

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212268Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 125707

MEETING MINUTES

Noven Pharmaceuticals, Inc.
Attention: Audrey B. Alivio
Associate Director, Regulatory Affairs
100 Town Square
5th Floor
Jersey City, NJ 07310

Dear Ms. Alivio:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for HP-3070 (asenapine (b) (4)).

We also refer to the meeting between representatives of your firm and the FDA on June 19, 2018. The purpose of the meeting was to discuss the proposed NDA for HP-3070 for the treatment of schizophrenia and to gain FDA feedback and agreement on the data package and the adequacy of overall submission package to support the NDA filing for HP-3070.

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

If you have any questions, contact Nam (Esther) Chun, Regulatory Project Manager at nam.chun@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: June 19, 2018, 11AM – 12:30PM (EST)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

Application Number: 125707
Product Name: HP-3070 (asenapine (b) (4))
Indication: Treatment of Schizophrenia
Sponsor/Applicant Name: Noven Pharmaceuticals, Inc.

Meeting Chair: Mitchell Mathis, MD
Meeting Recorder: Nam (Esther) Chun, PharmD

FDA ATTENDEES

Mitchell Mathis, MD	Director, Division of Psychiatry Products (DPP)
Tiffany Farchione, MD	Deputy Director, DPP
Gregory Dubitsky, MD	Clinical Reviewer, DPP
Jasmine Gatti, MD	Clinical Team Leader, DPP
Laura McGhee, PhD	Pharmacology/Toxicology Reviewer, DPP
Aisar Atrakchi, PhD	Pharmacology/Toxicology Supervisor, DPP
Peiling Yang, PhD	Biometrics Team Leader, Division of Biometrics I
Huixia Zhang, PhD	Clinical Pharmacology Reviewer, DPP
Hao Zhu, PhD	Clinical Pharmacology Team Leader, DPP
David Claffey, PhD	CMC Lead, Office of Pharmaceutical Quality (OPQ)
Caroline Strasinger, PhD	CMC Reviewer, OPQ
Kaushalkumar Dave, PhD	Biopharmaceutics Reviewer, OPQ
Gopichand Gottipati, PhD	Pharmacometrics Reviewer, Office of Clinical Pharmacology
Phuong Nguyen, RPh	Project Manager, Office of Surveillance and Epidemiology
Ofir Nevo, PharmD	Reviewer, Division of Pharmacovigilance
Vicky Chan, PharmD	Team Leader, Division of Pharmacovigilance
Nam (Esther) Chun, PharmD	Regulatory Project Manager, DPP

SPONSOR ATTENDEES

Audrey B. Alivio, MS	Associate Director, Regulatory Affairs
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Kanan Balakrishnan, PharmD	Director, Regulatory Affairs
Mariacristina Castelli, PhD	Executive Director, Clinical Pharmacology
Marilisa Chin, MBA	Associate Director, Clinical Research
Michelle DeSimone, PhD, DABT	Principal Scientist, Translational Science
Monica Escobar, PhD	Senior Director, CMC and Regulatory Operations
Naruhito Higo, PhD	Chairman of the Board
Yoshinobu Higashi, MS	Executive Director, Global Development Liaison
Swetha Inturi, PhD	Research Scientist, Toxicology
Marina Komaroff, DrPH	Director, Biostatistics
Ralph Lipp, PhD	Chief Scientific Officer, Product Development
Jeff Mihm	Chief Executive Officer
Alexandra Park, BSc	Executive Director, Regulatory Affairs & Pharmacovigilance
Katsumi Suzuki, MS	Director, Clinical Pharmacology
(b) (4), MD	Consultant

1.0 BACKGROUND

Asenapine is a second generation antipsychotic formulated as a sublingual tablet and marketed under the tradename Saphris. Saphris was approved in 2009 and is currently approved for the treatment of adult patients with schizophrenia and pediatric patients (ages 10 to 17 years) and adult patients with bipolar I disorder.

Noven Pharmaceuticals, Inc. (NP) has developed the HP-3070 Transdermal System (HP-3070), a transdermal delivery system for asenapine intended for daily application. HP-3070 doses of (b) (4) /24hours and (b) (4) /24 hours provide asenapine exposures comparable to Saphris® doses of 5 mg BID and 10 mg BID, respectively. NP plans to submit a 505(b)(2) NDA by the fourth quarter of 2018 for the use of HP-3070 in the treatment of adults with schizophrenia, using Saphris as the Listed Drug (LD).

The Division has had several interactions with NP regarding the HP-3070 development plan, to include:

- an End-of-Phase 2 meeting on June 25, 2015. The discussion included the adequacy of a single key efficacy trial to support filing and approval, the need to assess patch adhesion and the effect of heat on the release and absorption of asenapine from the patch, recommendations for assessing user risk and human factors, and a strong recommendation that the to-be-marketed product be used in the key efficacy trial.
- a Clinical Special Protocol Assessment (SPA) meeting to discuss the key efficacy trial on February 24, 2016. An SPA Agreement letter was issued on September 16, 2016.
- an Agreed initial Pediatric Study Plan (iPSP) was issued on March 17, 2017. This provides for a partial waiver for patients ages 0 to 11 years and deferred assessment of safety and efficacy for ages 12 to 17 years.

- Written Response Only (WRO) comments dated October 23, 2017, concerning the NDA content and format. These comments conveyed Division agreement that the 4-Month Safety Update for the NDA could be waived, advice on studies that require financial disclosure information, and feedback on datasets, Case Report Forms, and Narrative Summaries in the application.

The HP-3070 development program consists of six completed clinical studies: one formulation selection study, four phase 1 clinical pharmacology studies, and one phase 3 safety and efficacy trial. In addition, three studies are ongoing and expected to be completed in the third quarter of 2018: a cumulative skin irritation and sensitization study, a patch adhesion study, and a summative usability test.

The key efficacy trial for this application (Study HP-3070-GL-04) is 6-week, randomized, double-blind, placebo-controlled, fixed dose, inpatient study in 607 acutely ill, adult patients with schizophrenia. Patients were randomized in a 1:1:1 ratio to one of two HP-3070 doses (one or two (b) (4) 24 hours patches) or placebo. The primary efficacy endpoint was the change from baseline to Week 6 in the PANSS total score and the key secondary endpoint was the change from baseline to Week 6 in the CGI-Severity score. The Sponsor indicates that both HP-3070 doses were statistically superior to placebo on both endpoints after adjustment for multiplicity. The most frequently reported adverse events were application site reactions (most commonly minimal erythema), headache, weight gain, extrapyramidal symptoms, akathisia, and somnolence. Complete patch detachment was reported in 2% to 5% of patients and partial detachment in 7% to 9%.

The Sponsor's stated objectives for this meeting are:

- a. Share and discuss the top line data from the single pivotal phase 3 study, HP-3070-GL-04, and obtain agreement that these data form the basis of the NDA submission.
- b. Gain feedback on any additional analyses needed for the NDA filing.
- c. Obtain agreement and feedback on the proposed doses for marketing.
- d. Gain agreement that the overall clinical, clinical pharmacology and nonclinical development plan supports the registration of HP-3070 for the indication of "treatment of schizophrenia in adults."

2. DISCUSSION

2.1. CLINICAL PHARMACOLOGY/CLINICAL

Question 1: Noven has completed Study HP-3070-GL-04, the Phase 3 double-blind, placebo controlled, randomized fixed dose, 6-week, in-patient study in adults diagnosed with schizophrenia. The protocol and statistical analysis plan was discussed at the February 24, 2016

Type A meeting and agreed upon with FDA under a Clinical SPA. The study met its primary and key secondary objectives.

- a. Does the Agency agree that efficacy data from Study HP-3070-GL-04 provides adequate evidence of efficacy to support the filing of an NDA under 505(b)(2)?
- b. Does the Agency consider the results from Study HP-3070-GL-04 supports the efficacy and safety of the HP-3070 patch?
- c. Does the Agency agree that the safety database is sufficient to support NDA filing under 505(b)(2)?

