

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**211371Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**



IND 122279

**MEETING MINUTES**

SAGE Therapeutics, Inc.  
Attention: Debra B. Feldman, MPH  
Senior Director, Regulatory Affairs  
215 First Street, Suite 220  
Cambridge, MA 02142

Dear Ms. Feldman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SAGE-547 (allopregnanolone) injection.

We also refer to the meeting between representatives of your firm and the FDA on January 18, 2018. The purpose of the meeting was to discuss (i) the data cut-off date for studies to be included in the NDA, (ii) content & format of the ISS and ISE, and (iii) content & search terms of abuse liability package.

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](mailto:Kofi.Ansah@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Mitchell V. Mathis, MD  
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

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA Meeting

**Meeting Date and Time:** January 18, 2018; 2:00 pm EDT  
**Meeting Location:** FDA White Oak Campus, Bldg. 22, Room #1415  
10903 New Hampshire Ave, Silver Spring MD 20993

**Application Number:** IND 122279  
**Product Name:** SAGE-547 (allopregnanolone) injection  
**Indication:** Postpartum Depression (PPD)  
**Sponsor/Applicant Name:** SAGE Therapeutics, Inc.

**Meeting Chair:** Mitchell Mathis, MD

**FDA ATTENDEES:**

Robert Temple, MD	Deputy Director, Office of Drug Evaluation I (ODE-I)
Mitchell Mathis, MD	Director, Division of Psychiatry Products (DPP)
Tiffany Farchione, MD	Deputy Director, DPP
Marc Stone, MD	Deputy Director for Safety, DPP
Kofi Ansah, PharmD, RAC	Senior Regulatory Project Manager, DPP
Bernard Fischer, MD, PhD	Acting Clinical Team Leader, DPP
Michael Davis, MD, PhD	Medical Officer/Clinical Reviewer, DPP
Ikram Elayan, PhD	Pharmacology/Toxicology Supervisor, DPP
Antonia Dow, PhD	Pharmacology/Toxicology Reviewer, DPP
Hao Zhu, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Kofi Kumi, PhD	Clinical Pharmacology Reviewer, OCP
Peiling Yang, PhD	Biometrics Team Leader, DBI/OB
Jinglin Zhong, PhD	Biometrics Reviewer, DBI/OB
Alan Trachtenberg, MD, MPH	Medical Officer, Controlled Substance Staff (CSS)
Anna Sun, PhD	Mathematical Statistician, CSS Team, Division of Biometrics VI
Carolyn L. Yancey, MD	Clinical Reviewer, DPMH
Jenn Sellers, MD, PhD	Medical Officer/Reviewer, Office of Scientific Investigations (OSI)
Leah Hart, PharmD	Team Leader, OSE/Division of Risk Management (DRISK)

**SAGE Therapeutics, Inc's Attendees**

Name	Title
Steve Kanes, MD, PhD	Chief Medical Officer
Christopher Silber, MD	Senior Vice President, Clinical Development
Jim Doherty, PhD	Chief Research Officer
Helen Colquhoun, MD	Vice President Medical Science
Amy Schacterle, PhD	Senior Vice President, Regulatory Affairs and Quality Assurance
Debra Feldman, MPH	Senior Director, Regulatory Affairs
Corey Murphy, RAC	Associate Director, Regulatory Affairs
Leslie Williams, DVM, MPH	Vice President, Drug Safety/Pharmacovigilance
Abdul Sankoh, PhD	Vice President, Data Science
Haihong Li, PhD	Director, Biostatistics
Rob Pawliuk, PhD	Vice President, Nonclinical Development
Ethan Hoffmann	Senior Director, DMPK and Clinical Pharmacology
Lisa Herman, PharmD, MS, RPh	Director, Regulatory Affairs
Rebecca Warwick, MPH	Manager, Regulatory Affairs
	(b) (4)
	(b) (4)

## 1.0 BACKGROUND

SAGE-547 Injection (hereafter referred to as SAGE-547) is a 5 mg/mL solution of brexanolone (United States Adopted Name for allopregnanolone), a neuroactive steroid that is synthesized endogenously from progesterone. In the central nervous system (CNS), allopregnanolone is thought to function as a positive allosteric modulator of synaptic and extrasynaptic GABA<sub>A</sub> receptors and depress neuronal excitability. SAGE-547 is being developed, under IND 122279, for the treatment of postpartum depression (PPD) and is intended to be administered to patients as a continuous infusion over 60 hours. The Sponsor has (b) (4)

SAGE-547 was granted Breakthrough Therapy Designation for the indication of PPD on August 23, 2016, and a Type B Breakthrough Guidance Meeting was held on November 2, 2016, to discuss nonclinical and clinical development plans to support product approval. The clinical

development program under IND 122279 includes the following confirmatory studies intended to support the approval of SAGE-547 for the treatment of PPD:

