CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205422Orig1s009

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 205422

MEETING PRELIMINARY COMMENTS

Otsuka Pharmaceutical Development & Commercialization, Inc.
Attention: Dana Cahill, PhD
Senior Director, Global Regulatory Affairs
2440 Research Blvd.
Rockville, MD 20850

Dear Dr. Cahill:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rexulti (brexpiprazole).

We also refer to your July 22, 2022, correspondence requesting a meeting to discuss a Type B (pre-sNDA) meeting to discuss your supplemental new drug application (sNDA) for the proposed indication of agitation associated with Alzheimer's dementia.

Our preliminary responses to your meeting questions are enclosed.

You should provide a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented or discussed at the meeting.

In accordance with FDA policy, you should not make audio or visual recordings of the discussion at this meeting. Consistent with 21 CFR 10.65(e), the official record of this meeting will be the FDA-generated minutes.

If you have any questions, contact me at Sujin.Wolff@fda.hhs.gov or 301-796-1519.

Sincerely,

{See appended electronic signature page}

Sujin Wolff, PharmD
Regulatory Project Manager
Psychiatry Group
Division of Regulatory Operations for Neuroscience
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

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

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	Pre-sNDA
Meeting Date and Time:	September 28, 2022, 1:00 p.m. to 2:00 p.m. (EDT)
Meeting Location:	Teleconference
Application Number:	NDA 205422
Product Name:	Brexpiprazole oral tablets (REXULTI; OPC-34712 and Lu AF41156)
Proposed Indication:	Treatment of agitation associated with Alzheimer's dementia
Sponsor Name:	Otsuka Pharmaceutical Development & Commercialization, Inc.
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act

FDA ATTENDEES (tentative)

Tiffany R. Farchione, MD	Director, Division of Psychiatry (DP)
Bernard Fischer, MD	Deputy Director, DP
Michael Davis, MD, PhD	Clinical Team Leader, DP
Valentina Mantua, MD, PhD	Clinical Reviewer, DP
Aisar Atrakchi, PhD	Pharmacology/Toxicology Supervisor, Division of Pharmacology and Toxicology for Neuroscience (DPT-N)
Amy Avila, PhD	Pharmacology/Toxicology Team Leader, DPT-N
Julie Frank, PhD	Pharmacology/Toxicology Reviewer, DPT-N
Luning (Ada) Zhuang, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Huixia Zhang, PhD	Clinical Pharmacology Reviewer, OCP
Peiling Yang, PhD	Biometrics Team Leader, Office of Biostatistics (OB)
Yang (Kelly) Yang, PhD	Biometrics Reviewer, OB
Sujin Wolff, PharmD	Regulatory Project Manager, DRON—Psychiatry Group

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 28, 2022, at 1:00 p.m. between Otsuka Pharmaceutical Development & Commercialization, Inc. and the Division of Psychiatry. 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. 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

Brexpiprazole (REXULTI) was first approved in July 2015 for the treatment of schizophrenia in adults and as adjunctive therapy for the treatment for major depressive disorder (MDD). In December 2021 it was also approved for the treatment of schizophrenia in pediatric patients 13 to 17 years of age. Rexulti is currently being co-developed by two sponsors (OPC and Lundbeck) for the treatment of agitation associated with Alzheimer's dementia (AAD) under IND 115960. This program was granted fast track designation on March 16, 2015.

The Sponsor completed two 12-week, double blind, placebo-controlled studies (331-12-283 and 331-12-284) enrolling a total of 701 individuals with AAD who had a Mini-Mental State Examination (MMSE) score of 5 to 22, inclusive, and a Neuropsychiatric Inventory (NPI) agitation/aggression item total score of ≥ 4. Both studies used the Cohen-Mansfield Agitation Inventory (CMAI) as the primary outcome measure.

Study 331-12-283 (hereafter Study 283) was a fixed-dose trial with three arms (brexpiprazole 1 and 2 mg/day and placebo in a 1:1:1 ratio), which enrolled 432 subjects. The brexpiprazole 2 mg/day group was statistically superior to placebo (least squares mean difference (LSMD) -3.77, p = 0.0404) on the primary endpoint of mean change in CMAI total score from Baseline to Week 12. The lower dose group, 1 mg/day brexpiprazole, did not show any separation relative to placebo (LSMD = 0.23, p = 0.9015).

Study 331-12-284 (hereafter Study 284) was a flexible-dose trial with two arms (brexpiprazole 0.5 to 2 mg/day and placebo in a 1:1 ratio) which enrolled 269 subjects. The brexpiprazole 0.5 to 2 mg/day group (mean dose 1.54 mg/day) did not show statistical superiority relative to placebo on the CMAI total score at Week 12 (LSMD = −2.34, p = 0.1454). The Sponsor noted that in a subgroup of patients who exhibited aggressive behaviors at baseline, the effect of brexpiprazole was more robust.

During a Type C meeting on September 21, 2017, the Sponsor discussed the results of studies 283 and 284. The Division recommended that the Sponsor conduct a third phase 3 study as a 12-week, three-arm, fixed-dose, double-blind, placebo-controlled trial that would include one arm with a higher dose than previously studied (3 mg). During a Type C meeting held on January 31, 2018, the Division discussed the design of the third phase 3 trial 331-14-213 (hereafter Study 213) and agreed to the Sponsor's proposal to power the study to assess the efficacy of the brexpiprazole treatment arm (2 and 3 mg/day) versus placebo. However, the Division recommended that at least 100 patients should be randomized to the higher 3-mg dose. Additionally, the Division agreed on the enrichment strategy to ensure that enrolled subjects exhibited sufficient agitation at baseline (International Psychogeriatric Association (IPA) provisional consensus definition of agitation and CMAI Factor 1 aggressive behavior at baseline).