FDA Response to Question 1:

- a) *On face, Study HP-3070-GL-04 provides adequate evidence of efficacy in the treatment of adult patients with schizophrenia to support NDA filing. The adequacy of these data to support approval will be a matter for review.*
- b) *Data from Study HP-3070-GL-04 and the safety experience with the LD provide support for the safety of the HP-3070 transdermal system (TDS). The results from the cumulative skin irritation and sensitization study (Study HP-3070-US-06) will also be needed to evaluate the dermal safety of HP-3070. The overall assessment of safety will be a matter for review.*
- c) *A total of 166 patients received HP-3070 (b) (4) 24 hours for 6 weeks and 158 patients and received HP-3070 (b) (4) 24 hours for 6 weeks. We expect that safety data from this exposure along with safety data with the LD will be sufficient to support filing this application.*

Discussion: *No further discussion.*

Question 2: *Noven has also performed a sub-group analysis as defined in the GL-04 statistical analysis plan.*

Does the Agency require any additional analyses at this time?

FDA Response to Question 2: *Yes. Please conduct a demographic subgroup analysis of adverse event incidence by gender, race, and age (if there was a sufficient number of patients age 65 years and older). This analysis should be performed for any adverse event that was reported by at least 5% of HP-3070-treated patients and at a rate at least twice the corresponding placebo rate in Study HP-3070-GL-04.*

Discussion: *The Sponsor indicated that only three adverse reactions were reported by at least 5% of asenapine TDS-treated patients and at a rate at least twice the placebo rate (extrapyramidal symptoms, application site erythema, and weight gain). The Division agreed that the demographic analysis of adverse events would be limited to those three events. The Sponsor also proposed using 55 years and older versus under 55 years as the age criteria for defining age subgroups for purposes of the adverse event analysis. About 17% of the sample was age 55 years or older. The Division agreed with this proposal but requested that the*

Sponsor also provide an analysis using age 65 years or older (with a sample size of 10) as the cutoff. The Sponsor agreed to provide that analysis as well.

Question 3: Does the Agency agree that the positive data from the pivotal Phase 3 study HP-3070-GL-04 supports the proposed doses of (b) (4) /24 hours and (b) (4) /24 hours for the treatment of adult patients with schizophrenia?

In the upcoming NDA, Noven is considering the inclusion of the HP-3070-(b) (4) to support recommendations that will allow for dosing flexibility for prescribers and individualization of therapy. Does the Agency have feedback on the analyses approach and agree that it is acceptable?

FDA Response to Question 3: *On face, the data from the phase 3 trial support the proposed product in the treatment of adults with schizophrenia. However, the expression of your proposed labeled dosage strengths as (b) (4) 24 hours and (b) (4) /24 hours is not correct. (b) (4) and (b) (4) are your total drug loads for the respective sizes of your product and are not the amount of API expected to be delivered to the patient within 24 hours. The strength of a transdermal system should be presented as a rate (e.g., mg/24 hours) and derived from and supported by pharmacokinetic and/or residual drug data.*

In more detail, the following considerations should be adopted to provide a robust analysis of the residual drug:

- 1. Data should be determined based on analysis of used TDS and not a theoretical calculation.*
- 2. The amount of drug left on the skin surface should be assessed and any drug that may have been transferred to packaging or other components during storage or use should be accounted for in an attempt to perform a mass balance.*
- 3. Tape or overlays should not be used in studies where the TDS is used to calculate residual drug, unless the use of an overlay is necessitated by the product label.*
- 4. TDS adhesion assessments should be conducted over the entire period of wear to evaluate whether the TDS diffusional surface area remains in full contact with the skin during the entire period of the study.*
- 5. A control should include an analysis of a sufficient number of unused products from the same lot as those used in the trial to provide an estimate of drug load and not simply an expression of label claim.*

6. *Sample storage conditions before and after application of the TDS on the skin should be validated and the photostability and thermal stability of the active ingredient(s) in the TDS should also be considered when selecting the appropriate storage conditions.*
7. *Appropriately sensitive, valid analytical methods should be used to assay the residual drug content for the purpose of calculating drug depletion and delivery. A drug extraction method with a target extraction efficiency of close to 100 percent should be utilized to minimize error when estimating the amount of residual drug in the TDS.*

Assuming apparent safety and efficacy is demonstrated for the high and low strengths, and assuming size and dose proportional pharmacokinetics, the inclusion of an intermediate strength to allow flexible dosing seems reasonable.

Note: size proportionality of the TDS means i) that the amounts of active and inactive ingredients per unit of active surface area are identical for the different strengths of the product, and ii) that the ratio of the active surface area to the strength of the product matches the corresponding ratio of the active surface area to the strength for a higher or lower strength of the product.

Discussion: *The Sponsor clarified that, at this time, they are only seeking a 20 cm² and 40 cm² system and that the corresponding proposed strengths of (b) (4) mg/24 hours and (b) (4) mg/24 hours is based on the slope of the linear regression of all (b) (4) size products. The Sponsor stated in the submission they plan to provide additional details and multiple analysis of the residual drug data (e.g. mean amount delivered of each size, as well as strength as calculated per the regression line). The Division agreed that the proposal sounds appropriate, but could not agree to the specific numbers until the full breadth of data and analysis were submitted in the NDA. The Division stressed, and the Sponsor acknowledged, their understanding with respect to the importance of proportionality of size of product to the strength and will be mindful of the relationship when proposing the strengths of the product.*

The Sponsor inquired if all the data from the Phase I study could be utilized which includes systems that were taped to some extent (a corner or edge was taped, not all four edges, or covering the entire system). The Division agreed that on face, incorporation of the data of taped systems when used for residual drug calculation seems appropriate. The Division stated that this data could not be utilized to justify the need for taping, the safe use of taping by the patient, the impact of an overlay on delivery of drug, or that it could be used for adhesion assessment. The adequacy of the adhesion of the product is a separate review issue.

Question 4: Does the Agency agree that the completed PopPK/PD modeling is sufficient to adequately characterize HP-3070 PK in the target patient population?

FDA Response to Question 4: *Yes, the proposed PopPK/PD modeling plan seems reasonable. However, the adequacy of the modeling efforts to characterize the PK of HP-3070 in the target patient population will be a matter of review.*

Discussion: *No further discussion.*

Question 5: As it was agreed with the FDA at the EOP2/PIND Meeting in 2015, Noven has been collecting safety data of HP-3070 to support the NDA filing and registration of HP-3070 for the treatment of schizophrenia. The pivotal Study HP-3070-GL-04 demonstrated HP-3070 efficacy, safety and tolerability up to 6 weeks in schizophrenic patients.

Does the Agency agree that the efficacy and safety data are, on face, adequate to support chronic use, not limited to a specific duration of use?

FDA Response to Question 5: *Yes, given that long-term safety and efficacy have been established for the LD and presuming no dermal safety concerns with long-term use of the TDS, the efficacy and safety data are, on face, adequate to support longer-term use.*

Discussion: *No further discussion.*

2.2. REGULATORY

Question 6:

- a. Does the Agency agree with the safety and efficacy data that Noven intends to rely on from the approved sublingual asenapine formulation as described in the 505(b)(2) reference table and the proposed location of the table in Module 2.5?
- b. Noven intends to place the requested updated “Highlights of Clinical Pharmacology” as an appendix in Module 2.2 “Introduction to Summary”. Does the Agency agree with the content and the location of the table?

FDA Response to Question 6:

- a) *Yes, reliance on the indicated safety and efficacy data from the LD and inclusion of the 505(b)(2) reference table in Module 2.5 are reasonable. Final product labeling will be a matter for review.*
- b) *Instead of Module 2.2, we recommend you place the updated table in Module 2.7.2, Summary of Clinical Pharmacology Studies. In addition, please fill out the attached template for “Clin Pharm Summary” and place it in Module 2.7.2 as well to facilitate review. The above documents can be attached as appendices to “Summary of Clinical Pharmacology Studies.”*

Additionally, we have the following comments for you to consider when you submit the NDA:

1. *We recommend the content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application be consistent with [FDA Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format](#). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.*
2. *Please provide your SAS codes as *.txt files with each study report where the standard bioequivalence statistical test has been performed. Ensure your codes are executable to confirm your results.*
3. *It is our understanding that for your clinical study HP-3070-GL-04, 2 x (b) (4) patches instead of 1x of (b) (4) patch were used when evaluating the (b) (4) dose level. Please provide your scientific justification in the study report why you think the two are equivalent and whether there is a need to conduct an in vivo dose-strength equivalence study.*

Discussion: *No further discussion.*

Question 7: Noven intends to retain the combination product system documents onsite. Does the Agency agree with this proposal?