- 547-PPD-202A: Randomized, double-blind, placebo-controlled, parallel group study in which women with severe PPD (N=21 randomized; HAM-D total score  $\geq 26$  at Screening and Baseline) were treated with a 60-hour infusion of SAGE-547 (target dose = 90  $\mu\text{g}/\text{kg}/\text{hr}$ ) or placebo. The primary efficacy endpoint of the change from baseline of the HAM-D at 60 hours was reported as least squares mean (SE) -21.0 (2.9) for SAGE-547 vs. -8.8 (2.8) for placebo ( $p=0.008$ ). The Sponsor reports that a statistically significant difference between the treatment groups remained at 7 and 30 days after treatment initiation.
- 547-PPD-202B: Randomized, double-blind, placebo-controlled, parallel group study in which women with severe PPD (N=138 randomized) were treated for 60 hours with one of two doses of SAGE-547 (target dose of 60 or 90  $\mu\text{g}/\text{kg}/\text{hr}$ ) or placebo. The primary efficacy endpoint of the change from baseline of the HAM-D at 60 hours was reported as least squares mean (SE) -19.5 (1.2) for 60  $\mu\text{g}/\text{kg}/\text{hr}$ , -17.7 (1.2) for 90  $\mu\text{g}/\text{kg}/\text{hr}$ , and -14.0 (1.1) for placebo. The Sponsor reports that both doses were statistically superior to placebo ( $p=0.0013$  for 60 and  $p=0.0252$  for 90  $\mu\text{g}/\text{kg}/\text{hr}$ ), and statistically significant differences between both treatment groups remained at 30 days after treatment initiation.
- 547-PPD-202C: Randomized, double-blind, placebo-controlled, parallel group study in which women with moderate PPD (N=108 randomized; HAM-D total score of 20-25 at Screening and Baseline) were treated with a 60-hour infusion of SAGE-547 (target dose = 90  $\mu\text{g}/\text{kg}/\text{hr}$ ) or placebo. The primary efficacy endpoint of the change from baseline of the HAM-D at 60 hours was reported as least squares mean (SE) -14.6 (0.8) for SAGE-547 vs. -12.1 (0.8) for placebo ( $p=0.016$ ). The Sponsor reports that a statistically significant difference between the treatment groups remained at 7 days after treatment initiation.

The Sponsor has requested this Pre-NDA Meeting to discuss and reach agreement with the Agency on the format and content of an NDA for SAGE-547 for the treatment of PPD. Specifically, the Sponsor would like to discuss and obtain agreement on:

- The data cut-off date for studies to be included in the NDA,
- The content and format of the Integrated Summary of Safety/Summary of Clinical Safety and Integrated Summary of Efficacy/Summary of Clinical Efficacy, and
- The content and search terms of the abuse liability package.

## 2.0 DISCUSSION

### 2.1 Clinical

**Question 1 (Studies for Inclusion in the NDA): Does the Agency agree with the proposed cut-off date of 15 November 2017 for completed and ongoing studies in anticipation of NDA submission by April 2018?**

**Sponsor's Position and Justification:**

With the NDA planned for submission in April, Sage is proposing a cut-off date of 15 November 2017 for study data to be included in the NDA, a date which is approximately five months in advance of the planned submission date. Based on this date, only completed studies will be included in the NDA; no studies of brexanolone were ongoing on that date. We propose to include the three completed confirmatory efficacy studies to support the approval of brexanolone as a treatment for postpartum depression (547-PPD-202A, 547-PPD-202B and 547-PPD-202C), the open-label study 547-PPD-201, the completed studies from the supportive clinical pharmacology program (see Table 7), and a study in subjects with essential tremor disorder (547-ETD-201). Abbreviated clinical study reports will be provided for clinical studies from the SRSE program, which are complete. (b) (4)

**FDA Response to Question 1:** *We agree with the proposed cut-off date of November 15, 2017, for completed and ongoing studies, in anticipation of your NDA submission by April 2018.*

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

**Question 2 (Integrated Summary of Efficacy (ISE)):**

- a) Does the Agency agree with proposed studies for pooling (547-PPD-202A, 547-PPD-202B and 547-PPD-202C), and separately summarizing study 547-PPD-201 in the ISE?**
- b) Does the Agency agree with the approach to the SCE/ISE, specifically its placement in Module 2?**
- c) Does the Agency agree with the planned integrated analyses to evaluate both doses (60 and 90 µg/kg/h) for the treatment of PPD?**

**Sponsor's Position and Justification:**

Sage is proposing to integrate efficacy data from the three placebo-controlled pivotal clinical studies, 547-PPD-202A, 547-PPD-202B and 547-PPD-202C, as outlined in the statistical analysis plans (SAP) for the ISE (provided in Appendix B). Data from open-label clinical study 547-PPD-201 will not be integrated and will be described separately in the ISE due to the differences in study design and because efficacy was not the primary objective of this study. Data analysis for all subjects who received study treatment will be integrated and presented across all three placebo-controlled studies in the ISE and individually in the separate study reports. Sage plans to present both the 60 µg/kg/h and 90 µg/kg/h doses in the integrated tables, understanding that data on the 60 µg/kg/h dose will be from Study 547-PPD-202B only. The 90 µg/kg/h dose was evaluated in all three studies and a finding of efficacy was replicated in each

study. It is noted however, that the 60 µg/kg/h dose also demonstrated efficacy and no dose response was observed.

