CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211243Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 114345

MEETING MINUTES

Janssen Research & Development, LLC
Attention: Patricia Treichler, RAC
Associate Director, Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

Dear Ms. Treichler:

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

We also refer to the meeting between representatives of your firm and the FDA on June 28, 2018. The purpose of the meeting was to discuss results from the completed relapse prevention maintenance study and potential implications for dosing and administration, and proposed plans for risk minimization. In addition, you seek to reconfirm acceptability of inclusion of Javelin nonclinical data in the NDA.

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, call Hiren Patel, Regulatory Project Manager at (301) 796-2087.

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

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: June 28, 2018 from 2:30pm-3:30pm (EST)
Meeting Location: CDER WO Bldg. 22, Room 1311

Application Number: IND 114345
Product Name: esketamine (JNJ-54135419)

Indication: Treatment Resistant Depression
Sponsor/Applicant Name: Janssen Research & Development, LLC

Meeting Chair: Dr. Mitchell Mathis

FDA ATTENDEES

Ellis Unger, MD	Director, Office of Drug Evaluation I (ODE-I)
Robert Temple, MD	Acting Deputy Director, ODE-I; Deputy Center Director for Clinical Science
Naomi Lowy, MD	Acting Associate Director for Regulatory Science, ODE-I
Mitchell Mathis, MD	Director, Division of Psychiatry Products (DPP)
Tiffany Farchione, MD	Deputy Director, DPP
Keith Kiedrow, PharmD	Regulatory Project Manager Team Leader, DPP
Bernard Fischer, MD	Clinical Reviewer, DPP
Aisar Atrakchi, PhD	Pharmacology/Toxicology Supervisor, DPP
Shiny Mathew, PhD	Pharmacology/Toxicology Reviewer, DPP
Laura McGhee, PhD	Pharmacology/Toxicology Reviewer, DPP
Thomas Birkner, PhD	Biometrics Reviewer, Division of Biometrics I
Hao Zhu, PhD Clinical	Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Kofi Kumi, PhD	Clinical Pharmacology Reviewer, OCP
David Claffey, PhD	CMC Lead, Office of Pharmaceutical Quality (OPQ)
Thomas Wong, PhD	CMC Reviewer, OPQ
Jenn Sellers, MD	Reviewer, Office of Scientific Investigations
Jovita Randall-Thompson, PhD	Reviewer, Controlled Substance Staff
Jamie Wilkins, PharmD	Deputy Director, Division of Risk Management (DRISK)
Leah Hart, PharmD	Team Leader, DRISK
Theresa Ng, PharmD	Reviewer, DRISK

SPONSOR ATTENDEES

David Hough, MD	Compound Development Team Leader
Jaskaran Singh, MD	Clinical Team Leader
Ella Daly, MD	Medical Leader
Heddie Martynowicz, DM, MS	Global Regulatory Leader
Peter Zannikos, PhD	Clinical Pharmacology Leader
Eric De Waal, PhD	Nonclinical Leader
Pilar Lim, PhD	Mood Disorders Statistics Functional Leader
Rosanne Lane, MAS	Statistical Leader
Luc Truyen, MD, PhD	Head of Development
Patricia Treichler, BS, RAC	U.S. Regulatory Affairs Leader

1.0 BACKGROUND

Janssen Research & Development, LLC is developing intranasal esketamine, the S-enantiomer of ketamine, for the treatment of adult subjects with treatment-resistant depression (TRD; (b) (4) under IND 114345. They are also developing intranasal esketamine for the treatment of patients with major depressive disorder who are at imminent risk of suicide (b) (4)

The Agency and the Sponsor have met eleven times under IND 114345:

- 03/14/2018 – Type B Pre-NDA Meeting
- 03/01/2016 – Breakthrough Therapy Designation Guidance Meeting
- 12/14/2015 – Type C Guidance Meeting (regarding the suicidal ideation indication)
- 06/24/2015 – Type A Guidance Meeting
- 12/08/2014 – End of Phase 2 Meeting
- 09/12/2014 – Breakthrough Guidance Meeting
- 06/05/2014 – Breakthrough Guidance Meeting
- 03/13/2014 – Type B Guidance Meeting
- 03/13/2014 – Guidance Meeting
- 10/22/2013 – Type C Guidance Meeting (regarding the suicidal ideation indication)
- 05/08/2012 – Type B Guidance Meeting

Important decisions regarding product development relevant to the current meeting request include:

- The definition of treatment-resistant depression (as above)
- The length of the acute esketamine treatment phase (4 weeks)
- The need to initiate a new conventional, oral antidepressant treatment during the acute esketamine treatment phase
- The need for and design of a maintenance study in addition to two adequate and well-controlled acute treatment trials

- The need for and nature of an abuse potential study
- The primary endpoint (the difference in MADRS score from baseline to the end of 4 weeks) and key secondary endpoints (onset of clinical response, Sheehan Disability Scale, 9-item Patient Health Questionnaire)

This development program was granted Breakthrough Therapy Designation and there is an agreed iPSP granting a full waiver of pediatric studies in TRD (a pediatric Written Request was issued (b) (4)

The TRD Phase 3 development program includes three short-term studies (a fixed-dose study in adults (ESKETINTRD3001), a flexible-dose study in adults (TRD3002), and a flexible-dose study in patients 65 years and older (TRD3005)), one relapse prevention maintenance study (TRD3003), and one long-term safety study (TRD3004); see Table 1. The Sponsor is also conducting an open-label extension study to allow subjects completing the Phase 3 studies continued access to esketamine (TRD3008). The Sponsor projects that all studies will be completed in the next several months (except for Study TRD3008) and that the NDA will be submitted in September, 2018.

The Sponsor requested this meeting to discuss results from the completed relapse prevention maintenance study and potential implications for dosing and administration, and proposed plans for risk minimization. In addition, the Sponsor seeks to reconfirm acceptability of inclusion of Javelin nonclinical data in the NDA.

Table 1. Phase 3 Esketamine Studies for U.S. Registration.

Study	Description	Subjects	Dosing	Status
3001	4-week acute RCT	348	Fixed: 56 or 84 mg twice weekly x 4 weeks	Completed; Negative study *(p = 0.088)*
3002	4-week acute RCT	196	Flexible: 56 or 84 mg twice weekly x 4 weeks	Completed; Positive study *(p = 0.02)*
3003	*12-week dose optimization phase* Direct entry or from 3001/3002 -Open-label for direct entry -Continue drug for transfers *Maintenance phase* -If placebo, will continue -If esketamine, re-randomized to continue or switch to placebo	705 (437 direct entry)	*Optimization* Fixed: 56 or 84 mg weekly – every other week *Maintenance* Flexible: 56 or 84 mg weekly – every other week	Completed; Positive study *(p = 0.003)*
3004	52-week, long-term open-label safety study	691 direct entry, 111 from 3005	Fixed: 28, 56, 84 mg for direct entry Flexible: 28, 56, 84 mg for transfers weekly – every other week	Completed
3005	4-week acute elderly RCT (age ≥ 65)	148	Flexible: 28, 56, or 84 mg weekly x 4 weeks	Completed; Negative study *(p = 0.058)*
3008	Long-term	Variable	Flexible: 28, 56, 84 mg	Ongoing

	open-label extension		dosed weekly – every 4 weeks	

FDA sent Preliminary Comments to Janssen on June 22, 2018 [Background section has been revised].

2. DISCUSSION

2.1. Clinical and Biostatistics

Question 1: **Support for Dosing Recommendations and Long-term Treatment with Esketamine Nasal Spray for Patients with TRD**

Given the positive results from the relapse prevention study TRD3003, does the Division agree with the general approach to dosing recommendations and in principle with continued, long-term treatment with esketamine nasal spray for patients with TRD?

FDA Response to Question 1: *The ultimate determination of labeling (including dosing) is a review issue. However, we agree with your approach to dosing interval determination (basing the label on the results of Study TRD3003).*

Discussion: *The Sponsor presented the information from their briefing package in which they propose to base labeling on the TRD3003 study. They propose to start at 56 mg* (b) (4) (b) (4) *with subsequent doses of 56 or 84 mg. Initially, treatment will be twice per week for 4 weeks. After that, treatment is once weekly for Weeks 5 through 8, and weekly or every other week after that. The proposed label recommends periodic re-evaluation to determine the lowest frequency needed to maintain remission or response. Although the TRD3003 used a formal rating scale, the Sponsor believes this assessment can be based on clinical assessment.* (b) (4)

We agreed that study TRD3003 offers the best data to inform labeling on dosing and agree with this strategy. (b) (4)

Question 2: **Analysis by Stage for Studies TRD3001 and TRD3005**

A sample size re-estimation was conducted in 2 of the Phase 3 short-term studies (TRD3001 and TRD3005). In both studies the weighted combination test was used and, as prespecified in the statistical analysis plan, Stage 1 (before the interim analysis [IA]) and Stage 2 (after the IA) were weighted equally. As previously described in the 14 March 2018 Pre-NDA Meeting Briefing Document (13 Feb 2018/SN0233) and further discussed at the meeting, the results showed a

differential treatment effect by stage. Does the Division agree that the Sponsor's plan to explain the Stage 1 and Stage 2 differences as described below will satisfactorily address the Division's request for more information on why there might be different outcomes for subjects enrolled in TRD3001 and TRD3005 before and after the IA?

FDA Response to Question 2: *Your explanations are helpful. However, a thorough assessment of the issue will be postponed until after filing of the NDA.*

Discussion: *No further discussion.*

2.2. Clinical Pharmacology

Question 3: **Submission of Final Results from Study TRD1019**

The Sponsor has completed a single-dose study that evaluated the effect of esketamine on on-road driving in healthy subjects (TRD1006) and is currently conducting a second on-road driving study after single and repeated dosing (TRD1019) in subjects with MDD. An interim study report (based on an IA of the second driving study) will be submitted with the initial NDA. The final study report from this second study is expected to be available during the review of the NDA. The Sponsor proposes to submit the final study report to the NDA when available (targeted by the 4-month safety update [4-MSU]) or alternatively as a post-marketing commitment. Does the Division agree?

FDA Response to Question 3: *If the application is classified as a priority review, submitting the final study report at the 4-MSU could present a challenge. If the study results are unexpected or otherwise present a complex picture for review, we may consider this a major amendment.*

Discussion: *The Sponsor indicated that 21 out of 24 planned subjects have enrolled in the study. They will provide an interim report at filing based on the 21 subjects and intend to submit a final report after 24 subjects have completed the study. Based on the evaluation of the 21 subjects that have completed the study to date, the Sponsor plans to recommend that patients not drive for* (b) (4) *after dosing.*

The Agency agreed that the interim report would be adequate for filing and can submit the final report during the review. The Agency indicated that a consideration to extend the review clock would happen if the final and interim reports are significantly different that would affect the instructions in the label.

2.3. Risk Management

Question 4: **Adequacy of Risk Minimization Measures**

Does the Division agree with the Sponsor that known and potential adverse events and/or risks that may be related to esketamine can be adequately minimized through the product labeling, legal status (Schedule III), administration of the product in a clinical setting under the supervision of a health care professional, device design, and limited pack size supplied directly to site of care and therefore, a formal risk evaluation and mitigation strategy (REMS) program is not warranted?

FDA Response to Question 4: *Whether a risk evaluation and mitigation strategy (REMS) is necessary to ensure that the benefits of the drug outweigh the risks of misuse and abuse will be determined during the review of the application. However, the risk minimization measures that you proposed in your pre-meeting package closely resemble a REMS; therefore, we encourage you to submit a proposed REMS with your application. A complete review of the REMS, in conjunction with the full clinical review of the submission, will be necessary to determine if it is needed, if it adequately addresses the relevant safety risks, and if it meets the criteria set forth in section 505-1 of the Federal Food, Drug, and Cosmetic Act. If you chose to submit a REMS, provide details of the proposed suspicious order monitoring program. Please see our Guidance for Industry: Format and Content of a REMS Document for additional information.*

> ***Discussion:*** *The Agency conveyed to the Sponsor that, although the risk minimization measures described are reasonable, these measures resemble a REMS with ETASU. We therefore recommend that the Sponsor consider submitting a REMS with the NDA application (section 1.16 Risk Management Plan). Ultimately, whether a REMS is needed for this product is the subject of the application review, and risk mitigation will be addressed at an Advisory Committee meeting. At this time, the Agency and the Sponsor appear to be generally aligned regarding structure and elements of risk mitigation, as outlined in the briefing package, and for multiple reasons including Agency review and enforceability, it is likely that this product will require a REMS. The Agency further explained that a REMS with ETASU is generally assessed annually and although there are instances when a REMS may be eliminated due to new safety information thereby changing the characteristics of a risk mitigated by a REMS; unless this occurs, the REMS will remain in effect.*
>
> *There was further discussion on safe use of the product including whether the product requires the supervision of a prescriber in the context of vital sign changes and dissociation. The Sponsor indicated that there is data to suggest that the vital sign changes and dissociation dissipate over the course of treatment. The Sponsor was encouraged to submit this information to their application when that data is available to better inform any risk mitigation surrounding this safety issue.*

2.4. Regulatory

Question 5: **Adequate Support for Filing an NDA**

Subject to review of the file, does the Division agree that efficacy and safety data from completed Phase 3 Studies TRD3001, TRD3002, TRD3003, TRD3004, TRD3005 and 2 Phase 2

studies (TRD2003, SUI2001) are adequate to support filing of an NDA for esketamine for the following indication?

TRADENAME is indicated for treatment-resistant depression [redacted] (b) (4)

FDA Response to Question 5: *We agree that, on face, your program is adequate to support filing. The indication will be a matter of review after the NDA is filed.*

Discussion: *No further discussion.*

Question 6: **Safety Database**

Does the Division agree that the size of the safety database is adequate to support filing of an NDA for esketamine for TRD?