FDA Response to Question 7: *No, we do not agree. In general, because of the complexity of separating the constituent parts of transdermal systems, quality information on the combination product as a whole (not the separate constituent parts) should be located in 3.2.P with appropriate hyperlinks to 3.2.R. As such we recommend including information for 820.20, 820.30, 820.50 and 820.100 in section 3.2.R of the eCTD.*

For additional assistance with where and how to document combination product information in a submission refer to [eCTD Technical Conformance Guide: Technical Specifications Document](#).

Discussion: *No further discussion.*

Question 8: Does the Agency agree with the submission timing for the final study reports for Study HP-3070-US-08 (in vivo adhesion) and Study HP-3070-US-06 (cumulative irritation and sensitization), i.e. within 30 calendar days of the initial filing date?

FDA Response to Question 8: *No. Applications should be complete at the time of NDA submission.*

Discussion: *No further discussion.*

Question 9: Does the Agency consider that based on the efficacy and safety profile observed to date, HP-3070 could be considered for Priority Review?

FDA Response to Question 9: *HP-3070 is intended to treat schizophrenia, a serious condition, and may have some advantages over the marketed asenapine product. The decision regarding Priority Review status will be made at the time of filing the application.*

Discussion: *No further discussion.*

Additional Statistics Comments

When you submit the NDA, please include as part of the original submission:

- a) All raw as well as derived variables in .xpt format*
- b) The SAS programs that produced all efficacy results*
- c) The SAS programs by which the derived variables were produced from the raw variables*
- d) A listing of all interactions with the Agency pertaining to this IND/NDA including serial numbers and submission dates of the protocols, SAPs, amendments, and any relevant meetings*
- e) All SAS code used to conduct the interim analysis and all documentation relating to the interim analysis*
- f) All datasets used for the interim analysis, if possible*

Discussion: *No further discussion.*

Additional Biopharmaceutics Comment

In your NDA submission, if applicable, provide a table or figure to summarize the in vitro and/or in vivo data to support the bridging between the products to-be-marketed and those used in clinical studies.

Discussion: *No further discussion.*

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* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

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

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* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. 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: <http://www.fda.gov/ectd>.

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 <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>.

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).

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the Guidance for Industry, *Assessment of Abuse Potential of Drugs*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>

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), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. 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 <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)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication A</i>

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:

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

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

No action items were identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

HP-3070 Pre-NDA Meeting
FDA Response to Q3
June 19, 2018



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Dosage Strength

- The dosage strength will be reported as delivery rate (mg/24 hours) calculated based on residual drug data from worn patches

Patch Size	Asenapine (b) (4)	Asenapine (b) (4)	
	Drug Load	Drug Load	Dosage Strength
(b) (4)	(b) (4)	(b) (4)	(b) (4)
20 cm ²	(b) (4)	6.4 mg	(b) (4)
30 cm ²	(b) (4)	9.6 mg	
40 cm ²	(b) (4)	12.8 mg	

Pooled analysis for Dosage
Strength calculated by linear
regression

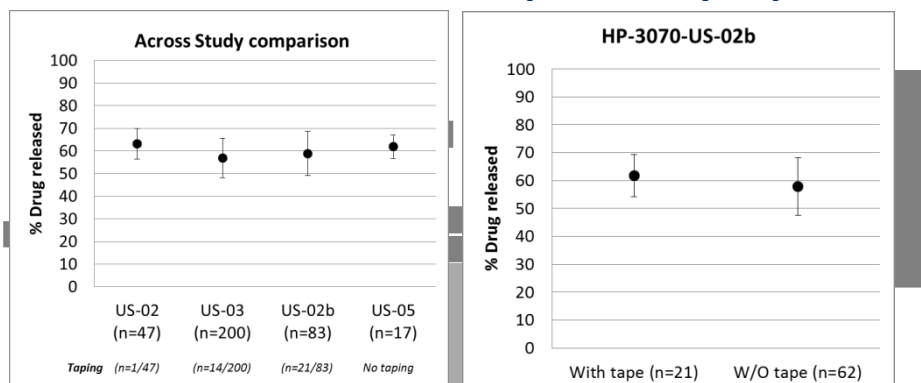
- $\text{Dosage Strength} = \text{Drug Load (Initial Drug Content in unused patch)} - \text{Residual Drug Amount in worn patch}$



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% of Drug released from patches worn in clinical studies was not impacted by tape use



- Limited and sporadic taping of the edge of patches across PK studies (i.e. at least one patch edge; not all 4 edges taped).
- Study sites were instructed that, if necessary (e.g., if the patch starts to peel off at the edges during the application period), adhesive tape (strips of Tegaderm™ Roll) could be used to keep a patch in place. It was, however, not allowed to cover the whole HP-3070 patch using adhesive tape.

NOVEN

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

/s/

MITCHELL V Mathis
06/25/2018



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 125707

MEETING MINUTES

Noven Pharmaceuticals, Inc.
Attention: Audrey B. Alivio, M.S.
Senior Manager, Regulatory Affairs
Empire State Building
350 Fifth Avenue, 37th Floor
New York, NY 10118

Dear Ms. Alivio:

Please refer to your Pre-Investigational New Drug Application (PIND) file for HP-3070 (asenapine ^{(b) (4)} Transdermal System.

We also refer to the meeting between representatives of your firm and the FDA on June 25, 2015. The purpose of the meeting was to discuss the development plan for HP-3070 transdermal patch for the indication of the treatment of schizophrenia. Our preliminary responses to your meeting questions are enclosed.

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

If you have any questions, please email Simran Parihar, PharmD, Regulatory Health Project Manager, at simran.parihar@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End-of-Phase 2

Meeting Date and Time: Thursday, June 25, 2015; 9:00 AM – 10:30 AM (ET)
Meeting Location: FDA, White Oak Building 22, Conference Room: 1315

Application Number: PIND 125707
Product Name: HP-3070 (asenapine (b) (4))
Indication: Schizophrenia
Sponsor/Applicant Name: Noven Pharmaceuticals, Inc.

FDA ATTENDEES (tentative)

Mitchell Mathis, M.D.	Director, Division of Psychiatry Products (DPP)
Robert Temple, M.D.	Deputy Center Director for Clinical Science
Jing Zhang, M.D.	Clinical Team Leader
Gregory Dubitsky, M.D.	Clinical Reviewer, DPP
Wendy Wilson-Lee, Ph.D.	Acting Branch I Chief, Office of Pharmaceutical Quality (OPQ)
Caroline Strasinger, Ph.D.	QPQ Reviewer
Sarah Ibrahim, Ph.D.	QPQ Reviewer
Amy Avila, Ph.D.	Pharmacology/Toxicology Reviewer, DPP
Kara Schmid, Ph.D.	Pharmacology/Toxicology Fellow, DPP
Kofi Kumi, Ph.D.	Clinical Pharmacology Reviewer, DPP
Peiling Yang, Ph.D.	Statistics Team Leader, DPP
Kelly Yang, Ph.D.	Statistics Reviewer, DPP
Denise Pica-Branco, Ph.D.	Regulatory Health Project Manager, Pediatric & Maternal Health Staff (PMHS)
Carrie Ceresa, Pharm D, MPH	Reviewer, Maternal Health
Ethan Hausman, M.D.	Reviewer, Pediatric Health
Danielle Harris, Pharm.D., BCPS	Team Leader, DMEPA
David Sze	PharmD Candidate, Pharmacy Student
Martin Kwok, Pharm.D.	Regulatory Fellow
Danbi Lee, Pharm.D.	Regulatory Health Project Manager, DPP
Tina Chhabra	Pharmacy Student
Simran Parihar, Pharm.D.	Regulatory Health Project Manager, DPP

SPONSOR ATTENDEES

Noven Pharmaceuticals, Inc.

Audrey B. Alivio, M.S.
Mariacristina Castelli, Ph.D.
Monica Escobar, Ph.D.
Marina Komaroff, M.S., M.P.H.
Jeffrey Klein, Ph.D., DABT
Joel Lippman, M.D.

