CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211321Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 077421

MEETING MINUTES

Proximagen, LLC
Attention: Encarnacion Suarez, PharmD
Director, Global Regulatory Affairs
505 Waterford Park, Hwy 169 N, Suite 850
Plymouth, MN 55441

Dear Dr. Suarez:

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

We also refer to the meeting between representatives of your firm and the FDA on January 16, 2018. The purpose of the meeting was to discuss the development plan for Nayzilam (midazolam nasal spray).

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 E. Andrew Papanastasiou, Regulatory Project Manager, at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	January 16, 2018, from 11:00 AM to 12:00 PM EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1419 Silver Spring, Maryland 20903
Application Number:	077421
Product Name:	Nayzilam (midazolam nasal spray)
Indication:	Rescue treatment of seizures in patients who require control of intermittent bouts of increased seizure activity (e.g., ARS, SC)
Sponsor/Applicant Name:	Proximagen, LLC

FDA ATTENDEES

Alan Stevens,	Branch Chief, General Hospital Devices
Angela Men, MD, PhD	Clinical Pharmacology Team Leader
Billy Dunn, MD	Division Director
Chad Morris, PharmD	Safety Evaluator, Division of Medication Error Prevention Analysis (DMEPA)
David Jones, MD	Clinical Reviewer
E. Andrew Papanastasiou PharmD, MS	Regulatory Project Manager (RPM)
Ebony Whaley, PharmD	Safety Evaluator, (DMEPA)
Edward Fisher, PhD	Nonclinical Reviewer
Eric Bastings, MD	Deputy Division Director
Jagan Parepally, PhD	Clinical Pharmacology Reviewer
John McMichael	Biomedical Engineer (CDRH)
Kun Jin, PhD	Supervisory Statistician
Lois Freed, PhD	Nonclinical Team Leader
Martha Heimann, PhD	Team Leader, Pharmaceutical Quality
Maryam Mokhtazedeh, MD	Senior Medical Officer, Office of Combination Products
Philip Sheridan, MD	Clinical Reviewer
Sandy Folkendt,	Regulatory Project Manager (RPM)
Shalini Bansil, MD	Medical Officer (Controlled Substances Staff)

Teresa Buracchio, MD	Clinical Team Leader
Xiang Ling, PhD	Statistical Reviewer
Yasmeen Abou-Sayed, PharmD	Pharmacist, Division of Risk Management

SPONSOR ATTENDEES

(b) (4)	Senior Medical Device Regulation Expert
David Seqeuira, PhD	Development Program Leader
(b) (4)	Statistical Consultant
Mark Gehrke, PhD	CMC Leader
Peter Van Ess PharmD, PhD	Chief Development Officer
Renee Gerhart, MS	Project Manager
William Pullman, MD, PhD, FRACP	President & Chief Scientific Officer

1.0 BACKGROUND

Nayzilam (midazolam nasal spray), formerly referred to as USL261, is an orphan designated drug under development for the rescue treatment of seizures in patients who require control of intermittent bouts of increased seizure activity (e.g., acute repetitive seizures, seizure clusters). Proximagen LLC is seeking to file a 505(b)(2) NDA for Nayzilam referencing NDA 18654 (midazolam HCl injection). A Type B Pre-NDA meeting was requested for Nayzilam on November 17, 2017, and the face to face meeting held on January 16, 2018.

FDA sent Preliminary Comments to Proximagen, LLC on January 11, 2018.

2. DISCUSSION

Question 1:

Does the Division concur that the planned PK approach and planned scientific justification are sufficient for the Division to make a determination regarding the following:

a) (b) (4)

b) Establishment of a body weight and/or age cut-off for dosing based on PK matching to the exposures observed in the P261-401 study in adults and adolescents for the 5-mg regimen and the 5mg + 5mg separated by 10 minutes regimen?

FDA Response to Question 1:

a) (b) (4)

b) See response to Question 1i.

Meeting Discussion:

(b) (4) applies only to the indication of partial-onset seizures. The sponsor indicated awareness that pediatric studies are not required because the drug has orphan drug designation, which exempts the application from PREA requirements; (b) (4)

Question 2:

Does the Division agree that the recommendations made to the sponsor at the EOP2 Teleconference held on 10 October 2013, and included in the Division's official minutes dated 07 November 2013, have been properly addressed by the sponsor, as described in this meeting package? Please note that the sponsor is no longer pursuing an alternative device, multiple dose strengths, an alternative manufacture or a secondary midazolam supplier.

FDA Response to Question 2:

It appears that you have addressed the previous comments from the October 2013 teleconference. However, refer to the Additional Comments below with regards to the device related information necessary to support any future marketing application.

Meeting Discussion:

No discussion. Refer to device discussion under Question 5.

