CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212690Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 049641

MEETING MINUTES

Jazz Pharmaceuticals
Attention: Paula Hines, PhD.
Senior Director, Global Regulatory Lead
CNS/Sleep Global Regulatory Affairs
3180 Porter Drive
Palo Alto, CA 94304

Dear Dr. Hines:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for JZP258.

We also refer to the pre-NDA meeting between representatives of your firm and the FDA on October 2, 2019.

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

If you have any questions, contact Vandna Kishore, Senior Regulatory Project Manager at vandna.kishore@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Acting Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	October 2, 2019 10 AM
Meeting Location:	FDA White Oak Campus, Building 22, Room 1313
Application Number:	049641
Product Name:	JZP-258
Indication:	Treatment of cataplexy and excessive daytime sleepiness in patients 7 years of age and older with narcolepsy
Sponsor Name:	Jazz Pharmaceuticals
Meeting Chair:	Eric Bastings, MD

FDA ATTENDEES

Billy Dunn, MD, Acting Deputy Office Director
Eric Bastings, MD, Acting Division Director
Ranjit Mani, MD, Clinical Reviewer
Alice Hughes, MD, Director for Safety
Sally Yasuda, PharmD, Team Leader for Safety
Dawei Li, PhD, Clinical Pharmacology Reviewer
Sharon Yan, PhD, Biometrics Reviewer
Martha Heimann, PhD, OPQ CMC Lead
Nandini Bhattacharya, PhD, Microbiology
Xia Xu, PhD, Microbiology Reviewer
Danielle Harris, PharmD, DMEPA Deputy Director
Chad Morris, DMEPA Reviewer
Donella Fitzgerald, DRISK Team Lead
Jamie Wilkins Parker, DRISK
Ingrid Chapman, PharmD, Risk Management Analyst
John Palmer, MD, NIH Fellow
Vandna Kishore, RPh, Regulatory Project Manager

SPONSOR ATTENDEES

(b) (4)	Clinical Pharmacology Consultant
Jed Black, MD	Senior Fellow, Sleep/Neuroscience, Clinical Development
Cuiping Chen, PhD	Senior Director, Clinical Pharmacology
Peng Chen, PhD	Director, Biostatistics

Nicole Damour	Associate Director, Global Regulatory Affairs, Chemistry, Manufacturing, and Controls
Sanja Gauthier, MD	Executive Director, Medical Safety
Paula Hines, PhD	Senior Director, Global Regulatory Lead, Regulatory Strategy
Robert Iannone, MD, MSCE	Executive Vice President, Head of Research and Development
Philip Jochelson, MD	Vice President, Therapeutic Area Head Clinical Development, Sleep and CNS
Gunjan Junnarkar, PhD	Senior Director, Process Development
Sherice Mills	Senior Director, Benefit Risk Management
Patricia Moore	Vice President, Research and Development Quality and Global Regulatory Affairs
Judith Profant, PhD, DBSM	Director, Medical Affairs
(b) (4)	Regulatory Consultant
Jeffrey Silverman, PhD	Vice President, Early Development
Franck Skobieranda, MD	Vice President, Clinical Development, Sleep
Roman Skowronski, MD, PhD	Executive Director, Clinical Development, Sleep and CNS Executive Director, Clinical Development, Sleep and CNS

Appears this way on original

1.0 BACKGROUND

This meeting is for a Pre-New Drug Application (Pre-NDA) discussion for JZP-258, also referred to as "oxybate" and previously referred to as an "oxybate mixed-salt oral solution (OMSOS)." The proposed NDA for JZP-258 is to be submitted under the Section 505(b)(1) pathway.

JZP-258 is an aqueous oral solution containing 0.413 g/mL of oxybate, stated to be equivalent to a 0.5 g/mL mixture of calcium, potassium, magnesium, and sodium oxybate. JZP-258 has been developed as a lower-sodium alternative to Xyrem® (sodium oxybate oral solution [500 mg/mL]), which is notable for its high sodium content.

Xyrem is currently approved for the treatment of cataplexy and excessive daytime sleepiness in narcolepsy in patients 7 years of age and older.

The proposed indications for JZP-258 are the same as those for which Xyrem® is currently approved. The proposed dosing regimen for JZP-258 is (b) (4) that currently recommended in the Prescribing Information for Xyrem.

The proposed NDA for JZP-258 is to contain reports for the following clinical studies, summary data for which are provided in this meeting package.