Senior Manager, Regulatory Affairs
Senior Director, Clinical Pharmacology
Director, CMC and Regulatory Operations
Associate Director, Biostatistics
Senior Manager, Pharmaceuticals – Preclinical
Executive Vice President, Product Development and Chief
Medical Officer
Senior Program Manager, Product Development
Senior Manager, Clinical Pharmacology
Senior Director, Regulatory Affairs and Pharmacovigilance
Senior Clinical Project Manager, Product Development
Senior Manager, Clinical Pharmacology
VP Research and New Technology, Product Development

Hisamitsu Pharmaceutical Co., Inc.

Naruhito Higo, Ph.D. Managing Director and Executive Officer and Head of
Research & Development

Consultants attending on Noven's behalf

(b) (4)

Independent Consultant
President and CEO, (b) (4)
Study Director, Medical, (b) (4) S
Senior Biostatistical Reviewer, (b) (4)

1.0 BACKGROUND

HP-3070 is a transdermal patch formulation of the atypical antipsychotic asenapine. Asenapine is approved and marketed as a sublingual tablet formulation (as Saphris in the US; Sycrest in the European Union) for the treatment of schizophrenia and manic or mixed mood episodes associated with bipolar I disorder. HP-3070 is designed for once daily application. Noven proposes to develop HP-3070 via the 505(b)(2) pathway, with Saphris as the reference listed drug (RLD).

The transdermal route of application will provide the patients with another treatment option that may have certain advantages over the sublingual formulation, such as:

- avoidance of oral hypoesthesia and/or dysgeusia that is commonly observed with sublingual asenapine,
- potentially improved tolerability resulting from less variability in absorption compared to the sublingual route of administration for Saphris, and
- providing a visual check of treatment compliance for physicians and caregivers.

To support initiation of the pivotal Phase 3 global study and approval of HP-3070 for the treatment of schizophrenia, Noven has conducted 42 nonclinical studies and four Phase 1 clinical studies of asenapine and HP-3070. In addition, Noven will be relying on the Agency's findings of the clinical pharmacology, safety, and efficacy of Saphris.

The following summary describes the development program of the HP-3070 to date and a planned study to support a 505(b)(2) application for the treatment of schizophrenia.

- ***Nonclinical***

HP-3070 was administered for up to 13 weeks in dogs; that Sponsor calculated that the no-observed-adverse-effect-level (NOAEL) doses of asenapine were 7.88 mg/kg/day and 2.61 mg/kg/day in males and females, respectively, providing safety margins of 10.5-fold (male) and 5.2-fold (female) based on AUC_{0-24} and 11.5-fold (male) and 5.7-fold (female) based on C_{max} . The steady state human plasma asenapine exposure levels observed at the highest tested dose of (b) (4) HP-3070 (in Study HP-3070-US02b) were similar to the asenapine exposure observed at the NOAEL in a toxicity study with rats and below those observed at the NOAEL in a toxicity study with dogs. A 39-week dermal study in minipigs to evaluate the long-term systemic and dermal safety of the patch is currently ongoing.

- ***Clinical***

To date, four Phase 1 studies have been conducted to evaluate the pharmacokinetics and tolerability of HP-3070 in healthy volunteers (HP-3070-US-01, HP-3070-US-02 and HP-3070-US-03) and in patients diagnosed with schizophrenia (HP-3070-US-02b). Reproducible pharmacokinetic performance for HP-3070 was confirmed across studies. No new or unexpected safety findings related to asenapine were reported in these studies. The completed Phase 1 studies are summarized below:

- **Study HP-3070-US-01 (First-In-Human Study):**

A single-center, single-dose, open-label, three-way-crossover study to evaluate the pharmacokinetics of two strengths of the HP-3070 patch compared to single-dose Sycrest 5 mg in healthy adult male and female subjects.

Two strengths of HP-3070, (b) (4) mg and (b) (4) mg, were evaluated and asenapine exposures from each dose were compared with asenapine exposure from a single sublingual administration of Sycrest 5 mg. The Sponsor states that mean asenapine exposure (AUC_{0-}) following the (b) (4) mg HP-3070 was slightly lower while the exposure following the (b) (4) mg HP-3070 was higher compared to the sublingual administration of a single 5-mg dose of Sycrest. Based on these results, a (b) (4) dose of HP-3070 was developed because this dose was expected to have comparable exposure to sublingual administration of Sycrest 5mg BID.

- **Study HP-3070-US-02:**

A single center, open-label, four-period single ascending-dose, and 7-day multiple-dose study to evaluate the pharmacokinetic profile of HP-3070 patch in healthy volunteers

Three doses of HP-3070 were evaluated in this study: (b) (4), (b) (4) and (b) (4). However due to tolerability issues of the (b) (4) dose in naïve healthy volunteers, the (b) (4) dose was not evaluated. This study was prematurely terminated and a new study (HP-3070-US-02b) was designed and conducted in patients diagnosed with schizophrenia to improve tolerability. The Sponsor notes that dose proportionality was observed between the (b) (4) and (b) (4) doses of HP-3070.

▪ **Study HP-3070-US-02b:**

An open-label, multiple ascending-dose study to evaluate the pharmacokinetic profile and D2 occupancy of HP-3070 patch in subjects diagnosed with schizophrenia

Study HP-3070-US-02b was conducted in subjects diagnosed with schizophrenia to evaluate the steady state pharmacokinetic of asenapine following 24-hour application of four strengths of HP-3070 for 7 days each: (b) (4), (b) (4), (b) (4) and (b) (4). The Sponsor asserts that dose proportional exposure and D2 receptor occupancy were confirmed, that there was low variability in key PK parameters over 24 hours, and that daily applications of HP-3070 for 7 days at each of the strengths from (b) (4) to (b) (4) were safe and well-tolerated. There were no reported clinically significant findings with respect to laboratory tests, vital signs, or ECGs. The Sponsor further notes that, when results of this study were compared with pharmacokinetic data from studies conducted using Saphris, the (b) (4) patch exhibited similar exposure (AUC_{0-24}) to Saphris 5mg BID while the (b) (4) patch had a similar steady state AUC_{0-24} as Saphris 10mg BID; the patch C_{max} was lower in each case.

▪ **Study HP-3070-US-03:**

A single center, open-label, single-dose, five-period crossover study to evaluate the pharmacokinetic profile and patch adhesion of HP-3070 patch following 24 hour application at five different patch application sites in Japanese and Caucasian healthy volunteers

Five application sites (upper arm, upper back, abdomen, upper chest, and hip area) were evaluated with the (b) (4) dose of HP-3070 to assess whether changing the transdermal patch application site would have an effect on the asenapine exposure. The reference application site was the upper arm. The Sponsor reports that all sites were within the 80% to 125% limits for C_{max} , AUC_{0-t} and AUC_{0-inf} , demonstrating bioequivalence of asenapine exposure among the different application sites, except for C_{max} for the abdomen. Compared with the upper arm, the lower boundary of the C_{max} for abdomen was out of bioequivalence range. According to the Sponsor, this study confirmed there was no ethnic difference in asenapine exposure between Caucasian and Japanese subjects.

Based on these data, HP-3070 doses of (b) (4) and (b) (4) doses have been selected for the Phase 3 global pivotal study in patients with schizophrenia to provide exposure comparable to Saphris 5mg BID and 10mg BID, respectively, the doses approved for treatment of schizophrenia. Because the safety and efficacy of asenapine in schizophrenia is well established, Noven proposes to conduct a single pivotal trial (HP-3070-GL-04) to demonstrate the safety and efficacy of HP-3070 in patients with schizophrenia who are in an acute exacerbation. This trial is described below.

• **Proposed Phase 3 Global Pivotal Study**

A Randomized, Double-Blind, Placebo-Controlled, Fixed-Dose, 6-Week In-Patient Study to Assess Efficacy and Safety of HP-3070 in Subjects Diagnosed with Schizophrenia in Acute Exacerbation

This will be a multicenter, randomized, double-blind, placebo-controlled, parallel group trial conducted on an inpatient basis. Approximately 750 adult patients with

schizophrenia in acute exacerbation will be randomized in a 1:1:1 ratio to 3 treatment arms: HP-3070 (b) (4), HP-3070 (b) (4), or placebo. Study treatment will be administered as two 20 cm² transdermal patches applied daily for 6 weeks as follows:

- HP-3070 (b) (4) arm – one (b) (4) patch and one placebo patch.
- HP-3070 (b) (4) arm – two (b) (4) patches.
- Placebo arm – 2 placebo patches.