Presentations of mean change from baseline in HAM-D total score and in individual HAM-D Items will be presented, with emphasis on the 60 hour (end of treatment) primary endpoint and durability of effect through 30 days. Subgroup analyses of the primary endpoint based on age, race, ethnicity and BMI are planned. Subgroup analyses for gender are not applicable to this patient population. All subjects were enrolled in the US, despite opening sites ex-US; therefore, regional subgroup analyses are not planned. While the subjects with PPD in these studies represents a narrow age group compared to other development programs, a subgroup analyses for age < 25 or ≥ 25 years was selected to coincide with the age groups referenced in the boxed warning for antidepressants.

Secondary endpoints data will be presented for subjects who had a response as defined by ≥ 50% reduction in HAM-D total score, subjects who achieved remission defined as HAM-D total score ≤ 7, as well as for the MADRS and CGI-Improvement endpoints. Data for those subjects who experienced worsening of symptoms, rebound following treatment or relapse during follow-up, as assessed by the HAM-D, will be presented.

A finding of effectiveness for brexanolone in the treatment of PPD is based on three adequate and well-controlled studies, all of which demonstrated statistically significant effects at the primary endpoint of Hour 60. Analysis of secondary endpoints show directional consistency with the primary endpoint, often with statistical significance being reached. Although the placebo response varied between the three studies, the efficacy profile of brexanolone was consistent and durable through 30 days, with no regression of effect that would have indicated a need for further medication. Thus, the discussion of efficacy and risk benefit is anticipated to be straight-forward and concise.

In accordance with FDA's guidance "Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document," Sage is proposing to present a Summary of Clinical Efficacy (SCE) in Module 2.7.3, which will serve as the Integrated Summary of Efficacy (ISE), with the datasets and tables presented in Module 5. The narrative portion of the ISE is considered appropriate and sufficiently concise for inclusion in Module 2, with appendices of tables, figures, and datasets located in Module 5, Section 5.3.5.3. A cross-reference in Module 5 will be provided to direct the reviewer to Module 2.7.3.

***FDA Response to Question 2:*** *In general, we have no objection to your proposed ISE because of its exploratory nature. We may ask for additional exploratory analysis during the NDA review.*

- a) *We agree with your proposal to pool studies 547-PPD-202A, -202B, and -202C in the ISE. You do not need to include Study 547-PPD-201 in the ISE, given its open-label, uncontrolled study design.*
- b) *We agree with your proposal for placing the narrative portion of the ISE in Module 2.7.3 and cross-referencing datasets and tables located in Section 5.3.5.3.*

- c) *On face, we agree with your proposed analyses to evaluate both doses of SAGE-547. In addition, we would like you to perform exploratory subgroup analyses according to baseline PPD severity (i.e., baseline HAM-D total score) and for the concomitant use of another antidepressant (at study entry, as well as initiation after infusion treatment).*

*We note that the 60 µg/kg/h infusion appears to have outperformed the 90 µg/kg/h infusion on HAM-D scores. We are interested in whether you have any hypotheses as to why this was the case. We also would like to discuss your reasoning behind choice of starting dose for potential labeling. Possible options (depending on the data submitted) could be:*

- *Target dose of 90 µg/kg/h*
- *Target dose of 60 µg/kg/h*
- *Starting target dose of 60 µg/kg/h, increase to 90 µg/kg/h for incomplete response*
- *Starting target dose of 90 µg/kg/h, taper to 60 µg/kg/h based on tolerability issues*

**Discussion at Meeting:**

*(a) No further discussion.*

*(b) No further discussion.*

- (c) The Sponsor presented efficacy data from the combined PPD studies and made the case that the 60 µg/kg/h dose appears to be as effective as the 90 µg/kg/h dose. However, because the 60 µg/kg/h dose was not replicated on the primary efficacy endpoint, and the results for this dose were from only 38 subjects, they proposed dosing recommendations that specify a target dose of 90 µg/kg/h but allow for a taper to 60 µg/kg/h based on tolerability. They noted that in previous studies, reducing the dose in this manner quickly resolved adverse events such as somnolence. However, they also noted that most AEs occurred at doses lower than 90 µg/kg/h. The Sponsor viewed this as favoring a 90 µg/kg/h target. However, the Division felt this could support a 60 µg/kg/h dose (i.e., if patients would be at risk for AEs during titration anyway, why target 90 µg/kg/h?).*