- Study JZP258-101, an open-label, randomized crossover study investigating the relative bioequivalence and bioavailability of JZP-258 and Xyrem under fasted conditions in healthy subjects.

- Study 13-010, an open-label, randomized crossover study investigating the relative bioequivalence and bioavailability of JZP-258 and Xyrem under fasted and fed conditions in healthy subjects.

- Study 15-003, a randomized, double-blind, placebo-controlled crossover study comparing the taste of JZP-258 with placebo in healthy subjects.

- Study 15-006, a double-blind, placebo-controlled, randomized withdrawal study of the efficacy and safety of JZP-258 in the treatment of cataplexy and excessive daytime sleepiness in narcolepsy.

All clinical studies of JZP-258 have been conducted in adult subjects only.

The clinical, chemistry, nonclinical, and clinical pharmacology data to be included in the proposed NDA for JZP-258 are summarized in this meeting package, as is the format in which those data are to be submitted in that application.

FDA sent Preliminary Comments to Jazz on September 27, 2019.

2. DISCUSSION

Please note the following regarding the text below: the Agency's initial responses to the sponsor's questions are in blue font, the sponsor's pre-meeting responses (dated September 30, 2019) are in purple font, the meeting discussion is summarized in green font, and a single Agency post-meeting comment is in brown font.

2.1. Chemistry, Manufacturing, and Controls

Question 1: Does the Agency agree that the proposed CMC package and control strategy outlined in the meeting package are adequate to support the registration of JZP-258?

FDA Response to Question 1:

In general, your proposed Chemistry, Manufacturing, and Controls (CMC) package and control strategy appear appropriate, pending review of the data provided in the proposed NDA. However, you should address the concerns outlined below in the original NDA submission.

Microbiology:

(b) (4)

For the NDA

submission for such a drug product, antimicrobial activity of the drug product should be demonstrated by performing a microbial challenge test such as USP <51> *Antimicrobial Effectiveness Test*.

In addition to the proposed microbial limits and absence of specified microorganism *E. coli*, the drug product specification for non-sterile aqueous drug products should also include a test for the absence of *Burkholderia cepacia* complex (BCC). Non-sterile aqueous drug products may potentially be contaminated with organisms in the BCC. BCC strains have a well-documented ability to ferment a wide variety of substrates and are known to proliferate in the presence of many traditional preservative systems. Thus, despite the presence of otherwise adequate preservative systems, BCC strains can survive and even proliferate in product during storage. For a recent review of the Agency's perspective on BCC, please see *PDA J Pharm Sci Tech 2011; 65(5): 535-43*.

In order to control for the presence of BCC in your product, you should consider the Following

1. Identifying potential sources for introduction of BCC during the manufacturing process and describing the steps to minimize the risk of BCC organisms in the final drug product. We recommend that potential sources are examined and sampled as process controls. These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.

2. Providing test methods and acceptance criteria to demonstrate that the drug product is free of BCC. Your test method should be validated and a discussion of those methods should be provided. Test method validation should address multiple strains of the species and cells should be acclimated to the conditions in the manufacturing environment (e.g., temperature) before testing. USP <60> *Microbiological Examination of Nonsterile Products – Tests for Burkholderia cepacia Complex*, although not yet official, is recommended as a source for reference. If BCC testing is not performed per USP <60>, we have provided suggestions for a potential validation approach and some points to consider when designing your validation studies. However, any validated method capable of detecting BCC organisms would be adequate. It is currently sufficient to precondition representative strain(s) of BCC in water and/or your drug product without preservatives to demonstrate that your proposed method is capable of detecting small numbers of BCC. Your NDA should describe the preconditioning step [time, temperature, and solution(s) used], the total number of inoculated organisms, and the detailed test method to include growth medium and incubation conditions. It is essential that sufficient preconditioning of the organisms occurs during these method validation studies to ensure that the proposed recovery methods are adequate to recover organisms potentially present in the environment.

For more information, we refer you *to Envir Microbiol 2011; 13(1):1-12* and *J Appl Microbiol 1997; 83(3):322-6*.

Product Stability and Shelf Life:

It appears that you intend to rely on stability data for drug product manufactured by (b) (4), (b) (4), to support an extended shelf life (60 months). As the commercial manufacturing site will be Jazz Pharmaceuticals Ireland Limited (JPIL), you should provide a detailed, side-by-side comparison of the manufacturing equipment and processes, in-process controls, equipment, container closure components and sources, and other related items, for the (b) (4)-manufactured stability batches versus the batches manufactured at JPIL to support reliance on the (b) (4) stability batch data. Additionally, you should provide executed batches records for the stability batches manufactured at each site. The expiration dating period will be determined based on review of the information provided in the NDA.