Question 3:

Does the Division concur with the following:

a) The proposed approach to integrate the efficacy data, specifically, the pooling strategy and the analyses?

b) The proposed approach to integrate the safety data, specifically, the pooling strategy and the analyses?

c) The plan to synthesize and summarize the peer-reviewed publications of adequate and well controlled trials as supporting evidence of the efficacy and safety of midazolam?

FDA Response to Question 3:

a) No, as indicated in the response to Question 3a of the meeting minutes of November 24, 2017, (b) (4)

Meeting Discussion:

The sponsor proposed to present a comparison of data from studies P261-401 and (b) (4) in side-by-side tables (b) (4) in the future NDA submission. The Division generally found this approach to be acceptable, but noted that the submission should clearly indicate that the data from the controlled study serve as the primary efficacy data, (b) (4) .

b) On face, this approach appears appropriate.

c) A Bayesian meta-analysis is not required. You should instead provide a summary of the published peer-reviewed publications of adequate and well controlled trials supporting the safety and efficacy of midazolam.

Question 4:

Does the Division agree with the following:

a) The proposed plan to provide data tabulation sets and Analysis Datasets for the clinical studies included in the NDA?

b) The proposed approach to split the components of the ISS and ISE across Modules 2 and 5 of the eCTD submission?

c) The proposed provision of CRFs in the NDA?

d) The organization of the abuse potential section of the NDA?

e) If any device specific information is needed [refer to Question 5) c)], where within the eCTD should the device specific information be included?

FDA Response to Question 4:

a) On face, the proposed plan appears acceptable.

b) Yes, your approach is acceptable if the summary is provided in m2 and the Tables, figures, etc., are provided in m5. Please refer to Guidance for Industry:- Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document, located here:- https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf

c) In addition to your proposal to submit CRFs for patients who had an adverse event in the category of Acute Central Respiratory Depression, who become pregnant, or who discontinue due to an adverse event, you should also include CRFs and patient narratives for all serious adverse events.

d) Comments about the organization of the abuse potential section will be provided in a separate communication.

Meeting Discussion:

CSS indicated that the proposed content and organization of the abuse potential section of the NDA appears acceptable.

Analysis of the human abuse potential study (P261-101) will be a review issue.

For additional details regarding the documentation of AEs and drug accountability issues consult the January 2017 CDER guidance for industry, *Assessment of Abuse Potential of Drugs*, available at:

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf

e) For the location of device information in the eCTD refer to the Section 5 in the September 2016 eCTD Technical Conformance Guide Technical Specifications Document: "Guidance for Industry *Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications"*(https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf).

Meeting Discussion

The sponsor asked how long it would take for the DEA to make a decision regarding the scheduling of Midazolam nasal spray once CSS made a scheduling recommendation under the Controlled Substances Act. CSS is of the opinion that unless there are data to support otherwise, or the Sponsor requests a different schedule, Midazolam nasal spray will be placed in Schedule IV, the same as other midazolam products and all benzodiazepines. The sponsor should submit a proposal for scheduling in the NDA.

Assuming CSS recommends that Midazolam nasal spray be placed in Schedule IV, no further action by the DEA will be necessary.

Question 5:

a) Does the Division concur that the proposed components of the Nayzilam prescribing information (ie, Medication Guide and Instructions for Use) are sufficient as elements to ensure the proper use of the drug for the labeled indication without the need for additional Risk Evaluation and Mitigation Strategy (REMS) elements?

b) Proximagen has completed usability engineering/Human Factors (HF) activities for the Nayzilam (midazolam nasal spray) device, and the summary report is included in this meeting package. Proximagen considers that this report addresses the Division's preliminary comments received on 24 November 2017 for the Type C meeting. Does the Division have any additional requirements or advice?

c) Does the Division concur with Proximagen's analysis of the regulatory requirements applicable to the Nayzilam nasal spray device? Specifically, does the Division concur that:

i. A separate Premarket Notification or 510(k) clearance is not required because the Nayzilam nasal spray device will be the subject of an NDA submission for a combination product? In addition, (b) (4)

ii. As such, it is exempt from (b) (4) ?And,

iii. 21 CFR Part 4.4 determines the CGMP compliance of this single entity / copackaged combination product? And,

iv. If 21 CFR Part 211 is elected as the primary CGMP compliance requirements under 21 CFR 4.4(b)(1), (b) (4) ?

d) For the planned NDA submission via the 505(b)(2) pathway, Proximagen intends to reference the Versed® Injection NDA 18-654, 1985, and Hospira's midazolam hydrochloride injection labeling. Does the Division concur with this approach?

e) Based on the FDA Guidance for Industry on Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014), does the Division consider that Nayzilam NDA meets the requirements for Priority Review Designation?