In Study 213, the brexpiprazole 2 and 3 mg/day group showed statistically significant improvement compared with placebo on the primary efficacy endpoint, the mean change in CMAI total score from baseline to Week 12 (LSMD = −5.32, p = 0.0026, as compared with the cutoff 0.035 due to interim analysis).

The Sponsor's stated purpose for this Type B pre-sNDA meeting is to reach agreement on:

- The analyses required to support the proposed indication of agitation associated with Alzheimer's dementia

- The components of the sNDA filing and if they are sufficient to facilitate a full and substantial review.

2.0. DISCUSSION

2.1. Clinical

Question 1: Does the Division agree that the efficacy data package support filing an sNDA for the treatment of agitation associated with Alzheimer's dementia?

> ***FDA Response to Question 1:*** *Based on the material in your meeting package and our background familiarity with your development program, the information you cite appears sufficient to support submission of a supplemental marketing application. A formal decision on filing your application would follow receipt of such a submission. The adequacy of such an application to support approval would be a matter of review, as would the wording of any eventually approved labeling.*

Question 2: Does the FDA agree that the proposed format of the CSRs for the planned submission could facilitate full and substantial review of this sNDA?

FDA Response to Question 2: *The format of the CSRs you proposed appears acceptable for review.*

Question 3: Does the Agency have any comments regarding the content and format of the proposed SCE?

FDA Response to Question 3: *The content and format of the summary of clinical efficacy appear acceptable. You should also provide efficacy analyses using individual component scores of the CMAI (domains). For Study 213, you should provide these analyses for the intended dose group (2 mg and 3 mg combined) and for the individual dose groups (2 mg and 3 mg separately).*

We consider analyses of pooled trials or pooled doses to be exploratory. Nevertheless, trial should be included as a factor in analyses of pooled studies/doses if a statistical model is used. We may request additional analyses during the NDA review.

Question 4: Does the Agency have any comments with regard to the content and format of the proposed SCS?

FDA Response to Question 4*: The format and content you propose for the summary of clinical safety appear acceptable; however, you should also include pooled analyses by brexpiprazole dose. Specifically, you should include a pooled safety analysis for the 2 mg and 3 mg dose arms combined and for the 2 mg and 3 mg dose arms separately. Given the dose titration periods in your studies, you should provide supportive safety analyses based on the doses that the patients were receiving at the time when they had the adverse event.*

2.2. Regulatory

Question 5(a): Does the Agency expect a PDAC meeting being convened for this indication?

FDA Response to Question 5(a): *Whether a Psychopharmacologic Drugs Advisory Committee (PDAC) is needed will be determined after receipt of a marketing application. However, we anticipate that a PDAC may be needed to discuss the safety of your product in the context of the broader boxed warning for the class of antipsychotics for the increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis.*

Question 5(b): If so, what are the potential topics the Agency would foresee being addressed at an PDAC meeting for brexpiprazole for this indication?

FDA Response to Question 5(b): *See our response to Question 5a.*

Question 6: While the Sponsor acknowledges that this will ultimately be a matter of review, does the Division agree that the proposed sNDA filing could be an appropriate candidate for Priority Review?

***FDA Response to Question 6*:** *Priority review is decided after receipt of a marketing application. If you seek priority review, you should include a rationale in your application.*

Question 7: Does the Agency agree with the presentation of these CRFs and Narratives?

FDA Response to Question 7: *Your proposal appears acceptable.*

Question 8: Does the Agency have any comments regarding the proposed content, as outlined in the draft Table of Contents (TOC)?

FDA Response to Question 8: *See the FDA's* Comprehensive Table of Contents Headings and Hierarchy*.*

Question 9: Does the Division agree with the following:

(a) The data cut-off date of 31 Oct 2022?

FDA Response to Question 9(a): *Your proposed data cut-off date appears acceptable.*

(b) The proposed content for the 120-day safety update?

FDA Response to Question 9(b): *Your proposed content for the 120-day safety update appears acceptable.*

Additional Comments from Biometrics

You should include the following items for the three efficacy studies (3321-12-283 ITT, 331-12-284 ITT, and 331-14-213 ITT) in your future sNDA submission:

1. *All raw as well as derived variables in .xpt format*

2. *Raw data in legacy format if data were not collected in CDISC*

3. *Executable SAS programs that produced all efficacy results*

4. *Executable 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)*

5. *A list of IND number with serial numbers and submission dates of the protocols, SAPs, amendments, and any relevant meetings*

6. *For study 331-14-213, the interim analysis results and DMC meeting minutes, as well as SAS programs (and the dataset) used to derive the primary efficacy variable for the interim analysis.*

Additional Comment from Clinical Pharmacology

We recommend that you include exposure-response analyses in the submission to support your application.

3.0. OTHER

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*.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

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[3] and Pregnancy and Lactation Labeling Final Rule[4] 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

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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 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.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* 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 ORA investigators who conduct those inspections. 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.

Please refer to the draft guidance for industry *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 Containing Technical Specifications*.[5]

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in

[5] https://www.fda.gov/media/85061/download

eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[6]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[7]

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

[6] http://www.fda.gov/ectd
[7] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

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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/

SUJIN J WOLFF
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