CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211964Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 108864

MEETING MINUTES

Supernus Pharmaceuticals, Inc.
Attention: Tami Martin, RN, Esq.
Vice President, Regulatory Affairs
1550 East Gude Drive
Rockville, MD 20850

Dear Ms. Martin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SPN-812V (viloxazine hydrochloride extended-release capsules).

We also refer to the meeting between representatives of your firm and the FDA on July 24, 2019. The purpose of the content and plans for submitting a new drug application (NDA) for this product.

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 CAPT Kofi Ansah, PharmD, Senior Regulatory Project Manager, at (301)796-4158 or email: Kofi.Ansah@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Tiffany R. Farchione, MD
Director (Acting)
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA Meeting
Meeting Date and Time:	July 24, 2019, 12:00 pm EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1313 Silver Spring, Maryland 20903
Application Number:	IND 108864
Product Name:	SPN-812V (Viloxazine Hydrochloride Extended-Release Capsules)
Indication:	Attention Deficit Hyperactivity Disorder (ADHD)
Sponsor Name:	Supernus Pharmaceuticals, Inc.
Meeting Chair:	Javier A. Muñiz, MD

FDA ATTENDEES

Ellis Unger, MD	Director, Office of Drug Evaluation-I (ODE-I)
Javier A. Muñiz, MD	Deputy Director (Acting), Division of Psychiatry Products (DPP)
Kofi Ansah, PharmD, RAC	Senior Regulatory Project Manager, DPP
Michael Davis, MD, PhD	Clinical Team Leader, DPP
David Millis, MD, PhD	Medical Officer, DPP
Aisar Atrakchi, PhD	Pharmacology/Toxicology Supervisor, DPP
Jia Yao, PhD	Pharmacology/Toxicology Reviewer, DPP
Luning Zhuang, PhD	Clinical Pharmacology, Team Leader, OCP
Praveen Balimane, PhD	Clinical Pharmacology Reviewer, OCP
Andrew Potter, PhD	Biometrics Reviewer, DBI/OB
Thomas Birkner, PhD	Secondary Biometrics Reviewer, DBI/OB
Douglas Warfield, PhD	Associate Director Biomedical Informatics, DPP
Hari Cheryl Sachs, MD	Team Leader, Division of Pediatric and Maternal Health (DPMH)
Ethan D. Hausman, MD	Medical Officer, DPMH
Jacquline Yancy, PhD	Senior Regulatory Health Project Manager, DPMH
Edward Hawkins, PhD	Pharmacologist, Controlled Substance Staff
Sangeeta Tandon, PharmD	Reviewer, DRISK/OSE

Supernus Pharmaceuticals Inc's Attendees

Stefan Schwabe, MD, PhD	Executive Vice President, Research and Development and Chief Medical Officer
Tami Martin, RN, Esq.	Senior Vice President, Regulatory Affairs
Azmi Nasser, PhD	Senior Director, Clinical Research
Shamia Faison, PhD	Manager, Clinical Pharmacology
Gopakumar Nair, BVSc, MS, AH DACVP, DABT	Director, Preclinical Toxicology
Chungping Yu, PhD	Director, Preclinical DMPK & Pharmacology
Tesfaye Liranzo, PhD	Senior Director, Biostatistics
Pebing Qin	Assistant Director, Biostatistics
Nicholas Fry	Clinical Program Manager
Catherine Huang	Associate Clinical Program Manager
Michael Viera, PhD	Senior Director, Drug Product Development
Tracy Acker, PharmD	Senior Director, Postmarketing Regulatory Affairs

1.0 BACKGROUND

Supernus Pharmaceuticals is developing an extended-release capsule formulation of viloxazine (SPN-812 ER) as a monotherapy treatment for attention deficit/hyperactivity disorder (ADHD) in pediatric patients, ages 6 to 17 years. Viloxazine is a norepinephrine reuptake inhibitor. The immediate-release formulation was initially marketed in Europe as an antidepressant in the late 1970s and subsequently withdrawn in 2002 for commercial reasons. Although viloxazine was previously marketed in Europe, it has never been approved or marketed in the United States. (b) (4)

The Sponsor expects the target total daily dose for viloxazine ER to be 100 to 400 mg for children ages 6 to 11 years and (b) (4) mg for children ages 12 to 17 years, administered once daily. Because viloxazine is a strong inhibitor of CYP1A2, the Sponsor proposes to include a statement in the label regarding concomitant use of viloxazine with CYP1A2 substrates.

The Sponsor plans to submit a 505(b)(1) New Drug Application for viloxazine ER for the treatment of ADHD in children and adolescents ages 6 to 17 years in approximately October 2019. Four phase 3 controlled efficacy and safety trials (812P301, 812P302, 812P303, and 812P304) are complete and clinical study reports are pending (see Table 1). The Sponsor states that all four phase 3 studies met their primary endpoint for at least one dose strength. An open-label, long-term study (812P310) is ongoing. For all four trials, the primary efficacy endpoint is the change from baseline to end of treatment in the ADHD Rating Scale-V (ADHD-RS-V) Total Score.

Table 1: Completed Phase 3 Trials for Viloxazine ER in the Treatment of ADHD

Study	Design	Age Range	Treatment Arms	N Completed
812P301	6-week, randomized, double-blind, placebo-controlled parallel-group efficacy and safety study	6 to 11 years	100 mg, 200 mg, placebo	399
812P302	6-week, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study	12 to 17 years	200 mg, 400 mg, placebo	266
812P303	7-week, randomized, double-blind, placebo-controlled, parallel-group efficacy and safety study	6 to 11 years	200 mg, 400 mg, placebo	279
812P304	7-week, randomized, double-blind, placebo-controlled, parallel-group efficacy and safety study	12 to 17 years	400 mg, 600 mg, placebo	300 planned (final count of completers not available)

The Sponsor plans to request a separate Chemistry, Manufacturing, and Controls meeting. The Sponsor has requested this pre-NDA meeting to discuss the planned contents of the NDA submission. Specifically, the Sponsor seeks:

- FDA commentary on the planned electronic presentation of information and if the planned presentation is agreeable to the Agency for review.

- FDA commentary on the manner in which Supernus plans to address key points identified for this submission.

- Confirmation that the package appears complete and suitable for review, when compiled as described.

2.0 DISCUSSION

General Comments:

You have indicated that all four of your phase 3 studies met the primary efficacy endpoint for at least one dose strength of viloxazine ER. However, we were unable to locate preliminary results for these studies and you indicated that the clinical study reports are not yet complete. Our responses, therefore, are limited by the extent of information that we have available in your background document.

2.1. Clinical

Question 1: [*Verification of Complete Program*] Supernus' clinical development program for the New Drug Application for SPN-812 for the indication of monotherapy treatment of ADHD in children ages 6-17 is summarized in the Table of All Studies (Appendix A) and discussed in Section 5 of this briefing package. Please confirm that completion of this development plan, and submission of the results of the investigations, will be adequate to permit an NDA review by the Division of Psychiatry Drugs for the stated indication.

FDA Response to Question 1: *From a clinical perspective, the studies summarized in Appendix A of your background package appear adequate to permit NDA review for your stated indication. However, the final filing determination will not be made until we complete our initial review of your submitted NDA.*

Additionally, we have the following clinical pharmacology comments:

- *Please confirm that the final to-be-marketed formulation was used in the pivotal efficacy/safety studies as well as the key clinical pharmacology studies (e.g., food-effect study, drug interactions study, etc.).*

- *Please clarify if the planned strengths are all compositionally proportional. Otherwise, you may need to conduct an in vivo strength proportionality/ equivalency study.*

- *Please confirm that the food-effect study was conducted using the final to-be-marketed formulation using the highest strength or the highest therapeutic dose.*

- *We recommend the content and format of information found in the Clinical Pharmacology sections (Section 7, 12, etc.) 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 (available at https://go.usa.gov/xn4qB). 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.*

- *Please confirm that the effect of hepatic impairment on PK has been assessed.*

- *Please confirm that a comprehensive assessment for drug-interaction (i.e., in vitro potential for substrate, inhibition and induction for key CYP enzymes and transporters as well as in vivo clinical interaction studies, as needed) for the product has been conducted as per the recent Agency guidances (available at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm). Clarify if any clinical drug interaction study with SPN-812 as a victim has been conducted.*

- *Please clarify if there are any unique human metabolite(s). If yes, confirm the complete characterization (i.e., PK, pharmacology, toxicology, etc.) of the unique human moieties. Additionally, please confirm that the metabolic pathways have been fully elucidated with the metabolite structures, fraction metabolized via different enzymes, etc. Provide concise tables listing the major metabolites (in plasma, in urine) in human and in animal species.*

  Discussion at Meeting: *The Sponsor confirmed that the final to-be-marketed formulation was used in pivotal efficacy and key clinical pharmacology studies. The planned strengths were compositionally proportional, and the food effect study was conducted using the highest strength.*

  The Sponsor clarified that they have conducted several drug interaction studies with their product. The Agency stated that because viloxazine is a substrate of CYP2D6, a drug interaction study to assess the effect of concomitant administration with a strong CYP2D6 inhibitor might be required depending on the data during NDA review.

  The Sponsor confirmed that they have not conducted a dedicated hepatic impairment study. The Agency expressed their concern because the drug is extensively metabolized via CYP pathways and is eliminated primarily as metabolites. The Agency encouraged the Sponsor to conduct the study prior to NDA submission; otherwise, it is likely to be a significant review issue.

  The Sponsor also clarified that they have fully characterized the metabolic pathway for viloxazine in human and animal species. There was some discussion on potentially unique human metabolites, U2 and U4, and the need for their appropriate characterization in pharmacology and toxicology panels prior to the NDA submission.

Question 2: [*Indication Statement*] Does the agency agree with this proposed indication statement, assuming the data are found to be sufficient for approval: “viloxazine is indicated as a treatment for pediatric patients ages 6 to 17 years with attention deficit/hyperactivity disorder”. Specifically, are ages to be included in the indication statement, or is specific “ages language” no longer desired? (See EOPII meeting minutes dated 7/26/2017, responses to Question 1)?

FDA Response to Question 2: *The final indication language will be a matter of review when you submit the NDA. You should include the age range in the indication statement. The Indications and Usage section should communicate the population for which safety and effectiveness have been established. In addition, we recommend that you include the drug class in the Indications statement in the Highlights section of the label and,* (b) (4) *we recommend that you include the formulation along with the drug name in*

the label. Further details on the Indications and Usage Section of Labeling can be found at https://www.fda.gov/media/114443/download.

Discussion at Meeting: *The Sponsor acknowledged the Agency's comments. Additional information on conveying the product name and formulation is provided in the Guidance entitled, "Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-title-and-initial-us-approval-highlights-prescribing-information-human-prescription-drug-and.*

Question 3: [*Confirmation of Adequate Exposures*] At the time of NDA submission, Supernus expects to have the following SPN-812 exposures: approximately 1848 subjects exposed, of whom 351 were in volunteer studies and 1497 were patients in clinical studies (812P202, 812P301, 812P302, 812P303, 812P304 and 812P310). Supernus will be submitting open label extension data from the 812P310 trial with a data cut off of 31 December 2018. As of that date, Supernus had 310 patients in the open label extension study for more than 6 months, and 59 patients in the open label extension study for more than 12 months. At the time of the 4-month safety update (data cut off of 31 July 2019), we expect to have exposures as follows: 698 for more than 6 months and 397 for more than 1 year. Please confirm that these exposures meet FDA criteria for adequate number of subject exposures to enable review of a New Drug Application for SPN-812.

FDA Response to Question 3: *The number of total exposures and the number of long-term exposures that you predict for the open-label extension study appear adequate to support an NDA.*

Please provide a table showing dose and duration of treatment by age group (for example, the number of patients 6 to 11 years, 12 to 17 years, and adults who received a given dose for 6 months and 12 months). To the extent possible, please also submit top-line (i.e., summary) safety data by age group and dose.

Discussion at Meeting: *No further discussion.*

Question 4: Please see Appendix B for a draft of one of our pivotal Clinical Study Reports. The CSR presentation is based both on guidance and American Medical Writers Association recommendations. Please comment on the acceptability of this clinical study report presentation for the New Drug Application review for phase 3 clinical study reports.