Patches will be applied at about the same time each morning, worn for 24 hours, then removed. They will be applied to one of the following sites: abdomen, hip, upper arm, upper back, or upper chest. All patients will have supportive tape applied to the edges of all patches each night prior to bedtime if tape was not applied earlier in the day. Adhesion will be rated prior to application of supportive tape.

The primary efficacy analysis will be conducted on the Full Analysis Set (FAS), defined as all consented and randomized subjects who have had at least one patch of study medication applied and have at least one valid post-baseline PANSS assessment. A global test of the treatment effect will be performed to determine if any treatment arms differ in terms of the mean change from baseline to week 6 in the PANSS total score at a significance level of 0.05. If the data are normally distributed, MMRM analysis will be used. Otherwise, an ANCOVA or Kruskal-Wallis test will be employed.

If the global test demonstrates any difference among the treatment arms, then key secondary efficacy analyses will be done to test each H-3070 dose arm with placebo in terms of the change from baseline in the PANSS total score using the same model as the primary analysis. The Step-Down Dunnett's method will be used to adjust for multiple comparisons.

Other secondary objectives are to evaluate the efficacy of HP-3070 using the following measures: the Clinical Global Impressions-Improvement score (CGI-I) and the Clinical Global Impressions-Severity score (CGI-S), PANSS positive, negative and general pathology subscales; proportion of PANSS responders, Calgary Depression Scale for Schizophrenia (CDSS), and Patient Satisfaction Questionnaire (PSQ) score.

The safety and tolerability of HP-3070 compared with placebo will be evaluated and include monitoring of vital signs, body weight, clinical laboratory tests (including serum prolactin), ECGs, C-SSRS, pregnancy testing, and movement disorder scales (AIMS, SAS, and BARS).. In addition, dermal assessments for skin irritation, discomfort, adhesion and adhesive residue will be conducted weekly or more often if a dermal adverse event is reported.

This study will also collect data to allow the assessment of the impact of covariates on asenapine exposure and to explore the exposure-response relationship at relevant endpoints through a model-based approach.

Noven plans to request a pediatric waiver for schizophrenia in patients under age 12 years because the very low incidence of schizophrenia in this age range would make a clinical trial impractical and clinical use would likely be minimal. A waiver for schizophrenia in patients 12 to 17 years of age will also be requested because a clinical trial with Saphris in this population failed to demonstrate efficacy.

Noven has requested this Pre-Investigational New Drug/End-of-Phase 2 meeting to address the following specific objectives:

- Gain feedback on the chemistry, manufacturing, and control (CMC) issues.
- Obtain agreement on the overall development program and use of Saphris data to support an NDA filing via the 505(b)(2) regulatory pathway.
- Obtain agreement that there are sufficient data to support initiation of the IND opening study HP-3070-GL-04, a global Phase 3 pivotal study.
- Gain feedback on the HP-3070-GL-04 study design and the appropriateness of the dose selection rationale used in support of this study.
- Obtain feedback on the adequacy of the safety database.
- Gain agreement that the overall clinical, clinical pharmacology, and non-clinical development plan intended to support the approval of HP-3070 for schizophrenia.
- Gain feedback on the content and format of the initial IND submission.

2. DISCUSSION

2.1. Chemistry, Manufacturing, and Control (CMC)

Question 1: The inactive ingredients in the HP-3070 patch are within the threshold limit according to the Food and Drug Administration's (FDA's) Inactive Ingredient Database, except for sodium acetate anhydrous and butylated hydroxytoluene.

Does the Agency agree the safety of each of these inactive ingredients at their proposed level in the HP-3070 patch is adequately characterized and that no further evaluation is necessary for human study and future registration?

FDA Response to Question 1:

As noted in our response to Question 6 below, it appears that the studies performed and planned will be adequate to qualify the levels of the proposed excipients, assuming that proper controls were used in the studies (untreated control, vehicle control and complete formulation). However, final determination will depend on the review of the final study reports.

We note that butylated hydroxytoluene has been reported to enhance transdermal penetration and therefore we propose you develop necessary drug product controls (in-process or drug product specification) for critical formulation excipients, (e.g. BHT) as development progresses.

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

Question 2: Noven plans to submit the HP-3070 CMC section in a Type II DMF in order to maintain product confidentiality in the event the application holder changes. The DMF will be submitted prior to the IND filing and will be updated on a regular basis as if it were included in the IND.

Does the Agency agree with this approach?

FDA Response to Question 2:

Yes, we find your approach reasonable. Be advised that a DMF is submitted solely at the discretion of the holder. The information contained in the DMF may be used to support an Investigational New Drug Application (IND). A DMF is NOT a substitute for your IND application and it is not approved or disapproved. The technical contents of a DMF are reviewed only in connection with the review of your IND application.

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

2.2. Nonclinical

Question 3: Noven proposes to develop HP-3070 under the 505(b)(2) regulatory pathway, relying on FDA's findings of nonclinical safety with regard to the pharmacokinetic, pharmacology, and toxicology data for SAPHRIS (sublingual asenapine ^{(b) (4)}) NDA 022117) as the RLD.

Does the Agency agree that Noven has established an adequate bridge to the proposed RLD and it is appropriate to rely on FDA's findings of nonclinical safety for SAPHRIS[®] as proposed in **Error! Reference source not found.**?

FDA Response to Question 3:

Yes, based on the nonclinical program provided here, it appears that there is an adequate bridge between HP-3070 transdermal patch and the reference listed drug (RLD), assuming human exposures following HP-3070 transdermal system (TDS) are not higher than that of the RLD and the nonclinical formulation used in nonclinical studies is the same as the clinical formulation of the patch. However, final determination of an adequate bridge will depend on full review of these studies.

Discussion at meeting: *The Sponsor clarified that human exposures of HP-3070 at the highest human dose ^{(b) (4)} are similar to the highest oral dose of reference listed drug (RLD) Saphris (10 mg BID) with respect to AUC, and the C_{max} is lower. Additionally, they acknowledged that the completed GLP nonclinical studies and ongoing 39-week minipig study utilize the same formulation as the clinical formulation. The Division acknowledged the clarification.*

Question 4: The IND-opening study is a pivotal, global, 6-week study in patients diagnosed with schizophrenia and who are in acute exacerbation.

Does the Agency agree the findings of nonclinical safety for SAPHRIS[®] (**Error! Reference source not found.**) and the nonclinical studies proposed to be included in the IND (**Error! Reference source not found.**) are adequate to support the initiation of the IND-opening study at the proposed clinical doses?

FDA Response to Question 4:

Yes, the completed and ongoing studies listed in Table 8 and the findings of safety for the RLD (Table 10), appear adequate to support initiation of the proposed IND-opening study. However, we recommend you submit the draft reports for all the studies listed in Table 9 that will be completed in June, 2015, preferably with the IND or as soon as feasible. In addition, if the HP-3070 patch has any component that has a molar extinction coefficient (MEC) greater than 1000 L mol⁻¹ cm⁻¹ at any wavelength between 290 and 700 nm, then the planned skin photosensitization study of the HP-3070 patch should be completed, and draft report submitted, prior to initiation of a Phase 3 clinical trial (ICH M3(R2), 2010; ICH S10 2015).

Discussion at meeting: *The Sponsor informed the Division that the UV absorption test will not be performed for all excipients, but the results from the ongoing photosensitization study (which utilizes the clinical formulation of the TDS) will be included in the original IND submission. The Division agreed with this approach, but the final determination of an adequate phototoxicity assessment will depend upon review of the final study report.*

Question 5: HP-3070 Specific Dermal Studies Including Carcinogenicity

- a) Does the Agency agree the dermal specific nonclinical studies proposed in **Error! Reference source not found.** are adequate to support registration?
- b) Does the Agency agree that based on the results of the ongoing 39-week minipig study and the FDA's findings of nonclinical safety for SAPHRIS[®] that a 2-year dermal carcinogenicity study is not required for registration and a waiver request is appropriate?