Sponsor Pre-Meeting Response:
The responses to the **Microbiology** and **Product Stability and Shelf Life** comments are provided below.

Microbiology:
In the planned JZP-258 NDA, Jazz intends to submit information regarding USP <51> Antimicrobial Effectiveness Test to demonstrate inherent anti-microbial activity of the drug product.

Jazz will conduct additional testing specifically for Burkholderia cepacia complex (BCC) based on USP <51>. This additional information will also be provided in the NDA. Also, Jazz will conduct validation studies based on USP <60> to demonstrate adequacy of the test method to detect BCC.

Jazz intends to conduct a risk assessment regarding the necessity for implementing a test for BCC and, based on the outcome, will determine if a specification for BCC is warranted.

Stability and Shelf Life:
Jazz agrees to submit detailed, side-by-side comparison of the manufacturing processes for the (b) (4)-manufactured stability batches versus the batches manufactured at Jazz Pharmaceuticals Ireland Limited (JPIL) to support reliance on the 60-month shelf life established by (b) (4) stability batch data. Jazz also will submit copies of executed master batch records for stability batches manufactured at both sites. Jazz intends to rely on stability data for drug product manufactured by (b) (4) to support an extended shelf life for drug product manufactured at JPIL.

Meeting Discussion:
Clarification was requested by the Agency regarding whether the absence of BCC in the finished drug product would be investigated per USP <51> or per USP <60>. The sponsor stated that those tests would be performed both per USP <51> and per USP <60>; the sponsor also stated that the tests per USP <51> would be performed to demonstrate that the drug product had inherent anti-microbial activity against BCC strain(s). The Agency conveyed that the drug product specification should include the absence of BCC. The sponsor stated that a risk assessment would also be conducted and agreed that BCC contamination would be evaluated in raw materials, manufacturing process/environment, and water system.

The sponsor's proposal to rely on the (b) (4) stability batch data to establish shelf-life would be a matter of review.

2.2 Nonclinical

Question 2: Does the Agency agree that the proposed nonclinical package outlined in the meeting package is adequate to support the registration of JZP-258?

FDA Response to Question 2:
As we have previously stated (please see the minutes of the Type C meeting held on December 2, 2013, and our Type C written response letter [pertaining to (b) (4)] dated February 6, 2017), no additional nonclinical studies will be needed unless safety issues (e.g., impurities) that require nonclinical assessment arise.

Sponsor Pre-Meeting Response:
No further discussion is needed at the meeting.

Meeting Discussion:
None.

2.3 Clinical Pharmacology

Question 3: Does the Agency agree that the clinical pharmacology package is adequate to support the registration of JZP-258?

FDA Response to Question 3:
The clinical pharmacology package that you have proposed is acceptable, in form, to support the registration of JZP-258.

Sponsor Pre-Meeting Response:
No further discussion is needed at the meeting.

Meeting Discussion:
None.

Question 4: Does the Agency confirm that the information from phase 1 Study 13-010 and the population pharmacokinetic (PPK) analysis are adequate to describe the dose proportionality of JZP-258 in adult and pediatric subjects?

FDA Response to Question 4:
Your proposed approach to describing the dose-proportionality of JZP-258 in adult and pediatric subjects is acceptable, in form.

Sponsor Pre-Meeting Response:

No further discussion is needed at the meeting.

Meeting Discussion:
None.

Question 5: Does the Agency agree that the proposed extrapolation approach is appropriate to support inclusion of pediatric patients (7 years of age and older) in the indication for JZP-258?

FDA Response to Question 5:
We do not think that an extrapolation analysis is necessary to support the inclusion of children 7 years and older in the indication for JZP-258. If the efficacy findings in adults are similar between JZP-258 and Xyrem, the dosage and administration instructions for JZP-258 in children aged 7 to 17 years will likely be similar to those in the Prescribing information for Xyrem.

Sponsor Pre-Meeting Response
As the available data support similar efficacy between Xyrem and JZP-258, Jazz does not intend to submit the pediatric extrapolation analysis in the NDA. No further discussion is required at the meeting.

Meeting Discussion:
None.

2.4 Clinical

Question 6: Does the Agency agree that the results of the primary and the secondary efficacy endpoints and the safety data from the JZP-258 phase 3 Study 15-006 presented in the meeting package will support the proposed indications?