FDA Response to Question 4: *This clinical study report format for the phase 3 studies appears to be acceptable for the NDA submission.*

Discussion at Meeting: *No further discussion.*

Question 5: Please see Appendix C for the draft Statistical Analysis Plans, which identify the table of contents, and a list of tables for the Integrated Summaries (ISS and ISE) planned for this New Drug Application. Please comment on the acceptability of this presentation for the New Drug Application review?

FDA Response to Question 5: *The planned formats for the Statistical Analysis Plans, ISS, and ISE appear to be acceptable for the NDA submission.*

Discussion at Meeting: *No further discussion.*

Question 6: [*Seizures*] The agency has expressed concern about provocation of seizures with the clinical use of SPN-812. See Supernus' materials submitted, particularly, as cover letter Attachment D to Serial Submission 0051, on this topic). In the recently completed/ongoing clinical studies in children age 6-17 we have seen nine (9) instances that fit the widened criteria set by FDA for preparation of seizure narratives (2 tonic clonic seizures, 1 pseudoseizure, and 6 cases of syncope). All nine reports were submitted as 15-Day adverse event reports to FDA.

Also see the clinical End of Phase 2 Meeting minutes (June 29, 2017) post meeting comments to Question 3(c). Apart from routine AE description and reporting in the CSRs, and providing the patient narratives on patients as agreed with the agency, are there any additional evaluations of the Phase III data/specific tables or listing etc., that the FDA would expect to need, to be able to review this matter fully as part of the NDA?

FDA Response to Question 6: *Your plan for reporting on occurrences of seizure appears to be adequate.*

Discussion at Meeting: *No further discussion.*

Question 7: [*Abuse Narratives*]
a) [*Content example*] Please see an example narrative (Appendix D) to be reviewed as a sample presentation of an abuse patient narrative. These abuse narratives were requested for all clinical studies with viloxazine (see clinical End of phase 2 meeting minutes, page 15). Is this presentation adequate for FDA review?

FDA Response to Question 7(a): *Yes, the example narrative you provided appears to provide the necessary information.*

Discussion at Meeting: *No further discussion.*

b) [*Location of Narratives and Location of Discussion*] Per discussion with the esubmissions team at FDA, these narratives will be located under a separate study tagging file (STF) following each report in Module 5. After a thorough review of all narratives, Supernus will determine in what way to discuss this topic in the NDA. Is a separate STF location for these narratives suitable for agency review?

FDA Response to Question 7(b): *Yes, Module 5 is the appropriate location for clinical data. You should provide links to the narratives in your final clinical study reports.*

> ***Discussion at Meeting:*** *No further discussion.*

c) [*DRAFT Narratives for Ongoing Study*] Because 812P310 is an ongoing, open label extension study, and individuals' patient narratives could change as the study continues, Supernus is presenting abuse narratives based on events occurring in Study 812P310 as draft documents. Study 812P310 safety data is being included in the ISS based on a December 31, 2018 data cut. Full data cleaning and database finalization for these narratives will, of course, occur at a later date. Does the agency agree that these 812P310 narratives may be presented in draft form?

FDA Response to Question 7(c): *We do not agree with presenting narratives in draft form. You should present final narratives which can be included as part of the 120-day safety update if necessary. Finalized reports are necessary because, although a human abuse potential study is not currently required, this decision could change based on the analysis of adverse events in your clinical trials.*

> ***Discussion at Meeting:*** *The Sponsor clarified that they used the term "draft" to describe the planned submissions for Study 812P310, because the study will be ongoing at the time of the December 31, 2018 data cutoff date. The available data will be cleaned and analyzed prior to the NDA submission.*

d) [*Drop Outs*] FDA has requested that abuse narratives be written for all subjects who have dropped out of the clinical studies. Supernus is proposing to write abuse narratives for all subjects who have dropped out of the efficacy phase 2 (812P202) and phase 3 studies (812P301, 812P302, 812P303, 812P304) but not write abuse narratives for subjects who have dropped out of the long-term open label study (812P310). Supernus' rationale for excluding 812P310 patients (b) (4) [redacted] Supernus would still write narratives for 812P310 patients based on adverse events and drug accountability. Does FDA agree with this plan?

FDA Response to Question 7(d): *We do not agree with excluding narratives from subjects who have dropped out of Study 812P310. In the NDA submission, please*

provide narratives, in electronic format and cleaned, through the December 31, 2018 data cutoff date for this study.

Discussion at Meeting: *Please see discussion for Question 7(c).*

e) [*Drug Accountability*] Please note that as to identification of missing clinical trial material, necessary to identify patients for whom abuse narratives must be written, drug accountability data was collected in three slightly different ways throughout the SPN-812 program. 1) for phase 2, drug accountability data was captured manually, and the database was cleaned for final report preparation and inclusion in the NDA, 2) phase 3 study data was electronically captured and is being fully quality control checked, and cleaned, and will be available at the time of NDA submission, 3) for the ongoing 812P310 study, data on drug accountability has been collected through the December 31, 2018 data cut off; however this data was not electronically collected and has not been subjected to full QC (cleaning).

Supernus is proposing providing all the draft abuse narratives based on missing clinical trial material for the phase 2 and phase 3 efficacy studies in the submission.

Supernus is proposing writing draft abuse narratives based on missing clinical trial material for the 812P310, an ongoing open label safety trial, with drug accountability data that has not been fully cleaned. These draft abuse narratives will be revised, if necessary, after the drug accountability data has been fully cleaned. Supernus is also proposing sending the fully cleaned drug accountability data electronically when available. Because of the ongoing status of the study, Supernus is not planning on providing drug accountability data on the 812P310 study which might be expected in order to correlate with the draft 812P310 abuse narratives written based on missing clinical trial material.

a) Is this acceptable to exclude drug accountability data from 812P310 at the time of NDA submission?

FDA Response to Question 7(e)(a): *Please see our response to Question 7(d).*

Discussion at Meeting: *Please see discussion for Question 7(c).*

b) Does the agency agree with this scope of included patients for abuse narratives based on drug accountability issues (e.g. all studies excepting 812P310)?

FDA Response to Question 7(e)(b): *Please see our response to Question 7(d).*

Discussion at Meeting: *Please see discussion for Question 7(c).*

Question 8: [*Narratives of SAE and Narratives on AEs of Special Interest*] Supernus plans to provide patient narratives for all studies for those patients who 1) discontinued

study participation due to an adverse event and 2) adverse events associated with seizures. Does the agency agree with Supernus' plans for patient narratives regarding Serious Adverse Events and Adverse Events of Special Interest?

FDA Response to Question 8: *We agree with your plan for submitting narratives for patients who discontinued study participation due to an adverse event and for adverse events associated with seizures. Narratives should also be included for all Serious Adverse Events.*

Discussion at Meeting: *No further discussion.*

Question 9: [*Drug-Drug Interaction (DDI) Studies*] Supernus conducted two clinical DDI studies using amphetamine and methylphenidate (812P113.2 and 812P113.3). In addition, preclinical *in vitro* metabolism and transporter-mediated DDI evaluation studies have been completed based on 2007/2017 draft guidance standards (see Sequence 120 to IND 108864). (b) (4)

FDA Response to Question 9: (b) (4) *will be a subject of review after the submission.*

Discussion at Meeting: *No further discussion.*

Question 10: [*1A2 Metabolic Pathway and Concomitant Drug Use*] SPN-812 is a strong inhibitor of the 1A2 metabolic pathway, (b) (4). Supernus intends to include language in the package insert and Medication Guide concerning effects of concomitant use of theophylline (b) (4) and SPN-812. Please comment on the adequacy of proposed language in the draft annotated label at Sections (b) (4) (Appendix F). The Medication Guide contents will be generated based on the final draft of the product label.

FDA Response to Question 10: *Please clarify if SPN-812 meets the criteria for in vivo drug interaction study with an index substrate of CYP1A2 (e.g., caffeine, tizanidine, etc.) and your plans to conduct the clinical study.*

Discussion at Meeting: *The Sponsor clarified that they have conducted a clinical PK study with caffeine.*

Question 11: [*QTc*] Supernus completed studies 812P120 and 812P117 with results about SPN-812 effects on cardiac physiology. Please confirm that completion of this work should be adequate to address any issues on this topic during the NDA review.

FDA Response to Question 11: *Our QT Interdisciplinary Review Team is reviewing the study reports and will provide Post-Meeting Comments to address this question.*

Discussion at Meeting: *No further discussion.*

Question 12: [*Key Secondary Endpoints*] Supernus has identified three key secondary endpoints in the phase 3 pivotal studies: CGI, Connors and Weiss. We would like to include information in the product label concerning the first key secondary endpoint, CGI. Please comment on the draft language in the attached draft labeling regarding secondary endpoint CGI in Section 14 (Appendix F).

FDA Response to Question 12: *The inclusion of key secondary endpoints and language used to convey study results will be a matter of review.*

Discussion at Meeting: *No further discussion.*

Question 13: [*Drug Administration*] Supernus intends to indicate that SPN-812 can be administered with or without food, and intact or sprinkled on (b) (4), based on the results of study 812P105. Does the FDA agree?

FDA Response to Question 13: *This will be a review issue.*

Discussion at Meeting: *No further discussion.*

Question 14: [*Pharmacogenomic Samples*] At the agency's direction, Supernus collected genomic blood samples and/or mouth swabs s from participants in the 812P301, 812P302, 812P303 and 812P304 clinical studies. At this time, we have no plans for analysis, based on a preliminary review of top line data results. Supernus will retain these samples until the NDA review is completed. Does the agency agree that no analysis of the pharmacogenomics samples is required for initial NDA submission? Assuming they are not utilized during the NDA review, Supernus may plan for their destruction. Does the agency have any comment on that plan of action?

FDA Response to Question 14: *Future plans for retaining or destroying the pharmacogenomics samples will be a review issue. However, you should plan for the initial NDA application to submit all the relevant data contrasting any observed differences in PK, AE, etc., between the PM's vs. the EM's of CYP2D6.*

Discussion at Meeting: *The sponsor clarified that they plan to save all genomics sample up to 10 years after the NDA submission.*

Question 15: [*Clinical Site Irregularities*]
a) During the conduct of studies 812P303 and 812P304, Supernus received a notification that an ex-clinical site employee was accusing the clinical site of improper procedures and data collection (Principal Investigator, Dr. Fallon). Supernus conducted an audit of the site; our findings were that there is no evidence of purposeful malpractice at this site. Supernus intends to include the data from this site in primary analyses. Does the agency agree with Supernus' treatment of data from this site?

FDA Response to Question 15(a): *We agree with your plan to include data from Dr. Fallon's site in the primary analyses. How the data from this site will be handled once it is received will be a review issue. You should consider submitting a copy of the audit report for Dr. Fallon's site as part of the NDA.*

Discussion at Meeting: *No further discussion.*

b) During the monitoring of the conduct of Study 812P303, Supernus learned that source documents for one patient evaluated at CRC Office at BioBehavioral Research of Austin (Dr. Divyansu Patel, Principal Investigator) could not be located. The source documentation is considered to be irretrievably lost. Supernus would like to continue to include the data from this patient at this clinical site as the electronic data capture is intact. Does the agency agree that this data can continue to be incorporated as if the source documentation was available?

FDA Response to Question 15(b): *We agree with your plan to include data from the patient at Dr. Patel's site in the primary analyses. How this patient's data will be handled once it is received will be a review issue. You should consider including a report of your efforts to locate this patient's source documents as part of the NDA.*

Discussion at Meeting: *No further discussion.*

Question 16: [*Four-month Safety Update – Data Cutoff*] Is July 31, 2019 suitable as a four-month safety update data cutoff point for an NDA planned for submission for October 2019? We expect this to be a safety data cutoff for only the 812P310 (Open Label Extension) study.

FDA Response to Question 16: *Your specified cutoff date of July 31, 2019 may be acceptable for the four-month safety update; however, please provide justification for why a later date would not be feasible.*

Discussion at Meeting: *The Sponsor stated that this cutoff date was chosen for practicality. They are now cleaning data in-house and feel that this date will give them adequate time to complete this process. This is acceptable to us.*

2.2. Nonclinical/Pharmacology-Toxicology

Question 17: [*Preclinical Program Completeness*] Under IND (b) (4), Supernus supplied a number of preclinical study reports conducted by (b) (4). Then, following FDA directions, Supernus conducted additional preclinical work, such as repeat dose toxicology studies (4-week rat, 13-week rat and 13-week dog), juvenile rat toxicity studies, full carcinogenicity studies in rats and Tg.rasH2 mice, and reproductive toxicology studies [see Appendix E]. We will be cross referencing IND (b) (4) for its preclinical contributions. It is our understanding that this cross reference, plus the Supernus-conducted studies will suffice to provide preclinical support a New Drug Application for SPN-812. Please confirm this understanding.

