuss the relevance of the *in vitro* findings for the drug of interest as an inhibitor or inducer for deciding which drug-drug interactions should be or need not be performed *in vivo* in humans. If appropriate use the [I]/K_i ratio as a means to assess the likelihood of an *in vitro* result to be clinically relevant. For each situation provide supporting evidence.

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

See 2.7.2.2 and 2.7.2.3. The instructions for the interactions of the drug of interest as substrate, inhibitor or inducer of transporters are analogous to those for enzymes.

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

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

Indicate extrinsic factors that impact significantly exposure and/or effectiveness and safety of the drug. Indicate extent of increase or decrease in exposure and/or response caused by extrinsic factors. State whether an adjustment of the dose is or is not required and provide supporting evidence for either case.

2.7.7 What are the drug-drug interactions?

Provide a list of the drug-drug interaction studies (PK or PD based mechanism) performed and give a rationale for conducting the listed studies. Indicate the suspected mechanism responsible for the interaction. For each of the *in vivo* studies performed provide a rationale for the design selected (single or multiple dose regimens, randomized/non-randomized cross-over or parallel design for perpetrator and/or victim).

a) Drug of interest is impacted by co-administered other drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report t_{1/2}, point estimates and 90% confidence intervals of the geometric mean ratios of AUC and C_{max} for the drug of interest in the presence and absence of each of the co-administered drugs. Provide a summary statement on the drug interaction liability of the drugs as victim. Indicate whether a dose adjustment is required or not. In either case provide a rationale. Define the required adjusted dose regimens.

b) Drug of interest impacts other co-administered drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Provide a summary statement on the drug interaction liability of the drug as a perpetrator. Report $t_{1/2}$, point estimates and 90% confidence intervals of the geometric mean ratios of AUC and C_{max} for each of the co-administered drugs in the presence and absence of the drug of interest.

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

2.7.9 What other co-medications are likely to be administered to the target population?

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

2.8 General Biopharmaceutics

For all *in vivo* studies performed in this section indicate study design, demographics and number of subjects enrolled, and type, composition, strength and lot number of the formulations used. Provide summary results with estimates for mean and inter-subject variability on AUC and C_{max} after single and multiple dose administration and peak to trough fluctuation after multiple dose administration.

IR Product

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

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

2.8.2.1 What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

2.8.2.2 If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and

efficacy data support the approval of the to-be-marketed product?

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

Indicate composition and calories of the food administered, and length of the pre-dose fasting period. State whether the impact of food is on the drug substance or the inactive ingredients of the formulation. Indicate the clinical relevance of findings. Indicate the temporal relationship between drug intake and food intake in the pivotal studies.

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

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

MR product (if an IR is already marketed)

2.8.6 What is the bioavailability of the MR product relative to the approved IR product? How does the plasma concentration time profile of the MR formulation compare to that of the IR formulation after single and multiple doses?

Indicate whether or not the pharmacokinetics of the drug of interest is linear, dose proportional or nonlinear after administration of the MR formulation. Summarize data on C_{max}, AUC and C_{min} of the IR and MR formulations after a single dose and multiple doses at steady-state. Provide information on the fluctuation factor at steady-state.

2.8.7 What is evidence that MR formulation *in vivo* consistently shows claimed MR characteristics?

2.8.8 What is evidence that MR formulation displays less variability in C_{max}, AUC and C_{min} than IR formulation?

2.8.9 Does the MR product show dose dumping *in vivo*?

Describe design, demographics and number of subjects participating in the studies performed to determine whether dose dumping occurs with the MR formulation when given in the fed state or when given together with alcohol. Present summaries of results.

2.8.10 Does ethanol *in vitro* have a dose-dumping effect on the MR product?

Provide the results of the *in vitro* dissolution testing of the various strengths of the ER product in pH 1.2, 4.5 and 6.8 media containing 0, 5, 10, 20 and 40% alcohol. Discuss any dose dumping observed. If an *in vivo* study was performed report the clinical relevance of the findings.

2.8.11 Are the MR and IR products marketed simultaneously?

If the intention is to market both the MR and IR products, indicate how patients are converted from the IR to the MR product and vice versa.

2.8.12 If the NDA is for an MR formulation of an approved IR product without supportive safety and effectiveness studies, what dosing regimen changes are necessary, if any, in the presence or absence of a PKPD relationship?

2.8.13 In the absence of effectiveness and safety data what data support the NDA for a MR formulation of an approved IR product?

2.9 Analytical Section

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

List all assays used and briefly describe the individual methods.

2.9.2 Which metabolites have been selected for analysis and why?

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

Indicate whether free, bound or total (bound+unbound) concentrations of the drug of interest and relevant metabolites are measured and give a rationale for your selection.