FDA Response to Question 6:
The efficacy and safety data for Study 15-006 that you have briefly summarized in this package suggest that those data may, in form, be sufficient to support the approval of JZP-258 for the entire range of indications that you are currently proposing for that product, subject to the Agency's full review of those data after your planned NDA is submitted.

Sponsor Pre-Meeting Response:
No further discussion is needed at the meeting.

Meeting Discussion:
None.

Question 7: Does the Agency agree that the statistical methods as described in the final statistical analysis plan (submitted in IND 49,641, Seq. No. 0332) are appropriate for the analyses of the primary and key secondary endpoints in Study 15-006 and adequate to support approval?

FDA Response to Question 7:
The primary analysis methods for the primary and key secondary endpoints, as described in the final statistical analysis plan for Study 15-006, are acceptable if missing values are limited. The appropriateness of the proposed methods of imputation for missing data and proposed sensitivity analysis for addressing possible missing data will be a matter of review.

Sponsor Pre-Meeting Response:
Jazz acknowledges FDA's comments on missing data and sensitivity analyses. No further discussion is needed at the meeting.

Meeting Discussion:
None.

Question 8: With regards to the supporting Xyrem safety information to be submitted in the JZP-258 NDA, does the Agency agree that cross-reference to the most recently submitted Xyrem Periodic Benefit Risk Evaluation Report (PBRER), and the approved United States Prescribing Information (USPI) is appropriate to demonstrate the most current and representative safety information for Xyrem?

FDA Response to Question 8:
It is acceptable for you to include the USPI and the most recent PBRER for Xyrem as supporting safety information in the proposed NDA for JZP-258. However, please do not cross-reference the current USPI and most recent PBRER for Xyrem; instead, please include those documents in your planned NDA.

Sponsor Pre-Meeting Response:
Jazz acknowledges FDA's response and will include the Xyrem PBRER and USPI in the JZP-258 NDA. No further discussion is needed at the meeting.

Meeting Discussion:
None.

Question 9: Based on the single pivotal trial registration plan, Jazz intends to summarize the clinical safety and efficacy data from Study 15-006 in Module 2 of the NDA, and does not plan to provide separate integrated summary of safety (ISS) and integrated summary of efficacy (ISE) documents. Does the Agency agree?

FDA Response to Question 9:
Your stated plan for summarizing the efficacy data for Study 15-006 in Module 2 of your planned NDA is acceptable.

Regarding your plan for summarizing the safety data for Study 15-006, it is acceptable to include the summary of safety in Module 2, with links between (i.e., to and from) the datasets, narratives, subject data listings, patient case report forms, and other relevant documents for Study 15-006 and the text and tables included in the safety summary in Module 2. We refer you to Appendix 1 for our general safety request document that includes details on additional specific aspects of the safety submission.

Please provide summaries and datasets separately for the open-label extension to Study 15-006.

Sponsor Pre-Meeting Response:
No further discussion is needed on FDA's comments in the first two paragraphs regarding Module 2.

Regarding FDA's request to provide summaries and datasets separately for the open-label extension (OLE), Jazz seeks agreement with the following strategy for the presentation of the OLE information within the NDA:

Study 15-006, main and OLE, is treated as a single study from the point of view of the protocol, Electronic Data Capture (EDC), associated submission ready (CDISC) datasets and clinical study report (CSR).

Information from the OLE part of Study15-006 will be readily identifiable within the submission ready CDISC datasets (SDTM and ADaM) in the NDA. SDTM datasets will identify OLE information via EPOCH variable. ADaM datasets will identify OLE information using APERIOD or other relevant flags. For example, within AE dataset (ADAE), main study and OLE study treatment emergent AEs will be identified via respective flags, MTRTEMFL and OTRTEMFL.

While a single CSR is planned for Study 15-006 with safety presented and discussed across all study periods, presentation of safety data from each period (e.g., main study, open-label extension) will be included.

Therefore, Jazz does not intend to provide summaries and datasets separately for the OLE part of Study 15-006.

Does the Agency agree?

Meeting Discussion:
The Agency agreed with the sponsor's proposal.

Question 10: Does the Agency agree that the proposal for clinical site datasets for Study 15-006 only will satisfy Office of Scientific Investigations requirements?

FDA Response to Question 10:

Your proposal to include clinical site datasets for Study 15-006 only is acceptable to the Office of Scientific Investigations.