FDA Response to Question 6: *We agree that your safety database (479 subjects exposed for at least 180 days and 178 subjects exposed for at least 350 days) is adequate to support NDA filing.*

Discussion: *No further discussion.*

Question 7: **Preparation for PDAC Meeting**

The Division has previously informed the Sponsor of their intention to seek the Psychopharmacologic Drugs Advisory Committee's (PDAC) advice and recommendations regarding the esketamine NDA once filed. At the Pre-NDA meeting held on 14 March 2018, the Division indicated in preparation for PDAC, a number of additional meetings will be held with JRD to discuss potential issues and the presentation to ensure alignment. The Sponsor requests additional information such as potential timing and logistical considerations for these meetings, and expectations.

FDA Response to Question 7: *The PDAC will be coordinated by the Division of Advisory Committee and Consultant Management (DACCM). The required deliverables and associated timelines will be communicated by DACCM if and after the application is filed. In addition, the Division will hold a teleconference with Janssen to provide a general overview of the scheduled PDAC including date, time, and location. The Division is amenable to additional teleconferences if necessary including holding a teleconference to reach alignment prior to the PDAC meeting.*

Discussion: *No further discussion.*

2.5. Nonclinical Development

Question 8: **Acceptability of Nonclinical Studies Conducted by Javelin Pharmaceuticals**

The Sponsor is seeking reaffirmation of the Division's prior agreement that inclusion of the nonclinical studies acquired from Javelin Pharmaceuticals is acceptable in the planned NDA. Specifically,

a. Does the Division agree with JRD's position to include *in vitro* and *in vivo* genotoxicity studies conducted with ketamine by Javelin Pharmaceuticals to complement the genotoxicity tests performed with esketamine, despite missing raw data?
b. Does the Division agree with JRD's position that the rat and rabbit embryo-fetal developmental toxicity studies conducted by Javelin Pharmaceuticals with ketamine may be included as supporting evidence in the esketamine NDA together with available scientific literature on ketamine, despite missing raw data and bioanalytical method validation reports?
c. Does the Division agree with JRD to provide Debarment Certification in the NDA for all JRD-sponsored studies and description of the efforts to obtain debarment certification for individuals involved in the conduct of Javelin studies?

FDA Response to Question 8a and b: *It is not clear to us what you mean by "missing raw data" given that we understand the data for individual plates/animals were provided for Javelin's genotoxicity and embryo-fetal developmental toxicity studies using PMI100. If you are referring to data formatting issues, we would like to clarify that all study reports prior to 2017 may be accepted in the absence of SEND format. We agree that you may submit the Javelin study reports to the NDA as you have done for your IND.*

> ***Discussion:*** *The Sponsor clarified that they do not have access to raw data given that Javelin's studies were conducted 15 years ago. Pharm/Tox reiterated that what we need for the NDA are the final study reports containing individual line listings of animal/plate data and signed histopathology reports like those submitted under IND.*

FDA Response to Question 8c: *Yes, we agree with your proposal to submit all Debarment Certifications for JRD-sponsored activities and a description of efforts to obtain Debarment Certifications from Javelin for their program. Whether the efforts are acceptable will be a matter of review.*

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

2.6. Clinical and Biostatistics

Question 9: Proposal to Submit an Interim Report with Select Data from Ongoing Study 54135419TRD3008

The Sponsor is currently conducting Study 54135419TRD3008, which is a multicenter, open-label, long-term extension safety study of esketamine in subjects with TRD. Given the potential value to the product labeling, the Sponsor proposes to submit an interim study report with select data from 54135419TRD3008 to the NDA when available (targeted by the 4-month safety update). Does the Division agree?

FDA Response to Question 9: *This proposal is acceptable. However, given the anticipated priority review for the esketamine NDA, you should be aware that any concerning safety signal submitted at the 4-month safety update has the potential to extend the review clock.*

> ***Discussion:*** *The Sponsor clarified that they had been considering submitting selected efficacy data from TRD3008 at the 120-day safety update. However, they have decided against this submission.*

3.0 OTHER

PREA REQUIREMENTS

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

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

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

PRESCRIBING INFORMATION

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

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

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.

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 items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent

with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

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

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ATTACHMENTS AND HANDOUTS

The attached handout was provided by Janssen during the meeting.

Reference ID: 4295682

The Sponsor proposes the following language in the dosage and administration section of the label:

2 DOSAGE AND ADMINISTRATION

The dosage recommendations for TRADENAME are shown in Table X. Dose adjustments should be made based on efficacy or tolerability to the previous dose.

Table X: Recommended Dosing for TRADENAME	
Induction Phase	**Maintenance Phase**
Weeks 1-4 (two dosing sessions/week): Starting dose*: 56 mg Subsequent doses: 56 mg or 84 mg	Weeks 5-8: 56 mg or 84 mg once weekly From Week 9: 56 mg or 84 mg every 2 weeks or once weekly**
Evidence of therapeutic benefit should be evaluated at the end of induction phase to determine need for continued treatment.	Periodically reexamine the need for continued treatment. (b) (4) .

* For patients ≥65 years Day 1 starting dose is 28 mg

** Dosing frequency should be individualized to the lowest frequency to maintain remission/response.

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/

MITCHELL V Mathis
07/24/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 114345

MEETING MINUTES

Janssen Research & Development, LLC
Attention: Patricia Treichler, RAC
Associate Director, Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

Dear Ms. Treichler:

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

We also refer to the meeting between representatives of your firm and the FDA on March 14, 2018. The purpose of the meeting was to discuss the proposed content and format of the New Drug Application in support of the proposed indication for the use of esketamine in the treatment of adult subjects with treatment-resistant major depressive disorder.

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, call Hiren Patel, Regulatory Project Manager at (301) 796-2087.

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

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: March 14, 2018 from 12:00pm to 2:00pm (EST)
Meeting Location: CDER WO Bldg. 22, Room 1311

Application Number: IND 114345
Product Name: esketamine (JNJ-54135419)
Indication: Treatment Resistant Depression
Sponsor/Applicant Name: Janssen Research & Development, LLC

Meeting Chair: Dr. Mitchell Mathis

FDA ATTENDEES

Ellis Unger, MD	Director, Office of Drug Evaluation I (ODE-I)
Naomi Lowy, MD	Acting Associate Director for Regulatory Science, ODE-I
Mitchell Mathis, MD	Director, Division of Psychiatry Products (DPP)
Tiffany Farchione, MD	Deputy Director, DPP
Hiren Patel, PharmD	Regulatory Project Manager Team Leader, DPP
Bernard Fischer, MD	Clinical Reviewer, DPP
Ikram Elayan, PhD	Pharmacology/Toxicology Supervisor, DPP
Shiny Mathew, PhD	Pharmacology/Toxicology Reviewer, DPP
Peiling Yang, PhD	Biometrics Team Leader, Division of Biometrics I
Thomas Birkner, PhD	Biometrics Reviewer, Division of Biometrics I
Hao Zhu, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Kofi Kumi, PhD	Clinical Pharmacology Reviewer, OCP
Kevin Krudys, PhD	Pharmacometrics Team Leader, OCP
David Claffey, PhD	CMC Lead, Office of Pharmaceutical Quality (OPQ)
Thomas Wong, PhD	CMC Reviewer, OPQ
Bernard Marasa, PhD	Product Quality Microbiology Reviewer, OPQ
Mark Johnson, PhD	Process Reviewer, OPQ
Katherine Windsor, PhD	Drug Substance Reviewer, OPQ
Jenn Sellers, MD	Reviewer, Office of Scientific Investigations
Jovita Randall-Thompson, PhD	Reviewer, Controlled Substance Staff
Keith Marin, MS, OCN, RAC	Reviewer, Center for Devices and Radiological Health
Leah Hart, PharmD	Team Leader, Division of Risk Management
Theresa Ng, PharmD	Reviewer, Division of Risk Management

Loretta Holmes, BSN, PharmD	Safety Evaluator, Division of Medication Error Prevention and Analysis

SPONSOR ATTENDEES

Husseini Manji, MD	Global Therapeutic Area Head for Neuroscience
Robert O'Donnell, PhD	Global Regulatory Affairs Head for Neuroscience
David Hough, MD	Compound Development Team Leader
Jaskaran Singh, MD	Clinical Team Leader
Peter Zannikos, PhD	Clinical Pharmacology Leader
Heddie Martynowicz, DM, MS	Global Regulatory Leader
Katrien Verbruggen, MS	CMC Leader
Pilar Lim, PhD	Mood Disorders Statistics Functional Leader
Rosanne Lane, MAS	Statistical Leader
Patricia Treichler, RAC	U.S. Regulatory Affairs Leader
Doug Mead, MS	Global CMC Regulatory Affairs, Devices
Tracy Lin, RPh, MS	Global CMC Regulatory Affairs
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1.0 BACKGROUND

Janssen Research & Development, LLC is developing intranasal esketamine, the S-enantiomer of ketamine, for the treatment of adult subjects with treatment-resistant depression (TR (b) (4) under IND 114345. They are also developing intranasal esketamine for the treatment of patients with major depressive disorder who are at imminent risk of suicide (b) (4).

The Agency and Sponsor have met nine times under IND 114345 (dates are based on Meeting Minutes):

- 03/31/2016 – Breakthrough Therapy Designation Guidance Meeting
- 01/05/2016 – Type C Guidance Meeting (regarding the suicidal ideation indication)
- 07/24/2015 – Type A Guidance Meeting
- 01/07/2015 – End of Phase 2 Meeting
- 10/02/2014 – Breakthrough Guidance Meeting
- 07/03/2014 – Breakthrough Guidance Meeting
- 06/02/2014 – Type B Guidance Meeting
- 04/11/2014 – Guidance Meeting
- 11/04/2013 – Type C Guidance Meeting (regarding the suicidal ideation indication)
- 05/16/2012 – Type B Guidance Meeting

Important decisions regarding product development relevant to the current meeting request include:

- The definition of treatment-resistant depression (as above)
- The length of the acute esketamine treatment phase (4 weeks)
- The need to continue conventional, oral antidepressant treatment during the acute esketamine treatment phase
- The need for and design of a maintenance study in addition to two adequate and well-controlled acute treatment trials
- The need for and nature of abuse potential studies
- The primary endpoint (the difference in MADRS score from baseline to the end of 4 weeks) and key secondary endpoints (onset of clinical response, Sheehan Disability Scale, 9-item Patient Health Questionnaire)

This development program was granted Breakthrough Therapy Designation on November 7, 2013. There is also an agreed iPSP granting a full waiver of pediatric studies in TRD.

The TRD Phase 3 development program includes three short-term studies (a fixed-dose study in adults [ESKETINTRD3001], a flexible-dose study in adults [TRD3002], and a flexible-dose study in patients 65 years and older [TRD3005]), one relapse prevention maintenance study (TRD3003), and one long-term safety study (TRD3004; see Table 1). The Sponsor is also conducting an open-label extension study to allow subjects completing the Phase 3 studies continued access to esketamine (54135419TRD3008). The Sponsor projects that all studies will be completed in the next several months (except for Study 54135419TRD3008) and that the NDA will be submitted in September, 2018. [Note: This paragraph has been modified from the Preliminary Comments dated March 9, 2018]

Table 1. Phase 3 Esketamine Studies for U.S. Registration.

Study Number	Description	Subjects	Dosing	Status
ESKETINTRD 3001	4-week Acute RCT + oral antidepressant[a]	348	Fixed: 56 or 84mg twice weekly x 4 wks	DB Completed
ESKETINTRD 3002	4-week Acute RCT + oral antidepressant	196	Flexible: 56 or 84mg twice weekly x 4 wks	DB Completed
ESKETINTRD 3003	12-weeks Dose optimization + oral antidepressant Direct entry or transfer from TRD3001 & TRD3002 • Open-label for direct entry • Continue drug for transfers Variable-week Maintenance + oral antidepressant • Continue PBO • Esketamine re-randomized to continue or switch to PBO	445 direct entry	Optimization: Fixed: 56 or 84mg dosed weekly – every other week Maintenance: Flexible: 56 or 84mg dosed weekly – every other week	Ongoing
ESKETINTRD 3004	48-week Long-term safety Open-label + oral antidepressant	691 direct entry 111 from TRD3005	Fixed: 28, 56, 84mg for direct entry Flexible: 28, 56, 84mg for transfers dosed weekly – every other week	Completed
ESKETINTRD 3005	4-week Acute elderly RCT + oral antidepressant	148 ≥65 yo	Flexible: 28, 56, or 84mg weekly x 4 wks	Completed
54135419TRD 3008	Long-term extension Open-label	Variable	Flexible: 28, 56, 84mg dosed weekly – every 4 weeks	Ongoing

[a]duloxetine, escitalopram, sertraline, or venlafaxine XR

The Sponsor requested this meeting to discuss the proposed content and format of the New Drug Application in support of the proposed indication.

2. DISCUSSION

2.1. Regulatory and General Overview of NDA and eCTD Content

Question 1: **Application Review**
In an email dated 15 September 2014, the Division indicated that the esketamine NDA would not be reviewed under "the Program" i.e., start of the PDUFA review clock following the 60-day filing review period. Please confirm the Division's current position has not changed.

FDA Response to Question 1: *Based on the available information, the application will not be reviewed under the Program.*

Discussion: *No further discussion.*

Question 2: **Content and eCTD Format of the NDA**
Does the Division agree that the proposed content and eCTD format of the NDA, as described in the eCTD Content Outline and discussed throughout this pre-NDA Briefing Document form the basis for a complete and fileable application?