FDA Response to Question 5:

- a) *The proposed dermal specific nonclinical studies listed in Table 8 appear adequate to support registration; however, a final determination will be made after all studies are reviewed.*
- b) *Assuming there are no preneoplastic lesions or evidence of any proliferative changes in the 39-week Gottingen minipig dermal toxicity study, or any other toxicity studies including the 26-week Tg rasH2 mouse carcinogenicity study, then a 2-year dermal carcinogenicity study may not be required. However, a final determination will be made after all studies are reviewed. In addition, it will be important to demonstrate that the skin dose/exposure of the drug from the transdermal patch is not higher than the skin dose/exposure from the RLD. According to the guidance on reformulated drug products ([Draft Guidance for Industry and Review Staff, Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route](#), March 2008), a dermal carcinogenicity study might be recommended for drugs with a chronic indication, even if systemic carcinogenicity studies are available, if there is a significant difference in the skin dose of drug with a new formulation.*

Discussion at meeting: *The Division clarified their statement regarding the skin dose/exposure from the patch compared the skin dose/exposure from the RLD in that it came from the draft guidance for industry on reformulated drug products (see above reference).*

The Sponsor informed the Division that they will be obtaining data on the skin/dose exposure in the ongoing 39-week minipig study along with data on long-term irritation, steady state PK, and histopathology of the skin and downstream lymph nodes. The Division acknowledged this approach and informed the Sponsor that they will review all data once the study report is submitted to the IND. The Sponsor stated the 39-week minipig study is due to be completed by March 2016.

Question 6: Does the Agency agree that the overall nonclinical development plan is adequate to support an NDA filing and registration for the proposed indication and no additional nonclinical studies are required?

FDA Response to Question 6:

The overall nonclinical development plan as presented in this package appears adequate to support NDA filing; however, a final decision will be made after review of all final study reports. One particular issue is the determination that proper controls were used in order to adequately evaluate the safety of the levels of excipients used in this formulation of the drug (HP-3070 transdermal patch). Additional nonclinical studies may be needed if any new or increased levels of impurities or potentially genotoxic impurities develop, or if any safety concerns arise in any ongoing nonclinical studies or during the course of clinical development.

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

2.3. Clinical

Question 7: Noven proposes to develop HP-3070 via the 505(b)(2) regulatory pathway and rely upon the Agency's findings of safety from the SAPHRIS data (NDA 022117) to fulfill the clinical pharmacology and safety evaluations as described in the rationale below. Noven has fully characterized the pharmacokinetic profile of HP-3070 transdermal following single (up to (b) (4)) and multiple doses (up to (b) (4))

- a) Does the Agency agree that Noven has established an adequate bridge to the proposed RLD and it is appropriate to rely on FDA's findings of clinical safety for SAPHRIS® as proposed below?
- b) Does the Agency agree no further clinical pharmacology studies are required for filing and registration for the proposed indication?

FDA Response to Question 7:

a) Yes.

b) No, we don't agree. We recommend that you evaluate the effect of heat on the release and absorption of asenapine.

Discussion at meeting: *The Sponsor agreed to conduct a study to evaluate the effect of heat on the release and absorption of asenapine. The Sponsor stated that they will use a protocol similar to that used for other transdermal products such as Daytrana. The Agency requested that the protocol for this study be submitted for review. The Sponsor agreed to submit the*

protocol for this study to the IND and the Agency would provide any comments on the protocol once received and reviewed.

Question 8: Noven proposes the IND-opening study, a global pivotal Phase 3, 6-week study (HP-3070-GL-04) to evaluate the efficacy and safety of HP-3070 in patients with schizophrenia. This study will have clinical sites in the US and rest of world. A full protocol is included in the briefing package.

- a) Does the Agency agree the doses that will be evaluated in the proposed Phase 3 study are appropriate?
- b) Does the Agency agree that the completed clinical and nonclinical program to date described in the briefing package will support the initiation of the proposed IND-opening study?

FDA Response to Question 8:

- a) *Yes. Based on the information provided, comparable steady state exposures of asenapine can be obtained when comparing*
 - i. the (b) (4) patch and 5mg RLD BID and
 - ii. the (b) (4) patch and 10mg RLD BID. The selected doses seem to be appropriate.
- b) *Please see our response to Question 4.*

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

Question 9: Design of Pivotal Study (HP-3070-GL-04) to Support Registration

- a) Does the Agency agree with the blinding strategy for the proposed study HP-3070-GL-04?
- b) Does the Agency agree with the proposed sample size for study HP-3070-GL-04?
- c) Does the Agency agree study HP-3070-GL-04 includes an adequate number of US subjects (one-third of the total study population) to establish efficacy representative of a generalizable US population for the proposed indication?
- d) Does the Agency agree in principle that the overall design for Study HP-3070-GL-04, is adequate to support registration for the proposed indication? Including the following:
 - Inclusion and Exclusion Criteria
 - Statistical Analyses of Primary (global test) and Secondary Endpoints for inclusion in the label
- e) Does the Agency agree with Noven's proposal to submit study HP-3070-GL-04 under a SPA if additional feedback is needed?

FDA Response to Question 9:

a) You should assess whether subjects can discriminate between the placebo and asenapine patches based on any dermal reactions, e.g., if the asenapine TDS produces an itchy sensation or hypoesthesia and the placebo patch does not. If not, the blinding strategy seems acceptable. If so, this potential source of unblinding should be addressed.

- b) We cannot comment on this because it is based on several assumptions about effect size and disease severity.*
- c) Yes, we would expect that efficacy findings will be reasonably consistent between the U.S. and non-U.S. sites.*
- d) You will have to be able to identify the efficacious dose(s) for inclusion in the label; i.e., winning on the global test alone would not be adequate to support an efficacy claim. The primary efficacy and safety analyses should compare each HP-3070 dose group to placebo and the efficacy analysis should adjust for multiplicity to limit the Type I error rate to 0.05. Also, any secondary endpoints intended for inclusion in the label must be prospectively and clearly declared, found to be acceptable to the Division, and be analyzed using acceptable statistical methodology, including any necessary multiplicity adjustment to control the overall type I error rate. In addition, the definition of the FAS should be revised to require that patients have a valid baseline score on the PANSS in addition to the proposed criteria to be included in the FAS. Refer to Question 13 for additional statistical comments on the study design and analyses.*
- e) Yes.*

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

Question 10: Overall Clinical Development Plan and Safety Database for the Treatment of Schizophrenia

- a) Does the Agency agree with the proposed safety database (global and US) is sufficient to support an NDA filing and registration for the proposed indication?
- b) Does the Agency agree that HP-3070-GL-04 is adequately designed to evaluate dermal characteristics (discomfort, irritation, adhesion, adhesive residue) of HP 3070 transdermal patch necessary for registration?
- c) Does the Agency agree, in principle, the proposed single pivotal study HP-3070-GL-04 and the Agency's findings of safety and efficacy data from SAPHRIS[®] (NDA 022117) support filing and registration of HP-3070 for the proposed indication?

FDA Response to Question 10:

- a) Assuming that efficacy is demonstrated and no new safety concerns arise with HP-3070, yes.*
- b) No. An in vivo adhesion study must be conducted as part of your development program for HP-3070. We note that the protocol for your proposed Phase 3 trial specifies that tape will be applied to the patch at bedtime each night, which suggests an anticipated problem with adhesion. Problems with adequate adhesion will need to be addressed in your program.*
- c) From a clinical standpoint at this time, yes. Please also see Additional Comments from OPQ, below.*

Discussion at meeting:

- a) There was no further discussion.*
- b) Because the largest size of the to-be-marketed product (40 cm²) will not be studied in the proposed Phase 3 trial, adhesion data from this trial alone will not suffice to*

demonstrate acceptable adhesion and a dedicated adhesion study must be conducted. Noven agreed to consider the effects of friction in designing an adhesion study because the systems may be worn under clothing which could result in edge lift or detachment. Also, the effects of physical movement in the areas of TDS application on adhesion will be considered (i.e., the patient should not be instructed to restrict movement while wearing the TDS). A proposed protocol for an adhesion study will be provided for Agency comment before initiating the investigation. Noven clarified that bathing will not be restricted in any way during the Phase 3 trial and that taping the edges is not permitted in any of the trials (adhesion or BE). The Agency also stated that there is the expectation that adhesion assessment would occur during the BE study, not just on the dedicated study of the largest product. Further the Agency generally recommended that when multiple sizes are intended to be marketed, an adhesion study be conducted in a bracketed fashion (largest and smallest sizes formally evaluated).

c) There was no further discussion.