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

Identify all studies that used a particular assay method. For each assay report

indicate the corresponding assay validation report.

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

For each method and analyte provide concentration range of calibration curve and indicate respective concentration range for relevant moieties with therapeutic regimens. Indicate fit type of the calibration curves.

2.9.5.1 What are the lower and upper limits of quantitation?

For each method and analyte indicate LLOD, LLOQ and ULOQ for undiluted and diluted samples.

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

For each method and analyte indicate inter-day and intra-day precision (CV%) and inter-day and intra-day accuracy (RE%).

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

For all studies in which concentrations of the drug of interest and relevant metabolites were measured provide information on initiation date of study, date of last sample analyzed and total sample storage time. For each method and matrix provide information on the stability of the analytes, i.e. number of freeze-thaw cycles, benchtop stability at room temperature and stability during long term storage at $\leq -20^{\circ}$ C.

2.9.5.4 What is the plan for the QC samples and for the reanalysis of the incurred samples?

For each study, method and analyte indicate precision (CV%) and accuracy (%RE) using the QC samples measured alongside samples with unknown concentrations. Indicate the concentrations of the QC and incurred samples used.

2.9.5.5 What evidence is available demonstrating that neither the assay of the drug on interest is impacted by co-administered other drugs and vice versa?

Applicable to therapeutic proteins only

2.9.5.6 What bioanalytical methods are used to assess therapeutic protein concentrations?

Briefly describe the methods and summarize the assay performance.

2.9.5.7 What bioanalytical methods are used to assess the formation of the anti-product antibodies?

Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference and matrix, etc.

2.9.5.8 What is the performance of the neutralizing assay(s)?

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

/s/

MITCHELL V Mathis
10/17/2017



IND 122590
IND 107203

**MEETING REQUEST-
WRITTEN RESPONSES**

Jazz Pharmaceuticals International III Limited
Attention: Lily Gong
Associate Director, Regulatory Affairs
3180 Porter Drive
Palo Alto, CA 94304

Dear Ms. Gong:

Please refer to your Investigational New Drug Applications (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for JZP-110.

We also refer to your July 6, 2017, containing a pre-NDA meeting request. The purpose of the requested meeting was to confirm the adequacy of the Chemistry, Manufacturing and Controls package of JZP-110 film-coated tablets.

Further reference is made to our Meeting Granted letter dated July 25, 2017, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your August 1, 2017, background package.

IND 122590
IND 107203
Page 2

If you have any questions, call Teshara G. Bouie, Quality Assessment Lead (Acting) at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Wendy Wilson-Lee, Ph.D.
Branch Chief (Acting)
Branch I, Division of New Drug Products I
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: Type B
Meeting Category: Pre-NDA (CMC)

Application Number: IND 122590
IND 107203

Product Name: JZP-110
Indication: to reduce excessive sleepiness and improve wakefulness
[REDACTED] (b) (4)
narcolepsy and obstructive sleep apnea

Sponsor/Applicant Name: Jazz Pharmaceuticals International III Limited

1.0 BACKGROUND

INDs 107203 and 122590 are being developed as a film-coated tablet for oral administration for excessive sleepiness in obstructive sleep apnea and narcolepsy. On July 6, 2017, the Sponsor submitted a meeting request to confirm the adequacy of the Chemistry, Manufacturing and Controls package of JZP-110 film-coated tablets. Specifically, the purpose of this meeting is to gain agreement on:

- 1) the biowaiver strategy to bridge to Phase 2 formulations
- 2) plans for process performance qualification of the drug product at the intended commercial facility
- 3) stability data package for NDA submission and plans for [REDACTED] (b) (4) [REDACTED] over the course of the NDA assessment period

Background packages were received on August 1, 2017.

2.0 QUESTIONS AND RESPONSES

Question 1: Does the Agency confirm that the data intended for submission in the Biowaiver request will be sufficient to facilitate a formal decision by the Agency or if not, can the Agency advise of additional data that may be required?

FDA Response to Question 1:

The data/information submitted in the Biowaiver Request Draft in Appendix A of this meeting package appears to be reasonable. However, the biowaiver request will be assessed during the review of the NDA.

Question 2: The Sponsor proposes to submit additional stability data (18 months for the (b) (4) tablet) once available (expected January 2018) to support a minimum shelf life at approval of 30 months. Does the Agency confirm that:

- a) Additional stability data specified above will be accepted during the NDA assessment period?
- b) (b) (4)
- c) The proposed bracketing approach for the first commercial lots is acceptable?
- d) The stability data available for the 75 mg unscored tablet can be leveraged to apply the same shelf-life to the 75 mg scored tablets (differing only in having a scoreline)?

