CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214275Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 104504

MEETING REQUEST-
WRITTEN RESPONSES

Janssen Research & Development, LLC.
Attention: Dana Leeds, Ph.D.
Associate Director, Regulatory Affairs
1820 Chapel Avenue West, Suite 300
Cherry Hill, NJ 08002

Dear Dr. Leeds:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Uptravi (selexipag).

We also refer to your September 19, 2019, correspondence requesting a meeting to discuss obtain agreement with the FDA on the format and content of an NDA for an IV formulation of Uptravi (selexipag) for treatment of patients with PAH who are currently prescribed oral selexipag (UPTRAVI) and who are temporarily unable to take oral medication.

Further reference is made to our Meeting Granted letter dated October 10, 2019, 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 October 16, 2019 background package.

If you have any questions, call Wayne Amchin, RAC, Regulatory Project Manager at 301-796-0421.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:

- Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: B
Meeting Category: Pre-NDA

Application Number: IND 104504

Product Name: Uptravi (selexipag)
Indication: Treatment of PAH
Sponsor Name: Janssen Research & Development, LLC
Regulatory Pathway: 505(b)(1)

1.0 BACKGROUND

The sponsor requested this meeting to obtain FDA agreement on the format and content of the NDA for an intravenous formulation (IV) of Uptravi (selexipag) for treatment of patients with PAH who are currently using the oral formulation but are temporarily unable to take oral medication.

Selexipag is a prostacyclin receptor agonist approved on December 21, 2015 for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH.

A teleconference was held with the sponsor on July 20, 2016 to discuss their development program for the IV formulation.

2.0 QUESTIONS AND RESPONSES

2.1. Chemistry, Manufacturing, and Controls

Question 1: Drug Product Stability Data: Does the Agency agree that the overall stability plan for drug product is adequate to support an NDA submission and that additional stability data (up to 18 months of registration batches) can be provided approximately 3 months after NDA submission?

FDA Response to Question 1: Your proposal to submit 12 months of long-term and six months of accelerated stability data for three registration batches is in alignment with ICH Q1A(R2) Guideline. The application is expected to be complete at time of submission, therefore, information submitted to the NDA subsequent to the original submission may or may not be reviewed as resources allow.

2.2. Clinical

Question 2: Proposed Infusion Rate: *The infusion rate applied in study AC-065A309 was adapted from the rate used in the absolute bioavailability study AC-065-110 in healthy subjects. No safety or tolerability issues were observed in either study. Based on the available data, the applicant proposes a twice daily 80 min infusion of IV selexipag at a constant rate. Does the Agency agree with this proposal?*

FDA Response to Question 2: Yes, the proposed infusion rate seems appropriate.

2.3. Regulatory

Question 3: Overall Submission Content / Administrative, Dossier Format:

a) The proposed submission includes a single study conducted in patients with PAH (AC-065A309). The study investigated the PK, safety and tolerability of selexipag in patients switching from an oral dose to an equivalent IV dose. Efficacy was not evaluated, and the safety data are fully described in the CSR. Consequently, the applicant requests a waiver for the requirement to provide the following:
- Integrated Summary of Effectiveness (ISE)
- Summary of Clinical Efficacy (SCE)
- Integrated Summary of Safety (ISS)
- Summary of Clinical Safety (SCS)

A summary of the safety data from the AC-065A309 study with reference to previously submitted safety and efficacy data for selexipag will be provided in the Clinical Overview. Does the Agency agree to this proposal?

FDA Response to Question 3a: Yes, we agree with your proposal and grant a waiver for the integrated and summary efficacy and safety documents.

b) The Sponsor plans to submit a nonclinical overview to discuss the data from the local tolerability study as agreed with the FDA together with an in-vitro hemolytic compatibility study. The report for the local tolerability study (T-16.036) that was previously submitted to the Agency under IND-104504 (Serial No. 0282) will be cross-referenced in the NDA. A cross-reference will also be made to NDA 207947; Serial No. 0000 for an additional local tolerance study report (T-12.570) that was previously submitted. Does the Agency agree with submission of the Non-Clinical Overview (Module 2.4), with cross-references to the previously submitted and approved information in NDA 207947?

FDA Response to Question 3b: *Yes, this seems appropriate for this submission.*

c) Does the Agency agree that the proposed overall eCTD Table of Contents, with appropriate cross-references to the previously submitted and approved NDA 207947, supports the NDA filing for the use of IV selexipag as a temporary substitute for oral selexipag in PAH?

FDA Response to Question 3c: Yes, we accept your proposal for cross-referencing to NDA 207947.

Question 4: Proposed Datasets: *Does the Agency agree with the proposed tabulation dataset and analysis dataset submission plan?*

FDA Response to Question 4: Yes, your proposal seems acceptable.

Question 5: 120-Day Safety Update: *The Sponsor proposes to submit the Development Safety Update Report (DSUR) in lieu of the required 120-day safety update for the planned submission. Is the Agency in agreement with this proposed substitution?*

FDA Response to Question 5: Yes, we agree with the DSUR can be a substitute for the 120-day safety update.

Question 6: Bioresearch Monitoring Program (BIMO) Waiver: *Does the Agency agree that a BIMO Report is not required for this NDA?*

FDA Response to Question 6: Yes, we agree.

Question 7: Orphan Drug Exemption: *On 30 August 2010, selexipag was granted Orphan Drug Designation (Designation Request # 10-3048) for the treatment of pulmonary arterial hypertension (PAH). Does the Agency agree that, as IV selexipag contains the same active moiety as the previously approved oral selexipag and is intended for the same PAH indication, submission of a pediatric assessment is not required to support the submission of an IV formulation of selexipag per the Pediatric Research Equity Act?*

FDA Response to Question 7: Yes, we agree.

Question 8: Published Literature: The Sponsor plans to submit published literature according to the following proposal:

a) The Sponsor will submit, in Module 5.4, copies of all published literature cited in Module 2.7 Clinical Summary.
b) The Sponsor plans to refer to the current DSUR for a list of published scientific literature for reports relevant to the clinical safety and effectiveness of selexipag.

Does the Agency agree?

FDA Response to Question 8: Yes, we agree with your proposal to submit published literature.

3.0 ADDITIONAL IMPORTANT MEETING INFORMATION

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

[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

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.

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 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.[3]

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.[4]

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.

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[3] http://www.fda.gov/ectd
[4] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

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)				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999).[5] In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov.[6]

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to

[5] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[6] http://www.regulations.gov

demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your

submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
(1) Example: Published literature	*Nonclinical toxicology*
(2) Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
(3) Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
(4)	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

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* (February 2018) and the associated *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*.[7]

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

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/

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