FDA Response to Question 17: *Based on the information in the briefing package, the nonclinical program under INDs 108864 and (b) (4) appears sufficient to support NDA submission. However, the adequacy of the studies will be a matter of review. In addition, because the proposed drug product is an extended release (ER) formulation (b) (4) we remind you that additional nonclinical studies may be needed if new or higher amounts of impurities, excipients, and/or degradation products are identified in the proposed drug product (ICH Q3A(R2) and Q3B(R2), and ICH M7); or if the exposure levels of the parent drug or any major human metabolites with the ER formulation exceed previously qualified levels in nonclinical studies under INDs (b) (4) and 108864.*

In your NDA submission, you should include an assessment of phototoxicity potential of the drug as per ICH M3(R2) and ICH S10 . The adequacy of this assessment will be a matter of review.

Discussion at Meeting: *The Sponsor stated that a human mass-balance study with the ER formulation is currently ongoing and will be submitted. The Sponsor stated that the nonclinical studies were conducted with the API in water solution. The Sponsor also stated that for impurities, they have identified two new potential impurities (in addition to 17 previously identified impurities), one of which is predicted to be mutagenic by QSAR and will be controlled under TTC levels per ICH M7 guidance.*

The Division asked the Sponsor to submit all relevant data with the NDA. The Division clarified that, because previous nonclinical studies were conducted with the API only, these studies have not qualified any formulation-related excipients for the proposed ER drug product. Therefore, additional nonclinical studies may be needed if impurities, excipients, or degradation products are above qualification levels as per ICH Q3A(R2) and Q3B(R2), and ICH M7. The Sponsor agreed.

For phototoxicity, the Sponsor agreed that they will submit the assessment with the NDA.

Question 18: [*Ictogenesis in Animal Models*] Supernus submitted a white paper regarding the potential mechanism of ictogenesis in animals and why this is unlikely to occur in humans. In the human clinical studies, there was specific monitoring and attention paid to seizures. Does the agency agree that this topic requires no additional preclinical evaluation?

FDA Response to Question 18: *It is premature to determine whether additional studies are needed. Safety evaluation, especially in light of seizures noted in nonclinical studies, necessitate that the differences between animal studies and humans are clarified. Please provide the location of the white paper referenced above or submit it.*

We recommend that you submit a detailed evaluation of the findings for seizure activity in all the nonclinical studies including findings in the carcinogenicity studies (see Information Requests to applicant submitted on June 16, 2017) and its relevance for clinical settings in the context of safety evaluation (with adequate safety margins).

> ***Discussion at Meeting:*** *The Sponsor provided hard copies of the white paper at the meeting and proposed that the seizure/convulsion findings in the nonclinical studies were due to animal specific metabolite(s) with limited clinical relevance.*
>
> *The Division expressed concern that seizures occurred in multiple species across different studies (rat, dog, and mouse). The Division asked the Sponsor to submit all available information and justification for why seizure findings are considered to be animal-specific with the application. The Sponsor agreed.*

Question 19: [*Reproductive Toxicology*] Supernus has provided the additional preclinical reproductive toxicity studies requested (see Sequence 0115 to IND 108864). Supernus' opinion is that the results mimic those of the studies conducted by (b) (4) , with low exposure margins in pregnant animals. No additional work is contemplated. Does the agency agree that no additional reproductive toxicology work is required?

FDA Response to Question 19: *Based on the information in the briefing package, the reproductive studies appear sufficient to support an NDA submission. However, the adequacy of the studies will be a matter of review.*

> ***Discussion at Meeting:*** *No further discussion.*

Question 20: [*Metabolic Scheme*] The agency has asked that Supernus supply "a detailed analysis of metabolic schemes involved in the biotransformation, elimination, excretions of the drug in animals and humans" (see page 17 of EOPII meeting minutes). Also see Sequence 0055 to IND 108664, which contained additional information about metabolic schemes in rats, dogs, and humans. For convenience, this information is repeated in Appendix G. The human metabolic scheme presented differs slightly from

that presented in Sequence 0055 in that it now provides detail about the metabolizing enzyme responsible for the hydroxylation of the parent compound, and also the glucuronidation of 5-hydroxyl viloxazine metabolite. Please see the metabolic schemes and confirm that these will satisfy the agency's request for detailed analysis of metabolic schemes in animals and humans?

FDA Response to Question 20: *Based on the information in the briefing package, the analysis of the metabolic profile of the drug in animals and humans appears acceptable. However, the adequacy of individual studies will be a matter of review.*

Discussion at Meeting: *No further discussion.*

2.3. Regulatory Affairs

Question 21: [*Advisory Committee*] At the time of the EOPII meeting, the agency was unable to comment on the probability of an Advisory Committee (AC) meeting for this program once the NDA is under review. Are there any more recent impressions about whether or not an AC meeting will be required for review of this program?

FDA Response to Question 21: *A decision on convening an Advisory Committee will be made following our preliminary review of your submitted NDA.*

Discussion at Meeting: *No further discussion.*

Question 22: [*Draft Labeling*] Please note the draft annotated PI provided for this briefing package. Does the agency agree that the AE table can group adolescent and children together, or would separate presentations of AE data be preferred? Please note other questions directing the agency to specific topics in this label. If any additional preliminary comments can be made about this draft package insert, please provide.

FDA Response to Question 22: *We will provide comments on the draft label as part of our review of the NDA submission. The choice between presenting a single combined AE table or separate AE tables for children and adolescents may depend on whether there are any differences in AE frequencies between the two age groups. Please see the FDA Guidance for Industry: Adverse Reactions Section of Labeling, located at https://www.fda.gov/media/72139/download.*

Discussion at Meeting: *The Sponsor noted that they have not observed significant differences between age groups in frequencies of AEs. At this time, they are expecting to prepare AE tables for all age groups combined. The Agency noted that our internal analysis of AEs will use queries that combine related AE terms and that such an approach may be useful for the Sponsor's own analyses. Please see Table 7 in the Post-Meeting Clinical Comments below for examples of the types of queries used by the Division for the analysis of AEs.*

Question 23: [*Risk Management*] Does the agency agree that a Risk Management Strategy consisting of patient education via a Medication Guide is suitable for the SPN-812 program?

FDA Response to Question 23: *At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether your proposed risk management strategy consisting of patient education via a Medication Guide will be adequate to ensure that the benefits of the drug outweigh the risks. We will determine the adequacy of your proposal during the review of your application.*

Discussion at Meeting: *No further discussion.*

2.4. Statistics

Question 24: [*Statistical Plans for Individual Studies*]: Statistical analysis plans (SAP) have been provided for all 4 pivotal clinical studies (SAP for 812P301, SAP for 812P302, SAP for 812P303, and SAP for 812P304). Are there any additional comments concerning the individual study SAPs and their use in analyzing our key pivotal trials?

FDA Response to Question 24: *Your overall statistical analysis plans are reasonable. We recommend that your final CSR include the results of a post hoc analysis including pooled site as a factor in your MMRM analysis of ADHD-RS-5.*
Any inclusion of key secondary endpoints in labeling will be a matter of review. As a reminder, key secondary endpoints should:

- *Not replicate information contained in the primary endpoint*
- *Be replicated in at least two studies*
- *Be agreed upon with the Agency*

We are concerned about the use of CGI-I as key secondary endpoint given its susceptibility to recall bias; change from baseline in CGI-S is preferred.

Discussion at Meeting: *During the meeting, the Sponsor stated that they only collected CGI-I during their four studies (P301 through P304). They also stated that they had reached agreement with FDA that CGI-I is acceptable as a key secondary endpoint and will provide documents with this agreement. FDA acknowledged that the Sponsor will submit a justification with these documents for the use of CGI-I as a key secondary endpoint. FDA reminded the Sponsor that inclusion of key secondary endpoints in labeling will be a matter of review.*

The Sponsor confirmed that they will include a post-hoc analysis including study site in the ISE.

Question 25: [*ISE Content*] Supernus intends to include the studies described in Table 2 in the Integrated Summary of Efficacy (ISE). Four studies will be included for ISE: Studies P301-P304. Does the agency agree that these studies are all suitable for inclusion in this analysis?

Table 2: Studies to be Included in the Integrated Summary of Efficacy

Study number	Study title
812P301	Evaluation of SPN-812 ER 100 and 200 mg Efficacy and Safety in Children with ADHD - A Double-Blind, Placebo-Controlled, Pivotal Trial ("low dose children")
812P302	Evaluation of SPN-812 ER 200 and 400 mg Efficacy and Safety in Adolescents with ADHD - A Double-Blind, Placebo-Controlled, Pivotal Trial ("low dose adolescents")
812P303	Evaluation of SPN-812 ER 200 and 400 mg Efficacy and Safety in Children with ADHD - A Double-Blind, Placebo-Controlled, Pivotal Trial ("high dose children")
812P304	Evaluation of SPN-812 ER 400 and 600 mg Efficacy and Safety in Adolescents with ADHD - A Double-Blind, Placebo-Controlled, Pivotal Trial ("high dose adolescents")

FDA Response to Question 25: *Yes, your list of studies appears reasonable. As a reminder, we consider the ISE to be an exploratory analysis. Our main interest are the individual study results because of heterogeneity in study designs. Interpretation of the integrated analysis may be challenging, especially if a simple pooling of data is applied.*

> ***Discussion at Meeting:*** *The Sponsor explained that they believe their plan to pool different titration schedules will lead to a conservative treatment effect estimate for SPN-812 because patients with a slower titration will dilute the efficacy estimate. FDA did not object to this plan because FDA considers the ISE an exploratory analysis. FDA recommended that the Sponsor include a summary table with all the individual study results.*

Question 26: [*ISS Content*] Supernus intends to include the studies described in Table 3 in the Integrated Summary of Safety. Does the agency agree that these studies are all suitable for inclusion in this analysis? Based on the Table of All Studies, does the agency agree that integration of safety data for these studies listed in Table 2 will meet FDA expectations for the ISS analysis?

Table 3: Studies to be Included in the Integrated Summary of Safety

Study number	Study title
Phase 3 trials	
812P301	Evaluation of SPN-812 ER 100 and 200 mg Efficacy and Safety in Children with ADHD - A Double-Blind, Placebo-Controlled, Pivotal Trial (“low dose children”)
812P302	Evaluation of SPN-812 ER 200 and 400 mg Efficacy and Safety in Adolescents with ADHD - A Double-Blind, Placebo-Controlled, Pivotal Trial (“low dose adolescents”)
812P303	Evaluation of SPN-812 ER 200 and 400 mg Efficacy and Safety in Children with ADHD - A Double-Blind, Placebo-Controlled, Pivotal Trial (“high dose children”)
812P304	Evaluation of SPN-812 ER 400 and 600 mg Efficacy and Safety in Adolescents with ADHD - A Double-Blind, Placebo-Controlled, Pivotal Trial (“high dose adolescents”)
812P310 (data cut 12-31-2018)	Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of SPN-812 ER for the Treatment of Pediatric Patients with Attention Deficit/Hyperactivity Disorder (ADHD)
Phase 2 Trials	
812P202	Evaluation of SPN-812 ER Efficacy and Safety in Children with ADHD - A Double-Blind, Placebo-Controlled, Dose-Ranging Study
Phase 1 Trials	
812P102	A Single-Center, Randomized, Open-Label, 3-Treatment Crossover Study Evaluating the Single- and Multiple-Dose Pharmacokinetics of Extended-Release and Immediate-Release Formulations of Viloxazine in Healthy Adults Under Fasting Conditions
812P103	A Single-Center, Randomized, Open-Label, 2-Treatment Crossover Study Evaluating the Single- and Multiple-Dose Pharmacokinetics of Extended Release and Immediate Release Formulations of Viloxazine in Healthy Adult Volunteers Under Fasting Conditions
812P105	Single Dose Study to Evaluate the Effect of Food and Sprinkling on the Bioavailability of SPN-812 Extended-Release in Healthy Adult Subjects
812P111	An Open-Label, Single-Dose, Mass Balance Study to Assess the Absorption, Metabolism, and Excretion (AME) of [^{14}C]-Labeled SPN-812V (Viloxazine) in Healthy Adult Male Volunteers
812P112.1	A Single Dose Study to Assess the Effect of Renal Impairment on the Pharmacokinetics of SPN-812 ER
812P113.1	The Effect of SPN-812 Extended Release on Select Cytochrome P450 Activity and the Evaluation of CYP2D6 Phenotypes on the Pharmacokinetics of SPN-812 Extended Release
812P113.2	Evaluation of the Drug-Drug Interaction Between SPN-812 Extended Release and Vyvanse® in Healthy Adults

Study number	Study title
812P113.3	Evaluation of the Drug-Drug Interaction Between SPN-812 Extended Release and Concerta® in Healthy Adults
812P115	Effect of Alcohol on the Bioavailability of SPN-812 Extended Release Capsules in Healthy Adult Males

FDA Response to Question 26: *Your list of studies appears to be reasonable for including in the ISS analysis. If you have excluded any studies from this list, please justify their exclusion.*

Discussion at Meeting: *The Sponsor noted that the QTc study was inadvertently omitted from Table 3. It will be included in the ISS. The Sponsor stated that Study 812P101, a single-dose pilot study examining different formulations, was so preliminary that they do not plan to include it in the ISS. The Agency agrees with this plan.*

Question 27: [*ISE Stat Plan, Tables and Figures*]: The Table of Contents, a list of tables and figures proposed for the Statistical Analysis Plan for the ISE, are presented as part of the draft Statistical Analysis Plan for the ISE (Appendix C). Is the SAP for the ISE acceptable? Also, please see Question 5 about adequacy of the list of tables.

