CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215431Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 135972

MEETING MINUTES

Axsome Therapeutics, Inc.
Attention: Melina Cioffi, Pharm.D
200 Broadway, 3rd Floor
New York, NY 10038

Dear Dr. Cioffi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AXS-07 (meloxicam and rizatriptan).

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, call Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Nick Kozauer, MD
Acting Director
Division of Neurology 2
Office of Neuroscience
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	**B**
Meeting Category:	**Pre-NDA**
Meeting Date and Time:	**July 16, 2020 from 1:00-2:00pm EDT**
Meeting Location:	**Teleconference**
Application Number:	**IND 135972**
Product Name:	**AXs-07 (rizatriptan and meloxicam)**
Indication:	**migraine**
Sponsor Name:	**Axsome Therapeutics**
Regulatory Pathway:	**505(b)(2)**
Meeting Chair:	**Nick Kozauer, MD**
Meeting Recorder:	**Lana Chen, RPh**

FDA ATTENDEES

Nick Kozauer, MD, Acting Director, Division of Neurology 2 (DN2)
Paul Lee, MD, PhD, Acting Deputy Director, DN2
Heather Fitter, MD, Clinical Team Leader, DN2
Laura Jawidzik, MD, Clinical Reviewer, DN2
Angela Men, PhD, Clinical Pharmacology Team Leader
Muzeeb Syed, PhD, Clinical Pharmacology Reviewer
Lana Chen, RPh, Project Manager
Minjeong Park, PhD, Statistical Reviewer

SPONSOR ATTENDEES

Axsome Therapeutics
Herriot Tabuteau, M.D., Chief Executive Officer
Mark Jacobson, M.A., Chief Operations Officer
Amanda Jones, Pharm.D., Senior VP, Clinical Research
Cedric O'Gorman, M.D., M.B.A., Senior VP, Clinical Development & Medical Affairs
Melina Cioffi, Pharm.D., Executive Director, Regulatory Affairs
Daniel Bigelow, Manager, Regulatory Affairs
Michael Chen, PhD, Statistician
John Dillberger, PhD, Nonclinical

DISCUSSION

Clinical

1. Axsome is planning a 505(b)(2) NDA submission for AXS-07 for the acute treatment of migraine, based on the results of the completed Phase 3 Study AXS-07-301 (MOMENTUM), conducted pursuant to a Special Protocol Assessment (SPA) Agreement, as agreed by the Division at the EOP2 Meeting. Axsome has also conducted an additional Phase 3 Study AXS- 07-303 (INTERCEPT) assessing drug response after treatment of acute migraine at the mild stage for description in labeling, in accordance with the FDA Guidance for Industry, "Migraine: Developing Drugs for Acute Migraine" (February 2018).

   In light of the positive results from these studies that are now available, does the Division agree with the Sponsor's plan to submit an NDA using these data to support a clinical review of AXS-07 for the acute treatment of migraine with or without aura in adults?

   See Section 5.2 for supporting justification.

   FDA Response:

   On face, your plan is acceptable. Whether a description of the results from Study AXS-07-303 could be included in any future product labeling will be a matter of review. At the time of your NDA submission, your application should be complete and should also include a safety database of at least 300 patients treated for 6 months and 100 patients treated for 1 year, treating a minimum of 2 migraines per month.

   Meeting Discussion: There was no meeting discussion.

2. Does the Division consider the Sponsor's anticipated NDA safety database to be acceptable?

   See Section 8.3 for supporting justification.

   FDA Response:

   On face, this is acceptable. Please see the response to Question 1.

   Meeting Discussion: There was no meeting discussion.

3. Does the Division concur with the Sponsor's plan to provide patient narratives?

   See Section 8.2.2 for supporting justification.

FDA Response:

You should provide narratives for deaths, adverse events leading to drug discontinuation, SAEs, pregnancies, and AEs of special interest. Please see Attachment 1 for more details regarding the preparation of the narratives and case report forms.

Meeting Discussion: There was no meeting discussion.

4. Does the Division concur with the Sponsor's planned content for the 120-day safety update?

   See Section 8.3.1 for supporting justification.