FDA Response to Question 2: *The proposed content and format of the NDA appears acceptable. Please also see our response to Question 9, below.*

Discussion: *The Sponsor clarified that Study TRD3003 is complete with data lock to occur by the end of this month (March). The full study report will be included when the NDA is submitted (Sponsor is targeting September, 2018).*

Question 3: **Submission of Technical Information**
Does the Division agree with the proposed plan for submission of Nonclinical legacy data, specifically, the Sponsor's plan to submit Nonclinical legacy data of eCTD sections 4.2.3.1, 4.2.3.2 and 4.2.3.4 in PDF format together with datasets as per the Agency's Technical Rejection Criteria for Study Data?

- Does the dataset for these legacy studies entail a Trial Summary (ts) dataset (ts.xpt), a Demographic (DM) dataset (dm.xpt) and a define.pdf file or is a single ts.xpt file sufficient?

- Can the Agency confirm that the eCTD location "M4/datasets/tabulations/legacy" is appropriate for this/these legacy dataset(s)?

FDA Response to Question 3: *The dataset for the legacy studies does not entail a Trial Summary (ts) dataset (ts.xpt), a Demographic (DM) dataset (dm.xpt), and a define.pdf file. Based on the information provided a single ts.xpt file is sufficient. Additionally, it is not necessary to submit a ts.xpt file if reports in PDF format are submitted.*

Discussion: *No further discussion.*

Question 4: **Financial Disclosure**
Does the Division agree with the proposed list of covered studies to provide financial disclosure information for clinical investigators in the NDA?

FDA Response to Question 4: *No, we do not agree. In addition to the financial disclosure information for Phase 1 and 3 investigators, we will require the financial disclosure information for all Phase 2 investigators as well.*

> ***Discussion:*** *The Sponsor agreed to submit financial disclosures for the Phase 2 studies in the TRD development program. If the Sponsor submits supporting studies conducted under the development program for the treatment of patients with major depressive disorder who are at imminent risk of suicide, then financial disclosures for those investigators will be required as well. The Division acknowledged that no financial disclosures are needed for the open-label safety study.*

Question 5: **Applicant Orientation Presentation Meeting**
After submission of the NDA, the Sponsor would welcome the opportunity to orient the review team regarding the content and format of the application in an Applicant Orientation Presentation meeting. Does the Division agree that such a meeting with the Sponsor would be helpful to facilitate the Agency's review of the NDA and would agree to the scheduling of such a meeting at the appropriate time?

FDA Response to Question 5: *The Division appreciates this offer, but we do not anticipate the need for such a meeting.*

> ***Discussion:*** *The Sponsor extended the offer of an orientation meeting based on the unique aspects of the development program, the anticipated priority review timeline, and the PDAC. The Division reassured the Sponsor that we will be in regular contact with them during the review and will coordinate PDAC preparation with them. We also requested that the Sponsor ensure their data define files are complete and accurate.*

Question 6: **PDAC Review of the NDA**
The Division has previously informed the Sponsor of their intention to seek the Psychopharmacologic Drugs Advisory Committee's (PDAC) review and evaluation of the esketamine NDA once filed. Please confirm if this is still the Division's intention and if yes, we request the Division provide the main topics that you anticipate requesting for PDAC's review.

FDA Response to Question 6: *Yes, the Division intends to seek PDAC review and evaluation of the esketamine TRD NDA. We anticipate a broad discussion of benefits and risks, as well as the appropriate conditions of use.*

> ***Discussion:*** *The Division confirmed that the PDAC will likely take place in January or February (based on a September NDA submission). Because of the possibility of inclement*

weather during those months, the Agency will investigate the possibility of having an alternate date pre-scheduled.

2.2. Clinical and Biostatistics

Question 7: **Submission of SAS Programs**
The Sponsor plans to submit statistical analysis system (SAS) programs to derive and analyze the primary and key secondary efficacy endpoints for the Phase 3 studies TRD3001, TRD3002, TRD3003 and TRD3005. As part of the electronic submission, the Sponsor will also provide the raw and derived datasets for Phase 1, 2 and 3 studies. Does the Division agree with this proposal?

FDA Response to Question 7: *On face your proposal seems acceptable. Please clarify, whether you plan to submit raw and derived datasets for all studies listed in the table on pages 19 and 20 of the meeting package. Please also submit the SAS programs to derive and analyze the primary efficacy endpoint in your Phase 2 TRD2003 study.*

Please include a complete listing of the regulatory history (indicating dates and submission numbers and whether FDA comments were issued) for all Phase 2 and 3 studies (protocols, amendments, SAPs, advice requests) supporting the planned NDA. Organizing such listing by study and including agreements achieved during meetings with FDA (with references to meeting minutes) would enhance the reviewability of your application.

Discussion: *The Sponsor confirmed that raw and derived datasets for all completed studies listed in the meeting package table will be submitted. The Sponsor also confirmed that the SAS programs described above will be submitted for the Phase 2 TRD2003 study as well as for any other clinical studies intended to support an efficacy claim. The Division encouraged the Sponsor to utilize hyperlinks in the regulatory history section whenever appropriate.*

Question 8: **Summary of Efficacy**
It is the Sponsor's position that the efficacy data for the pivotal Phase 3 acute studies TRD3001 (fixed dose: 56, 84 mg and placebo) and TRD3002 (flexible dose: 56 mg or 84mg and placebo) cannot be combined due to differences in the study designs. Does the Division agree with the Sponsor's proposal to provide a comprehensive efficacy analysis of the esketamine data within the Summary of Clinical Efficacy (Module 2.7.3) and to waive the requirement for a separate Integrated Summary of Efficacy (Module 5.3.5.3)?

FDA Response to Question 8: *Yes, we agree that combining the fixed-dose and flexible-dose studies for the primary efficacy analysis is inappropriate. Therefore, we agree to waive the requirement for a separate Integrated Summary of Efficacy. However, we request that exploratory analyses of demographic subsets use data from the combined studies.*

Discussion: *The Sponsor confirmed that they will conduct demographic subset exploratory analyses with pooled data from the acute studies (TRD3001 and TRD3002). Planned*

analyses will examine sex, age, region, country, number of previous treatment failures, baseline MADRS score, baseline Sheehan Disability Scale scores, and class of oral antidepressant.

Question 9: **Adequate Support for Reviewable NDA Based on the Data from Completed Phase 3 Esketamine Studies**

With the results from the relapse-prevention study TRD3003 expected to be available in the coming months, does the Division agree that the (b) (4) is adequate to support a reviewable NDA for TRD? The Sponsor is also seeking the Division's input regarding any additional analyses that should be included in the application that would aid the review of the NDA.

Response to Question 9: *No, we do not agree. The results of TRD3003 are important for determining safe use and labeling of intranasal esketamine and should be submitted when the NDA is filed. You may consider requesting a Rolling Review. Although we typically require complete modules for submission under Rolling Review, we are willing to allow you to submit Module 5 without TRD3003 to allow substantive review to begin prior to NDA filing. When the results of TRD3003 are available, they can be submitted and the NDA filed.*

Discussion: *The Division asked the Sponsor whether they would have two positive studies for an NDA submission. The Sponsor acknowledged that TRD3001 was negative, but hoped that positive Phase 2 studies (including TRD2003) could be used to support the application. The Division explained that TRD3003 could serve as one of two positive adequate and well-controlled studies to support an NDA submission. Another possibility could be to use a positive study from the MDD with suicidal ideation program (as both programs are focused on MDD). In either case, this will be a matter of review.*

The Sponsor noted that both arms in Study TRD3003 include an oral antidepressant. Therefore, deciding what results constitute a "positive study" may be problematic. The Division acknowledged this and suggested we revisit the issue when we see the study results. The Sponsor is planning a second pre-NDA meeting to discuss the maintenance studies and risk mitigation.

The Division also requested more information on why there might be different outcomes for subjects enrolled in TRD3001 and TRD3005 before and after the interim analysis.

Question 10: **Support for Inclusion of 56-mg and 84-mg Doses in the Draft Label**

Does the Agency agree that the efficacy and safety data from all completed Phase 3 studies potentially support inclusion of the 56-mg and 84-mg doses as the effective dose range for intranasal esketamine even though no dose response was observed for efficacy in the TRD3001 study?

FDA Response to Question 10: *The determination of labeling, including information on dosing, is a review issue. You may include your dosing suggestions in submitted draft labeling along with justification for their selection.*

> ***Discussion:*** *The Sponsor clarified that they intend to include 84 mg in the effective dose range because it was the most frequently used dose in the flexible-dose study and because there did not seem to be a tolerability difference between 56 and 84 mg.*

Question 11: **Inclusion of Change from Baseline Over Time in MADRS Total Score in the Draft Label**

Does the Agency agree that the graphical representation of the change from baseline over time in MADRS total score intended for inclusion in the Clinical Studies section of the label could be based on results from the flexible-dose Study TRD3002?

FDA Response to Question 11: *The Division does not usually include graphs based on flexible-dose study results. You may propose a graphical representation from Study TRD3002, but this will ultimately be a review issue.*

> ***Discussion:*** *The Sponsor reasoned that use of a flexible dose more closely mirrors clinical practice. The Division agreed that communicating the esketamine effect over time is clinically important. However, there is no precedent for using a flexible-dose study to produce this type of graph. We requested that the graph account for dosing changes during the study.*

Question 12: **Summary of Safety**

Does the Division agree with the Sponsor's plan for safety data presentation, which includes the following:

a. the proposed strategy of pooling safety data for TRD3001 and TRD3002 studies that will include (b) (4),
b. no pooling of acute study data (TRD3001 and TRD3002) with TRD3003 or TRD3004 (due to differences in study design and duration)
c. considering this limited pooling strategy, the proposal to present the safety data (including all supportive documentation) in the Integrated Summary of Safety (Module 5.3.5.3) and use the main text of that Integrated Summary of Safety as a Summary of Clinical Safety (Module 2.7.4).

FDA Response to Question 12:

a. No, we do not agree. We ask that pooled safety data from TRD3001 and TRD3002 include all AEs (b) (4).

b. Yes, we agree that the acute study safety data should not be pooled with data from Studies TRD3003 or 3004.

c. Yes, your proposal for presentation of the safety data is acceptable.

Discussion: *The Sponsor clarified that all AEs will be included in the pooling and provided a table (see Appendix) specifying which parameters and scales would be pooled and which would not. This was acceptable to the Division.*

The Division requested that a two-column list of verbatim and preferred terms be submitted to the IND in advance of the NDA. This will enable the clinical reviewer to assess the preferred terms prior to the Sponsor using those terms for their safety analysis.

Question 13: **Narratives and Case Report Forms**
Does the Division agree with the proposed plan for providing narratives and case report forms in the NDA?

FDA Response to Question 13: *We agree with your plan for providing narratives and case report forms for the NDA with one caveat—please provide CRFs for any deaths, SAEs, or AEs leading to discontinuation for the ongoing trials.*

Discussion: *The Sponsor agreed to provide CRFs for any deaths, SAEs, or AEs leading to discontinuation for the ongoing trials.*

Question 14: **Reporting of Safety Data**
Does the Division agree with the Sponsor's proposal regarding the reporting of safety data, specifically:

a. to report safety data in the NDA from ongoing studies using a cutoff date of 6 months prior to NDA submission?
b. the proposed content and cutoff date of the 4-month safety update? Additionally, does the Division agree with the Sponsor's proposal to submit the safety update earlier than 120 days from submission of the NDA?

FDA Response to Question 14: *Yes, we agree with your plan. Please confirm an additional safety update inclusive of the month that is immediately prior to NDA submission will be submitted prior to the action date.*

Discussion: *The Sponsor clarified that they were willing to submit the safety update earlier in the review process to avoid submitting it around the same time as the PDAC. The Division appreciated this offer, but felt the standard timelines were acceptable.*

Question 15: **Published Literature**
Does the Division agree with the following proposal for submission of published literature in the clinical sections of the NDA?

a. The Sponsor will perform a search of the published scientific literature for reports of adult data (safety and efficacy) of ketamine and esketamine using a cutoff date of 6 months prior to submission of the NDA. The search will focus (b) (4) Relevant published literature identified by the search will be summarized in a report to be included in Module 5, Section 5.3.5.4. Copies of all relevant references will be provided in Module 5, Section 5.4. Late breaking articles of importance will also be included

b. The Sponsor will submit in Module 5, Section 5.4 copies of all published literature cited in Module 2.5, Clinical Overview and in Module 2.7, Clinical Summaries, in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline M4E.

c. References cited in the individual study reports will not be included in the submission but will be available upon request.

FDA Response to Question 15:

a. No, we do not agree. Esketamine and ketamine literature from pain and anesthesia indications must be included if the primary focus of the reference is safety. Pain and anesthesia references where the primary focus is efficacy, and safety is mentioned incidentally, do not need to be included.

b. & c. We agree with your proposal.

Discussion: *The Sponsor questioned the relevance of pain and anesthesia studies where dosing is significantly higher than for TRD. However, the Division feels an examination of safety findings from pain and anesthesia studies are relevant. We agreed that only review articles focused on safety need to be included from pain and anesthesia indications.*

Question 16: **Abuse Potential Assessment**

In accordance with FDA's Guidance for Industry Assessment of Abuse Potential of Drugs, the Sponsor proposes to review the content and the adequacy of the abuse potential assessment data that will be included in the NDA. Does the Division agree with the following:

a. the clinical data presented by the Sponsor from the recently completed study of esketamine abuse potential are supportive of esketamine remaining in Schedule III,

b. the content and the intended organization of the abuse potential assessment to be provided in the NDA,

c. the Sponsor's proposal to provide detailed case narratives for treatment emergent adverse events potentially suggestive of abuse in a tabular format.