FDA Response to Question 27: *Your plan is acceptable. See response to question 25.*

Discussion at Meeting: *No further discussion.*

Question 28: [*ISS Stat Plan, Tables and Figures*]: The Table of Contents, a list of tables and figures proposed for the Statistical Analysis Plan for the ISS, are presented as part of the draft Statistical Analysis Plan for the ISS (Appendix C). Is the SAP for the ISS acceptable? Also, please see Question 5 about adequacy of the list of tables.

FDA Response to Question 28: *We note in Section 8.6.1.8 of the draft SAP for the ISS that the only Adverse Events of Special Interest are seizures and adverse events that might represent a seizure. Because norepinephrine reuptake inhibitors may have some pharmacologic properties similar to stimulants, we recommend that you also include sleep disturbances and appetite disturbances as Adverse Events of Special Interest. In the final SAP for the ISS, please include the list of search terms that will be used to query the preferred terms and verbatim terms in the AE database for these adverse events. In addition, the ISS should include descriptive summary statistics of height and weight changes compared to population norms to assess for any evidence of growth delays in Study 812P310. In the SAP for your ISS, you should pre-specify an estimator for all adverse event rates stratified by study.*

Discussion at Meeting: *Please see discussion of Question 22. During the meeting, FDA clarified that the ISS AE rates should be estimated using a stratified estimator to prevent Simpson's paradox. See discussion on page 13 of FDA's meta-analysis guidance, https://www.fda.gov/media/117976/download.*

Question 29: [*ISE Analysis Pools*]: Supernus intends to group the analysis by age (children 6-11; adolescents 12-17) and by dose strength (200mg dose across three studies, 400 mg dose across three studies) for a total of 4 analysis pools.

Table 4: Studies for inclusion in integrated dataset for ISE by age

Study number	Dose	Age	Endpoint
812P301	Placebo, 100 mg and 200 mg	6-11	Day 42
812P302	Placebo, 200 mg and 400 mg	12-17	Day 42
812P303	Placebo, 200 mg and 400 mg	6-11	Day 56
812P304	Placebo, 400 mg and 600 mg	12-17	Day 49

Table 5: Studies for inclusion in integrated dataset for ISE by dose strength

Analysis pool	Studies included	Comparison	Age	Endpoint
1	812P301, 812P303	200 mg vs. Placebo	6-11	Day 42
2	812P302**,** 812P304	400 mg vs. Placebo	12-17	Day 42
3	812P301, 812P302 and 812P303	200 mg vs. Placebo	6-11, 12-17	Day 42
4	812P302, 812P303 and 812P304	400 mg vs. Placebo	6-11,12-17	Day 42

If not commented on under ISE/ISS comments about SAPs in previous questions, please specifically comment on Supernus' choices for pooled analysis. Does the agency agree?

FDA Response to Question 29: *For the ISE, you may propose any pooled analysis that you believe is useful. However, the interpretation of these results may be challenging. See response to question 25 for more information. In addition to ISE analyses grouped by age (6 to 11 and 12 to 17 years) and dose strength, you may wish to consider conducting exploratory efficacy analyses according to bodyweight, divided into two or three bands.*

Discussion at Meeting: *The Sponsor noted that they are working on multiple approaches to exploration of efficacy data for the ISE analyses and will include the results of all analyses in the NDA submission.*

Question 30: [*Analysis of primary endpoint*]

a) End of study Visit: For the primary end of study visit, Supernus plans to use Day 42 since it the last common endpoint visit day for all studies, due to differing titration schedules. Does the FDA agree?

b) Analysis data pools: Analysis pool 1 consists of the two pivotal studies in children (812P301 and 812P303). Placebo and 200 mg dose are the 2 doses that are collected in both studies, so the comparison of interest in this pool is between placebo and the 200 mg dose. The other 2 randomized doses, 100 mg and 400 mg were each used in one of the studies only which do not provide the advantage of having the larger representation from the pooled data in treatment comparisons. Both of these doses will be used in the analyses and will be summarized descriptively since they were the original randomized groups in the individual studies, but they will not be presented in the tables for treatment comparisons.

   Analysis pool 2 consists of the two pivotal studies in adolescents (812P302 and 812P304) and the comparison of interest is between placebo and the 400 mg dose. Similar to analysis pool 1, both 200 and 600 doses will be used in the analyses and will be summarized descriptively, but they will not be presented in the tables for treatment comparisons.

   Analysis pool 3 consists of the three pivotal 812P301 (children), 812P302 (adolescents) and 812P303 (children), which combines data from children with adolescent population. The comparison of interest in this pool is similar to analysis pool 1 but the MMRM analysis model excludes age group, which was included in the individual study MMRM model, since the age group is not distributed across the studies. The benefit of this pooling is that it provides larger sample size for the 200 mg and Placebo group compared to analysis pool 1, since the 200mg dose strength is common in these three clinical trials.

   Analysis pool 4 consists of the three pivotal 812P302 (adolescents), 812P303 (children), and 812P304 (adolescents), which combines data from children with adolescent population. The comparison of interest in this pool is similar to analysis pool 2 but the MMRM analysis model excludes age group, which was included in the individual study MMRM model, since the age group is not distributed across the studies. The benefit of this pooling is that it provides larger sample size for the 400 mg and Placebo group compared to analysis pool 2, since the 400mg dose is common in these three clinical trials.

   Does the FDA agree with the planned analysis pools?

c) Analysis model: Supernus analyzed the primary endpoint using Mixed Model for Repeated Measures (MMRM) in the individual Phase III studies. The model for analysis pool 1 and 2 will include fixed effect terms for baseline ADHD-RS-5 Total Score, age group, treatment, visit, and treatment-by-visit interaction as independent variables as per FDA agreement. For the integrated analysis, Supernus proposes to include Study and Study-by-Treatment interaction. For Analysis pools 3 and 4, the age group will be dropped from the model since age group not distributed across 3 studies. More the age group covariate was not statically significant in any of the individual studies. Does FDA agree with the analysis model?

FDA Response to Questions 30(a) to 30(c): *We consider the ISE to be an exploratory analysis because of challenges interpreting the pooled results.*

a) We are concerned that differing titration schedules will cause challenges in interpreting any results from any pooled analyses.

b) See our answer to Question 30(a).

c) We do not object.

For the individual studies, please use the pre-specified timepoints for the primary analysis.

Discussion at Meeting: *See discussion under Question 26.*

Question 31: *[ISS Pooling*]

Please see Table 5 below regarding planned ISS pooling. Is this ISS pooling acceptable for NDA review?

Table 6: Studies for inclusion and pooling plans for Integrated Safety Summary

Pool	Studies	Age (years)	Doses of SPN-812 in the Study (mg)	Duration of Treatment
1: **Pediatric Subjects with ADHD: 5 Studies**	812P202 812P301 812P303 812P302 812P304	6-12 6-11 6-11 12-17 12-17	100, 200,300,400 100,200 200,400 200,400 400,600	8 weeks 6 weeks 8 weeks 6 weeks 7 weeks
2: Healthy Subjects: 5 Studies (Note: 812P112.1	812P103 812P105 812P112.1 (Renal) 812P117	> 18 > 18 > 18 > 18 > 18	200 200 200, 400 1800	21 days 11 days 1 day 12 days 7 days

contains renally impaired subjects, but only healthy subjects will be included in ISS)	812P120		300, 600, 900,1200,1500,1800,2100	

FDA Response to Question 31: *In addition to your two proposed ISS pools, we recommend that you present analyses according to age group (i.e., age 6 to 11 and 12 to 17). You may also wish to consider conducting exploratory safety analyses according to bodyweight (divided into two or three bands).*

> ***Discussion at Meeting:*** *The Sponsor stated that they will conduct analyses according to body weight bands for the ISS, using the median body weight to define the groups.*

Additional Biometrics Comments

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

- *All raw and derived variables in .xpt format.*
- *The SAS programs that produced all efficacy results.*
- *The SAS programs by which the derived variables were produced from the raw variables.*
- *A listing of all interactions with the Agency pertaining to clinical efficacy and safety for this IND/NDA including serial numbers and submission dates of the protocols, SAPs, amendments, and any relevant meetings.*

Post-Meeting Clinical Comments

We discussed the decision by the previous manufacturer to withdraw viloxazine from the market in several European countries, where it had been marketed for the treatment of depression. The Sponsor previously contracted a research consultant to clarify the reason for the withdrawal. The conclusion of the consultation was that the withdrawal was for commercial reasons. There was no evidence that the withdrawal was related either to a safety issue or to lack of efficacy as an antidepressant. Documentation of the consultation was previously submitted to (b) (4) *IND 108864.*

The following table is presented in reference to our responses to Question 22 and Question 28.

Table 7: Examples of Queries Used by the Division of Psychiatry Products for the Analysis of Adverse Events

Query Title	Individual MedDRA Terms Comprising Query
Anorexia, Decreased Appetite	Anorexia; Decreased appetite
Insomnia, Sleep Disturbance	Abnormal dreams; Abnormal sleep-related event; Advanced sleep phase; Breathing-related sleep disorder; Circadian rhythm sleep disorder; Delayed sleep phase; Dyssomnia; Hypersomnia; Hyposomnia; Initial insomnia; Insomnia; Irregular sleep phase; Middle insomnia; Nightmare; Parasomnia; Poor quality sleep; Rapid eye movements sleep abnormal; Sleep disorder; Sleep talking; Sleep terror; Somnambulism; Terminal insomnia
Seizure	Clonic convulsion; Complex partial seizures; Convulsion; Convulsions local; Drug withdrawal convulsions; Epilepsy; Febrile convulsion; Generalised tonic-clonic seizure; Grand mal convulsion; Hyperglycaemic seizure; Hypoglycaemic seizure; Partial seizures; Partial seizures with secondary generalisation; Petit mal epilepsy; Post-traumatic epilepsy; Seizure; Seizure anoxic; Simple partial seizures; Status epilepticus; Temporal lobe epilepsy; Tonic convulsion

3.0 OTHER

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion was held on the need for a REMS, other risk management actions. It was concluded that the need for REMS or other risk management strategies would be determined during the review of your application.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

In addition, we note that a chemistry pre-submission meeting is scheduled for September 16, 2019. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

PRESCRIBING INFORMATION

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

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

Information[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, which include:

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

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

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

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

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

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

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

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

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA,**

ANDA, BLA, Master File (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[5]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[6]

STUDY DATA REQUIREMENTS

The applicant should refer to and adhere to the specific guidance provided in the following resource for collecting and submitting study data and programs:

Study Data Standards Resources:
https://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

Study Data Technical Conformance Guide:
https://www.fda.gov/media/122913/download

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*.[7]

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

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

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

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*.[8]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor's handouts.