   FDA Response:

   Yes, your plan for the 120-day safety update is acceptable.

   Meeting Discussion: There was no meeting discussion.

5. Does the Division agree with the Sponsor's proposal to utilize the text portion of the integrated summaries of safety and efficacy (Module 5.3.3) as the Clinical Summaries of Efficacy (Module 2.7.3) and Safety (Module 2.7.4)?

   See Section 8.5 for supporting justification.

   FDA Response:

   We are unclear about what you are proposing; we refer you to the Guidance for Industry that you have cited in your meeting package, stating that if the narrative portion of the ISE or ISS is suitable for use in section 2.7.3 or 2.7.4, the narrative portion should be submitted only once and referenced in both Module 2 (section 2.7.3 or 2.7.4) and Module 5, section 5.3.5.3. The intention of sections 2.7.3 and 2.7.4 is to serve as a summary, and not to provide all of the detail that would be found in the ISE and the ISS.

   Meeting Discussion: The Division indicated that the text of the ISE and ISS should be sufficiently detailed, while the SCS and SCE should be a summary. The Division reiterated to the sponsor that the text of the ISE and ISS did not need to be repeated in the SCS or the SCE.

Statistics

6. Does the Division agree with the Sponsor's planned integrated presentation of efficacy and safety?

   See Section 8.1 and 8.2 for supporting justification.

FDA Response:
The ISE should be an overall integrated analysis that comprehensively examines the effectiveness data derived from individual clinical studies. It is not intended to include only analyses of pooled efficacy data from multiple studies. There are situations when pooled efficacy analyses may be useful, such as when evaluating effectiveness in subgroups, such as, age, [redacted] and race, and such an analysis could be presented in the ISE. Please refer to the Guidance for Industry: Integrated Summary of Effectiveness: https://www.fda.gov/downloads/drugs/guidances/ucm079803.pdf

For the ISS, please clarify your planned safety analysis pools. At a minimum, you should have a safety pool that includes the two Phase 3 pivotal studies. You should include integrated datasets so that we can conduct analyses as needed on this pool. The safety parameters you have listed on page 45 of the briefing booklet do not include vital sign analyses. We would expect to see analyses of vital signs presented in your ISS.

Meeting Discussion: For the pooled efficacy analyses of the ISE, the sponsor stated it will analyze age above and below the median age, [redacted] and race categories of White and non-White. The Division stated race categories should be White, Black, Asian, American Indian/Alaskan Native, Native Hawaiian, or other. However, ultimately this will depend on the number of patients the sponsor has in each category. It may be acceptable to pool American Indian, Native Hawaiian, and other if there few patients in each category.

The sponsor agreed to provide a safety pool that includes the two Phase 3 studies and the integrated datasets for this pooled safety data. The sponsor also agreed to provide vital sign analyses for the two clinical studies, as well as the requested safety pool.

7. Does the Division concur with the Sponsor's proposed dataset package?

   See Section 8.4 for supporting justification.

FDA Response:
From technical standpoint, the format of your proposed dataset package is acceptable.

We have the following comments about the efficacy dataset:

a. You should include a patient-level flag to indicate rescue medication use before the 2-hour timepoint.
b. You should include a patient-level flag to indicate missing data status for each of the two co-primary endpoints (pain severity and the MBS) at the 2-hour timepoint.

Meeting Discussion: There was no meeting discussion.

Clinical Pharmacology

8. The potential for QT prolongation with AXS-07 will be addressed in the NDA via a comprehensive assessment of ECGs from patients treated with AXS-07 in our clinical trials, reference to the thorough QT study information for meloxicam found in the label for Anjeso (meloxicam IV), and reference to the arrhythmias section of the label for Maxalt (rizatriptan). Axsome believes that this approach is appropriate and that a thorough QT study is not needed since 1) both of the components of AXS-07 (meloxicam and rizatriptan) are approved drugs that are widely prescribed with a long history of clinical use, 2) the systemic exposures from dosing with AXS-07 are either significantly lower than or at most similar to those with achieved with the reference listed drugs, 3) no significant effect on the QT interval has been reported with rizatriptan or meloxicam, and 4) the expected safety database with AXS-07 is expected to be large and includes ECG assessments.