FDA Response to Question 16:

a. *We agree. Based on your assessment of the human abuse potential study you recently completed (i.e., Study 54135419TRD1015), the data appear to support that esketamine is appropriately placed in Schedule III of the CSA. Note that our final determinations about the abuse potential of a proposed drug product are made following our comprehensive review of all abuse potential-related data submitted under an NDA.*

b. *We agree with the content and the organization of the abuse potential assessment.*

c. *We agree with your proposal to provided case narratives of abuse-related AEs in a tabular format.*

Discussion: *No further discussion.*

Question 17: **Study in the Elderly**

Does the Division agree with the Sponsor's position regarding the positive benefit-risk assessment for the population of elderly subjects 65 years of age and older as observed in Study TRD3005 and the proposed recommendation to treat this population?

FDA Response to Question 17: *The determination of risk-benefit in an elderly population is a review issue.*

Discussion: *No further discussion.*

2.3. Clinical Pharmacology

Question 18: **Proposed Analysis Plans**

Does the Division agree with the Sponsor's opinion that the proposed analysis plans for population pharmacokinetics and exposure-response for efficacy and safety endpoints, when executed, adequately support the clinical pharmacology package for the sought indication?

FDA Response to Question 18: *On face, the plan appears adequate. However, whether it supports the proposed indication will be a matter of review.*
In your NDA submission, please include datasets used for model development as SAS transport files (.xpt) as well as a define.pdf file with a description of each data item. Model codes, control streams and output listings should be submitted as ASCII text files with *.txt extension.*

Upon initial review of your exposure-response analysis plan we have the following comments:

- *As part of your population PK plan you should detail how you will evaluate whether the PK model allows for accurate and precise individual prediction of Cmax to be used in exposure-response models.*

- *We share your concern regarding confounding of dose and subject sensitivity from studies with flexible dose design. We recommend that in addition to the planned analysis, you perform an analysis only using data from studies with fixed dose design.*

  Discussion: *The Sponsor agreed to perform the requested analyses and to include the requested files in the NDA submission.*

2.4. Chemistry, Manufacturing and Control

Question 19: **Module 3 Drug Substance Presentation Plan**
Does the Agency agree with the Sponsor's proposed Module 3 presentation plan for the two commercial drug substances?

FDA Response to Question 19: *Your plan to provide two separate 3.2.S. drug substance sections in the NDA submission for the two respective proposed manufacturers of commercial drug substance appears reasonable. For the drug substance manufactured by* (b) (4) *include the release test results according to the Janssen drug substance specification for all* (b) (4) *batches in section 3.2.S.4, as you have proposed. Available stability data for the batches tested according to the Janssen drug substance stability protocol should be provided in section 3.2.S.7. Consult with the DMF holders to ensure that a copy of the relevant letter of authorization (LoA) is included in each respective DMF.*

We note your statement that the drug substances from both suppliers are of comparable quality. We remind you that your comparison of drug substance batch data from both suppliers should demonstrate that the drug substance impurity profiles resulting from the (b) (4) *and Janssen manufacturing processes are comparable.*

Discussion: *No further discussion.*

Question 20: **Proposed Drug Substance Specifications**
Recognizing that the specification limits will be reviewed at the time of the NDA submission, does the Agency agree with the proposed specifications for Esketamine Hydrochloride drug substance?

FDA Response to Question 20: *The proposed specifications for esketamine hydrochloride drug substance generally appear reasonable. Provide in your NDA the justifications–including batch data where appropriate–to support your proposed exclusion of certain tests from the release and/or stability protocol (i.e., appearance of solution, chiral purity, and microbiological purity). As you noted, a final determination regarding the proposed limits will be made at the time of NDA review.*

We note that the esketamine hydrochloride drug substance specification does not include microbiological testing. The NDA submission should include a risk assessment and justification for excluding microbiological testing of the drug substance.

Discussion: *The Sponsor agreed to include the requested justifications in the NDA, including a risk assessment and justification for excluding microbiological testing.*

Question 21: **Proposed Specifications for The Esketamine Nasal Spray Drug Product**
Recognizing that the specification limits will be reviewed at the time of the NDA submission, does the Agency agree with the proposed specifications for the Esketamine Nasal Spray drug product?

FDA Response to Question 21: *The acceptability of the deletion of the weight loss and chirality tests will be a review matter after submission of the NDA. We encourage you to continue to carry out these tests as these data may be used to justify your approach.*

Please note that the overfill volume of the nasal spray solution in the vial should be appropriately justified. Refer to Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation published by the FDA in July 2002.

Since the drug product is non-sterile and unpreserved, the NDA submission should contain results from microbial challenge studies showing that the drug product formulation is at least inherently bacteriostatic/fungistatic. If the drug product formulation does not inhibit microbial growth, we recommend that the drug product be manufactured as a sterile drug product.

From a CDRH perspective you have proposed using specifications such as spray pattern, spray content uniformity, droplet size distribution according to the FDA guidance in the future NDA filing. This appears acceptable.

Note that NDAs are required to include a control strategy for elemental impurities as described in USP <232> and <233> and ICH Q3D for both the drug substance and drug product. Alternatively, include justification based on data and a risk assessment, as to why an elemental impurities control strategy is not needed.

Discussion: *The Sponsor stated that they agreed with each of the Agency's comments and will include the requested information in the NDA. They agreed to continue to carry out the weight loss and chirality tests on the registration batches. They stated they will provided justification for the 30 ul overfill. They will include data to show that the drug substance is bacteriostatic and fungistatic and that they will include stability data showing no microbial proliferation on storage. They plan to include an elemental impurities control strategy based on a risk assessment for both the drug substance and drug product.*

Question 22: **Proposed Verification and Validation Strategy for The Drug-Device Combination Product**
Does CDRH agree with the proposed verification and validation strategy for the drug-device combination product as outlined in the briefing document?

FDA Response to Question 22: *You have provided a plan for the verification testing and identified the essential performance characteristics appropriate for the device. Your response and proposed plan is acceptable.*

Regarding your human factors validation study, we acknowledge your plan and refer you to previous advice given regarding your study protocol.

Discussion: *No further discussion.*

Question 23: **Implementation of the Automated Optima Filling Line**
Does the Agency agree that the proposed plan to implement a (b) (4) at the (b) (4) site can be filed as an Annual Report?

FDA Response to Question 23: *No. This change appears to require a CBE-0 or CBE-30 supplement submission; however, a decision cannot be made at this time as it will depend on the final approved process and the risk to product quality from this operation– which will be evaluated during review of the NDA. Submission of a Comparability Protocol in the NDA to request a reduction in reporting category may be a means to obtaining a more definitive filing category at application approval. For more information refer to our Guidance for Industry: Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information.*

Discussion: *The Sponsor stated that they will include the recommended Comparability Protocol in the NDA.*

Question 24: **Submission of an Executed Batch Record**
Does the Agency agree with the Sponsor's proposed plan to submit an executed batch record from one representative batch of Esketamine Nasal Spray drug product?

FDA Response to Question 24: *No. We request that you submit executed batch records for each of the registration drug product batches. This will allow a more thorough review of the consistency of your manufacturing process.*

Discussion: *The Sponsor agreed to include the requested executed batch records in the NDA.*

Question 25: **Response to the FDA Request for Clarification of 24 November 2015**
Does the Agency agree with the Sponsor's response to the FDA's request for clarification on the proposed drug substance registration batches received on 24 November 2015?

FDA Response to Question 25: *We agree with your proposal to provide a minimum of 12 months of stability data for the three registration batches (b) (4) and 1 month of stability data for the three validation batches (b) (4) at the time of NDA submission, provided that you (1)*

include comparative data for the two DS sources to demonstrate equivalency and (2) commit to provide a 3-month stability update for the validation batches during the review period as soon as the data become available.

> ***Discussion:*** *The Sponsor agreed to provide comparative data for the registration batches and the validation batches. Additionally, the Sponsor will provide the 3-month stability data for the validation batches in the original NDA submission.*

Additional Division of Risk Management Discussion
At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. However, if you believe a REMS is needed, we encourage you to submit a proposed REMS with your application. We refer you to our October, 2017, Draft Guidance for Industry: Format and Content of a REMS Document.

3.0 OTHER

PREA REQUIREMENTS

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

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

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

PRESCRIBING INFORMATION

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

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

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.

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.				

NEW MOLECULAR ENTITY STATUS

FDA has made a preliminary determination that the application for this product would not be reviewed as a new molecular entity (NME) and would not be subject to the Program under PDUFA VI. Please note that this is a preliminary determination, based on information available to FDA at this time, and will be re-evaluated at the time your application is submitted. This determination is based on our understanding of the active moiety (21 CFR 314.108(a)) and whether another marketing application containing the same active moiety is approved or

marketed. Please also note that the NME determination for an application is distinct from and independent of the new chemical entity (NCE) determination and any related exclusivity determinations, which are made after approval of an NDA.

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 (available at the following links https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) 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.

4.0 ATTACHMENTS AND HANDOUTS

The attached handout was provided by Janssen.

Pooled Safety Variables

Variable	**DB Pooled Studies TRD3001, 3002**
Demographics	Yes
Disposition	Yes
Con Meds	Yes
Exposure	Yes
AEs	Yes
Labs	Yes
Vitals	Yes
ECGs	Yes
C-SSRS	Yes
Nasal Examination	No
Nasal Symptom Questionnaire	No
MOAA/S	No
CADSS	No
CGADR	No
PWC-20	No
BPRS	No
Cogstate Battery	No
Smell Threshold Test	No
UPSIT	No

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
04/13/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 114345

MEETING MINUTES

Janssen Research & Development, LLC
Attention: Patricia Treichler, RAC
Associate Director, Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

Dear Ms. Treichler:

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

We also refer to the meeting between representatives of your firm and the FDA on December 8, 2014. The purpose of the meeting was to discuss 1) the safety of proceeding to Phase 3, 2) the adequacy of the proposed Phase 3 protocols to assess the safety and effectiveness of intranasal esketamine in treatment resistant depression (TRD), and 3) the adequacy of the overall development program to support a New Drug Application for intranasal esketamine in TRD.

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, call Dr. Hiren Patel, Regulatory Project Manager at (301) 796-2087.

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:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	December 8, 2014 from 1:00pm-2:30pm (EST)
Meeting Location:	CDER WO Bldg. 22, Room 1315
Application Number:	IND 114345
Product Name:	Esketamine (JNJ-54135419)
Indication:	Treatment Resistant Depression
Sponsor/Applicant Name:	Janssen Research & Development, LLC
Meeting Chair:	Dr. Mitchell Mathis

FDA ATTENDEES

Mitchell Mathis, M.D.	Director, Division of Psychiatry Products (DPP)
Tiffany Farchione, M.D.	Deputy Director (Acting), DPP
Jing Zhang, M.D.	Clinical Team Leader, DPP
Lucas Kempf, M.D.	Clinical Reviewer, DPP
Peiling Yang, Ph.D.	Biometrics Team Leader, DPP
Thomas Birkner, Ph.D.	Biometrics Reviewer, DPP
Linda Fossom, Ph.D.	Pharmacology/Toxicology Supervisor, DPP
Hao Zhu, Ph.D.	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Andre Jackson, Ph.D.	Clinical Pharmacology Reviewer, OCP
Olen Stephens, Ph.D.	Branch Chief, CMC
Thomas Wong, Ph.D.	CMC Reviewer
Monica Calderon, PharmD	Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)
Hiren Patel, PharmD	Regulatory Project Manager, DPP

SPONSOR ATTENDEES

Ivo Caers, Ph.D.	Compound Development Team Leader
Wayne Drevets, M.D.	Mood Disease Area Leader, CNS
Robert O'Donnell, Ph.D.	Global Regulatory Affairs TA Head, CNS
Jaskaran Singh, M.D.	Clinical Team Leader, CNS
Ella Daly, M.D.	Project Physician, CNS
Peter Zannikos, Ph.D.	Clinical Pharmacology Leader
Pilar Lim, Ph.D.	Psychiatry Statistical Team Leader
Rosanne Lane, MAS	Statistical Leader
Eric de Waal, Ph.D.	Preclinical Leader
Katrien Verbruggen, Ph.D.	CMC Leader

Ilias Jimidar, Ph.D.	Analytical Development Leader
Romi Behbehanian	Drug Product Development Leader
Jingli Wang, Ph.D.	Device Leader
Heddie Martynowicz, M.S.	Global Regulatory Leader, CNS
Patricia Treichler, BS, RAC	US Regulatory Leader, CNS
Carol Jamieson, BSc	Patient Reported Outcomes Leader
Barry Fong, BS	CMC Regulatory Leader
Doug Mead, MS	Regulatory Affairs, CMC and Medical Devices
Tracy Lin, RPh, MS	Global CMC Regulatory Affairs
Marc Walton, M.D., Ph.D.	Quantitative Sciences Leader

1.0 BACKGROUND

A. Background

Janssen Research & Development LLC (JRD) is developing intranasal esketamine, the S enantiomer of ketamine, for the treatment of patients with treatment-resistant major depressive disorder (TRD) under IND 114,345. The sponsor is currently conducting their Phase 2a study ESKETINTRD2003 to assess the efficacy, safety, and dose response of intranasal esketamine in the treatment of TRD.

On September 16, 2013, the sponsor submitted a request for Breakthrough Therapy designation for this IND, which was granted on November 7, 2013. A Type B meeting to discuss the scope and design of the Phase 3 clinical development and clinical pharmacology programs was held on March 13, 2014 (with a follow-up teleconference on May 6, 2014 to discuss several questions that could not be addressed due to time constraints). A second Type B meeting to review remaining aspects of the development program, with focus on topics related to the intranasal device design, Chemistry Manufacturing and Control (CMC), and abuse potential assessment was held on June 5, 2014.

On September 12, 2014 the sponsor had another Type B meeting to discuss and receive agreement with the Division on the design of their proposed Phase 3 pivotal short-term and maintenance studies. Now, with the first results from their Phase 2 study, the sponsor wishes to discuss their new proposed designs for two acute studies, their randomized withdrawal maintenance study, the long-term extension study, and the geriatric studies.