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

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

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

/s/

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08/23/2019 07:25:42 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 108864

MEETING MINUTES

Supernus Pharmaceuticals, Inc.
Attention: Tami Martin, RN, Esq.
Vice President, Regulatory Affairs
1550 East Gude Drive
Rockville, MD 20850

Dear Ms. Martin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SPN-812V ER (Viloxazine Hydrochloride Extended-Release Capsules).

We also refer to the meeting between representatives of your firm and the FDA on June 29, 2017, and your post-meeting correspondence dated July 13, 2017. The purpose of the meeting was to discuss the Phase 3 development plans for the use of SPN-812V ER in treating ADHD in children.

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

If you have any questions, contact CAPT Kofi Ansah, Pharm.D., Senior Regulatory Project Manager, at (301)796-4158 or email: Kofi.Ansah@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. 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 (EOP2) Meeting

Meeting Date and Time: June 29, 2017; 1:00 pm EDT
Meeting Location: FDA White Oak Campus, Bldg. 22, Room #1311
10903 New Hampshire Ave, Silver Spring MD 20993

Application Number: IND 108864
Product Name: SPN-812V (viloxazine Hydrochloride Extended-Release Capsules)
Indication: Attention Deficit Hyperactivity Disorder (ADHD)
Sponsor/Applicant Name: Supernus Pharmaceuticals, Inc.

FDA ATTENDEES:

Robert Temple, MD	Deputy Director, Office of Drug Evaluation-I
Mitchell Mathis, MD	Director, Division of Psychiatry Products (DPP)
Tiffany Farchione, MD	Deputy Director, DPP
Naomi Lowy, MD	Associate Director for Regulatory Science, ODE-I
Kofi Ansah, PharmD, RAC	Senior Regulatory Project Manager, DPP
Jean Kim, MD	Clinical Team Leader, DPP
Michael Davis, MD	Medical Officer/Clinical Reviewer, DPP
Antonia Dow, PhD	Pharmacology/Toxicology Reviewer, DPP
Jerry Cott, PhD	Pharmacology/Toxicology Reviewer, DPP
Hao Zhu, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Praveen Balimane, PhD	Clinical Pharmacology Reviewer, OCP
Peiling Yang, PhD	Biometrics Team Leader, Office of Biostatistics (OB), Division of Biometrics I (DBI)
Yang Wang, PhD	Biometrics Reviewer, OB/DBI
Edward Hawkins, PhD	Reviewer, Controlled Substance Staff
Andrei Pontas, PhD	CMC/Quality Reviewer, Office of Pharmaceutical Quality
Yeruk Mulugeta, MD	Medical Officer, Division of Pediatric & Maternal Health
Daniel Reed, MPH	Regulatory Project Manager, Division of Pediatric & Maternal Health
Lars Johannesen, PhD	Reviewer, QT-Interdisciplinary Review Team

Supernus Pharmaceuticals, Inc.'s Attendees

Stefan Schwabe, MD, PhD	Executive Vice President, Clinical Development & Chief Medical Officer

Tami Martin, RN, Esq.	Senior Vice President, Regulatory Affairs
Tracy Acker, PharmD	Senior Director, Regulatory Affairs
Monica Little, MS	Assistant Director, Regulatory Affairs
Maria Pittaras, BS, BA	Senior Director, Portfolio Management
Gopala Krishna, PhD, DABT, FATS, MBA	Vice President, Preclinical Evaluation
Gopakumar Gopalakrishnan, DVM, MS	Associate Director, Preclinical Evaluation
Chungping Yu, PhD	Preclinical Drug Metabolism
Erika Roers, BS	Assistant Director, Clinical Pharmacology
Tesfaye Liranso, PhD	Director, Biostatistics
Gabriela Tulloch	Clinical Program Manager
Nicholas Fry, BS	Associate Clinical Program Manager
Janet Johnson, PhD	Senior Director, Clinical Research
Michael L. Vieira, PhD	Director, Drug Delivery Services
(b) (4) (b) (4)	Consultant to Supernus Pharmaceuticals, Inc. Child and Adolescent Psychiatrist & Consultant to Supernus Pharmaceuticals, Inc.

1.0 BACKGROUND

Supernus Pharmaceuticals is developing an extended-release capsule formulation of viloxazine (SPN-812 ER) as a monotherapy treatment for Attention-Deficit/Hyperactivity Disorder (ADHD) in pediatric patients, age (b) (4)-17 years. Viloxazine is a norepinephrine reuptake inhibitor that was initially marketed in several non-US countries as an antidepressant in the late 1970's and subsequently withdrawn in 2002 for commercial reasons. In addition to this current application (IND 108864), (b) (4) The Sponsor expects the target total daily dose for SPN-812 ER to be 100 to 400 mg/day for children ages (b) (4)-11 years and (b) (4) mg/day for children ages 12-17 years, administered once daily.

A pre-IND meeting was held on June 13, 2013. Advice regarding the IND application, including the pursued pediatric ADHD indication and design aspects of planned clinical studies, were communicated to the Sponsor. On June 22, 2015, the Sponsor submitted the IND application, which included the protocol for the Phase 1 Study 812P103 (A Single-Center, Randomized, Open-Label, 2-Treatment Crossover Study Evaluating the Single- and Multiple-Dose Pharmacokinetics of Extended Release and Immediate Release Formulations of Viloxazine in Healthy Adult Volunteers). The IND study was permitted to proceed on July 27, 2015. The development program for IND 108864 has thus far comprised of the following studies:

<u>Completed Studies</u>

- 812P101: single-dose PK/tolerability study in 22 healthy adults (submitted to (b) (4))
- 812P102: single- and multiple-dose PK/tolerability study in 27 healthy adults

- 812P103: single- and multiple-dose PK/tolerability study comparing viloxazine formulations in 28 healthy adults
- 812P105: single-dose study evaluating the effect of food and sprinkling on viloxazine bioavailability in 27 healthy adults
- 812P111: single-dose mass balance study in 7 healthy male adults
- 812P120: single- and multiple-ascending dose study to evaluate safety and effect on QTc intervals in 56 healthy adults
- 812P202: Phase 2, 8-week, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study in 222 pediatric patients with ADHD, age 6-12 years. Doses included 100, 200, 300, and 400 mg/day. This study incorporated an optional PK sub-study with 79 subjects.

Ongoing Studies

- 812P310: open-label, uncontrolled, flexible-dose extension study to collect long-term safety and efficacy data in pediatric patients with ADHD, age 6-12 years. Doses include 100, 200, 300, and 400 mg/day for up to 36 months. Of note, on May 20, 2016, the Division requested interim safety reports from the Sponsor every 6 months, given the limited available data supporting the long-term use of SPN-812 ER in pediatric patients.

The Sponsor is currently planning to conduct the following Phase 3 pivotal trials and Phase 1 studies:

Planned Studies

Phase 3

- 812P301: Randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and safety of SPN-812 ER in 432 pediatric patients with ADHD, age (b)(4)-11 years. Subjects will be randomized to receive SPN-812 ER 100 mg/day, 200 mg/day, or placebo, with a 1-week titration and 5-week maintenance treatment period. The primary efficacy endpoint is the change from baseline to end of study in the clinician-administered ADHD-RS-V total score. Secondary endpoints include the change from baseline in the CGI-ADHD-S scale and functional impairment measurements (to be determined).

- 812P302: Randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and safety of SPN-812 ER in 300 pediatric patients with ADHD, age 12-17 years. Subjects will be randomized to receive SPN-812 ER 200 mg/day, 400 mg/day, or placebo, with a 1-week titration and 5-week maintenance treatment period. The primary efficacy endpoint is the change from baseline to end of study in the clinician-administered ADHD-RS-V total score. Secondary endpoints include the change from baseline in the CGI-ADHD-S scale and functional impairment measures (to be determined).

- 812P303: Randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and safety of SPN-812 ER in 300 pediatric patients with ADHD, age (b)(4)-11 years. Subjects will be randomized to receive SPN-812 ER 200 mg/day, 400 mg/day, or placebo, with a 1-3 week titration and 5-week maintenance treatment period. The primary efficacy endpoint is the change from baseline to end of study in the clinician-administered ADHD-RS-V total score. Secondary endpoints include the change from baseline in the CGI-ADHD-S scale and functional impairment measures (to be determined).

- 812P304: Randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and safety of SPN-812 ER in 234 pediatric patients with ADHD, age 12-17 years. Subjects will be randomized to receive SPN-812 ER 400 mg/day, 800 mg/day, or placebo, with a 1-3 week titration and 5-week maintenance treatment period. The primary efficacy endpoint is the change from baseline to end of study in the clinician-administered ADHD-RS-V total score. Secondary endpoints include the change from baseline in the CGI-ADHD-S scale and functional impairment measures (to be determined).

Phase 1

- 812P112.1: evaluation of SPN-812 in healthy adults with CYP2D6 poor metabolizer vs. extensive metabolizer phenotype.
- 812P113.1 (under consideration): drug-drug interaction study evaluating the effect of SPN-812 on CYP1A2, CYP3A4, and CYP2D6 activity.
- 812P113.2 (under consideration): drug-drug interaction study evaluating the interaction between SPN-812 ER and Vyvanse in healthy adults.
- 812P113.3 (under consideration): drug-drug interaction study evaluating the interaction between SPN-812 ER and Concerta in healthy adults.
- 812P115: evaluation of the effect of alcohol on the bioavailability of SPN-812 ER in healthy adult males.

Supernus has requested this End-of-Phase 2 meeting to discuss plans for the pivotal Phase 3 studies and whether the completed and planned nonclinical and clinical development programs will be sufficient to support a New Drug Application review. The Sponsor also requests preliminary comment on a Target Product Profile.

2.0 DISCUSSION

Following are Supernus Pharmaceuticals specific questions and FDA/DPP's responses and the discussion at the meeting.

2.1. Clinical

Question 1: Does the agency accept the stated indication for this product (see enclosed Target Product Profile)?

FDA Response to Question 1: *On face, the stated indication ("as treatment for patients with attention deficit/hyperactivity disorder (ADHD)") is appropriate, but this will be a matter of review under the NDA. In addition, the indication in the product label should specify the age range (for example, "in pediatric patients, ages (b)(4) to 17 years").*

Discussion at Meeting: *The Sponsor indicated that, according to their proposed Phase 3 protocol revisions, they would pursue the indication for pediatric patients ages 6 to 17 rather than ages (b)(4) to 17 years (see discussion for Question 2a).*

Question 2: Phase III program population and exposures questions (See Section 5 of Briefing Package)

a) (b) (4) We propose to include children down to age (b)(4) in two of our Phase III studies. Does the agency agree with inclusion of children down to age (b)(4) in two key pivotal clinical studies?

FDA Response to Question 2(a): *We agree with the general approach of including children as young as age (b)(4) years in the Phase 3 clinical studies. Please refer to our responses to Questions 2(a)(i), 2(a)(ii), and 3(c) for comments about endpoints and dosages relating to this age range.*

Discussion at Meeting: *Prior to the meeting, the Sponsor submitted proposed revisions to the Phase 3 study protocols. These revisions (b) (4) the lowest age in Studies 812P301 and 812P303 from (b) (4) years of age.* (b) (4) *. The Division had no objections to this plan at the meeting, but it will need to be reviewed following submission of a Pediatric Study Plan.*

i. Does the agency agree with the use of the ADHD RS-V as the measure of the primary endpoint in subjects down to age (b)(4) years?

FDA Response to Question 2(a)(i): *In principle, use of the ADHD RS-V as the primary efficacy measure in subjects as young as age (b)(4) years appears reasonable. We note that this scale is designed for use in children as young as 5 years;* (b) (4)

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

ii. The Phase III study designs include the use of the C-SSRS to monitor potential suicidality. The authors of the C-SSRS suggest the use of the Children's version for ages 7-11. Based on this information and the difficulty in assessing possible suicidal intent in children ages (b) (4) years does the agency agree with the use of the C-SSRS only in ages 7 and above?

FDA Response to Question 2(a)(ii): *We agree with your proposal of using the C-SSRS only in ages 7 and above, as suggested by the scale's authors. However, you should propose an alternative method for assessing suicidal ideation (or a clinically appropriate proxy) in this age group. One reference you may consider reviewing regarding this topic is Whalen et al. J Am Acad Child Adolesc Psychiatry 54(11):926-937 (2015). You may consider other assessments of changes in mood or behavior, such as the Aberrant Behavior Checklist (ABC) irritability subscale, for this age group.*

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

b) Supernus believes that the Phase II, 812P202 study in children ages 6-12 provides significant details about use of SPN-812 at various doses. Because viloxazine was also studied for ADHD in adults with the immediate release formulation (812P201), Supernus believes that this supports the inclusion of adolescents in our Phase III program. Does the agency agree that four clinical trials, two in ages (b) (4) 11 and two in ages 12-17 will be sufficient to support a marketing application for ages (b) (4) -17? (See clinical study synopses submitted to IND 108864).