   Does the FDA agree with the proposed approach to addressing the potential for QT prolongation in our NDA?

   See Section 6.4 for supporting justification.

   FDA Response:

   Yes, we agree.

   Meeting Discussion: There was no meeting discussion.

9. Does the Division agree with the Sponsor's plan to reference Drug-Drug Interaction data and data on Special Populations already available for the reference listed drugs (RLDs) Mobic® (oral meloxicam), Anjeso™ (IV meloxicam), and Maxalt® (rizatriptan)?

   See Section 6.3, Appendix 2: Proposed Drug Interaction Section for Labeling for AXS-07, and Appendix 3: Proposed Special Populations Section for Labeling for AXS-07 for supporting justification.

   FDA Response:

   You claim that a pharmacokinetic bridge between the LDs has been established using 30 mg IV meloxicam and 30 mg rizatriptan. Although a food effect study is planned, the exposure is unlikely to be higher than 30 mg of reference products. It seems reasonable to refer to the LD labels for information about drug-drug interaction (DDI) and special populations. In the NDA submission, you will need to submit complete bridging information including the comparison with meloxicam and the food effect.

Meeting Discussion: There was no meeting discussion.

Nonclinical

10. Axsome has completed the 3-month repeat dose toxicity study of AXS-07 requested by the FDA at the EOP2 meeting to support the planned NDA filing. In addition, the Sponsor will utilize existing nonclinical data for meloxicam and rizatriptan from the FDA labels for the reference listed drugs (RLDs), Mobic® (oral meloxicam), Anjeso™ (IV meloxicam), and Maxalt® (rizatriptan), and in the literature. Does the Division agree that this nonclinical package is adequate to support the filing of a 505(b)(2) NDA for AXS-07 for the acute treatment of migraine?

    See Section 7 for supporting justification.

FDA Response:

Based on the information provided in the briefing document, the nonclinical package is sufficient to support filing of an NDA. A final determination as to the adequacy of nonclinical studies will be a matter of review.

Meeting Discussion: There was no meeting discussion.

Procedural

11. Does the Division agree that the Sponsor's planned content and format of our NDA is adequate to support the filing of an application of AXS-07 for the acute treatment of migraine?

    See Appendix 1: NDA Table of Contents for AXS-07 in the Treatment of Acute Migraine with or without Aura in Adults for supporting justification.

FDA Response:

From technical perspective (and not content related), the planned format of the NDA is acceptable. However, please note that for Modules 1.6, 1.9, 1.14, and 3.2, additional nodes will need to be added under the Modules to further specify the content submitted. For example, under Module 1.6, Meeting Request content should be provided under Module 1.6.1 and Meeting Background Materials should be provided under Module 1.6.2. Please follow

https://www.fda.gov/media/76444/download for more details regarding the eCTD structure specifications.

In addition, throughout your briefing document, including the table in Appendix 1, you refer to three listed drugs, Mobic, Maxalt, and Anjeso, on which you appear to intend to rely to support approval of your proposed NDA. Please identify the following for these or any listed drugs on which you propose to rely for approval of your application:

1. The name of the listed drug and application number
2. The information needed for approval of your application that reliance on the specific listed drug will provide (e.g., your proposed application will rely on FDA's findings of nonclinical safety for listed drug X to support the nonclinical safety of your proposed combination product)
3. Your plan for bridging to that specific listed drug on which you intend to rely (i.e., your plan for scientifically justifying reliance on the listed drug)

Please note that if you intend to rely for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish a "bridge" between your proposed product and each listed drug on which you propose to rely to demonstrate that such reliance is scientifically justified.

Meeting Discussion:

Although the briefing package described the sponsor's plan to utilize both Mobic (oral meloxicam) and Anjeso (IV meloxicam) as the planned listed drugs for the future NDA submission, during the meeting, the sponsor clarified that its updated plan is to rely only on the Anjeso (IV meloxicam) label (Section 7, 8, 12, and 13) and use Anjesco as the only listed drug in the NDA submission. The Division stated that it acknowledged the sponsor's plan and indicated that its acceptability will be a matter of review. The Division stated that the sponsor should include adequate bridging information in the proposed NDA submission.