B. Proposed Design for the Fixed Dose Short-term Pivotal Phase 3 Efficacy Study (ESKETINTRD3001)

The primary objective of Study ESKETINTRD3001 is to evaluate the efficacy of intranasal esketamine plus a newly initiated oral antidepressant compared with a newly initiated oral antidepressant active comparator plus intranasal placebo in improving depressive symptoms in subjects with treatment-resistant depression (TRD). This will be a randomized, double-blind, active-controlled, multicenter study in approximately 348 male and female adult subjects with TRD to assess the efficacy, safety, and tolerability of intranasal esketamine (56mg or 84mg) plus an oral antidepressant compared to intranasal placebo and an oral antidepressant alone (active comparator).

Each subject will participate in up to three phases:

- A 6-week Screening/ Prospective Open-Label Antidepressant Treatment Response Observation Phase.
- After six weeks, if clinically indicated, an optional antidepressant taper period of approximately one week is permitted.
- A 4-week Double-Blind Induction Phase.
- A 24-week Follow Up and Observational Phase.

For all subjects who receive at least one dose of study medication in the Double-Blind Induction Phase and who are not participating in the subsequent maintenance clinical trial (ESKETINTRD3003), the maximum duration of the subject's participation will be between 10 to 34 weeks. This will depend upon whether a subject is determined to be responder or non-responder and, if a responder in the Double-Blind Induction Phase, whether the subject elects to participate in the subsequent clinical trial (ESKETINTRD3003). The end of the study will occur when the last subject in the trial completes his/her last study assessment.

C. Proposed Design for the Flexible Dose Short-term Pivotal Phase 3 Efficacy Study (ESKETINTRD3002)

ESKETINTRD3002 is a randomized, double-blind, active-controlled, multicenter study in a maximum of 196 male and female adult subjects with TRD to assess the efficacy, safety, and tolerability of intranasal esketamine plus an oral antidepressant compared to intranasal placebo plus an oral antidepressant (active comparator). ESKETINTRD3002 has a very similar design to ESKETINTRD3001; however, ESKETINTRD3002 is a 2-arm flexible dose study.

D. Combined Screening/Prospective Open-Label Antidepressant Treatment Response Observation Phase in Both Short-Term Studies

The proposed studies will be conducted in male and female adult subjects (aged 18 to 64 years) with severe MDD (Inventory of Depressive Symptomatology Clinician Rated, 30 item [IDS-C30] total score ≥40), without psychotic features. They must have had non-response to at least two, but fewer than six, antidepressant treatments (of adequate dose and duration, documented retrospectively) in the current episode, with one of the failed antidepressant treatments ongoing at screening. Once entered in the trial, subjects will continue their current antidepressant treatment for six weeks to confirm non-response.

E. Optional Antidepressant Taper Period in Both Short-Term Studies

Following six weeks of prospective treatment and subsequent assessment of antidepressant treatment response, the antidepressant medication may, if clinically indicated, be tapered over a period of up to one week per the country-specific prescribing information.

F. Double-Blind Induction Phase in Both Short-Term Studies

During this phase, subjects who did not respond to treatment in the previous phase will switch to a new oral open-label antidepressant. In addition to receiving the oral antidepressant, subjects will be randomized to receive either intranasal esketamine or intranasal placebo twice per week for 4 weeks. ESKETINTRD3001 is a fixed-dose study, ESKETINTRD3002is a flexible-dose study.

For ESKETINTRD3001, subjects will be randomized to one of the following double-blind treatment groups in a 1:1:1 ratio (up to 116 subjects per group):

- Intranasal esketamine (56 mg)
- Intranasal esketamine (84 mg)
- Intranasal placebo

For ESKETINTRD3002, subjects will be randomized to one of the following double-blind two treatment groups:

- Intranasal esketamine (flexibly dosed)
- Intranasal placebo

For both studies, the randomization will be stratified by country and type of oral antidepressant (selective serotonin reuptake inhibitors [SSRIs] or serotonin norepinephrine reuptake inhibitors [SNRIs]).

G. Selection and Dosing Regimen of Oral Antidepressants (Active Comparator) in Induction Phase

On Day 1 of each study, a new open-label oral antidepressant treatment will be initiated. Options for this new antidepressant include duloxetine, escitalopram, sertraline, or venlafaxine XR. The antidepressant medication assigned will be one which the subject has not previously had a non-response to in the current episode, has not been previously intolerant to (lifetime), and is available in the participating country. Dosing follow the country-specific prescribing information for the respective product, with a forced titration to the maximally tolerated dose (see below).

Oral Antidepressant Options for All Countries, except Japan

Oral Antidepressant (Active Comparator)	Titration Schedule			
	Week 1 (starting Day 1)	Week 2 (starting Day 8)	Week 3 (starting Day 15)	Week 4 (starting Day 22)
Duloxetine	30 mg	60 mg	60 mg	60 mg
Escitalopram	10 mg	20 mg	20 mg	20 mg
Sertraline	50 mg	100 mg	150 mg	150 mg
Venlafaxine XR	75 mg	150 mg	225 mg	225 mg

Oral Antidepressant Options for Japan

Oral Antidepressant (Active Comparator)	Titration Schedule			
	Week 1 (starting Day 1)	Week 2 (starting Day 8)	Week 3 (starting Day 15)	Week 4 (starting Day 22)
Duloxetine	20 mg	40 mg	60 mg	60 mg
Escitalopram	10 mg	20 mg	20 mg	20 mg

H. Dosing Regimen of Intranasal Study Medication in Induction Phase

All subjects will self-administer the intranasal study medication at treatment sessions occurring twice a week for four weeks at the clinical site.

For ESKETINTRD3001, the dose will be esketamine 56 mg or 84 mg, or placebo.

For ESKETINTRD3002, subjects randomized to intranasal esketamine will receive 56 mg on Days 1 and 4.On Day 8, the dose may be increased to 84 mg or remain at 56 mg, as determined by the investigator based on efficacy and tolerability. On Day 11 the dose may be increased to 84 mg (if Day 8 dose was 56 mg), remain the same, or be reduced (if Day 8 dose was 84 mg) as determined by the investigator based on efficacy and tolerability. On Day 15, a dose reduction for tolerability from 84 mg to 56 mg is permitted, if required for tolerability; no dose increase is permitted on Day 15. After Day 15, no further adjustments are permitted.

At the end of the Double-Blind Induction Phase, responder subjects (>50% reduction from baseline) will be eligible to enter the subsequent maintenance clinical trial (ESKETINTRD3003).

To maintain study blinding, all responder subjects, including responders to the active comparator (ie, oral antidepressant and intranasal placebo), are eligible to enter ESKETINTRD3003. Those subjects that do not enter ESKETINTRD3003 will proceed into the Follow Up and Observational Phase.

I. Follow Up and Observational Phase

During this phase, further clinical/standard of care for the treatment of depression will be arranged by the study investigator and/or the subject's treating physician. All subjects who

received at least 1 dose of study medication in the Double-Blind Induction Phase and are not participating in the subsequent ESKETINTRD3003 study will have two safety follow up visits--a telephone contact one week after the last dose of study medication, and a clinic visit two weeks after last dose. After the last follow up visit, subjects will be eligible to proceed into a 22-week observation period during which the course of the subject's major depressive episode will be assessed.

J. Rationale for Dose Selection in Phase 3 Studies

Dose selection for the Phase 3 studies was based on the sponsor's previous clinical data, in particular the results from Study ESKETINTRD2003. The sponsor plans to use the 56 mg and 84 mg doses in the Phase 3 studies.

K. Efficacy and Safety Assessments for Studies ESKETINTRD3001 and ESKETINTRD3002

- The primary efficacy endpoint is the change from baseline (Day 1 pre-randomization) in MADRS total score to the end of the 4-week Double-Blind Induction Phase.

- The first key secondary efficacy endpoint is the onset of clinical response [i.e., ≥50% reduction from Day 1 (prior to randomization) in MADRS total score] with an onset by Day 2 (i.e., the day after the first administration of double-blind intranasal study medication) that is maintained through the end of the 4-week Double-Blind Induction Phase. Subjects who discontinue the study prior to the end of the Double-Blind Induction Phase will not be considered to have maintained clinical response.

- (b) (4)

- Other secondary efficacy evaluations include PHQ-9, response and remission rate (MADRS), Clinical Global Impression – Severity (CGI-S), Generalized Anxiety Disorder 7-item scale (GAD-7), EuroQol – 5 Dimensions – 5 Levels (EQ-5D-5L), and assessment of medical resource utilization.

- Safety assessments will include monitoring of treatment-emergent adverse events, clinical laboratory measurements, vital signs, electrocardiograms (ECGs), physical examination, local nasal examination, assessment of nasal tolerability, effects on suicidal ideation/behavior using the Columbia Suicide Severity Rating Scale (C-SSRS), effects on cognition (eg, CogState computerized test battery, Hopkins Verbal Learning Test-Revised [HVLT-R]), effects on cystitis or bladder-related symptoms using the Bladder Pain/Interstitial Cystitis Symptom Score (BPICSS), and assessment of sense of smell. At

the end of the Double-Blind Induction Phase, those subjects who will not be entering the ESKETINTRD3003 study will have withdrawal symptoms following cessation of intranasal esketamine measured by the 20-item Physician Withdrawal Checklist (PWC).

- Additional safety endpoints to assess short-term adverse events seen on treatment session days will include:

  - Assessment of potential dissociative symptoms, using the CADSS.

  - Evaluation of potential psychosis-like side effects using a 4-item positive symptom subscale (consisting of: suspiciousness, hallucinations, unusual thought content, and conceptual disorganization) of the Brief Psychiatric Rating Scale (BPRS+) Assessment of treatment-emergent sedation using the Modified Observer's Assessment of Alertness/Sedation scale (MOAA/S), and a global assessment of alertness using the Clinical Global Assessment of Alertness scale (CGAA) Pulse oximetry, heart rate, blood pressure, and respiratory rate.

L. Statistical Methods for Studies ESKETINTRD3001 and ESKETINTRD3002

The sponsor provides a sample size rationale based on the following assumptions:

- Treatment difference of 8 points in MADRS total score between any dose of esketamine and the active comparator
- Standard deviation of 12
- One-sided significance level of 0.0125 (ESKETINTRD3001) or 0.025 (ESKETINTRD3002)

Based on these assumptions, the sponsor estimates a sample size of either 58 (ESKETINTRD3001) or 49 (ESKETINTRD3002) subjects per each treatment arm will provide 90% power. The actual number of subjects to be randomized in the studies will be adjusted to account for the assumed drop-out rate of 25%. As detailed below, an interim analysis is planned to re-estimate sample size, and, if necessary, increase the sample size.

M. Interim Analysis for Sample Size Re-estimation

One interim analysis is planned when 30 (ESKETINTRD3001) or 25 (ESKETINTRD3002) intent-to-treat (ITT) subjects per treatment group have completed the Double-blind Induction Phase of the study. The purpose of the interim analysis is to either re-estimate sample size or to stop the study due to futility. The sample size may be adjusted to achieve the desired power while maintaining control of the overall Type I error. The maximum sample size for this study is 116 (ESKETINTRD3001) or 98 (ESKETINTRD3002) subjects per treatment group. The sample size re-estimation (SSR) at the interim analysis will be based on the unblended estimation of treatment efficacy effect. For the hypotheses of interest, conditional power (CP) is calculated assuming that the estimated treatment effect at the interim analysis is the true effect using the formula , where Φ is the cumulative distribution function of the standard normal distribution; t is the information fraction and z is the observed normalized test statistic. If 30% < CP <80% for at least one esketamine dose comparison to active comparator, then the sample size will be increased in order to achieve 88

(ESKETINTRD3001) or 75 (ESKETINTRD3002) subjects who have completed the Double-blind Induction Phase in all treatment groups. To account for sample size reassessment, the p-value combination test will be used for each hypothesis of interest before adjusting for multiplicity. The combination test will be defined according to the approach described in Wassmer et al 2001 (also Cui et al 1999), which defines test statistics as a weighted sum of the Stage 1 (before the interim analysis) and Stage 2 (after the interim analysis) test statistics. The two stages will be weighted equally in the combination test. The sponsor states that a rigorous interim statistical analysis plan (SAP) and charter will be developed detailing the algorithm for a SSR based on the interim data and how the analysis will be executed. An independent, external statistician will perform the interim analysis and will make recommendations for any sample size adjustment based on the rules defined in the interim analysis SAP. Any changes to sample size will be communicated by the independent, external statistician to an internal statistician not involved with the esketamine program who will coordinate with the interactive web response system (IWRS) vendor to ensure that the appropriate number of subjects is enrolled in the trial.

N. Efficacy Analyses

Efficacy analyses will be performed on the ITT analysis set, which will be defined to include all randomized subjects. For the US dossier, the primary efficacy variable (change from baseline in MADRS total score at Week 4 in the Double-blind Induction Phase) will be analyzed using a mixed-effects model for repeated measures (MMRM). The model will include baseline MADRS total score as a covariate, and treatment, country, type of AD (SSRI, SNRI), day, and day-by-treatment interaction as fixed effects, and a random subject effect. The comparison of each esketamine plus AD arm with AD plus intranasal placebo will be performed using the appropriate contrast.

For the analysis of the first of two key secondary efficacy endpoints, the proportion of subjects showing onset of clinical response by Day 2 that is maintained for the duration of the Double-blind Induction Phase in each esketamine plus AD arm will be compared with the AD plus intranasal placebo arm using a Cochran-Mantel-Haenszel chi-square test adjusting for country and type of AD (SSRI, SNRI). (b) (4)

A serial gatekeeping approach will be applied to adjust for multiplicity and to strongly control type I error across the primary and the two key secondary efficacy endpoints, and across the 2 dose-control comparisons (for ESKETINTRD3001 only). For ESKETINTRD3001, the two dose control comparisons corresponding to each efficacy endpoint are considered as a family of hypotheses. Further details of these approaches will be provided in the SAPs.