Please refer to the updated draft Guidance for Industry entitled "Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions" (February 2018) and the associated "Bioresearch Monitoring Technical Conformance Guide" (February 2018) containing technical specifications, which are available at the following links, respectively:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf

Sponsor Pre-Meeting Response:
No further discussion is needed at the meeting.

Meeting Discussion:
None.

2.5 Regulatory

Question 11: Does the Agency agree that consistent with the USP Salt Policy the nonproprietary name for JZP-258 will be (b) (4) ?

FDA Response to Question 11:
(b) (4) a final determination of that matter will be made during the review of the NDA. The proposed dosing regimen for JZP 258 should be weight-based and include an initial dosage, maximum weekly dosage increase, and a maximum recommended dosage that account for exposure to the inactive ingredient of salt.

Sponsor Pre-Meeting Response:
Jazz acknowledges FDA's response, and would like to confirm that FDA agrees that dosing of JZP-258 will be (b) (4) **Can FDA confirm this?**

Meeting Discussion:
The Agency indicated that labeling the product (b) (4) is not acceptable (b) (4) The Agency further noted that the requirement for consistency between established name and labeled potency (USP Chapter <7>) is separate from the "USP Salt Policy"

and has been in effect for several years. Additionally, labeling should reflect concentration of the individual salts present in solution, (b) (4) The Agency acknowledged the sponsor's concerns with respect to potential medication error (b) (4)

The inclusion of information in labeling to clarify that the concentration of the active moiety in JZP-258 and Xyrem is the same would be acceptable to the Agency.

The sponsor may request an exception to the USP Salt Policy, if adequately supported by clinical considerations. However, based on recent discussions within the Agency, the use of an established name such as "(b) (4)" would not be acceptable.

Agency Post-Meeting Note:
Please see the minutes of the Type C teleconference held on May 8, 2017, under NDA 21196, and specifically the text under Question 6 regarding the (b) (4) for a previous discussion regarding the established name and label potency. Please also refer to USP Chapter <7> Labeling, specifically the section titled "LABELS AND LABELING FOR DRUG PRODUCTS AND COMPOUNDED PREPARATIONS EXPRESSED AS ACTIVE MOIETY IN NAME AND STRENGTH" for current USP labeling requirements.

Question 12: Does the Agency agree with the proposed content and cross reference plan of the NDA as outlined in Section 4.7 and Appendix 3?

FDA Response to Question 12:
We note that Section 4.7 of this meeting package omits reference to the Quality Overall Summary in Module 2 and states, with respect to Module 3, that "A summary of the drug substance and drug product information, including the control strategy, will be provided in the JZP-258 NDA." We assume that this is an error, and that a full CMC package will be submitted as outlined in Appendix 3 of the meeting package. The proposed content related to product quality microbiology appears acceptable, although a final determination will be made during NDA review based on the information that is provided in that application.

Sponsor Pre-Meeting Response
Jazz confirms that the NDA will include a Module 2.3 Quality Overall Summary as well as complete Module 3 CMC package, as described in Appendix 3 of the meeting package.
Jazz considers that there will be adequate information to support the anti-microbial effectiveness of the formulation over its in-use period in the final Module 3 for submission (as discussed in the response to FDA Question 1. No further discussion is needed at the meeting.

Meeting Discussion:
None.

ADDITIONAL COMMENTS

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

Controlled Substances Staff
You should provide data on abuse-related adverse events that have occurred in Study 15-006, in tabular form, for all reports that occurred in the following categories: abuse; overuse; and lost, stolen, missing, or unaccounted-for product. Those data should include subject ID number and detailed narratives.

Sponsor Pre-Meeting Response:
Jazz acknowledges FDA's requests, which will be provided in the NDA. No further discussion is needed at the meeting.

Meeting Discussion:
None.

Human Factors
We understand that you intend to market JZP-258 as an oral solution containing 0.413 g/mL of oxybate. However, we are unclear if you intend to co-package JZP-258 with an oral dosing device. If you intend to co-package your product with an oral dosing device, we recommend that you conduct a comprehensive use-related risk analysis if you have not already completed one. The comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis) the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures.

We also recommend you consider the Agency's Response to Question 11 above in your use-related risk analysis. If models of the same or similar combination products exist, your use-related risk analysis should incorporate applicable information on known use-related problems with those products. Useful information can be obtained from your own experience as well as from public sources such as the literature, adverse event reports, and product safety communications. Please see the draft Guidance for Industry entitled "*Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development.*"1

Additionally, if models of the same or similar combination products exist, it may be useful to conduct comparative analyses such as a labeling comparison, a comparative task analysis, and a physical comparison between your proposed product and the comparator for the purposes of identifying what differences exist between the user interfaces and where the same or similar risks may apply to your proposed product.