The sponsor stated that:

- The AXS-07-102 formulation is the formulation that was used in the completed pivotal efficacy studies, the ongoing safety study, and planned food effect study.
- The AXS-07-102 formulation is also the to-be-marketed formulation.
- A Phase 1 prototype was used in Study AXS-07-101.

Abuse Potential

12. The Sponsor plans to assess the abuse potential of AXS-07 by performing an analysis of abuse-related AEs in our clinical trials and by referencing the FDA's prior findings of abuse potential for the reference listed drugs (RLDs), Anjeso™ (meloxicam), and Maxalt® (rizatriptan). Does the Division agree with the Sponsor's plan for assessing the abuse potential of AXS-07 in the NDA submission?

    See Section 8.6 for supporting justification.

    FDA Response:
    Yes, we agree with your proposed abuse potential assessment for AXS-07.

Additional Clinical Pharmacology Comments:

Exposures (AUC 0-inf) with the formulation used in Study AXS-07-101 appeared to be much higher compared to the AXS-07-102 formulation (73556 ng.h/mL vs 46865 ng.h/mL). Moreover, there was no information on the formulation used in the completed pivotal efficacy/safety and future food effect studies. Please describe which formulation was used , or will be used, in the following studies:

1. AXS-07-301 (MOMENTUM) Study (efficacy and safety)
2. AXS-07-303 (INTERCEPT) Study (Efficacy and safety)
3. AXS-07-302 (Open label long term safety study)
4. AXS-07-103 (Planned BA and food effect study)

Please note that the bridging information is needed if the formulation used in the above studies is different from the to-be marketed formulation.

Meeting Discussion:

Please refer to the meeting discussion for Question 11.

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.

[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

- 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 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.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the guidance for industry *Assessment of Abuse Potential of Drugs*.[5]

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).[6] 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.[7]

[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] 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.
[7] http://www.regulations.gov

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 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*

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,* 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*.[8]

ATTACHMENTS AND HANDOUTS

Slides provided by Axsome Therapeutics are attached.

6 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

[8] 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/

NICHOLAS A KOZAUER
08/12/2020 10:09:21 AM

IND 135,972

MEETING MINUTES

Axsome Therapeutics, Inc.
Attention: Cedric O'Gorman, MD, MBA
200 Broadway, 3rd Floor
New York, NY 10038

Dear Dr. O'Gorman:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AXS-07 (meloxicam and rizatriptan).

We also refer to the meeting between representatives of your firm and the FDA on May 30, 2019. The purpose of the meeting was to discuss your Phase 3 development program.

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, call Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Nick Kozauer, MD
Associate 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:	**End of Phase 2**
Meeting Date:	**May 30, 2019**
Meeting Location:	**FDA White Oak**
Application Number:	**IND 135,972**
Product Name:	**AXS-07 (meloxicam and rizatriptan)**
Indication:	**Migraine**
Sponsor Name:	**Axsome Therapeutics**
Meeting Chair:	**Billy Dunn, MD, Director**
Meeting Recorder:	**Lana Chen, RPh, Project Manager**

FDA ATTENDEES

Office of Drug Evaluation I
Ellis Unger, MD, Director

Division of Neurology Products
Billy Dunn, MD, Director
Eric Bastings, MD, Deputy Director
Nick Kozauer, MD, Associate Director
Heather Fitter, MD, Clinical Team Leader
Laura Jawidzik, MD, Clinical Reviewer
Viveca Livezey, MD, Clinical Reviewer
Lois Freed, PhD, Supervisory Pharmacologist
Edmund Nesti, PhD, Pharmacology Reviewer
Minjeong Park, PhD, Statistical Reviewer
Sreedharan Sabarinath, PhD, Clinical Pharmacology Team Leader
Mariam Ahmed, PhD, Clinical Pharmacology Reviewer
Lana Chen, RPh, Project Manager