O. Proposed Design for the Maintenance Study (ESKETINTRD3003)

The proposed study is a randomized, double-blind, parallel-group, multicenter study to evaluate the efficacy and safety of intranasal esketamine plus an oral antidepressant compared with an oral antidepressant and intranasal placebo in delaying relapse of depressive

symptoms in adult male and female subjects with TRD who are in remission following an induction and stabilization course with intranasal esketamine plus an oral antidepressant. Subjects will enter the study either directly or after completing the Double-Blind Induction Phase of one of the short term efficacy studies (ESKETINTRD3001 or ESKETINTRD3002). Each subject will participate in up to 6 phases:

- A 6-week Combined Screening and Prospective Open-Label Antidepressant Treatment Response Observation Phase
    - Subjects who enter the study after completing the Double-Blind Induction Phase of one of the short-term efficacy studies (ESKETINTRD3001 or ESKETINTRD3002) will not participate in this phase; they will start from the Stabilization Phase.
    - For directly recruited subjects, after six weeks, if clinically indicated, an optional antidepressant taper period of approximately one week is permitted prior to starting the Open-Label Induction Phase.
- A 4-week Open-Label Induction Phase
- A Stabilization Phase of up to 12 weeks (variable)
- A Randomized Withdrawal Phase of variable duration
- An Optional Open-Label Extension Phase of variable duration
    - Subjects that relapse during the Randomized Withdrawal phase will be eligible to participate in this phase and receive intranasal esketamine in a second Induction Phase followed by a Stabilization Phase.
- A 2–week Follow Up Phase
    - All subjects who receive at least one dose of intranasal study medication in this study will have follow-up visits performed at one and two weeks after the last dose of intranasal study medication.

Subject selection for the direct recruitment is similar to that used in the short term efficacy studies (ESKETINTRD3001 and ESKETINTRD3002).

Open-Label Induction Phase
During this phase, subjects will self-administer open-label treatment with intranasal esketamine at treatment sessions occurring twice a week for four weeks. In addition, subjects will simultaneously initiate a new, open-label oral antidepressant.

On Days 1 and 4, subjects will receive 56 mg of intranasal esketamine. On Day 8, the dose may be increased to 84 mg or remain at 56 mg, as determined by the investigator based on efficacy and tolerability. On Day 11 the dose may be increased to 84 mg (if Day 8 dose was 56 mg), remain the same, or be reduced (if Day 8 dose was 84 mg) as determined by the investigator based on efficacy and tolerability. On Day 15, a dose reduction for tolerability from 84 mg to 56 mg is permitted, if required for tolerability; no dose increase is permitted on Day 15. After Day 15, no further adjustments are permitted.

Also on Day 1, a new, open-label oral antidepressant treatment will be initiated. The titration schedule and antidepressant selection will be the same as those in the ESKETINTRD3001 and ESKETINTRD3002 studies.

Stabilization Phase
Responder subjects (>50% reduction from baseline in MADRS total score) at the end of the Open-Label Induction Phase will immediately enter the Stabilization Phase and continue intranasal esketamine and an oral antidepressant.

Subjects who enter the study after completing the Double-Blind Induction Phase of one of the short term efficacy studies (ESKETINTRD3001 or ESKETINTRD3002) will start from the Stabilization Phase. To maintain study blinding, all responder subjects from these two studies, including responders to the active comparator (i.e., oral antidepressant and intranasal placebo), will be eligible to participate in this study. At the start of the Stabilization Phase, these subjects will continue their same treatment from the Double-Blind Induction Phase (intranasal esketamine or placebo and an oral antidepressant).

During the Stabilization Phase, frequency of intranasal esketamine or placebo treatment sessions will be reduced as described in the tables below. The dose of intranasal esketamine administered at each session will remain unchanged. The sponsor states that "it is recommended that the antidepressant dose remains stable," but does not provide details regard how or why dose adjustments may be made.

Intranasal Treatment Session Schedule for Stabilization Phase

	Week			
	0	1	2	3 through end of the Stabilization Phase
Intranasal Treatment Session	X	X	X[a]	See Table 2

[a] If the MADRS total score is > 12 at the beginning of Week 2, the subject will receive a treatment session in Week 2. No further change to the treatment session frequency is permitted for the remainder of the Stabilization Phase. The subject will continue to have weekly sessions until stable remission is achieved or the Stabilization Phase ends at 12 weeks, whichever occurs first.

Determination of Intranasal Treatment Session Frequency (from pre-dose Week 3 through end of 12-week Stabilization Phase; sponsor Table 2)

Predose MADRS Total Score from prior intranasal treatment session	Treatment Session Frequency for subsequent treatment session
≤ 12	Every other week
>12 [a]	Weekly[b]

[a] If this is the 2nd consecutive occurrence of the MADRS total score ≥ 22, assess for relapse. If relapse criteria are met, the subject must be discontinued from the Stabilization Phase.

[b] Once a subject requires a weekly treatment session, no further change to the treatment session frequency is permitted for the remainder of the Stabilization Phase. The weekly sessions will continue until stable remission is achieved or the Stabilization Phase ends at 12 weeks, whichever occurs first. Stable remission is defined as a MADRS total score ≤12 for 4 consecutive weeks and at the same session frequency for these 4 weeks.

Subjects who are in stable remission (MADRS total score ≤12 for 4 consecutive weeks, at the same dose frequency for those 4 weeks) will proceed into the Randomized Withdrawal Phase. The MADRS total score at Week 4 is the first MADRS total score that can contribute to the stable remission criteria. For subjects on a weekly treatment session frequency, when assessing the four consecutive weeks of remission, one excursion of a MADRS total score up to 15 is allowed in the second of the four consecutive weeks.

At the end of the 12-week Stabilization Phase subjects with stable response (≥50% reduction from baseline score in Induction Phase and MADRS total score ≤18 for 4 consecutive weeks in the Stabilization Phase) who do not achieve stable remission will proceed into the Randomized Withdrawal Phase but will not be included in the primary analysis. All other subjects will discontinue the study. After completing the Follow-up phase, appropriate follow up care will be arranged.

Rationale for Duration and Design of the Open-Label Stabilization Phase
The duration of the stabilization phase is consistent with the typical time to relapse in TRD patients (i.e., 8-12 weeks). The symptom severity-based algorithm described above allows for an individualized titration and subsequent individualization of the session interval dosing frequency.

Randomized Withdrawal Phase
Subjects who are in stable remission at the end of the Stabilization Phase will be randomized in a 1:1 ratio to oral antidepressant plus either intranasal esketamine or intranasal placebo.

Subjects with stable response (≥50% reduction from baseline score in Induction Phase and MADRS total score ≤18 for 4 consecutive weeks in the Stabilization Phase) that do not achieve stable remission at the end of the Stabilization Phase will also be randomized in a 1:1 ratio to oral antidepressant plus either intranasal esketamine or intranasal placebo. These subjects will not be included in the primary analysis. The data will provide additional information for assessment of outcomes.

During this phase, the dose of intranasal esketamine will remain unchanged from the Stabilization Phase. It is recommended that the antidepressant dose remains stable. All subjects will begin this phase at the same session frequency (weekly or every other week) as they had at the end of the stabilization phase. Thereafter, determination of subsequent intranasal treatment session frequency (i.e., every other week or weekly) will be based on the pre-dose MADRS total score from the prior intranasal treatment session. The algorithm for determination of treatment session frequency based on the MADRS total score is described below.

Predose MADRS Total Score from prior intranasal treatment session	**Treatment Session Frequency for subsequent treatment session [a, b]**
≤ 12	Every other week [b]
>12 [c]	Weekly

[a] For any subject in whom the treatment session frequency is increased from every other week to weekly, the weekly session frequency must be maintained for a minimum of 4 weeks. Once the patient has a MADRS total score of ≤ 12 for 4 consecutive weeks, the subject is permitted to return to an every other week session frequency.

[b] Subjects that enter the Randomized Withdrawal Phase on a weekly intranasal treatment session frequency are required to remain on this frequency for the first 4 weeks of this phase. After a minimum of 4 weeks of weekly treatment sessions, if the subject meets the MADRS total score criteria for stable remission on an every other week frequency (i.e., MADRS total score ≤ 12 for 4 consecutive weeks), the treatment session frequency can be changed to every other week.

[c] If this is the 2nd consecutive occurrence of the MADRS total score ≥ 22, assess for relapse. If relapse criteria are met, the subject must be discontinued from the Randomized Withdrawal Phase.

Subjects who enter the Randomized Withdrawal Phase from the Stabilization Phase while on a weekly intranasal treatment session frequency are required to remain on this frequency for the first four weeks of this phase. After a minimum of four weeks of weekly treatment sessions, the treatment session frequency can be changed to every other week if the subject meets the MADRS total score criteria for stable remission.

Subjects who enter the Randomized Withdrawal Phase on an every other week dosing frequency may continue on this dosing frequency depending on their MADRS total score with an increase in session frequency to weekly if the MADRS total score is >12.

Time to relapse will be assessed by evaluating the time between randomization into the randomized withdrawal phase and the confirmation of a relapse event. Relapse will be defined by any one of the following criteria:

- MADRS total score >22 for at least 2 consecutive weeks (the date of the second MADRS assessment in the 2-week period will be used for the date of relapse);

- Discontinuation for lack of efficacy, defined as a need for additional or alternate treatment for depression;
- Hospitalization for worsening depression or hospitalization for suicidal attempt or to prevent suicide.

Rationale for Duration and Design of the Randomized Withdrawal Phase
The Randomized Withdrawal Phase is of variable duration until the number of relapses is met. The sponsor asserts that using the proposed approach of also allowing symptom severity-based individualization of dosing frequency in the Randomized Withdrawal Phase will also help to reduce the risk of relapse in those subjects for whom the relapse is delayed.

Planned Safety Assessments in the Maintenance Study
After expert consultation, the sponsor has chosen the following assessments of olfactory function:

- The University of Pennsylvania Smell Identification Test (UPSIT), which assesses a patient's ability to identify odors.
- Odor detection, which will be assessed using a forced-choice single staircase threshold procedure.

These tests will be administered bilaterally (ie, both nostrils at the same time). Testing will occur during the screening phase to establish a subject's baseline sensitivity. The degree of change from this baseline will be determined subsequently over time. Initially, testing will occur on a once every two weeks basis. However, after the first month, testing will occur every four weeks. The percent change from baseline will serve as the dependent measure for each subject for each test.

Other safety assessments included in this study include assessment for any long-term effect on cognitive function, assessments for cystitis, and risk for suicide. These safety assessments are the same as those in the long-term study and are described in greater detail above.

P. Proposed Design for the Open-Label Long-Term Study (ESKETINTRD3004)

This is an open-label multi-center, long-term study to evaluate the safety and efficacy of intranasal esketamine in combination with an oral antidepressant in subjects ≥18 years of age with TRD. It is anticipated that approximately 700 subjects will be included in this study. At least 100 of the 700 subjects will be elderly (i.e., 65 years of age) and will be exposed to variable esketamine treatment durations up to 12 months. This is in line with the ICH E7 guideline entitled Studies in support of special populations.

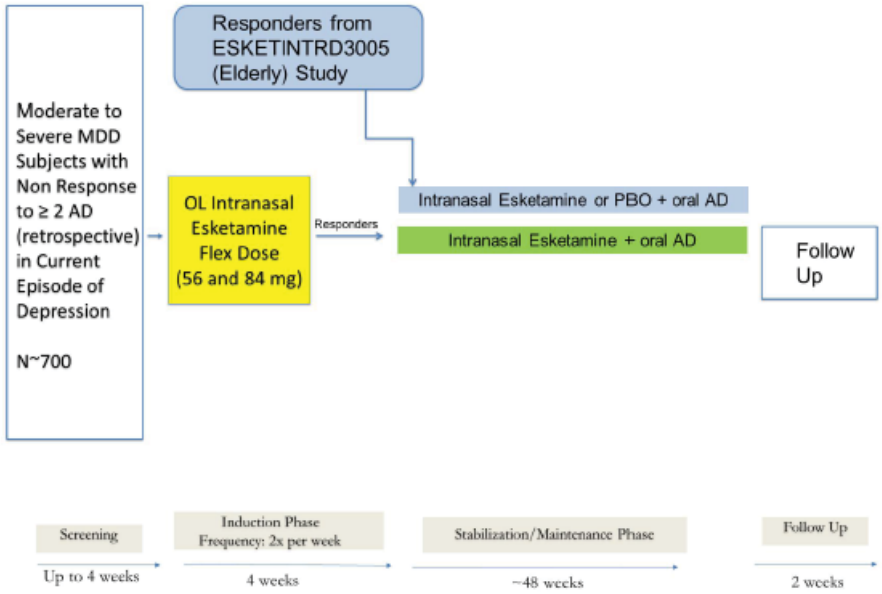
Each subject will participate in up to 4 phases:

- An up to 4-week Screening Phase
    - Elderly subjects who enter the study after completing the Double-Blind Induction Phase of the short-term efficacy study (ESKETINTRD3005) will not participate in this phase; they will start from the Stabilization/Maintenance Phase.

  - For directly recruited subjects, during the last week of the Screening Phase, if clinically indicated, an optional antidepressant taper period of approximately one week is permittedfor subjects currently taking an antidepressant.
- A 4-week Open-Label Induction Phase
- A 48-week Open-Label Treatment Stabilization/ Maintenance Phase
- A 2-week Follow-up Phase
  - All subjects who receive at least 1 dose of intranasal study medication in this study will have follow-up visits performed at 1 and 2 weeks after the last dose of intranasal study medication.