FDA Response to Question 2(b): *On face, we agree that two Phase 3 trials in ages (b) (4) to 11 and two in ages 12 to 17 will be sufficient to support a marketing application for ages (b) (4) to 17. Please refer to our response to Question 3(c) regarding dosages in the Phase 3 trials.*

Discussion at Meeting: *Please refer to the discussion for Question 2(a) regarding changes in age ranges in the proposed Phase 3 studies.*

c) Supernus intends to administer SPN-812 to a total of 844 subjects with ADHD in four Phase III clinical trials. An additional 193 children with ADHD were treated in 812P202. Supernus believes that these exposures, in addition to the 97 healthy adults treated with extended-release SPN-812, and 26 adults with ADHD treated in Study 812P201 with the immediate-release formulation of viloxazine should suffice for the marketing application for a pediatric indication. This will total 1160 exposures.

In addition to 1160 individual exposures described above, please note that open-label extension study (812P310), currently in progress with participants from Phase II evaluations, will be offered to all patients who complete the Phase III studies. Therefore, longer term data on patient exposure will be available and presented at the time of NDA submission.

Assuming completion of the plan as described, will 1160 total exposures combined with long term open label safety data be adequate for the marketing application for SPN-812?

FDA Response to Question 2(c): *On face, the anticipated safety database will be adequate for marketing application submission provided that a sufficient number of subjects participate in the open-label extension study. The ICH E1 guideline (The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-Life Threatening Conditions) recommends a total exposure of 1000-1500 patients, with at least 300 patients exposed for 6 months and at least 100 patients exposed for 12 months at the relevant doses.*

Safety monitoring in your protocol should include ophthalmologic exams as well as evaluation for urinary retention.

> ***Discussion at Meeting:*** *The Sponsor queried why the Division asked for ophthalmologic and urinary retention evaluations. Dr. Mulugeta indicated that this was derived from warnings in the French label for viloxazine (marketed as Vivalan). The Sponsor indicated that the warning in the French label was not based on human safety findings but on theoretical or medication class-related concerns. The Sponsor does not intend to specifically monitor participants with ophthalmologic examinations or evaluations for urinary retention. The Division requested that the Sponsor submit a copy of the Vivalan package insert.*

FDA Post-Meeting Comments: *The Sponsor referenced a translated version of the French Vivalan label (Sequence 0000, Module 1, Foreign Marketing History EU Status, Attachment 1). This label describes the following Precautions:*

> *Viloxazine will have to be used with prudence in patients suffering from or at risk for angle-closure glaucoma or in patients suffering from urinary retention connected with uretroprostatic problems. Even though the clinical trials have not given evidence in subjects with glaucoma or prostate problems of aggravation or deterioration of their diseases, the risk of angle-closure glaucoma or urinary retention connected with uretroprostatic disturbances should not be ruled out because of the anticholinergic properties of viloxazine.*

This is consistent with the Sponsor's points at the meeting. The Division is in agreement with the Sponsor's position.

Question 3: Phase III pivotal study design questions

a) Does the agency agree with the primary endpoint, ADHD-RS-V total score, as described in the four Phase III clinical synopses?

FDA Response to Question 3(a): *In principle, we agree with the primary endpoint (change from baseline to end of treatment in the clinician-administered ADHD-RS-V total score). However, we note that there are multiple versions of this scale that are validated for different age ranges. We recommend that, within a given study, you use a single version of the ADHD-RS-V and include subjects who are within the age range for the scale version.*

> ***Discussion at Meeting:*** *The Sponsor indicated that they would use a single version of the ADHD-RS-V within a single study. There was no further discussion.*

b) Does the FDA agree with inclusion/exclusion criteria and study design?

FDA Response to Question 3(b): *On face, the study eligibility criteria appear appropriate; however we have some suggestions you may wish to consider. We note that you specify a minimum ADHD-RS-V total score for entry of 26. You may wish to consider specifying different scores for boys and girls (according to the scale's scoring profiles) to target equivalent baseline ADHD severity. Otherwise, the disorder severities may not be equivalent, on average, between*

sexes. It would also be preferable to enroll subjects with a lifetime history of Major Depressive Disorder, as long as they are not in a current episode.

Discussion at Meeting: *The Sponsor considered this suggestion and determined they did not want to have different entry criteria based on gender given that they were assessing the change in symptoms captured by the scale rather than a change in gender-normalized ADHD severity. The Division indicated that this was a suggestion to consider, rather than a requirement, and that the Sponsor's plan was acceptable.*

c) Please confirm that the dose ranges for ages (b) (4)-11 and for ages 12-17 are acceptable for investigation in Phase III.

FDA Response to Question 3(c): *We recommend that you propose fixed dosages based on bodyweight rather than age. The rationale is that the pharmacokinetics (PK) appear to be weight-dependent, bodyweight can vary significantly for a given age, and there are significant exposure-based safety concerns in preclinical studies with little to no safety margin in proposed human dosages. You should propose 2 to 3 bodyweight bands with 2 to 3 doses for each band, so the product label can specify a dose range based on bodyweight.*

Regarding your proposed dosages, we have particular safety concerns about the proposed higher dosages in youngest patients (i.e., 300 mg to 400 mg in (b) (4) *year-olds) as well as the highest dosage in adolescents (i.e.,* (b) (4) *mg). Please provide additional justification as to why you believe that exposures at these dosages are appropriate in terms of safety, particularly given the lack of safety margin from preclinical studies. In the adult ADHD study with the immediate-release formulation of viloxazine (Study 812P201), subjects received a maximum of 300 mg/day for six weeks.* (b) (4) *. Thus, we are not convinced that the safety of the 300 to 400 mg/day dosage in* (b) (4) *year-old patients and* (b) (4) *mg/day dosage in adolescents are adequately supported.*

Additionally, given that the drug is metabolized via CYP2D6, you need to include genotyping and provide a dosage adjustment strategy in CYP2D6 poor metabolizers in Phase 3 trials.

Discussion at Meeting: *Based on the Agency's preliminary comments, the Sponsor revised their study designs and presented plans to study patients ages 6 to 11 years up to a 400 mg dose level and patients ages 12 to 17 years up to a 600 mg dose level.* (b) (4) *The Division indicated that the revised study designs appeared to be more appropriate than the initial proposed studies. However, the larger issue of dose safety margins, in relation to preclinical findings of seizures and deaths, had not been adequately resolved and required further discussion during this meeting.*

The Sponsor made the case that viloxazine had been on the market in European and other countries for 20 years with only a small number of documented seizures in humans. Furthermore, many of the seizure cases were confounded by other factors that limited causal attribution to viloxazine. In addition, the previously approved viloxazine product was an immediate release (IR) formulation and the Sponsor's extended release (ER) formulation would be anticipated to have fewer adverse events if the events were associated with Cmax.

The Division expressed some skepticism, noting that it is unusual for humans to be the least sensitive species for a concerning adverse event detected in preclinical toxicology studies and, furthermore, seizures did not always develop early in treatment but were sometimes observed in the context of long-term exposure. Study 812P120 had too few patients exposed for too short a duration to provide robust evidence of safety at higher dosages.

The Sponsor discussed the case of seizure in a pediatric patient in Study 812P310, stating that the seizure was most likely due to an epilepsy that had not yet been diagnosed. The Division queried how we could be sure that the drug had not provoked a long-term seizure disorder. The Division asked whether there was an explanation as to why seizures occurred in multiple animal species at lower exposures than humans seemed to tolerate in studies thus far. The Sponsor indicated that they did not know, but hypothesized that it could be related to a kindling phenomenon, which has been reported in animals but not reported in humans. The Agency clarified that the previously approved product was an IR formulation and was administered twice or thrice a day; therefore the current ER product could lead to Cmax levels similar to the Cmax from the IR product and might have a similar AE profile.

The Division recommended that the Sponsor provide additional information about the safety of proceeding with Phase 3 studies using the proposed doses. The information should include usage data and post-marketing safety information related to seizures/convulsions with previously-marketed viloxazine; a report on seizures observed in preclinical studies, including plasma levels when they occurred and on what days of the study the seizures initially appeared; and elaboration of hypotheses as to why humans might be less sensitive to seizures than the other animal species tested. Additionally, the Sponsor should present the comprehensive mechanistic work-up to explain the species difference (i.e., human vs. other animal species) with regards to seizures. These should include, but should not be limited to: detailed metabolic differences between species, unique metabolites, differences in tissue distribution, etc. The Sponsor should also propose additional safety parameters for the Phase 3 studies (e.g., study stopping criteria, screening criteria related to history of seizures/convulsions).

The Sponsor also agreed to collect and bank the samples from all the subjects included in the studies. The pharmacogenomics assessment of the samples will be performed later based on the response (PK or PD).

FDA Post-Meeting Comments: *The Sponsor submitted a documented entitled, "White Paper: Review of Clinical Safety Data on Viloxazine." This document had the stated objective of identifying and analyzing published clinical studies on viloxazine to gain a comprehensive understanding of safety risks, including adverse events or side effects, and reasons for treatment*

discontinuation/study withdrawal. Information in this document was derived from a literature search.

The duration of the majority of viloxazine trials was four weeks, and dosing ranged from 100 to 800 mg/day (with most using doses between 150 and 300 total mg/day, divided into 3x/day dosing). The Sponsor described four studies that reported seizure-related events associated with viloxazine treatment (including 7,644 viloxazine-treated patients) and four studies on drug-drug interactions between viloxazine and an anticonvulsant (including 30 patients with epilepsy). These studies described three patients who had seizures while receiving viloxazine; two cases had clear confounding factors (known diagnosis of epilepsy; benzodiazepine withdrawal). A review article entitled, "Does viloxazine have epileptogenic properties?" (Edwards et al. J Neurol Neurosurg Psychiatry 47(9): 960-964 (1984)) described eight cases of convulsive seizures reported to regulatory authorities and the product manufacturer and concluded that in only two cases was it possible that viloxazine was the cause of the seizures. The authors also reviewed 120 clinical studies of viloxazine and calculated the incidence of seizures associated with viloxazine treatment to be 0.01%, concluding that viloxazine "even if possessing convulsive properties like other anti-depressants, is probably less epileptogenic than conventional tricyclics and is not contraindicated in epileptic patients requiring antidepressant medication."

Overall, from historical viloxazine clinical studies and foreign marketed use, the Division agrees that clinically there did not appear to be a clear seizure risk associated with viloxazine (with the caveat that the formulation and dosages used historically were different than SPN-812 ER).

d) In addition to the primary endpoint analysis of change from Baseline to End of Study (EOS) for ADHD RS-V Total Score, Supernus would be interested in adding the results of additional analyses from the Phase III studies in the product label, including:

   1) (b) (4)

   2)

   If the results of these predefined analyses provide significant results regarding response to SPN-812, Supernus would be interested in including this information in the product label. Please comment about these plans.

FDA Response to Question 3(d): *You may wish to denote secondary endpoints intended for product labeling as "key secondary endpoints." Statistical testing on these endpoints will need to be controlled for multiplicity, and the results will need to be substantiated. Whether specific proposed key secondary endpoints are appropriate for product labeling would be a matter of review, based on whether they are well-documented, prospectively-defined, and statistically and clinically meaningful.* (b) (4)

[1] Supernus notes recent FDA initiatives considering importance of real world evidence, pharmacoeconomics, and health outcomes in decision-making. (*see* "Manufacturer approved communication regarding unapproved uses of approved or cleared medical products", transcript of FDA public hearing held November 9, 2016.) Although this meeting discussed unapproved uses, use of the same types of evidence regarding approved uses reasonably follows.

(b) (4)

Discussion at Meeting: *The Sponsor indicated they would provide additional information as requested, including a proposal for key secondary endpoints.*

Question 4: Overall Scope of completed and remaining development program

a) Does FDA agree that conduct and presentation of the studies identified in the "Summary of Studies Completed, Planned" will constitute a full development program suitable for New Drug Application review?