SPONSOR ATTENDEES

Herriot Tabuteau, M.D. Chief Executive Officer
Cedric O'Gorman, M.D., M.B.A. Senior VP, Clinical Development & Medical Affairs
Amanda Jones, Pharm.D. Executive Director, Clinical Research
Karen TenHuisen Senior Director, CMC
Daniel Bigelow Associate Manager, Regulatory
Michael Chen, Ph.D. Statistician

1. DISCUSSION

Chemistry, Manufacturing and Controls Questions

1. Axsome intends to manufacture registration batches at a minimum batch size of 1/10th the proposed commercial batch size, according to ICH guideline Q1A (R2). Axsome is in the process of finalizing the intended commercial batch size. Axsome intends to submit the final determined registration batch sizes to the Division for approval prior to commencing initiation of manufacturing. Is this acceptable to the FDA?

FDA Response: Note that, per ICH Q1A (R2), a pilot scale batch for a solid oral form is generally, at a minimum, 1/10th of full production scale or 100,000 tablets or capsules, whichever is larger.

Meeting Discussion: There was no meeting discussion.

2. The completed, ongoing, and planned clinical trials of AXS-07 utilize the to-be-commercialized formulation and dose of AXS-07. CMC information for this drug product was previously submitted to the IND and is being continuously updated. In addition, Axsome plans to submit the required protocol for the registration batches as well as data from the registration batches prior to NDA submission. Is this CMC package adequate to support an NDA submission?

FDA Response: We are unable to determine from the limited information in the briefing package whether your CMC package would be adequate to support an NDA filing. If you would like feedback regarding specific aspects of your CMC development program, we recommend that you submit a Type C CMC-only request for written responses.

Meeting Discussion: There was no meeting discussion.

Nonclinical Questions

3. To support an NDA filing, Axsome intends to utilize existing nonclinical and clinical data on rizatriptan and meloxicam in the current FDA product inserts for Maxalt® (rizatriptan) and Mobic® (meloxicam), and in the literature, combined with the required long-term clinical safety data with AXS-07 (meloxicam and rizatriptan) from at least 300 patients treated for 6 months and 100 patients treated for 1 year, treating a minimum of 2 migraines/month. Does the FDA agree that this will be an adequate nonclinical package to support an NDA submission?

FDA Response: To support initiation of expanded (Phase 3) clinical studies, you will need to conduct a 3-month study of the combination in one species; justification should be provided for the species selected. The study should test at least three dose levels of the combination and a high dose of each drug alone. A primary safety concern is the potential for increased cardiovascular risk with the combination. This possibility should be evaluated in a rigorous manner either in the 3-month study or in a separate study.

Regarding the use of literature, published studies typically do not provide sufficient detail to allow for an independent review of the data.

Meeting Discussion: The sponsor stated that expanded clinical studies are ongoing and asked if the 3-month combination study may be conducted concurrent with those studies. The Division agreed but noted the 3-month study should be initiated as soon as possible.

Clinical Pharmacology Questions

4. Axsome has completed a parallel-group pharmacokinetic trial of the to-be-marketed formulation of AXS-07 (meloxicam and rizatriptan) and of the rizatriptan reference listed drug (Maxalt®) in healthy volunteers (Study AXS-07-102). Axsome has examined the pharmacokinetics of the meloxicam reference listed drug (Mobic®) in healthy volunteers in a separate trial (Study AXS-06-101). Axsome also intends to conduct a food effect pharmacokinetic study of AXS-07. In addition, Axsome intends to reference the pharmacokinetic information for specific populations and the clinical drug interaction information in the FDA package inserts for Maxalt® (rizatriptan) and Mobic® (meloxicam).

Does the Division agree that the above completed clinical pharmacology studies, the planned food effect pharmacokinetic study, together with the information from the FDA package inserts for Maxalt® (rizatriptan) and Mobic® (meloxicam) will be an adequate package of clinical pharmacology studies to support an NDA filing?