*The Division asked the Sponsor to perform an analysis to determine if any subjects who had not shown a treatment benefit at 24 hours (prior to titrating the dose to 90 µg/kg/h) demonstrated therapeutic benefit at later time points (after titrating to the 90 µg/kg/h dose).*

*Regarding exploratory subgroup analyses, the Sponsor asked whether the Division would accept a HAM-D cut-off of  $\geq 25$  and  $< 25$  to describe subjects with severe vs. moderate PPD; the Division accepted this definition.*

**Question 3 (Integrated Summary of Safety (ISS)):**

- a) Does the Agency agree with proposed studies for safety pooling and separately summarizing study 547-CLP-102 in the ISS?**

**b) Does the Agency agree with the approach to the SCS/ISS, specifically its placement in Module 2?**

Sponsor's Position and Justification:

Sage is proposing to include data from 13 clinical studies in subjects treated with brexanolone alone or brexanolone with a placebo control. The ISS will integrate data from all studies with the exception of the subjects in the clinical pharmacology study 547-CLP-102 (Human Abuse Potential; HAP). Data from the HAP study will be presented separately with links to the study reports but not included in the safety pools. The proposal for the HAP study to be presented separately is based on the study design employing a dose range portion to determine the maximum tolerated dose for this distinct subject population and who were subsequently all administered suprathreshold doses of brexanolone (up to three times the planned maximum maintenance dose of 90 µg/kg/h). The administration of suprathreshold dose levels may result in a number of adverse event reports for somnolence attributed to study drug in the non-PPD population. Inclusion of this study in the overall safety assessment would likely adversely impact the ability to draw reasonable conclusions related to safety and tolerability of brexanolone in the PPD population.

Data from the oral dosing cohorts in the clinical study 547-CLP-107 (Oral Bioavailability) will be integrated but not pooled with the other studies for presentation. This is because the route of administration is different from the intended commercial route of administration and the resultant plasma concentrations following the single oral doses were generally very low. The data from the IV cohort will be integrated and pooled within the ISS, in keeping with presenting the overall safety analysis solely on the intended commercial route of administration. The full data from all cohorts in the 547-CLP-107 study will be presented in the clinical study report. As previously agreed to at the Breakthrough Designation Meeting, safety data from unconscious subjects with SRSE will not be presented in the ISS (individual study reports will be provided for reference). The proposed pooling for safety will include the following pools of subjects:

**Sponsor’s Table 25: Safety Pools Study.**

Study	All Studies Pool	PPD Pools		Health Volunteer Pool
	All	All	PC	All
PPD-201	X	X		
PPD-202A	X	X	X	
PPD-202B	X	X	X	
PPD-202C	X	X	X	
CLP-101	X			X
CLP-102*	HAL study to be presented separately			
CLP-103	X			X <sup>^</sup>
CLP-104	X			X <sup>^</sup>
CLP-105	X			X
CLP-106	X			X
CLP-107 <sup>#</sup>	X			X
CLP-108	X			X
ETD-201	X			

All = All Studies Pool; PC = Placebo Controlled Studies Pool \* Study 547-PPD-102 is the human abuse potential study which included supratherapeutic dose levels ^ Only subjects with normal renal or hepatic function will be included in the healthy volunteer pool. # Only subjects and their data from Part 3 of Study CLP-107 in which an IV infusion was given will be included.

Based on the safety profile to date and in compliance with FDA’s guidance “Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document”, Sage is proposing to present a Summary of Clinical Safety (SCS) in Module 2.7.4, which will serve as the Integrated Summary of Safety (ISS) with the datasets presented in Module 5. To date, the safety profile is favorable with limited safety events that would lead to a large ISS, therefore, the narrative portion of the ISS in Module 2 is considered appropriate with appendices of tables, figures, and datasets located in Section

**FDA Response to Question 3:**

a) *We generally agree with your classification of proposed studies for safety pooling. You do not need to integrate the oral dosing cohorts in Study 547-CLP-107 (assessing oral bioavailability) in the ISS, because it will be of little value for assessing safety and tolerability of SAGE-547 when used as intended. We agree that you do not need to include data from Study 547-CLP-102 (human abuse potential study) in the safety pool given its design and the supratherapeutic doses used. However, presenting these data separately may be useful for assessing safety at doses higher than recommended (as can sometimes occur with off-label use). Finally, it appears that some of the pools consist of randomized trials with different randomization ratios. Naïve pooling of these studies can lead to Simpson’s paradox.*

- b) We agree with your proposal for placing a SCS/ISS in Module 2.7.4 and cross-referencing datasets and tables located in Section 5.3.5.3.