FDA Response to Question 4(a): *On face, from a clinical perspective, the completed and planned studies would constitute a full development program suitable for NDA review.*

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

b) No adult or elderly population studies are planned for the initial marketing application. Please confirm that no additional adult or elderly clinical work is expected to support the original application for a pediatric population.

FDA Response to Question 4(b): *No additional adult or elderly clinical studies are expected to support the original application for the pediatric population.*

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

c) Due to the age of the target population, and further rationale presented regarding the metabolism of viloxazine, Supernus does not intend to conduct special population studies in renally impaired, or hepatically impaired patients. Please comment on the acceptability of this plan.

FDA Response to Question 4(c): *Organ impairment studies (i.e., renal impaired and hepatic impaired) are typically required for appropriate labelling and safe use in the clinic. Given that viloxazine is extensively metabolized and is eliminated via the urine both as parent and metabolite(s), organ impairment can lead to significant increase in exposure requiring dose adjustment. We request you to provide a detailed justification for the waiver of such studies.*

If you believe that your product should not be used in patients with compromised organ function and you do not plan to conduct relevant studies, you must address it in the label appropriately. Additionally, the future clinical studies should exclude subjects who are organ impaired.

Discussion at Meeting: *Regarding organ impairment studies, the Sponsor reiterated that based on the target population (younger ADHD patients), the product is unlikely to be administered to individuals with organ impairments and, thus, the organ impairment studies might not be helpful. However, based on the mass balance data suggesting that the primary route of drug elimination is via the kidneys, the Sponsor agreed to conduct a renal impairment study to assess the impact of renal impairment on the PK of the product. Similarly, the Sponsor has agreed to carefully consider all the information regarding metabolism/mass balance data to assess the potential impact of hepatic impairment. Subsequently, they will either conduct a hepatic impairment study or provide a comprehensive justification for the waiver of the study.*

d) As for cardiac evaluations - Supernus has completed and supplied the clinical study report for Study 812P120 (See Sequence 0034), which evaluated cardiac prolongation using concentration effect modeling in a single- and multiple-ascending dose trial as mentioned in ICH E14 Q&A Revision 3. Does the agency agree that this cardiac evaluation precludes the need for a full QTc study?

FDA Response to Question 4(d): *No. We do not agree that the cardiac evaluation in Study 812P120 precludes the need for a full QTc study. The analysis provided included only a 1.4-fold exposure margin over the geometric mean C_{max} of the highest proposed therapeutic dose (800 mg/day in adolescents, assumed to be comparable to 900 mg/day in adults). Because the highest clinically relevant drug exposure has not been defined and the exposure margin over the normal therapeutic exposures with the highest dose is only 1.4-fold, it does not appear likely that the 2-fold margin required to waive the inclusion of a positive control can be met. Thus, we recommend that you perform a TQT study.*

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

Sponsor's Response (Post-Meeting Comments): At the meeting on June 29th, Supernus provided a handout on this topic, however there was no time for discussion of this topic. See Attachment E for the meeting handout, titled "Table 14.2.2.1 Descriptive Statistics for Pharmacokinetic Parameters of SPN-812 ER in Plasma after Single Oral Dose Administration on Day 1 (Cohorts 1-7)", from Study 812P120.

Supernus has repeated our calculations and could not arrive at the "1.4-fold exposure margin" of the geometric Cmax of the highest proposed therapeutic dose (400 mg/day in children 6-8, assumed to be comparable to 900mg/day in adults) arriving, instead, at a 2-fold margin when compared to 2100mg (maximum tolerated dose). Further, the overall results of the concentration-QTc effect modeling (PK-PD; Figure 3-6 of Cardiac Expert Report) show a negative slope of the relationship between plasma concentration and change in QTcF. Supernus has held discussions with cardiac safety experts (including Dr. (b) (4)), and continues to feel that there is no cardiac safety issue, and that the 812P120 study should suffice for cardiac evaluation of SPN-812. **We request that the FDA review their calculations in light of our response; Supernus anticipates a continued dialogue with the agency on this topic**.

FDA Post-Meeting Comments: *The Sponsor is correct that the geometric mean Cmax of the 2100 mg dose is 2-fold above the Cmax of the 900 mg single dose as shown in Attachment E. However, when considering the expected Cmax,ss we still arrive at a 1.4-fold margin (10.7 µg/mL/7.6 µg/mL).*

Moreover, in order to waive the requirement for a positive control, a 2-fold margin over the supratherapeutic exposure for the parent drug as well as all major moieties is required (ICH E14 Q&A (R3), 5.1) and, per the provided materials, it appears that the supratherapeutic exposure is still unknown.

Therefore, we still disagree that the concentration-QTc analysis based on Study 812P120 can serve as a replacement for a thorough QT study.

e) Supernus has completed, and will supply, a draft study synopsis and Tables, Listing and Figures concerning the conduct of Study 812P202 titled "Evaluation of SPN-812 ER Efficacy and Safety in Children with ADHD - A Double-Blind, Placebo-Controlled, Dose-Ranging Study". This study provided PK data in children. Supernus will continue to evaluate PK in the Pivotal Phase III studies as an optional population PK substudy. Does the agency agree that no additional PK specific trials need be conducted?

FDA Response to Question 4(e): *You must perform adequate PK assessment within the Phase 3 studies to fully characterize the PK in all the pediatric age groups (i.e., (b) (4)) and conduct exposure-response analysis for both efficacy and safety.*

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

f) Supernus has conducted Study 812P105 which evaluated the product in the fed and fasted state, administered either intact or as sprinkle product. A draft study synopsis and Tables, Listing and figures for Study 812P105 were submitted in Sequence 0036. Does the FDA agree that this study supports instructions to take the product without regard to food, and that the product may be taken intact or sprinkled on (b) (4) if necessary?

FDA Response to Question 4(f): *On face, the food effect study seems acceptable. However, please confirm that the food effect study has been conducted with the highest strength of the planned commercial formulation of the product. The acceptance of the results will be a review issue after the NDA submission.*

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

Question 5: Forward thinking questions - Clinical

a) Although Supernus is seeking a monotherapy indication, we are considering conducting two Drug-Drug Interaction studies (stimulant, and nonstimulant, see Table [TBD]). Does FDA feel these are required for the marketing application for a monotherapy indication, (b) (4) ?

FDA Response to Question 5(a): *It is acceptable* (b) (4) *Please see additional comments at the end of section 2.*

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

(b) (4)

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

2.2. Nonclinical/Pharmacology-Toxicology

On June 16, we submitted an Information Request to the Sponsor requesting the completion of exposure data from animal studies and humans. In addition, we requested justification as to why the observed nonclinical toxicities are not seen in humans. This request stems from our concern about the incidence of seizures in animal studies. The concern was highlighted by the recently completed carcinogenicity studies in rats and transgenic mice where the high dose had to be lowered in both studies to reduce seizures. We would like a complete report of these seizures, including plasma levels when they occurred and on what day of the study the seizures initially appeared.

Question 6: Supernus' juvenile rat toxicity study was conducted in animals that correspond to human age groups of ages 2 to 18 (See juvenile rat toxicity report 812V-TOX2012-001 in Sequence 0004). Please confirm that this is sufficient to allow dosing of children down to age (b) (4)?

FDA Response to Question 6: *On face, this study appears to fulfil the requirement for the Juvenile Animal Study for the age group you are proposing* (b) (4) *to 12 years).*

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

Question 7: A battery of reproductive toxicology studies was conducted by the original innovator (b) (4) in support of marketing authorization for viloxazine, using good scientific practices appropriate for the time period (1970s). Please see tabular summaries provided in Section 4.2 of this briefing package. Does the agency agree that the reproductive toxicology program for this product is sufficient to permit a) the participation of adolescents in the Phase III clinical program and b) a marketing application including an indication for adolescents?

FDA Response to Question 7: *The details available from these old studies are marginal and generally contain only summary data. This is especially of concern for the Segment III perinatal and postnatal rat study since it does not conform to current testing standards (lacks evaluation of neurobehavioral endpoints and other developmental endpoints in F1 generation). This study will need to be repeated using current GLP standards and procedures of testing as described in the ICHS5(R2) guideline. In addition, an embryotoxicity study in a second species (rabbit) will be required. We note that the toxicity findings observed at the high dose in the rat embryo toxicity study are not mentioned in any of your summaries or in the investigator brochure. These findings must be included there.*

Discussion at Meeting: *The Division reiterated our position on the reproductive studies that would be required. We also noted our general concern that there is no safety margin between NOAEL exposures for seizure in animals and blood levels already attained and exceeded in human trials (including children). We stated at the outset of the meeting that there is no nonclinical support for doses of viloxazine above 100 mg in adults or children. The Sponsor reiterated that serious adverse effects have not been seen in short-term clinical trials. The Division suggested that, if a mechanism (and thus a threshold) for the most worrisome non-clinical effect (seizures in three species) could be determined, it might help provide a way forward. The Sponsor hypothesized that there may be a kindling effect in rats given that seizures were not observed in short-term studies. The Sponsor stated that no kindling effect appears to exist in humans, suggesting that this might be one mechanistic difference between humans and animals. We requested that the Sponsor submit data in support of this or any other hypotheses as to how humans could be the least sensitive species.*

Question 8: Based on preclinical work described in Section 4.2, and because as a norepinephrine reuptake inhibitor, SPN-812 is not expected to stimulate the dopaminergic reward system in the central nervous system that leads to drug abuse issues. Does the agency agree that no abuse studies either preclinically or clinically will be required?

FDA Response to Question 8:

- *The Agency agrees that, at this time, preclinical and clinical abuse potential studies are not necessary to assess the abuse potential of viloxazine. However, please submit the label that was accepted for use in Europe as well as a report of any instances of abuse or abuse-related adverse events that were recorded while SPN-812 was on the market in Europe. You should also continue to monitor for abuse-related adverse events as part of your clinical trials and for other possible cases of abuse as outlined below.*

- *For all Phase 1, 2, and 3 clinical studies, you should report all potentially abuse-related adverse events (AEs) and provide detailed narratives for these AEs. Also, you should provide a list of MedDRA terms that will prompt these reports (including abuse-related AE terms such as euphoria, dissociative effects, hallucinations, psychosis, changes in mood, impaired cognition, attention, and psychomotor effects, inappropriate affect, patient dropouts, overdoses; misuse, and lost or unaccounted for medication and unjustified dose increases). Narratives should include time of onset and duration of the event, dose of drug taken, severity and outcome. AE reporting should be broken down by gender, age (18 to 55 and*

>55), and by population (e.g., healthy volunteers, patients with MS disease, and patients with other disorders). See also section V.B. of FDA's Guidance for Industry: Assessment of Abuse Potential of Drugs for additional details and recommendations for monitoring and reporting abuse-related AEs.

- *You should also monitor for other possible cases of abuse (subjects taking the drug for non-therapeutic purposes, e.g., for psychoactive effects such as high or euphoria) in all clinical trials. Investigators should obtain more information and explanations from the subjects when there are drug accountability discrepancies. Towards this end:*

    - *Train investigators to capture cases of abuse, misuse, and addiction before starting trials and provide definitions for these cases.*
    - *Provide data in tabular form for all reports of abuse, overuse, lost/stolen/missing or unaccounted product that occurred in clinical trials. These data should include study number and type of study, subject ID number, narratives, case description and details.*
    - *Provide narratives for cases where the patients drop out from studies for reasons that might be coded as "protocol violation," "lack of efficacy" (to capture aberrant behavior in patients who drop out of the study supposedly due to lack of efficacy), "lost to follow up," "non-compliance to study medication or procedures," "over compliance," or for "other." Case reports should be provided separately.*
    - *Report any use of the investigational formulation by individuals other than the subjects (family member, health care practitioner, etc.).*

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

Sponsor's Response (Post-Meeting Comments): Bullet point #1: Supernus agrees and accepts the agency's comment that abuse potential studies are not necessary at this time. For a review of the French label for Vivalan, please refer to Module 1.13.10, EU Regulatory Status document, Attachment 1 of Sequence 0000.

Bullet point #2: Alternatively, Supernus proposes to provide a patient narrative of any Adverse Event(s) that could point to abuse related behavior that resulted in a patient dropout. In addition, Supernus will include, in the investigator training, a segment concerning identification of abuse, misuse and addiction behaviors as noted in the FDA's preliminary response. **Please advise if you can accept this alternative proposal**.