The maximum duration of the subject's participation will be 58 weeks for subjects directly entering the study, and 61 weeks for those who enter from study ESKETINTRD3005. The End of Study will occur when the last subject in the trial completes his/her last study assessment.

Figure 10: Design for Open-Label Safety and Efficacy Study of Intranasal Esketamine in the Treatment of Subjects with TRD (ESKETINTRD3004); Subjects' Study Flow



AD = antidepressant; MDD = Major Depressive Disorder; OL = open-label; PBO = placebo

Screening Phase

Elderly subjects who enter the study after completing the Open-Label Induction Phase (ESKETINTRD3005) will not participate in this phase; they will start from the Stabilization/Maintenance Phase. This phase is only for subjects who enter the study directly. Subjects must meet DSM-5 diagnostic criteria for recurrent MDD, without psychotic features, based upon clinical assessment and confirmed by the MINI. In addition, the subject must have a MADRS total score ≥24. Subjects must have had non-response to at least 2 antidepressant treatments in the current episode of depression, assessed using the MGH-ATRQ and confirmed by documented medical history/prescription records.

Optional Antidepressant Taper
Subjects not currently taking an antidepressant at Screening are eligible to participate. Subjects currently taking antidepressant treatment will discontinue their antidepressant treatment prior to start of the Induction Phase. If clinically indicated, the antidepressant medication will be tapered according to the country-specific prescribing information.

Open-Label Induction Phase
During this phase, subjects will self-administer open-label treatment with intranasal esketamine at treatment sessions occurring twice a week for 4 weeks. In addition, subjects will simultaneously initiate a new, open-label oral antidepressant. The dosing procedures for the Open-Label Induction Phase of this study are the same as those in ESKETINTRD3001, ESKETINTRD3002, and ESKETINTRD3003.

Stabilization/Maintenance Phase
Responder subjects (≥50% reduction from baseline in MADRS total score) at the end of the Open-Label Induction Phase will immediately enter the Stabilization Phase/Maintenance, continuing intranasal esketamine and an oral antidepressant. After giving informed consent for this study, elderly subjects who enter the study after completing the Double-Blind Induction Phase of the short-term efficacy study (ESKETINTRD3005) will start from the Stabilization Phase. To maintain study blinding, all responder subjects, including responders to the active comparator (i.e., oral antidepressant and intranasal placebo), are eligible to participate in this study. At the start of the Stabilization Phase, these subjects will continue their same double-blind treatment from the Double-Blind Induction Phase.

During the Stabilization/Maintenance Phase, the frequency of intranasal esketamine or intranasal placebo treatment sessions will be reduced from the frequency of the Induction Phase (twice per week) according to the same principles described above for ESKETINTRD3003. The dose of intranasal esketamine will remain unchanged. It is recommended that the antidepressant dose remains stable. Weekly MADRS assessments will be performed during this phase.

Relapse will be defined by any one of the following criteria:

- MADRS total score >22 for 2 consecutive weeks (the date of the second MADRS assessment in the 2-week period will be used for the date of relapse);
- Discontinuation for lack of efficacy defined as a need for additional or alternate treatment for depression;
- Hospitalization for worsening depression or hospitalization for suicidal attempt or to prevent suicide.

Follow-up Phase
All subjects who receive at least one dose of intranasal study medication in this study will have follow-up visits performed at one and two weeks after the last dose of intranasal study medication.

Safety Assessments
Safety assessments will include assessment of any long-term adverse reactions, with special attention to cognitive function, cystitis and bladder symptoms, potential withdrawal from esketamine, and suicidal thoughts.

Q. Proposed Design for Geriatric Short-term Study (ESKETINTRD3005)

The design of this study is similar to that described above for the ESKETINTRD3002 flexible-dose study. Responders at the end of the double blind induction phase will have the option of entering the open-label safety study (ESKETINTRD3004) as described above.

Based on the Panel A double-blind results of the ESKETINTRD2003 study, together with the preliminary PK data obtained from the ESKETINTRD1003 study described below, the two doses selected for the geriatric study (56 mg and 84 mg) are the same as the doses proposed for the two acute adult studies.

The ESKETINTRD1003 study was conducted in 14 healthy elderly subjects (≥65 years of age, with 3 subjects ≥75 years of age) and 20 healthy younger adult subjects (18 to 55 years of age, inclusive) who received a single intranasal treatment of esketamine 28 mg. The PK profile observed in the elderly cohort was similar to that observed in the younger adults. Median time to reach the maximum plasma concentration (tmax) of esketamine was approximately 30 minutes for both age groups. The geometric means of maximum plasma concentration (Cmax), area under the plasma concentration-time curve from time 0 to infinite time (AUC∞) for esketamine were approximately 21%, and 17% higher, respectively, in the elderly compared with younger adult subjects. The incidences of the TEAEs were slightly higher in young subjects (100% [20 subjects]) as compared with elderly subjects (85.7% [12 subjects]). The most commonly reported TEAEs by preferred term (>20%) in elderly subjects were dysgeusia and vertigo (9 [64%], of 14 subjects each), and TEAEs were similar in nature to those seen in the younger adult group.

2. DISCUSSION

2.1. Questions

CLINICAL

Question 1: Does the Agency agree with the designs of the two pivotal Phase 3 short-term studies (one fixed dose study, ESKETINTRD3001 and one flexible dose study, ESKETINTRD3002), as described in the supporting rationale and attached protocol outlines? Specifically does the Agency agree with the following?

a) Dose selection based on the results of the Phase 2 study ESKETINTRD2003
b) Efficacy and safety assessments in the ESKETINTRD3001 and ESKETINTRD3002 studies, specifically the key secondary endpoints of
   - onset of clinical response
   - change from baseline in the [redacted] (b) (4)

c) Selection and dosing regimen of oral antidepressants in the induction phase
d) The statistical methods, including the multiplicity adjustment for the primary and 2 key secondary efficacy endpoints (and across two dose-control comparisons for ESKETINTRD3001) and the interim analysis for sample-size re-estimation or futility?

FDA Preliminary Response to Question 1:

a. *Dose selection appears to be reasonable based on the submitted efficacy data, but the safety data provided is not adequate to conduct a thorough benefit-risk analysis. Please submit a full report of your safety analysis prior to submitting the protocols for review.*

b. *We have no objection to the first key secondary endpoint, intended to compare the proportion of patients with clinical response as defined in the briefing document.* (b) (4) *. Please provide further rationale for your choice of this instrument.*

c. *The selection of antidepressants and dosing regimens appear adequate, but details of the variation of the dosing in different countries need to be clearly stated. In addition, the screening for concomitant medications need to exclude other antidepressants, antipsychotics (typical and atypical), and lithium. The investigator needs to be aware that, because this is a global study, the sites in different countries may have different antidepressants and different names for the same antidepressant than what is represented on the MGH screening form. These drugs may also be used for other indications (e.g., pain, smoking, hot flashes, insomnia) that are not represented on the screening form and need to be probed to avoid violating the inclusion/exclusion criteria. Provide a plan that adjusts for these issues in your upcoming and ongoing protocols.*

d. *The statistical methods are generally acceptable. We may provide further comments once the SAPs have been received.*

Discussion at Meeting:

a. *The sponsor intends to provide topline safety data from Panel A of ESKETINTRD2003, as well as preliminary safety data (e.g., narratives for SAEs) from Panel B, by the end of January, 2015. The sponsor anticipates that a full safety report will be submitted by the end of 2015. The targeted start date for ESKETINTRD3001 is May, 2015. The division agreed that this plan is acceptable.*

b. *The sponsor inquired about ways in which time-to-response could be represented in labeling. The division stated that a graphical representation of the data (e.g., similar to that in the clinical studies section of the vortioxetine label) with a time scale in days would be acceptable, if that is how the data are acquired.*

(b) (4) *further discussion and analysis with the Study Endpoints and Labeling Development (SEALD) team is required before we*

c. The sponsor stated that generic names of prohibited medications will be listed for future studies. The Agency stated that ongoing protocols need not be amended.

Question 2: Does the Agency agree that the Phase 3 maintenance of effect study (ESKETINTRD3003), as described in the supporting rationale and appended protocol outline, will be adequate to support registration of esketamine for the treatment of TRD? Specifically does the Agency agree with the following?

a) Esketamine treatment session frequency selection, including a stabilization phase of variable duration between 6 to 12 weeks
b) Efficacy and safety assessments, including assessment of any effects on sense of smell
c) The statistical methods, including the interim analysis for sample size re-estimation, futility, or efficacy?

FDA Preliminary Response to Question 2:

a. The attempt to find the minimal effective dosing strategy is appreciated. The variable duration stabilization phase appears to be adequate and reflective of projected clinical usage.

b. Safety assessments appear adequate and reflect prior discussions. The results of the CogState safety data is absent from the submitted material, so we are unable to advise on the adequacy of your longer term studies.

c. The statistical methods are generally acceptable. However, we discourage a sample size decrease for the final analysis based on the interim result, particularly from a small number of events. We may provide further comments once the SAP has been received.

Discussion at Meeting:
Clinical 2b:
The sponsor included the cognitive assessments in Panel A of the ESKETINTRD2003 study following the division's request. However, the study was already ongoing and, to date, there are only eight patients with post-baseline CogState data. The sponsor plans to submit the data from this cognitive battery in May, 2015.

Statistics 2c:
The sponsor agreed to not decrease the sample size.

Question 3: Does the Agency agree with the following?

a) The proposed study design and assessments in the Long-term Safety Study (ESKETINTRD3004) are adequate to support registration of esketamine for TRD
b) The proposed clinical development program for TRD in elderly patients, which includes the proposed study design and assessments in the evaluation of short-term efficacy Geriatric Study (ESKETINTRD3005) and long-term safety (ESKETINTRD3004) of patients 65 years and older, is sufficient to support registration of esketamine for TRD

FDA Preliminary Response to Question 3:

a) On face the long-term safety study appears adequate, but a detailed review will be necessary at the time of submission of the protocol.

b) The design appears adequate, but a detailed review will be performed when the full protocol is submitted.

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

CLINICAL PHARMACOLOGY

Question 4: Does the Agency agree that the completed and proposed clinical pharmacology studies are sufficient to support an NDA submission for the proposed indication, and that no additional clinical pharmacology studies are required?

FDA Preliminary Response to Question 4:
Based upon Table 8 of your briefing book, on face, we would agree that the proposed clinical pharmacology studies are sufficient to support an NDA submission.

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

NONCLINICAL DEVELOPMENT

Question 5: In the pre-IND meeting of 8 May 2012, the Agency questioned the adequacy of the embryo-fetal developmental toxicity studies conducted by Javelin Pharmaceuticals with racemic ketamine to support the clinical use of esketamine. To address this concern, the Sponsor conducted toxicokinetic studies with racemic ketamine in pregnant rats and rabbits to determine the esketamine enantiomer exposure. Similar toxicokinetic studies were conducted in non-pregnant rats and dogs as well.

a) Does the Agency agree that the racemic ketamine systemic exposures generated in the intravenous toxicokinetic studies with racemic ketamine conducted by the Sponsor accurately mimic the systemic exposure range of racemic ketamine achieved in the embryo-fetal developmental and general intranasal toxicity studies with racemic ketamine acquired from Javelin Pharmaceuticals?

b)

c)

(b) (4)

FDA Preliminary Response to Question 5:

a) Yes, we agree that the AUCs appear to be fairly comparable in most cases, but we do not think this is relevant (see below).

b) No, we do not agree.

(b) (4)

(b) (4)

PK/TK studies conducted with (racemic) ketamine administered intranasally would be the most direct way to estimate the systemic exposures to esketamine (and metabolites) in the toxicology studies conducted with (racemic) ketamine administered intranasally and should be provided with the NDA.

We remind you that women of childbearing potential should be adequately protected from becoming pregnant, based on the potential for apoptotic brain lesions in fetuses exposed to NMDA receptor channel blockers like esketamine.

c) *No, we do not agree. See our response to Questions 5b, above.*

Discussion at Meeting: (b) (4)

Question 6: Does the Agency agree that the genotoxic potential of esketamine has been characterized adequately?

FDA Preliminary Response to Question 6:
Yes, we agree. You have currently submitted to the Agency a complete genotoxicity battery (Ames test, in vitro mouse lymphoma assay, in vivo bone marrow micronucleus assay) all using PMI-100. In addition, you have submitted a non-GLP in vitro micronucleus study in human TK6 lymphoblastoid cells and a Comet assay in liver cells with esketamine to further investigate the positive findings from PMI-100 in the in vitro mouse lymphoma assay.

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

Question 7: Does the Agency agree that the 14-day neurotoxicity study with intranasally administered esketamine in rats shows an adequate safety margin for histopathological brain lesions?

FDA Preliminary Response to Question 7:
On face, we agree. However, the adequacy of the 14-day neurotoxicity study to support Phase 3 clinical trials and/or NDA submission will be a matter of review when we receive the final study report.

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

Question 8: Does the Agency agree that the completed nonclinical studies support entry into Phase 3, and that no additional studies are required?

FDA Preliminary Response to Question 8:
No, we do not agree. The adequacy of the neurotoxicity assessment of esketamine will be a matter of review when the final report for the 14-day study has been submitted; see our response to Question 7. However, your complete genotoxicity battery, as well as your studies conducted with intranasal esketamine [fertility and early embryonic development toxicity study and your chronic toxicity studies of up to 6 months duration in rats and your ongoing 9-month toxicity study in dogs (when completed)], appear adequate to support Phase 3 clinical trials. Additionally, women of childbearing potential should be adequately protected from becoming pregnant.