**Discussion at Meeting:** The Sponsor presented safety data from their PPD study program and made the case that, although 60 and 90 µg/kg/h doses will be presented individually, the focus of the ISS presentation will be on the combination of both SAGE-547 doses vs. placebo. They noted that most adverse events occurred shortly after treatment initiation, before subjects had been titrated to 90 µg/kg/h, and there did not appear to be any clear safety differences between the two doses. The Division accepted this proposal but reiterated its initial comment that naïve pooling of studies could lead to Simpson’s paradox. The Division noted that we would assess the data in review and ask for additional analyses, if indicated.

**Question 4 (Safety Database): Does the Agency confirm that the size of the proposed clinical safety database is adequate to support filing of the NDA?**

**Sponsor’s Position and Justification:**

Sage anticipates the safety database will contain 144 subjects with PPD exposed to brexanolone as well as 224 subjects in Phase 1 and other indications for a total of 368 subjects exposed to brexanolone. Sage believes this is adequate for the evaluation of safety in the PPD population in the context of the endogenous nature of the active substance, the short duration of treatment, and the fact that target plasma concentrations approximate those observed at the end of pregnancy. Sage does not anticipate there would be rare events in the PPD population with brexanolone treatment due to the natural exposure at similar levels in pregnant women, therefore the size of the safety database would be sufficient to detect a safety signal in this population. Further, based on the data from the three placebo-controlled studies, the overall safety profile of brexanolone is comparable to placebo.

**Sponsor’s Table 26: Exposure to Brexanolone.**

Study Number	Number of Subjects Exposed to Brexanolone	Estimated Total per Indication
<b>PPD</b>		
547-PPD-201	4	144
547-PPD-202A	10	
547-PPD-202B	79	
547-PPD-202C	51	
<b>ETD</b>		
547-ETD-201	25	25
<b>Clinical Pharmacology</b>		
547-CLP-101	8	199
547-CLP-102	65	
547-CLP-103	32	

547-CLP-104	17	
547-CLP-105	26	
547-CLP-106	30	
547-CLP-107	9	
547-CLP-108	12	
<b>Total Exposure</b>	<b>368 subjects</b>	

At the Breakthrough Designation Meeting, it was agreed that an estimated 327 subjects exposed to brexanolone (122 with PPD) would be considered an adequate safety database. Because studies 202B and 202C included increases in sample size from what was discussed at the breakthrough designation meeting, the number of subjects with PPD exposed to brexanolone in the placebo-controlled studies is 140, resulting in an overall increase in the number of subjects exposed to brexanolone in subjects with PPD at the time of NDA submission. Due to emphasis on enrollment in studies 202B and 202C, (b) (4)

**FDA Response to Question 4:** *We agree that the size of your proposed clinical safety database (144 subjects with PPD and 224 subjects in Phase 1 or with essential tremor exposed to SAGE-547) is adequate to support filing of the NDA.*

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

**Question 5 (Case Report Forms):** **Does the Agency agree with the proposal for submission of the CRFs?**

**Sponsor's Position and Justification:**

Case report forms (CRFs) will be submitted for all subjects who were treated with study drug (brexanolone, placebo or other study drug administered in Phase 1 studies) and who experienced a Serious Adverse Event (SAE) or discontinued due to an adverse event in any completed non-SRSE study. There were no deaths in any study unrelated to SRSE. It is anticipated that there will be very few such CRFs submitted. In addition, an annotated sample CRF will be provided. Narrative descriptions will also be provided for each subject who experienced other significant AEs such as loss of consciousness, medication errors and syncope. As agreed at the Breakthrough Designation Meeting, data from the SRSE population is not considered relevant for the PPD population and CRFs will not be provided for these subjects.

**FDA Response to Question:** *We agree with your proposal for CRF submission.*

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

**Question 6 (Safety Update):**

**a) Does the Division agree to waive the requirement for a 120-day safety update?**

(b) (4)

***FDA Response to Question 6:*** *We agree to waive the requirement for a formal 120-day safety update. However, if any deaths or serious adverse events occur after the NDA inclusion cut-off date and prior to the completion of our NDA review, we would review the IND Safety Reports that are submitted to the Division and incorporate their information in our NDA review.*

***Discussion at Meeting:*** *The Sponsor* (b) (4) *asked the Division whether we would accept a shorter follow-up period than the initially proposed* (b) (4) *The Division agreed to shortening the follow-up period, because most adverse events occurred shortly after initiating the treatment infusion and it would be difficult to infer causality for events occurring long after the single treatment dose.*

**Question 7 (Abuse Potential):**

- a) Does the Agency agree with the proposed plan for assessing abuse liability and presentation in the NDA including the proposed pooling strategy, exclusion of SRSE subjects from the analysis, assessment of discontinuation effects, list of abuse liability terms, and placement in the NDA?**
- b) Given the potential for an expedited NDA review under priority review/breakthrough designations, is there anything that Sage can do to allow for completion of both Controlled Substance Staff and DEA reviews prior to NDA approval?**

**Sponsor's Position and Justification:**

Sage has completed a nonclinical and clinical program to assess the abuse potential of brexanolone. Sage will be proposing a scheduling for brexanolone based on the completed nonclinical and clinical studies, which is consistent with other neuroactive steroids and compounds that interact with GABA receptors. Sage is proposing a scheduling recommendation of not more than Schedule IV. The SAP for the drug abuse liability assessment (DALA) is provided in [Appendix C](#).