Based on the aforementioned information and data, you should determine whether you need to submit the results of a human factors validation study conducted under simulated use conditions with representative users performing necessary tasks to demonstrate safe and effective use of the product. If you determine that human factors validation study does not need to be submitted for your product, you should submit your risk analysis, comparative analyses, and justification for not submitting the human factors validation study to the Agency for review under this IND. When submitting the requested information to the IND, you should place that information in

eCTD Section 5.3.5.4. The Agency will notify you if we concur with your determination. Guidance on human factors procedures to follow can be found in the following guidance documents.2

1. Applying Human Factors and Usability Engineering to Medical Devices.
2. Guidance on Safety Considerations for Product Design to Minimize Medication Errors.

Please note that we have also recently published three draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling.3

1. Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development.
2. Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.
3. Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications.

Sponsor Pre-Meeting Response
Jazz acknowledges FDA's comments.

JZP-258 is an oral solution containing 0.413 g/mL oxybate, equivalent to 0.5 g/mL of active ingredient. (b) (4) . The dosing syringe to be provided with JZP-258 is the same as that currently used for Xyrem for which a human factors (HF) study was conducted to support the pediatric supplement submitted on 27 April 2018 for Xyrem (NDA 021196, S-030, approved 26 October 2018). As such, Jazz intends to include the risk analysis and the HF study performed for Xyrem in the JZP-258 NDA to support use of the same dosing syringe.

Jazz will submit a risk analysis, comparative analyses, and justification for not repeating an HF study in the NDA.

Meeting Discussion:
The Agency acknowledged the sponsor's proposal to reference the Human Factors (HF) study performed with Xyrem (and referred to in the sponsor's pre-meeting response) in the planned NDA for JZP-258 to support use of the same dosing syringe. The Agency recommended that the sponsor design its HF development program taking into consideration the Agency's initial response to Question 11 and the meeting discussion under that question. Specifically, the use-related risk analysis (URRA) and comparative analyses should consider the product's established name, statement of strength, and labeled potency. The Agency strongly recommended that Jazz submit its planned analyses and HF development plan to this IND for Agency review, and will notify the sponsor if it concurs with those proposals.

Risk Evaluation and Mitigation Strategy (REMS)
Based on the information available at this time, a risk evaluation and mitigation strategy will be necessary to ensure that the benefits of JZP-258 (b) (4) outweigh its risks. JZP-

258 [redacted] (b) (4) should be incorporated into the currently approved Xyrem REMS. This REMS should be included in the initial NDA submission.

Sponsor Pre-Meeting Response:
No further discussion is needed at the meeting.

Meeting Discussion:
None.

ADDITIONAL SPONSOR PRE-MEETING COMMENTS/QUESTIONS:

1. JZP-258, [redacted] (b) (4), contains the active moiety oxybate, the same active moiety in Jazz's marketed product, Xyrem (sodium oxybate), and thus would not be considered as a new molecular entity (NME) according to FDA's definition.

   Does the FDA agree that JZP-258 qualifies as a non-NME, and thus the NDA target review period will be 10 months (standard review) or 6 months (priority review) from the receipt of the submission?

   Meeting Discussion:
   The Agency concurred that JZP-258 qualified as a non-NME.

2. The notable high sodium content in Xyrem is reduced by up to 1.5 grams a day when taking JZP-258. Reduction in sodium is associated with reduced cardiovascular risk, as supported by numerous authoritative bodies, including a 2019 National Academy of Sciences Consensus Study Report (National Academies of Sciences, Engineering, and Medicine. Dietary Reference Intakes for Sodium and Potassium. Washington, DC: The National Academies Press: 2019).

   In addition, narcolepsy is a serious, chronic condition associated with increased risk of comorbid conditions including hypertension and cardiovascular disease. Jazz believes that a reduction of sodium up to 1.5 grams a day for this chronically administered medication will provide a significant improvement in safety.

   Does FDA agree that the JZP-258 NDA would be appropriate for priority review?