Question 11: Pediatric Development Plan - An outline of the draft pediatric plan is provided in **Error! Reference source not found.** Noven plans to request a pediatric waiver for the proposed indication in patients less than 12 years of age as well as adolescents (ages 12-17), based on the rationale below.

Does the Agency agree it is appropriate to submit the proposed pediatric waivers?

FDA Response to Question 11:

A waiver request for patients under age 12 years seems reasonable based on the low prevalence of schizophrenia in this age group. However, there is an appreciable prevalence of schizophrenia in the 12-17 year age group and we are not convinced that asenapine is not safe and effective in adolescents. Therefore, a request for deferral of the PREA requirement for trials in adolescent schizophrenia is more appropriate.

Discussion at meeting: *The Sponsor acknowledged our comments and agreed to submit an initial Pediatric Study Plan (iPSP) to the IND.*

2.4. Administrative

Question 12: Noven plans to submit the IND in eCTD format, as described in the FDA Guidance for Industry, “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications” (June 2008, Electronic Submissions, Revision 2).

Does the Agency agree with the documents and data planned for inclusion in this IND as described in the Briefing Document?

FDA Response to Question 12:

Yes.

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

Question 13: Does the Agency have any additional points for Noven's consideration regarding this proposed IND filing or development of HP-3070 transdermal patch for the proposed indication?

FDA Response to Question 13:

OPO:

We strongly recommend that you perform the pivotal clinical trial with your proposed commercial formulation. Any changes to the proposed commercial formulation from developmental formulations require sufficient bridging studies. In addition, we strongly encourage you to make all possible changes to your manufacturing process and design of the system prior to initiation of pivotal clinical trials; we believe that clinical trials are the best validation of the performance of complex dosage forms. As development progresses and prior to conducting Phase 3 trials you may want to consider the following:

Adhesives

We recommend that you qualify adhesives both prior to and post drug formulation. This ensures both optimum product quality attributes in transdermal and topical formulations, and a seamless post-approval change process, in case the raw materials, manufacturing process, or manufacturer of the adhesive(s) is changed. The following tests are not required for release of the drug product but rather to qualify the adhesive component. Proper qualification of the adhesives used to formulate the drug product may include the following:

- *Readily available polymer - molecular weight distribution, polydispersity, spectroscopic analysis (IR), thermal analysis, intrinsic viscosity, and measurement of residual monomers, dimers, solvents, heavy metals, catalysts and initiators.*
- *Adhesive as a Lamina (without drug substance or other adhesive matrix excipients) - residual solvents, extractable and leachables, and an evaluation for peel, tack, shear, and adhesion.*
- *Adhesive in the final Drug Product - residual monomers, dimers and solvents, IR identification, loss on drying, impurities, and content uniformity. Functionality parameters to be assessed include but are not limited to peel, shear, adhesion, tack, in vitro drug release, and in vitro drug permeation.*

Residual Drug

We recommend you include sufficient scientific justification to support the amount of residual drug in a TDDS in the 3.2.P.2 section of the common technical document (CTD) format discussion of the product and process development and justification for the final formulation and system design. The level of information in the submission should be sufficient enough to demonstrate product and process understanding and assure that a science and risk based approach has been taken to minimize the amount of residual drug in a system after use. The justification for the percent of residual drug and the overall amount of remaining drug will be assessed during review. Note, residual drug should be determined from analysis of worn systems after prescribed use and not a theoretical calculation. Refer to the [Guidance for](#)

[Industry – Residual Drug in Transdermal and Related Drug Delivery Systems](#) for additional information.

Biopharmaceutics

1. *We have the following advice comments for the information that should be provided in your NDA regarding the development of in vitro release method and establishing in vitro acceptance criteria for your product:*
 - a) **Drug Release Testing:** *Provide the drug release method development and validation report supporting the selection of the proposed test method ensuring a proper quality control with adequate discriminatory ability to reject bad batches from both formulation and process control point of views.*
 - b) **Drug Release Acceptance Criteria:** *The in vitro drug release specifications should be based on multi-point drug release profiles with at least three specification time points covering the initial, middle, and terminal phases of drug release in vitro, and encompassing the timeframe over which the maximum amount of drug release can be achieved with a valid, discriminating method prior to the attainment of plateau in the release profile. The percentage of in vitro drug release at the last time point cannot be less than the percent of drug delivered in vivo during the maximum indicated period of wear, based on in vivo residual drug analysis and/or pharmacokinetic data. Results of in vitro drug release testing should be provided for the lots used in the clinical trials and in primary stability studies.*

Note that the final determination on the acceptability of the drug release method is a review issue that can be determined during the IND or NDA. However, the acceptability of the proposed drug release acceptance criteria for your product will be made during the NDA review process based on the totality of the provided data.

2. *If an in vitro human skin permeation study is conducted, provide the full study report including the study design, analytical method and permeation results with raw data. Clearly state the objective of the in vitro human skin permeation study in the study report.*

Manufacturing Process

- *Provide a table summarizing all hold times utilized during the manufacturing process including but not limited to those associated with drug/adhesive blend, laminating manufacturing steps, die cutting steps, and pouching steps. Additionally, provide justification for all hold times.*

Drug Product Release Specification and Stability Testing

- *Establish a test and acceptance criteria for pouch integrity.*
- *Establish a test and acceptance criteria for cold flow to be used at release and on stability. Assessment of cold-flow may be a combination of quantitative and qualitative methods. Appearance criteria can assess potential use issues caused by cold flow if systems are difficult to remove from pouches, if release liners detach from the adhesive matrix during attempted removal due to cold flow adhering the backing membrane to the pouch, as well as adhesive residue transferred to the pouch after removal of the system. A*

quantitative cold flow method captures the degree to which cold flow extends beyond the parameter of the backing membrane.

- *Establish a test and acceptance criteria for the absence of crystals to be used at release and on stability. Microscopic and photometric methods are preferred rather than a simple visual count.*
- *Establish a test and acceptance criteria (including upper and lower bounds) for peel from release liner, adhesion to steel or other substrate, shear and tack.*
- *Test the final laminate for residual monomers and other adhesive impurities. Additionally, perform an extractable study on the final drug product to identify any potential leachables of the backing membrane, release liner and ink. We suggest at minimum performing the extraction with solvents utilized by the adhesive system of your product. Identify all quantifiable impurities and provide test and acceptance criteria in the drug product specification with justification for any impurities if of toxicological relevance.*
- *Provide solubility information with regard to the API in the adhesive blend and laminates in the drug development section of NDA*
- *As migration of the drug substance and excipients within the individual drug product throughout its shelf life is of major concern, a complete drug product matrix description with regard to the drug substance in the adhesive matrix and/or backing membrane is suggested. A full understanding of the drug product, specifically where the drug is within the adhesive matrix (e.g., emulsion system, suspension, completely dissolved in the matrix) and what changes the matrix may undergo from the time of manufacture to product expiry is recommended.*

Useful tools to support your explanation for the above may include confocal microscopy, light microscopy, SEM imaging and Elemental Mapping (SEM-EDX) of the cross-section and surface of the drug product at manufacture and throughout stability. The tools listed above may not be appropriate for every drug product application; those utilized must be scientifically justified.

Identifying Label

On the backing membrane of the drug product, include an identifying label which at minimum includes the drug product name and strength. The impact of the identifying label on stability of the drug product should be assessed; therefore, you are encouraged to incorporate a representative label early in development. Assure inks utilized for printing do not interact with the drug product and assess any inks utilized for leachables and/or extractables.

Expression of Strength

Express the strength of the product as a transdermal delivery rate (e.g. XX mg/day).