#### Proposed Pooling Strategy

Subjects from SAGE-547 studies included in the ISS who received any study drug will be included in the pooled analyses of abuse liability and will be labeled as the Overall Abuse Liability Population. As unconscious subjects with SRSE are unable to report on events related to abuse liability or dependence, the three SAGE-547 studies enrolling unconscious subjects (547-SSE-201, 547-SSE-301, 547-SSE-302) will not be included in the abuse liability analyses. Analysis populations will be defined by the treatment received at any time during the trials, regardless of treatment duration. Subjects who received more than one treatment within the same study (e.g., crossover studies) will be counted once in each applicable treatment group; adverse events will be assigned to the last treatment received prior to the time of the onset of the AE. In the Placebo-Controlled analysis pools, subjects will be categorized as receiving either SAGE-547 (All SAGE-547) or Placebo. Subjects receiving SAGE-547 will have treatment groups further categorized as SAGE-547 <100µg/kg/h, SAGE-547 100-200 µg/kg/h, or SAGE-547 >200 µg/kg/h. Dose categories refer to the received treatment and reflect the targeted maintenance dose for that subject.

To evaluate for events potentially related to abuse liability, the following four subject populations will be used: (*see Briefing Package pages 64-68 for continuation*).

#### **FDA Response to Question 7:**

a) *The pooling strategy, described in the briefing materials, may be included in the analysis to be submitted for the NDA, if this is provided in addition to, and not instead of, the analyses recommended in the guidance for industry, Assessment of the Abuse Potential of Drugs, available at:*

<https://www.fda.gov/downloads/drugs/guidances/ucm198650.pdf>

*Abuse-related AEs, in comparison to placebo, should be reported by study, population, and dose, and displayed in tabular format including study number and type of study, subject ID number, narratives, case description and details. Narratives describing these events should be provided in tabular form, and should include timing of the event in relation to drug administration, duration, severity; including whether multiple events were observed simultaneously, and if other drugs were involved. Any pharmacokinetic measures available in relation to the events should be provided.*

*Details of the Statistical Analysis Plan provided in the briefing materials are being reviewed by FDA biostatisticians and the results of that review will be provided as soon as they are available. The recommended list of abuse-related AEs described in the briefing materials appears to be consistent with our guidance. We agree that patients with super-refractory*

*status epilepticus (SRSE) may be omitted from the pooling data. However, any potentially relevant data, pre-clinical or clinical, from your development programs for SRSE or any other potential indications for allopregnanolone, should be included in the overall assessment of abuse liability in this NDA. Proper placement of abuse-related data within the NDA is described on page 8 of the Guidance, and the abuse potential section of the NDA should include (or cross-reference) the Integrated Summary of Safety (ISS).*

- b) *Under the 2015 legislation, the Improving Regulatory Transparency for New Medical Therapies Act, the Drug Enforcement Administration (DEA) has 90 days to issue an interim final rule to schedule a drug, counting from the later of the following two dates: (1) the date DEA receives, from the Department of Health and Human Services, the scheduling recommendation for the new drug; or (2) the date FDA notifies DEA that FDA has approved an NDA for the new drug product. Both events must occur in order for DEA to proceed with drug scheduling. See additional details of the drug scheduling process in Section III. E of the Guidance.*

*Once DEA has issued a final scheduling decision and assigned a controlled substance schedule, the controlled substance symbol, e.g., C-II, C-III, C-IV or C-V, must be included in the product labeling as required under 21 CFR 201.57(c)(10) (i) and 1302.03. To update the labeling following the scheduling action, a supplement to the NDA must be submitted by the applicant to update product labeling to reflect the DEA scheduling action described in the final rule or interim final rule (see 21 CFR 314.70). Following that, the appropriately labeled FDA-approved drug product may be marketed.*

**Discussion at Meeting:**

- (a) *For tables modeled on your slide # 19, you should also make sure that the data set includes all relevant timing (dates and/or hours from baseline). This would include date of last contacts, first and last exposure to treatment, times and dates of event, last visit, and time of AE and time of administration relative to date of delivery (of the child). Also, include time of day and context within the sleep cycle (if known) for events related to maternal sedation or arousal.*

**Post Meeting Note**

*As stated in the FDA pre-meeting response, the pooled analyses described specifically in the SAP are acceptable in addition to, but not instead of, those described in the guidance. Further consultation with FDA biostatisticians yielded the general advice that in performing pooled analyses, study-size adjusted pooling was preferred over crude pooling, as a matter of statistical practice. We also stated at the meeting that study-size adjustment has not typically been required in the past for post-hoc pooled analysis of AEs.*