FDA Response: Based on Study AXS-06-101 and Study AXS-07-102, there appears to be 70% higher Cmax for meloxicam following AXS-07 administration, as compared to the approved Mobic® dose. Your rationale of comparing the cumulative monthly exposures between Mobic and AXS-07 may not be adequate to bridge meloxicam exposures to the listed drug. Since the dose and exposure to meloxicam is higher from AXS-07, in vitro drug-drug interaction studies for meloxicam with major CYPs and transporters may be needed to rule out DDI liability. For more information, please refer to the FDA guidances for industry on drug-drug interactions[1,2]. Moreover, you should include information on the PK drug-drug interaction between meloxicam and rizatriptan.

Additionally, for your proposed food effect study, a Maxalt® arm is not needed. Instead we recommend including Mobic® administered in the fasted state. This will allow you to

reliably estimate the bioavailability of meloxicam following AXS-07 relative to the listed drug (i.e., Mobic®).

1) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/vitro-metabolism-and-transporter-mediated-drug-drug-interaction-studies-guidance-industry
2) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-drug-interaction-studies-study-design-data-analysis-and-clinical-implications-guidance

Meeting Discussion: There was no meeting discussion.

Clinical Questions

5. As requested by the FDA in the response to Question 7a in the Pre-IND meeting minutes dated August 25, 2017, Axsome intends to support its NDA for AXS-07 with a long-term safety database of at least 300 patients treated for 6 months, and 100 patients treated for 1 year, treating a minimum of 2 migraines/month. Axsome is planning to initiate an open-label, long-term safety study (Study AXS-07-302) to build this required safety database. Axsome is proposing to submit the NDA with the safety data available once 300 patients have been treated for 6 months, and to submit the remaining required safety data during the NDA review. Is this acceptable to the FDA?

FDA Response: No. At the time of NDA submission, your application should be complete and therefore should include safety data on 300 patients treated for 6 months and 100 patients treated for 1 year.

Meeting Discussion: There was no meeting discussion.

6. Axsome intends to file an NDA for AXS-07 for the proposed indication with a single adequate and well-controlled Phase 3 efficacy trial, which is being conducted pursuant to an SPA (Study AXS-07-301), in conjunction with the required long-term clinical safety data (at least 300 patients treated with AXS-07 for 6 months and 100 for 1 year, treating a minimum of 2 migraines/month). Does the FDA agree that this single adequate and well-controlled efficacy study, combined with the required long-term safety data, is acceptable to support an NDA submission?

FDA Response: On face, positive efficacy results from a single study, such as Study AXS-07-301, along with the required long-term clinical safety data, may provide sufficient support for an NDA for AXS-07 for the acute treatment of migraine. Ultimately, the acceptability of the results of those data would be a matter of review.

Meeting Discussion: There was no meeting discussion.

7. (b) (4)

(b) (4)

Consistent with this guidance, Axsome is proposing to (b) (4)

Does the FDA agree?

FDA Response: No, we do not agree. (b) (4)

(b) (4)

Meeting Discussion: The sponsor proposed that (b) (4)

(b) (4) a proposal that the Division did not find acceptable. (b) (4)

(b) (4)

Post-Meeting Comment: (b) (4)

(b) (4)

(b) (4)

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]

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

[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] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm

process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[3]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format--- Standardized Study Data.* 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,[4] 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 started after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[5] 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 started on or 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.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov.[6] For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical

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[3] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

[4] http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

[5] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

[6] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide[7] (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site.[8] When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[9]

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned

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[7] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

[8] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

[9] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

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[10] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[11]

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).

[10] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[11] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the guidance for industry *Assessment of Abuse Potential of Drugs*.[12]

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).[13] 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.[14]

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 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

[12] 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.
[13] 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.
[14] http://www.regulations.gov

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*

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.[15]

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

(1) Study phase
(2) Statement of whether the study is intended to support marketing and/or labeling changes
(3) Study objectives (e.g., dose finding)
(4) Population
(5) A brief description of the study design (e.g., placebo or active controlled)
(6) Specific concerns for which you anticipate the Division will have comments
(7) For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

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

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/s/

NICHOLAS A KOZAUER
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