OCP/OND:

In Vivo Adhesion

We consider in vivo adhesion studies to provide the greatest predictor of adequate adhesion of the proposed commercial drug product during use. In general, a mean adherence of greater than 90% should be expected and no instances of detachment should be seen. Poor adherence events should be investigated and possible causes and risk factors determined. The transdermal system should be used as proposed and product reinforcement, such as taping the edges or use of overlays, or occluding the product from water during bathing should not be permitted during the in vivo adhesion evaluation.

Investigation of Heat

It is well known that heat can affect the rate of drug release and adsorption of many drug substances from transdermal systems. The Sponsor is encouraged to consider investigating the impact of applied heat (e.g., heating pad, heating blanket, whirlpool, or sauna) and exercise on the delivery profile of the drug product.

DMEPA:

TDS Color

Consider the following as you move forth in the development of your transdermal system. Transdermal systems that are difficult to locate and identify present safety issues. Transdermal systems that are clear, translucent or are colored to match human skin colors can make it difficult to find the patch on the patient, and have also led to administration errors when patients or caregivers fail to remove old systems and apply more than one system at a time. We refer you to the draft [Guidance for Industry: Safety Considerations for Product Design to Minimize Medication Errors](#).

Use-Related Risk and Human Factors

Given the indication for which your proposed asenapine ^{(b) (4)} transdermal system will be used, there may be unique considerations for use of the transdermal system in this treatment population. Therefore, we recommend that you conduct a comprehensive use-related risk analysis of the product. Your comprehensive risk analysis must include a comprehensive evaluation of all the steps involved in using your transdermal product (e.g., based on a task analysis for your transdermal system and known problems with similar marketed transdermal systems), the errors that users might commit or the tasks they might fail to perform, the potential negative clinical consequences of use errors and task failures, the risk mitigation strategies you employed to reduce any use errors or failures, and the method of validating your risk mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and that all residual risks are acceptable (i.e., not easily reduced further and outweighed by the benefits of the product). Based on the comprehensive use-related risk hazard analysis, you will have a better idea of the extent to which simulated use testing is required. The risk analysis will also guide you in the design of a human factors validation protocol study for your product if it is warranted based on the risk analysis.

Guidance on human factors procedures to follow can be found in [Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management](#).

Note that we have also published three draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors and product design:

- a. [Applying Human Factors and Usability Engineering to Optimize Medical Device Design \(Draft\).](#)
- b. [Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors \(Draft\).](#)
- c. [Safety Considerations for Product Design to Minimize Medication Errors \(Draft\).](#)

Statistics:

- Randomization: Please plan to stratify patients at randomization by country or region, if not feasible by center.
- Use of Same Data Set for Model Fitting And Hypothesis Testing: You propose to switch the analysis from MMRM to ANCOVA or non-parametric, depending on the data normality. This is problematic because it may inflate the overall type I error rate. Given such a large sample size, normality assumption is unlikely to be violated. However, you would still need to plan to explore the normality assumption. Nevertheless, we recommend that you use MMRM as the primary analysis, and non-parametric analysis as a supportive analysis.
- Primary Statistical Model: It is not clear whether you plan to include all 3 dose groups in the primary statistical model. We strongly recommend that you do so in order to have a common estimate of placebo response as well as to reduce variance. In your future SAP:
(i) Please provide the method of estimation (e.g., ML or ReML) and the method for approximating the degree of freedom of the denominator (e.g., Kenward-Roger, Satterthwaite). (ii) The stratification factor for randomization should be included as a factor in the primary statistical model; if randomization is stratified by center and you plan to include pooled-center in the model (because of very sparse data in few centers), you will need to pre-specify the pooling algorithm.
- Primary Analysis Set: The protocol states that “The assessment of PANSS score will be considered valid if it was taken within 48 hours from study drug administration. Only valid assessments will be included in the analysis.” Please clarify this. This should not be used as an exclusion criterion for the primary analysis set.
- Sample Size Re-calculation: Please provide the details on who will be involved in the interim blinded data review for possible sample size re-estimation (in same company or from external referral). Please provide a standard operating procedure for this blinded data review and sample size adjustment (including, for example, the cap of sample size).
- Sensitivity Analyses: The proposed MCAR-based ANCOVA analysis may not be a sensible sensitivity analysis, because it requires a stronger assumption (Missing Completely at Random) compared to the proposed primary analysis (MMRM)). Please pre-specify the details of sensible sensitivity analyses in SAP to explore the impact in case the missing data mechanism assumed in the primary analysis appears to be violated.

Discussion at meeting:

DMEPA: The Sponsor confirmed they will conduct a comprehensive use-risk analysis to determine the need for human factors studies and submit their results to the Agency for DMEPA

review. The Sponsor asked whether a cross-disciplinary review of the analysis results that would include DMEPA and the clinical review team could be requested. The Agency stated that this was reasonable, but asked that such a request indicate the particular area(s) of concern to be addressed by such a review.

Statistics: *The Sponsor agreed with our comments. Specifically, the Sponsor clarified the following: (1) Randomization will be stratified by country (8 countries anticipated). (2) The statistician from Quantiles will conduct the interim blinded data review. A standard operating procedure will be provided in the SAP.*

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP 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 PSP 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 PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation 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. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order

to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

For general toxicology, supporting nonclinical toxicokinetic and carcinogenicity studies we encourage sponsors to both use Standards for the Exchange of Nonclinical Data (SEND) for regulatory submissions and to submit sample or test data sets before implementation becomes required. Sponsors will be provided feedback on the suitability of these test data sets.

Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

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 [CDER/CBER Position on Use of SI Units for Lab Tests](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm) (<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>).

Office of Scientific Investigations (OSI) Requests

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

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

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

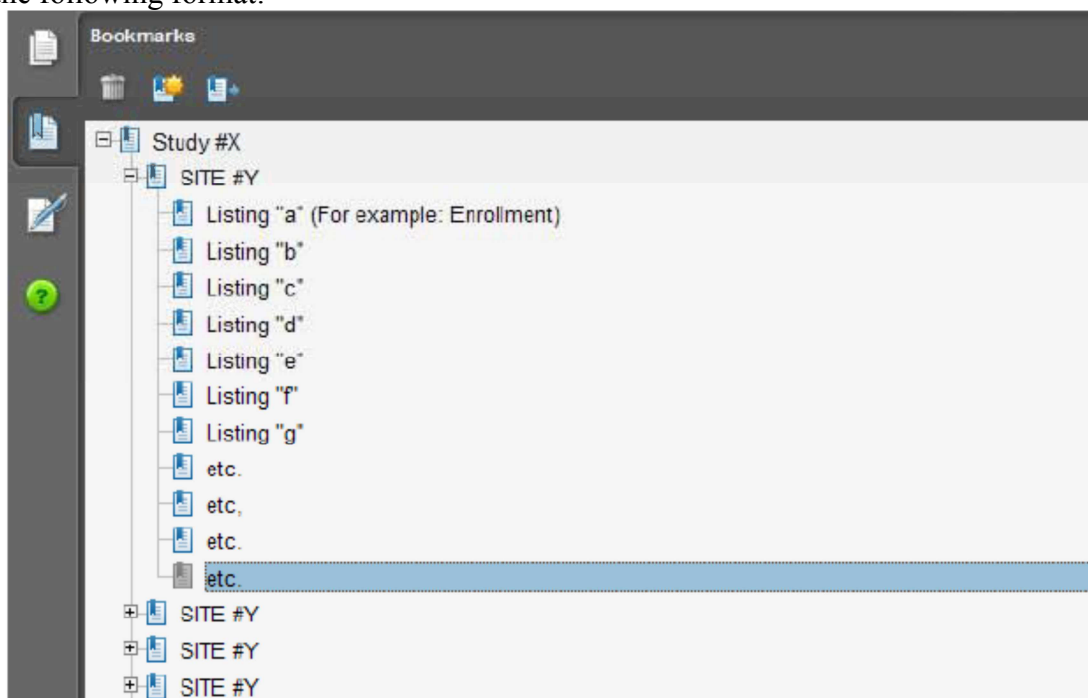
- I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:

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



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily

provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

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

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

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

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



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

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

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

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

FDA eCTD web page

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

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

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

/s/

MITCHELL V Mathis
07/22/2015