FDA Response to Question 5:

a) We do not have sufficient 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, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

b) We acknowledge that you have submitted a summary report of your human factors validation study. Please note we expect that your proposed 505(b)(2) submission include the detailed HF validation study report. The acceptability of the HF Validation Study results is a review issue.

c)

i. Regarding the submission type for the combination product, the NDA is sufficient. A separate device application is not required for your combination product.

Regarding the briefing document (b) (4) we disagree with your exemption assessment.

Nayzilam, is proposed for "the acute treatment of seizures in patients who require control of intermittent bouts of increased seizure activity (e.g., seizure clusters, acute repetitive seizures)." (b) (4)

ii-iv. As stated above under the response to 5c(i), (b) (4) does not apply to Nayzilam. As described in the briefing document, Nazyzilam is a single entity combination product. The combination is subject to 21 CFR Part 4. (b) (4)

Meeting Discussion:

In reference to "Proximagen's Responses to Preliminary FDA Comments" dated January 15, 2018 (see attachment), FDA stated that a response to the new information would be provided as a post meeting comment.

Post-Meeting Comment:

As noted above, the Agency acknowledges the additional information you provided during the meeting for question 5.c with respect Quality System Regulation exemptions for devices regulated under (b) (4), as well as your identification of devices registered and listed under product code (b) (4). Manufacturers register and list with FDA using product codes at their discretion; however, this does not mean that the Agency has determined that the device is correctly classified. In any case, your product raises distinct issues that place it outside the scope of both regulations.

Specifically, your product's use, administration to the nasal cavity of a drug with a systemic or central-nervous-system targeted mechanism of action for rescue treatment of seizures, is beyond the scope of intended uses of delivery devices under (b) (4) and raises distinct safety and effectiveness questions. Therefore, we do not agree that the device constituent part of your product is covered by 21 CFR (b) (4) or 21 CFR (b) (4).

You state: (b) (4). As discussed above, the intended use of the Nayzilam device is new as compared to devices classified under 21 CFR (b) (4) and, as such, the device constituent part of your combination product is not covered by either regulation and, therefore, your combination product is subject to the 21 CFR 820 provisions as described in 21 CFR 4.

d) In general, reference to US approved Versed® Injection and Hospira's midazolam hydrochloride injection labeling is acceptable for 505(b)(2) pathway. However, as described in the EOP2 meeting minutes (28 January 2013), midazolam drug interaction information should be updated based on the information obtained from concomitant administration of Nayzilam with known CYP3A4 inducers and inhibitors. The IV midazolam is approved for use in a different indication and is used in the hospital settings under continuous monitoring for respiratory and cardiac function. IN midazolam appears not to be used under such closely monitored conditions.

Meeting Discussion:

The Agency reiterated that the labeling updates should be based on the sponsor's own data and scientific literature, which include datasets and bioanalytical assay information to be reviewed. The sponsor proposed providing justification for the labeling statements (b) (4). The Agency agreed to review the information provided to justify the updated proposed labeling.

e) This determination will be made after the NDA is submitted.

2.0 ADDITIONAL INFORMATION

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.
Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

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

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

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

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

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

ABUSE POTENTIAL ASSESSMENT

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

MANUFACTURING FACILITIES

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

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation

conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

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

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

Corresponding names and titles of onsite contact:

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

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
4.	

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

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

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

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

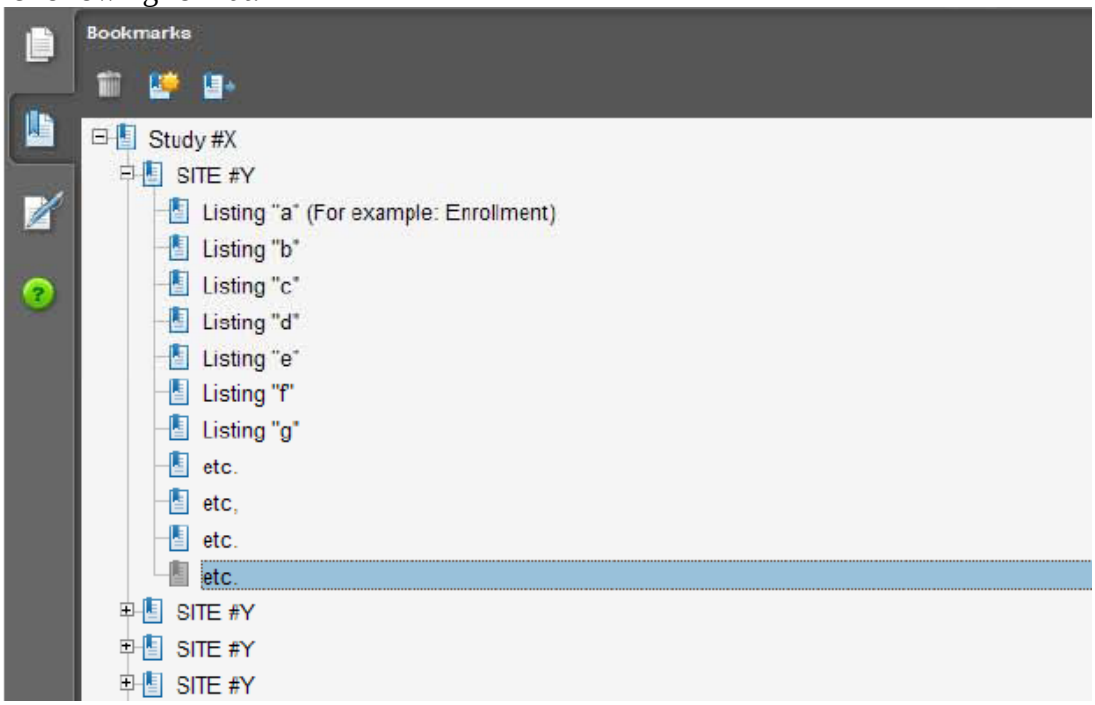
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