*We will not require any special or specific pooled analyses of clinical studies in the application beyond the analysis of AEs already described in the guidance. The results and statistical analyses of data from the HAP study you are conducting will be sufficient as a quantitative pre-specified analysis informing our understanding of the abuse liability for the new drug.*

*(b) No further discussion.*

**Question 8 (Data Standardization Plan): Does the Agency agree with the proposed Data Standardization Plan and the presentation of electronic datasets and documentation in the NDA?**

Sponsor's Position and Justification:

Please see the SAGE-547 Study Data Standardization Plan provided in Appendix D.

**FDA Response to Question 8:** *Yes, your Data Standardization Plan and proposed organization of electronic datasets and documents are acceptable.*

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

## 2.2. Regulatory

**Question 9:**

- a) Does the Agency agree with the plan to request Priority Review?
- b) Is there any additional information that the Agency would require for justification for Priority Review that would assist in granting this request?
- c) Is there any guidance, suggestions or methods for communicating which have been successful for other sponsors that would aid review of NDA submission that the Agency can share?
- d) Does the Agency agree that the waiver request for the filing fee is appropriate for Sage Therapeutics?
- e) Does the Agency agree that acceptance for filing of the NDA is not directly dependent on the initiation of the adolescent study, (b) (4) given Sage's commitment and progress toward initiation of this study?

Sponsor's Position and Justification:

Sage is proposing that brexanolone be indicated for the treatment of postpartum depression. There are no approved therapies for PPD, a serious condition which can be life-threatening with potentially morbid consequences for mothers, children, and their families. Therefore, Sage plans to request Priority Review, with a justification that is consistent with that provided for the Breakthrough Therapy Designation. In particular, the potential for brexanolone to have "an improved effect on a serious outcome(s) of the condition compared with available therapy" as measured by time to and magnitude of response on depression scales in patients with PPD, as evidenced by the 547-PPD-202 studies. Brexanolone may further provide an advantage over available therapies (approved for MDD but used for PPD) by providing "efficacy comparable [and potentially improved] to those of available [MDD] therapy, while (1) avoiding serious toxicity that occurs with available therapy, (2) avoiding less serious toxicity that is common and causes discontinuation of treatment of serious condition, or (3) reducing the potential for harmful

drug interactions.” Preliminary clinical evidence from studies of brexanolone as a treatment for PPD demonstrates a substantial and clinically meaningful improvement compared to currently available therapies while potentially avoiding prolonged exposure to side effects associated with available therapies.

As Sage is a small business with less than 500 employees and this is the first human new drug application to be submitted, Sage is planning to request a waiver for the filing fee under Section 736(d)(1)(E) of the FD&C Act prior to the NDA submission.

The pediatric study plan for brexanolone has been agreed to with the Agency and Sage has recently submitted the Proposed Pediatric Study Request for the Agency’s consideration to issue a pediatric Written Request. The planned adolescent study is on track to be initiated in April 2018. Sage may submit the NDA prior to this study initiation.

**FDA Response to Question 9:**

- a) *We agree with your plan to request Priority Review.*
- b) *Please refer to the [Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics](#) for additional details. Your information supporting the priority review designation request should include the basis for considering the drug to be intended to treat a serious condition and the basis for the assertion that the drug would be a significant improvement in the safety or effectiveness of the treatment of a serious condition.*
- c) *Our review team will submit information requests during the process of NDA review. Prompt, detailed, and clear responses will help us review your NDA efficiently. There will also be opportunities for meetings/teleconferences during the NDA review cycle for communication with the review team.*
- d) *We agree that Sage Therapeutics can request a waiver from the filing fee. For additional information on user fee waivers please refer to the "Guidance for Industry: User Fee Waivers, Reductions, and Refunds for Drug and Biological Products". If you have further questions, contact the Division of User Fee Management and Budget Formulation at [CDERCollections@fda.hhs.gov](mailto:CDERCollections@fda.hhs.gov) or at (301) 796-7900.*
- e) *We agree that acceptance for filing the NDA is not directly dependent on initiating the adolescent study, [REDACTED] (b) (4) As communicated in the Agreed iPSP (dated October 17, 2017), Section 11, Timeline of the Pediatric Development Plan, Efficacy/Safety Studies, the estimated protocol submission date will be no later than January 2018 and the estimated study initiation date will be no later than April 2018. Therefore, you should submit your proposed protocol for the study of allopregnanolone in adolescent subjects with PPD as soon as possible. As communicated on June 15, 2017, we ask that anticipated completion of the adolescent study is within a short time following the NDA decision date.*

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

**Post Meeting Note**

*We would like to remind you that a drug that is first to treat an indication and/or that has a different mechanism of action is, by default, a candidate to be discussed at a public advisory committee meeting.*