   Meeting Discussion:
   The Agency indicated that a decision regarding whether the proposed NDA for JZP-258 qualified for priority review status would be possible only at the time of the filing meeting to be held after submission of the planned NDA. At the same time, the information provided so far did not support the grant of priority review status, based as that information was on theoretical/speculative considerations. If the sponsor does indeed feel that the NDA for JZP-258 qualifies for priority review status, that argument should be made in the NDA.

The sponsor asked whether the timing of the safety update would be changed from 120 days if the NDA is granted a priority review. The Division noted that the safety update is generally submitted earlier than 120 days in the case of a priority review NDA, but the timing of the safety update for JZP-258 would have to be discussed following the submission of the planned NDA for that product.

3.0 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[1] and Pregnancy and Lactation Labeling Final Rule[2] 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.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and

[1] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[2] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information 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*.

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

No attachments from the meeting.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIC P BASTINGS
10/30/2019 08:14:08 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 049641

MEETING PRELIMINARY COMMENTS

Jazz Pharmaceuticals
Attention: Janice Mallison
Senior Director
Regulatory Affairs
3180 Porter Drive
Palo Alto, CA 94304

Dear Ms. Mallison:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Sodium Oxybate Oral Solution.

We also refer to your May 20, 2015, correspondence requesting a meeting to discuss the development plan for a low-sodium alternative formulation to Xyrem (sodium oxybate) oral solution, referred to as oxybate mixed-salt oral solution (OMSOS). Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting.

Our preliminary responses to your meeting questions are enclosed.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me/Vandna Kishore, Regulatory Project Manager, at (301) 796-4193.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: [B]
Meeting Category: [End of Phase 2]

Meeting Date and Time: [September 24, 2015, 11-12 PM EST]
Meeting Location: [WO Building 22, Room 1309]

Application Number: [049641]
Product Name: [Sodium Oxybate Oral Solution]
Indication: **[**Narcolepsy]
Sponsor/Applicant Name: [Jazz]

FDA ATTENDEES (tentative)

Billy Dunn, MD, Division Director
Eric Bastings, MD, Deputy Division Director
Ranjit Mani, MD, Senior Medical Officer
Alice Hughes, MD, Deputy Director for Safety
Sally Yasuda, PharmD, Team Leader for Safety
Kun Jin, PhD, Biometrics Team Leader
Lois Freed, PhD, Supervisory Pharmacologist
Melissa Banks-Muckenfuss, PhD, Nonclinical Reviewer
Angela Yuxin Men, MD, PhD, Clinical Pharmacology Team Leader
Bei Yu, PhD, Clinical Pharmacology Reviewer
Martha Heimann, PhD, Chemistry Manufacturing Controls Lead\
Reema Mehta, Pharm.D., M.P.H., DRISK
Jamie Wilkins Parker, Pharm.D., DRISK
Jasminder Kumar, Pharm.D., DRISK
James Hunter, RPh., MPH, Pharmacist Reviewer, CSS
Vandna Kishore, RPh., Project Manager
Susan Daugherty, R.N., Project Manager

SPONSOR ATTENDEES

- Jed Black, MD, Vice President, Therapeutic Area Head, Sleep Medicine
- Diane Guinta, PhD, Vice President, Clinical Development, Development Team Leader, Sleep Medicine
- Jennifer Ekelund, Vice President, United States Regulatory Affairs
- P.J. Honerkamp, Vice President, Business Unit Head, Sleep
- Gunjan Junnarkar, PhD, Director, Process Development
- Chinglin Lai, PhD, Vice President, Biostatistics

• Joel Selcher, Ph.D., Senior Director, Head of United States Regulatory Affairs Strategy
• Wheatley Spence, Senior Manager, Regulatory Affairs, Regulatory Strategy
• Roman Skowronski, MD, PhD, Executive Director, Clinical Development
• Karen Smith, MD, PhD, MBA, LLM, Global Head of Research and Development, Chief Medical Officer
• Katie Zomorodi, PhD, Senior Director, Early Development and Clinical Pharmacology

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for September 24, 2015 between Jazz and the Division of Neurology. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Xyrem oral solution is approved under NDA 21-196 for the treatment of cataplexy in narcolepsy and excessive daytime sleepiness (EDS) in narcolepsy. Jazz Pharmaceuticals (Jazz) is developing a new, low-sodium formulation for the same indications. The new formulation is an oral solution containing mixed-salt oxybate and is hereafter referred to as oxybate mixed-salt oral solution (OMSOS).

This meeting was requested to discuss the development plan for OMSOS now that the nonclinical studies agreed upon with the Agency have been completed and data are available from the agreed upon clinical pharmacokinetic study of OMSOS.