Discussion at Meeting: *The division clarified that it would need adequate time to review the final report for the 14-day neurotoxicity study thoroughly before Phase 3 clinical trials could be initiated.*

Question 9: Does the Agency agree that the completed and proposed nonclinical studies are sufficient to support the planned NDA, and that no additional studies are required pending regulatory review and the absence of emerging safety issues from the clinical trials that would warrant nonclinical follow-up?

FDA Preliminary Response to Question 9:
On face, we agree, except for the deficiencies noted under Questions 5b and 8. We note that you have submitted a pre- and post-natal development study and have an ongoing 2 -year carcinogenicity study using esketamine and are planning a 6-month transgenic mouse study.

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

CHEMISTRY, MANUFACTURING AND CONTROL

Question 10: The Sponsor is developing the capability for in-house production of esketamine HCl drug substance as an additional source of API supply. After demonstrating comparability of the internal drug substance to the (b) (4) GmbH drug substance, the Sponsor intends to use a matrix approach to test the drug product stability. Does the Agency agree with our matrix proposal?

FDA Preliminary Response to Question 10:
Yes, we agree with your approach, i.e., two of the three registration batches will utilize the (b) (4) *manufactured drug substance.*

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

Question 11: Does the Agency agree with our proposed drug product manufacturing and control strategy for registration stability batches? Specifically:

a) Release testing strategy on vials and devices
b) Stability protocol and approach for manufacturing of registration batches
c) Extractable and leachable testing plan

FDA Preliminary Response to Question 11:

a) Yes, we agree with your proposed release and stability testing strategy on vials and devices as listed in Table 23 of the meeting package, including the proposed stability sample storage conditions.

b) For your stability protocol approach:
i) Because there is no information in the meeting packaging indicating that the solution is in full contact with the stopper, we recommend that the position of both the vials and devices be tested in inverted position instead of horizontal position.
ii) Inverted stability samples of vials stored at 25ºC/40% RH and 30ºC/40% RH at 9 month- and 18 month- time points should be tested for A(Appearance, assay, chromatographic purity, pH) and C (Assay of disodium edetate, color and clarity). The vials in vertical position at 9-month and 18-month time points should also be tested for A and C.
iii) Stability samples of devices stored at 25ºC/40% RH and 30ºC/40% RH at 9-month and 18-month time points should be tested for P (Appearance, assay, chromatographic purity, spray droplet size distribution, spray content uniformity by weight).

For manufacturing of registration batches approach:
i) We agree with your proposed registration batch size provided that the proposed third filled vial batch of (b) (4) *vials is a representative of a full filled vial operation, i.e., the beginning, middle and the end of the full vial filling operation.*
ii) We also agree with your proposed assembled devices batch size of (b) (4) *per stability batch provided that the assembled device samples are representative of*

a full device assembly operation, i.e., the beginning, middle and the end of the full device assembly operation.

c) *We agree with your proposed extractable and leachable testing plan except that the horizontal position of the stoppered glass vials is recommended to be tested in inverted position instead since there is no information in the meeting packaging indicating that the solution is in full contact with the stopper.*

Discussion at Meeting: *The sponsor agreed to test the filled vials and devices in the inverted position as requested for the registration stability study and extractable and leachable study.9- and 18-month time points will be added to the stability protocol. The sponsor also noted errors in the percent relative humidity in the stability protocols; corrections will be made for follow-up documents.*

Question 12: Does the following information address the Agency's concerns/requests discussed at the 05 June 2014 Type B meeting concerning a, b, and c below?

a) The Sponsor is providing a technical assessment of the dose gauge's ability to confirm the complete delivery of doses in Phase 3 devices
b) The Sponsor is providing the schematics of the dot indicator that is incorporated into the marketed product and will replace the dose gauge used for the Phase 3 studies
c) The Sponsor is providing a description of the minor device changes (previously presented to the Agency) that will be undergoing additional verification and validation testing

FDA Preliminary Response to Question 12:
Regarding 12a, you have provided an adequate assessment of the dose gauge's ability to confirm complete delivery of doses in Phase 3 devices. Regarding 12b, you have provided adequate descriptions and figures of the dot indicator that is incorporated into the marketed product. Regarding 12c, you have provided an adequate description of minor device changes, including the changes previously presented to FDA, as well as minor changes to increase manufacturing and performance robustness that were not previously presented to FDA.

DMEP's response to Question 12c:
Yes, we agree that should conduct a formal human factors summative study to validate all changes to the commercial device to include the addition of the dot indicator task, and the instructions for use. We recommend you submit the risk analysis and study protocol for our review prior to commencing the summative validation study.

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

Question 13: Does the Agency agree that additional modifications to the dual spray nasal device that improve manufacturability and/or increase the robustness of device performance can be made after the start of Phase 3 with appropriate device qualification?

FDA Preliminary Response to Question 13:
The changes that have been identified by the sponsor appear to be minor. We agree that additional modifications can be made after the start of Phase III as long as the changes are fully assessed with a design verification study that confirms the robustness of the device to being distorted or deformed when exposed to forces utilized during normal use.

DMEPA's response to Question 13:
We recommend the validated to-be-marketed commercial device be used in Phase III studies so that it will be used in a larger population, and any unforeseen problems that arise can be addressed early, prior to marketing the device. However, we agree the additional modifications can be made after the start of Phase III as long as the changes are fully assessed within the human factors summative validation study.

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

REGULATORY

Question 14: Does the Agency agree that the labeling concepts (goals of the esketamine drug development program) as summarized in the draft target product profile (TPP) are supported by the proposed Phase 3 clinical development program? The Sponsor recognizes that the Agency's concordance with the TPP does not represent a commitment to approve the identical language in the final label (*FDA Guidance for Industry and Review Staff Target Product Profile — A Strategic Development Process Tool*, March 2007).

FDA Preliminary Response to Question 14:
The proposed indication appears to accurately represent the study population. The labeling will need to provide clinicians with accurate instructions for the proper use of the medication based on the available information.

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

Additional Discussion:
The sponsor proposed a change in dosing for the ESKETINTRD3001 protocol. For the 84-mg dose group, the sponsor proposes titrating from 56mg rather than initiating treatment at 84 mg to improve tolerability and decrease dropouts. The sponsor noted that the severity of dissociative symptoms appears to be dose-related, but diminishes with repeat doses; therefore, adding a titration period should result in improved tolerability of the higher dose. The 84-mg dose also allows the treatment response to be maintained with a reduced dosing frequency, ideally once every other week following induction treatment. It appears that lower doses would require more frequent esketamine administration to maintain the antidepressant effect, because the duration of response appears to be diminished with lower doses. The division agreed to this modification.

The division asked for clarification regarding the sponsor's plan to address increases in blood pressure, and whether the blood pressure changes were correlated with dose or other factors.

The sponsor stated that blood pressure will be monitored prior to each dose, and the dose will be held if the blood pressure is outside the acceptable range. The sponsor noted that blood pressure peaks approximately 40 minutes post-dose, and typically returns to baseline within 2 hours. Patients with cardiovascular or cerebrovascular risk factors will be excluded from the study. Modifications are being made to the inclusion and exclusion criteria to lower the acceptable blood pressure range for study entry. The division noted that it will be important to allow patients with well-controlled hypertension into the study. Otherwise, the product label may have a Limitation of Use. The division added that the label may include instructions to monitor blood pressure or to discontinue use if an increase in blood pressure is observed. The Phase 3 protocol will include a dose reduction of the concomitant antidepressant if a significant increase in blood pressure is observed.

The sponsor intends to reduce the Prospective Screening/Observational Phase from 6 weeks to 4 weeks because of concerns from investigators that a 6-week screening/observation period without initiating a new treatment is excessive. Shortening the observation period still results in a cumulative time on the failed antidepressant of at least 10 weeks. The division agreed to this change.

3.0 PREA REQUIREMENTS

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

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

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Pediatric and Maternal Health Staff 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.

4.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

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

5.0 LABORATORY TEST UNITS FOR CLINICAL TRIALS

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

6.0 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 draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

7.0 OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators

who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

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

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

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

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions

transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.

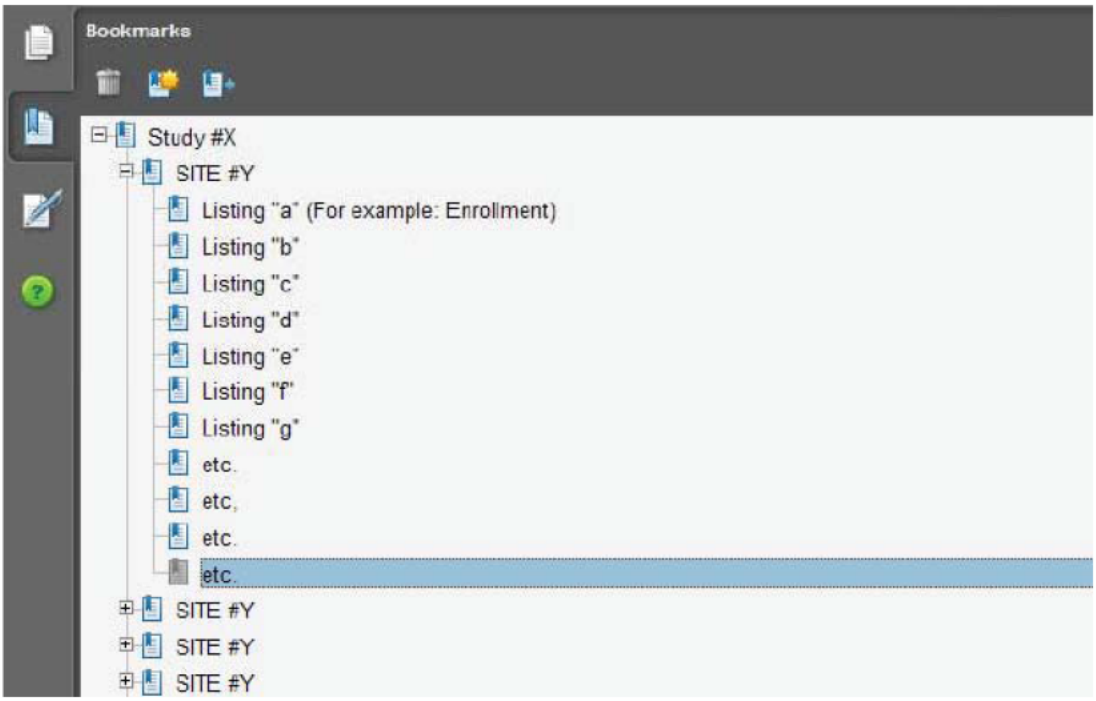
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

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

II. Request for Subject Level Data Listings by Site

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

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

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

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

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

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

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.

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

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

8.0 ATTACHMENTS AND HANDOUTS

The attachment below was presented as updates to the Drug Product Stability Protocol Tables 24 and 25 of the Meeting Briefing Document. The updates were made to address our proposals in the Preliminary Comments and correct the percent relative humidity of the intermediate and accelerated storage conditions to align with ICH Q1A.

Table 1: Proposed Drug Product Stability Testing of Vials in Inverted Position

Months	Long Term Storage Conditions				Accelerated Condition		Stress Condition	
	5°C	25°C/40%RH	30°C/35%RH	30°C/75%RH	40°C/75%RH	40°C/NMT25%RH	Light ICH	50°C
Initial	NA	NA	ABCD	NA	NA	NA	NA	NA
8 hours	NT	NT	NT	NT	NT	NT	A	NT
1	NT	NT	NT	A	A	A	NT	A
3	NT	NT	AC[a]	AC	ABC	ABC[a]	NT	ABC
6	AC	AC	AC[a]	AC[a]	ABCD[a]	ABCD[a]	NT	NT
9	NT	AC	AC[a]	A	NT	NT	NT	NT
12	ABCD	ABCD	ABCD[a]	ABCD[a]	NT	NT	NT	NT
18	NT	AC	AC[a]	AB	NT	NT	NT	NT
24	ABCD	ABCD	ABCD[a]	ABCD[a]	NT	NT	NT	NT
36	ABCD	ABCD	ABCD[a]	ABCD[a]	NT	NT	NT	NT

[a] Time point also tested in vertical position
A = Appearance, Assay, Chromatographic Purity, pH
B =Chiral Purity
C = Assay of Disodium Edetate, Color and Clarity
D = Particulate Matter
Light ICH = integrated near UV energy not less than 200 W·h/m^2, overall illumination not less than 1200 klux·hr
NT = Not Tested
NA = Not Available

Table 2: Proposed Drug Product Stability Testing of Devices in Inverted Position

Months	Long Term Storage Conditions				Accelerated Condition		Stress Condition	
	5°C	25°C/40%RH	30°C/35%RH	30°C/75%RH	40°C/75%RH	40°C/NMT25%RH	Light ICH	50°C
Initial	NA	NA	PQ	NA	NA	NA	NA	NA
8 hours	NT	NT	NT	NT	NT	NT	P	NT
1	NT	NT	NT	P	P	P	NT	P
3	NT	NT	P[a]	P	P	P[a]	NT	P
6	P	P	P[a]	P[a]	PQ[a]	PQ[a]	NT	NT
9	NT	P	P	P	NT	NT	NT	NT
12	PQ	PQ	PQ[a]	PQ[a]	NT	NT	NT	NT
18	NT	P	P	P	NT	NT	NT	NT
24	PQ	PQ	PQ[a]	PQ[a]	NT	NT	NT	NT
36	PQ	PQ	PQ[a]	PQ[a]	NT	NT	NT	NT

[a] Time point also tested in vertical position
P = Appearance, Assay, Chromatographic Purity, Spray Droplet Size Distribution, Spray Content Uniformity by Weight
Q = Microbiological Purity, Weight Loss
Light ICH = integrated near UV energy not less than 200 W·h/m^2, overall illumination not less than 1200 klux·hr
NT = Not Tested
NA = Not Available

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
01/07/2015