FDA Response to Question 2:

- a) *The additional stability data submitted prior to mid-cycle may be accepted provided that the appropriate resources are available. As the commercial drug product lots will be manufactured at a different site from the development lots, the use of development site lot stability data as indicative data for commercial lot stability will be a matter for review. Additional factors under consideration for stability data comparability at both sites include similarity of the equipment, packaging, SOPs, environmental conditions, and controls used in the manufacturing process.*
- b) *We cannot comment on any (b) (4)*
- c) *The proposed bracketing approach for the first commercial lots in line with ICH guideline Q1D is reasonable.*
- d) *The stability data for the 75 mg unscored tablet may be leveraged to apply the same shelf-life to the 75 mg scored tablets, but will be a matter for review based on considerations described in our response to question 2a). We consider the functional scoring to be a critical quality attribute. Therefore, we will review the submitted stability data to determine whether it is sufficient to show equivalency between the scored and unscored tablets.*

Additionally, we recommend that the stability study data submitted for the scored tablets fully comply with the requirements as outlined in “FDA Guidance for Industry: Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation.”

Question 3: Does the Agency confirm that the process validation plan proposal is suitable to support the application for this small molecule chemical drug product?

FDA Response to Question 3:

The proposed process validation plan appears reasonable. Process qualification activities are not required to be completed prior to submission of the NDA. FDA does not pre-approve process performance qualification approaches, protocols, or specific number of batches to be used in process performance qualification studies. The actual protocols, acceptance criteria, and study outcomes will be evaluated during an inspection. It is the company’s responsibility to conduct all studies necessary to assure that the commercial manufacturing process is capable of consistently delivering quality product prior to distribution of any commercial product. For further guidance refer to “FDA Guidance for Industry: Process Validation: General Principles and Practices, 2011”.

Question 4: Does the Agency confirm that the proposal for submission of executed batch records is sufficient for NDA filing?

FDA Response to Question 4:

Per 21 CFR 314.50(d)(1)(ii)(b), the executed production records for each batch used in bioavailability study, bioequivalence study, or primary stability studies and supporting production information must be provided. To facilitate the manufacturing process review, it is expected that summarized process related information (e.g. manufacturing equipment, process parameters, in-process controls, etc.) from developmental/clinical batches to scale up batches and the proposed commercial batches be provided in the submission that can help the reviewer to determine adequacy of the application from the perspective of manufacturing process and control.

Question 5: Does the Agency confirm that the mean results, and ranges, for dissolution will be sufficient to be reported in the batch analysis section of the planned NDA, or will the full results (individual results per tablet) be required?

FDA Response to Question 5:

Submit the complete data (i.e., individual, mean, range, %CV and plots) in the NDA.

We note that the proposed film coated tablets are scored. Therefore, we have the following recommendations for the dissolution information that should be provided to support the approval of the scored tablets:

1. *Dissolution Testing Sample Size:*
 - *N=6 tablets split by hand (for a total of n=12 halves or n=18 for trisects, etc.)*
 - *N=6 tablets split mechanically (for a total of n=12 halves or n=18 for trisects, etc.)*
2. *Each individual segment should be tested in its own vessel in proposed QC dissolution medium using the proposed dissolution method. Each tested segment should be properly identified and tracked. For example, tablet 1.1, 1.2, 2.1, 2.2, 3.1, 3.2, and so forth.*
3. *The individual vessel and mean data for each segment, total (segment1 + segment 2), and whole tablets should be reported in tabular format (see table below as an example), in addition to the mean dissolution data presented in graphical format.*
4. *The dissolution profiles from each segment (actual and normalized to label claim) and total (split by hand & mechanically) vs. the whole tablets should be compared using the similarity f2 test and the values reported. For example, if the tablet is split in two halves, to calculate the normalized percentage of drug dissolved, the individual values of each segment are normalized to 50% of label claim instead of 100%.*

An Example Table could be:

Percentage of Drug Dissolved with respect to Label Claim (Normalized and Actual)																		
Tablets	5 min					Whole Tablets	10 min					Whole Tablets	15 min					Whole Tablets
	Segments						Segments						Segments					
	Normalized		Actual				Normalized		Actual				Normalized		Actual			
	1	2	1	2	Total		1	2	1	2	Total		1	2	1	2	Total	
1																		
2																		
3.0																		
3																		
4																		
5																		
6																		
MA																		
NU																		
FA																		
CT																		
Mean																		
SD																		

URING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation

conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

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

/s/

TESHARA G BOUIE
08/29/2017

WENDY I WILSON-LEE
08/29/2017