2.0 DISCUSSION

Clinical Pharmacology
Question 1: Does the Agency agree that no additional clinical pharmacology studies are required for the registration of OMSOS?

FDA Response to Question 1:
The pharmacokinetics of Xyrem have been observed to be non-linear over the dose range of 4.5 grams/night to 9.0 grams/night. However, the pharmacokinetic linearity of oxybate mixed-salt oral solution over the same dose range is unknown. Therefore, you should characterize the pharmacokinetics of oxybate mixed-salt oral solution over the 4.5 grams/night to 9.0 grams/night dose range in a sub-group of your proposed Phase 3 study, during the up-titration phase.

Clinical

Question 2: Given the pharmacokinetic data from Study 13-010 and existing clinical safety and efficacy data for Xyrem,
a. does FDA require a confirmatory Phase 3 study
b. does FDA agree that a single confirmatory Phase 3 study is adequate for approval of OMSOS?

FDA Response to Question 2:
Question 2a
Yes.

Question 2b
Yes.

Question 3: Does the Agency agree that a double-blind, placebo-controlled, randomized withdrawal, Phase 3 efficacy and safety study of OMSOS in subjects with narcolepsy with cataplexy is sufficient to support registration for the proposed indications?

FDA Response to Question 3:
Yes.

Question 4: Does the Agency agree that to support registration of OMSOS for the proposed indications the proposed study design is appropriate, including the following?
a. the primary endpoint: number of cataplexy attacks
b. the key secondary endpoint: change in ESS
c. adequacy of the proposed placebo, based on electronic taste sensor testing, to maintain subject masking to treatment

FDA Response to Question 4:
The following responses are based only on the protocol outline provided in this submission and are subject to change following review of the full clinical protocol for the proposed Phase 3 study.

Question 4a
Yes.

Question 4b
Yes.

Question 4c
We agree that use of electronic sensor technology ("e-tongue") may inform development of a matching placebo formulation. However, we recommend that you verify suitability of the chosen placebo formulation in human subjects.

Question 5: Does the Agency agree that the statistical methods for the analysis of the primary efficacy endpoint in the proposed study are acceptable to support registration?

FDA Response to Question 5:
The comments below are based only on the abbreviated statistical analysis plan for your Phase 3 study that has been included in this submission. The ultimate acceptability of the methods that you have proposed for analysis of the primary efficacy endpoint, to support the approval of oxybate mixed-salt oral solution for the treatment of cataplexy in narcolepsy, will be a matter of review, once a detailed plan for that analysis is submitted together with the full protocol for the Phase 3 study.

Despite the limitations of the statistical analysis plan that you have submitted, the statistical methods for the primary analysis that you have proposed are, in form, reasonable. However, in addition to the approach that you have described, you should take steps to ensure that the numbers of unreported days in subjects' diaries are minimal. You should specify sensitivity analyses to address unreported diary days, although if there are many such days, the analysis results may be uninterpretable. You should also specify a test of normality so that the determination of normality is not highly subjective.

Question 6: Does the Agency agree that the existing Xyrem clinical safety database and 13 years of postmarketing experience, in addition to any agreed-upon clinical study for OMSOS, can serve as the complete safety database to support registration of OMSOS for the treatment of cataplexy and EDS in patients with narcolepsy?

FDA Response to Question 6:
We agree that the clinical safety database as described by you in this question is likely to be sufficient to support the registration of oxybate mixed-salt oral solution for the treatment of cataplexy and excessive daytime sleepiness for narcolepsy. However, should any currently-unanticipated concerns about the safety of that product emerge during its further clinical development, it is possible that the database that you have proposed may warrant expansion.

General and Administrative

Question 7: Does the Agency agree that the marketing application for OMSOS can be submitted as a Supplemental New Drug Application (sNDA) to NDA 21-196?

FDA Response to Question 7:
No. A marketing application for oxybate mixed-salt oral solution should be submitted as an Original New Drug Application. Oxybate mixed-salt oral solution is considered by the Agency to have an active ingredient that differs from that in Xyrem, i.e., a new active ingredient.

For a more detailed explanation of the above, please see Section III. A.1.a (and Footnote #7) of the Guidance for Industry entitled "Submitted Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees," that was published in December 2004. That document is available at the following link.

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079320.pdf

3.0 DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format.

This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

4.0 LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

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

/s/

VANDNA N KISHORE
09/18/2015