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

**Additional Biostatistics Comments**

*For each efficacy trial to support an efficacy claim, please include the following items in your NDA submission:*

- (a) all raw as well as derived variables in .xpt format,*
- (b) the executable SAS programs for primary and sensitivity analyses of endpoints intended to be described in the labeling,*
- (c) the executable SAS programs by means of which the derived variables were produced from the raw variables,*
- (d) all the meeting minutes of Independent Data Monitoring Committee (IDMC) and letters sent from IDMC to the sponsor, and*

*(e) a list of serial numbers and submission dates for all protocols, all protocol amendments, and any statistical amendments [including Statistical Analysis Plans] submitted to all relevant INDs.*

**Sponsor's Response:** Sage would like to request clarity on the meeting minutes of the IDMC. For the PPD program, an IDMC was not used, however, Sage intends on providing the minutes from the sample size re-estimation decision that occurred in Clinical Study 547-PPD-202A in the NDA.

**Discussion at Meeting:** *The Sponsor's proposal appears acceptable.*

### **Additional Nonclinical Comments**

*We remind you that we need additional information on three circulating major human metabolites (M133, M136, and M137) before we can provide you a definitive answer on whether a nonclinical assessment of these metabolites will be needed (as per our Information Request dated April 12, 2017).*

**Sponsor's Response:** Sage also plans to provide the additional information requested in support of the nonclinical assessment for the three major metabolites as part of the NDA submission.

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

## **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 and, where applicable, the development of a Formal Communication Plan.
- 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.

### **PREA REQUIREMENTS**

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

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

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email [Pedsdrugs@fda.hhs.gov](mailto:Pedsdrugs@fda.hhs.gov). For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

## **PRESCRIBING INFORMATION**

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

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

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

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

### **SUBMISSION FORMAT REQUIREMENTS**

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. 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>.

### **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>.

**MANUFACTURING FACILITIES**

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

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

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 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).

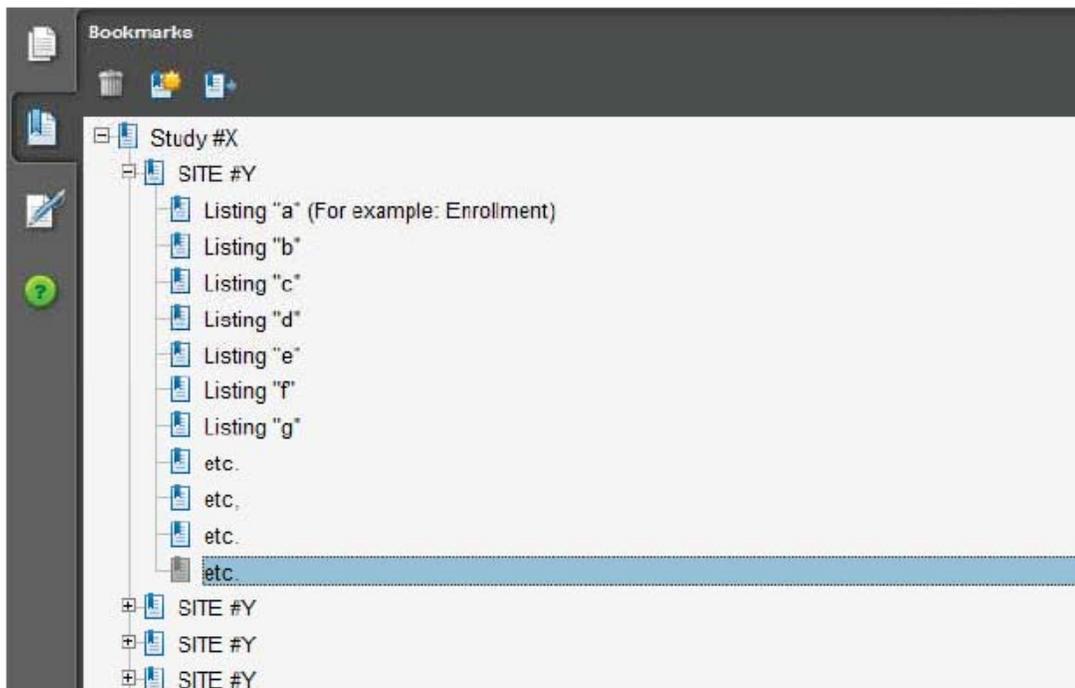
**I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

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 <sup>1</sup>	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:



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](mailto:ESUB@fda.hhs.gov)

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

#### **4.0 ISSUES REQUIRING FURTHER DISCUSSION**

*None.*

#### **5.0 ACTION ITEMS**

*None.*

#### **6.0 ATTACHMENTS AND HANDOUTS**

*Sponsor's Slides.*

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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.**  
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/s/  
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MITCHELL V Mathis  
02/08/2018