FDA Post-Meeting Comments:
Bullet point #1: Thank you for the information and reference to the label for Vivalan.

Bullet point #2: Providing narratives for adverse events related to abuse only from subjects who drop out of the study is not acceptable. Although information on why a subject drops out of a study is important, it is just as important to have this information for subjects who have adverse events related to abuse and remain in the study. It is only in this manner that potential causal factor(s) can be evaluated. You should provide the information as specified in our response to Question 8.

We note that you will include investigator training on the identification of abuse, misuse, and addiction behaviors as part of your studies.

Question 9: Supernus believes that none of the human metabolites are of toxicological concern and the human metabolism information is adequate for the NDA. Does the Agency agree?

FDA Response to Question 9: *No, we disagree. With significant toxicity observations in several animal species, we are very concerned about the toxicological potential of the parent as well as several circulating metabolites. You must plan to provide a detailed analysis of metabolic schemes (e.g., all metabolites that are formed, enzymes involved in the pathways etc.) involved in the biotransformation, elimination, excretion of the drug in human as well as animal species. We can plan to have additional discussion once the comprehensive in vitro metabolism data across all animal species (human and animal) has been provided.*

Potential toxicity of drug metabolites is discussed in guidance: Safety Testing of Drug Metabolites.

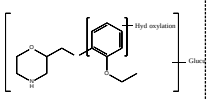
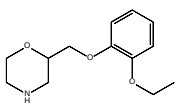
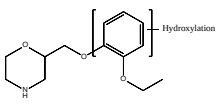
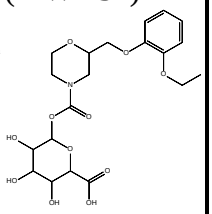
Discussion at Meeting: *There was no further discussion.*

Sponsor's Response (Post-Meeting Comments): Supernus wishes to continue this discussion, please note in particular the findings of Clinical Study 812P111.

Supernus completed the human mass balance study, Study 812P111. Based on the findings, the concentration of the major human metabolite P1 (5-hydroxy glucuronide; ~11% of total plasma radioactivity) is notably less than hydroxyl glucuronide metabolites (M1 and M2) in rats. Additionally, P1 is not a reactive acyl glucuronide metabolite. Given this information, Supernus believes that none of the human metabolites are of toxicological concern and no additional human metabolism need be explored. 5-hydroxy glucuronide metabolite in human (P1) is also detected in animal species.
The results from human mass balance study (QBR Report SPN/04) are summarized in Table 1 below. Additional investigations were performed to confirm metabolite P1 as 5-hydroxyviloxazine glucuronide and metabolite U2 as 5-hydroxyviloxazine (QBR Report SPN/08). A comparison of the relative concentrations of human and rat plasma metabolites is shown in Table 2 below.

Table 1: A summary of the relative proportions of the human plasma and urine metabolites (QBR SPN/04)

P1	P2	U2	U4

	$C_{19}H_{27}O_{10}N$ (MW 429)  (5-hydroxy-viloxazine glucuronide)	$C_{13}H_{19}O_3N$ (MW 237)  (Unchanged SPN-812V)	$C_{13}H_{19}O_4N$ (MW 253) 	$C_{20}H_{27}O_{11}N$ (MW 457) 
Sample Pool	**(% of total sample radioactivity)**			
Subject (b) (6) AUC pool	12.48	69.81	4.94	4.80
Subject AUC pool	10.11	71.72	2.46	5.79
Subject AUC pool	NO	71.38	3.48	6.34
Subject AUC pool	NO	63.40	4.16	7.24
Subject AUC pool	12.15	63.84	2.82	7.34
Subject AUC pool	16.20	57.32	3.31	6.79
Subject AUC pool	14.64	55.68	3.62	6.50
Subjects (b) (6) 1hr pool	NO	71.05	4.39	6.40
Subjects 8hr pool	10.57	53.05	2.78	4.42

NO Not observed above 10% of the total sample radioactivity

Table 2: Comparison of the relative concentrations of human and rat plasma metabolites

	Human metabolite P1	Male Rat Metabolite M1	Male Rat Metabolite M2
	Mean concentration (µg equivalent/mL)	Mean concentration (µg equivalent/g)	Mean concentration (µg equivalent/g)
1 hour	<0.23	1.16	1.00
4 hours	No equivalent data	1.14	0.64
8 hours	0.118	0.786	0.632

Concentrations expressed as µg equivalents ^{14}C-viloxazine/mL or /g plasma
Source data for human: Table 4 of QBR SPN/03; Table 3 of QBR SPN/04
Source data for rat: Tables 27 and 28 of study report 809V-TOX2007-023

Based on this additional information, can the agency confirm that no additional human metabolism data will be necessary for the NDA review?

FDA Post-Meeting Comments: *Please provide detailed information (in addition to your post-meeting comments) to address all our earlier comments/questions.*

Question 10: Supernus has been following the recommendations from the agency regarding preclinical development for viloxazine (please refer to pre-IND meeting minutes for IND (b) (4) 108,864). Does the agency agree that the preclinical development program as described for this product will be sufficient to support an NDA?

FDA Response to Question 10: *This will be a matter of review. Some of the reproduction studies will need to be repeated as discussed in the answer to Question 7.*

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

2.3. Regulatory/Procedural

Question 11: As a new chemical entity in the United States, would this program be subjected to review by an Advisory Committee, despite its previous approvals and sales in Europe for the indication of depression?

FDA Response to Question 11: *At this time, we are not able to state whether the program would be subjected to review by an Advisory Committee. This decision would be made after NDA submission, depending on whether there were issues that would benefit from independent expert advice to the Agency.*

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

Question 12: Please note the first presentation of a Target Product Profile for SPN-812. Please comment on the planned content of the product label.

FDA Response to Question 12: *On face, the draft labeling outline appears to be a reasonable initial framework. However, it is premature to discuss specifics on section contents at this time.*

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

Question 13: Supernus' understanding is that ADHD cannot be diagnosed in children under 4 years of age. Assuming adolescents are included in the original NDA submission, must Supernus submit an Initial Pediatric Study Plan to request a waiver for those ages birth to age 4? Or will that be understood based on the indication for use?

FDA Response to Question 13: *You will need to submit an iPSP within 60 days of your End-of-Phase 2 (EOP2) meeting. Your iPSP should include a plan for partial waiver in patients less than 4 years of age* (b) (4) *. Please see below additional information on the iPSP submission.*

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

Question 14: Following the implementation of open label extension study 812P310, Supernus committed to the provision of safety updates for study participants every six months, including laboratory and ECG data follow-up. By the time Phase III trials are initiated we will have

provided two if not three safety updates. With the initiation of the Phase III program, may Supernus discontinue the safety updates on the open label extension study?

FDA Response to Question 14: *We appreciate your provision of safety updates on a more frequent basis, as previously requested. We agree that upon initiating Phase 3 trials, you may return to standard reporting requirements.*

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

Question 15: Is it acceptable, in the absence of other data, to reference (b) (4)

FDA Response to Question 15: (b) (4) *assessments may not be relied upon as these are* (b) (4) *If the studies* (b) (4) *have been published, you may be able to rely upon that literature.*

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

Question 16: Are there any class labeling requirements expected based on the chemical moiety?

FDA Response to Question 16: *The language included in the label will depend on the characteristics of the drug and review of the data; it is premature to discuss at this time.*

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

Question 17: Viloxazine was marketed in Europe as an antidepressant. Will class labeling pertaining to antidepressants be required on labeling for viloxazine for an ADHD indication in children?

FDA Response to Question 17: *See our response to Question 16 above.*

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

Additional Clinical Pharmacology Comments

In addition to the studies listed in Table 3 (Completed and Planned Studies), we have the following comments regarding additional clinical study requirements:

- *Strength proportionality study (with final commercial formulation), if similarity in composition or in vitro dissolution across multiple strengths cannot be established.*

- *Drug interaction studies as per the Guidance (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf)*
    - *Viloxazine as an enzyme substrate (i.e., as a victim drug)*
    - *Transporter interaction study (either as a victim or a perpetrator), if any, based on the in vitro data*
- *Confirm that the food effect study has been conducted with the highest strength and the planned commercial formulation of the product.*
- *Drug interaction study with pH modulators (e.g., PPI), if your formulation is coated with pH-sensitive polymers.*
- In vitro alcohol dose-dumping study

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

Additional Statistical Comments:

1) *For studies 812p301 and 812p303: Randomization needs to be stratified by age group (* (b) (4) *).*
2) *For all four Phase 3 studies 812p301, 812p302, 812p303 and 812p304:*
    - *According to Recommendation 10 in "the Prevention and Treatment of Missing Data in Clinical Trials" by panel on handling missing data in clinical trials, National Research Council, single imputation method (i.e., LOCF) "should not be used as the primary approach to the treatment of missing data unless the assumptions that underlie them are scientifically justified." Please plan to propose alternative justifiable methods for your primary analysis and to handle missing data.*
    - *Please plan to clarify the estimand of the primary interest and justify the suitability of the primary analysis for the proposed estimand. You should also pre-specify in detail sensitivity analyses to assess the impact of the violation of the missing data assumptions required for the primary analysis. Please be aware that Office of Biostatistics in CDER is contemplating different approaches to handling statistical analyses in the presence of missing data; for example, whether all dropouts should be treated as treatment failures instead of assuming MAR (missing at random) in the primary analysis. We suggest that you start to explore this and justify for your trials.*

Discussion at Meeting: *There was 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 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

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

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

and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

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

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

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. 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.

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)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
4.	

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

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the 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.

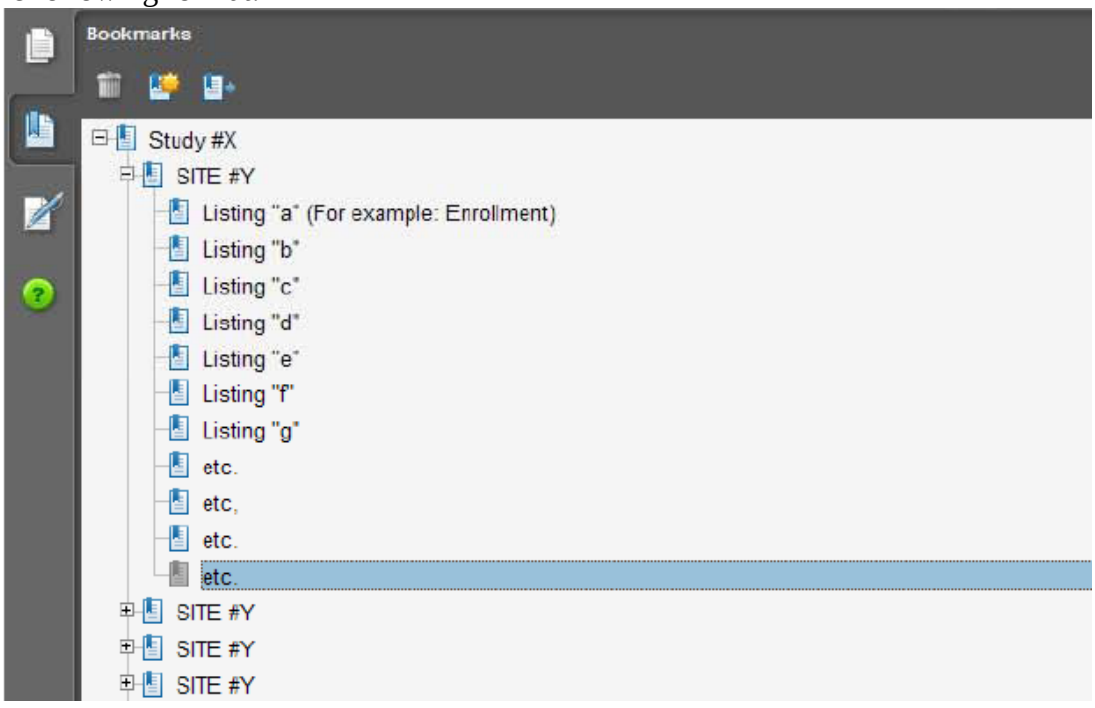
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

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[2]	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:

[2] 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

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

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

1. Study phase

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

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

The Sponsor should submit additional information to address the Agency's concerns as outlined under Question 9.

6.0 ATTACHMENTS AND HANDOUTS

Revised protocol design handouts (2) provided at the meeting and another handout from the meeting related to the QTc discussion.

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

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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
07/28/2017