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

II. Request for Subject Level Data Listings by Site

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

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



III. Request for Site Level Dataset:

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

Attachment 1

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

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

DSI Pre-NDA Request Item[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

PROSPECTIVE ASSESSMENTS OF SUICIDAL IDEATION AND BEHAVIOR IN CLINICAL PROTOCOLS

Treatment-emergent suicidal ideation and behavior have been identified as a concern for a number of drugs and drug classes. For example, meta-analyses of clinical trial data for both antiepileptic drugs and antidepressants have demonstrated that these drugs increase the risk of suicidal ideation and behavior. Spontaneous reports have led to similar concerns with other drugs as well, e.g., isotretinoin and other tretinoins, beta blockers, reserpine, smoking cessation drugs, and drugs for weight loss. Because of these concerns, a prospective assessment for suicidal ideation and behavior should be included, when appropriate and feasible, in clinical trials involving all drugs and biological products for neurological indications. These assessments should generally be included in every clinical protocol, at every visit, and in every phase of development, with the exception of single-dose trials in healthy volunteers. These assessments should be conducted whether or not a particular product is known or suspected to be associated with treatment-emergent suicidal ideation and behavior. A sponsor considering the omission of the assessment of suicidal ideation and behavior from a particular clinical protocol should prospectively discuss this omission with the Division of Neurology Products

4.0 ISSUES REQUIRING FURTHER DISCUSSION

During the meeting, CDRH recommended the submission of a reliability testing protocol of the intranasal device for review before testing is initiated. CDRH recommended that this review take place in the context of a Type C meeting.

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

Proximagen, LLC provided responses to the FDA preliminary comments which were discussed during the meeting. A copy of these comments is attached to this document.

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

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

/s/

ERIC P BASTINGS
02/15/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 77,421

MEETING MINUTES

Upsher-Smith Laboratories, Inc.
Attention: Encarnaction Suarez, PharmD
Director, Regulatory Affairs
6701 Evenstad Drive
Maple Grove, MN 55369-6026

Dear Dr. Suarez:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for intranasal midazolam (USL261).

We also refer to the telecon between representatives of your firm and the FDA on October 10, 2013. The purpose of the meeting was to discuss and obtain feedback on the proposed and ongoing development program for USL261.

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

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Olen Stephens, Ph.D.
Acting Branch Chief
Branch I, Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End-of-Phase 2 CMC
Meeting Date and Time:	October 10, 2013; 11:00 am – 12:00 pm
Meeting Location:	Teleconference
Application Number:	IND 77,421
Product Name:	intranasal midazolam (USL261)
Indication:	rescue treatment of seizures
Sponsor/Applicant Name:	Upsher-Smith Laboratories, Inc.
Meeting Chair:	Olen Stephens
Meeting Recorder:	Teshara G. Bouie

FDA ATTENDEES

Office of New Drug Quality Assessment
Olen Stephens, Ph.D., Acting Branch Chief
Martha Heimann, Ph.D., CMC Lead
Lyudmila Soldatova, Ph.D., CMC Reviewer
Sandra Suarez, Ph.D., Biopharmaceutics Reviewer
Teshara G. Bouie, Regulatory Health Project Manager

SPONSOR ATTENDEES

Encarnacion Suarez, Pharm.D., Director, Regulatory Affairs
Michele Heintz, M.S., Associate Director, Regulatory Affairs CMC
Stephen M. Berge, Ph.D., R.Ph., Vice President, Pharmaceutical Sciences
Ron Ortiz, Ph.D., M.S., Principal Scientist, Pharmaceutical Development
Jim Jensen, Ph.D., Principal Chemist, Chemistry and Analytical Services
Leslie Helou, Pharm.D., Project Leader, USL261

1.0 BACKGROUND

IND 77,421 USL261 (Midazolam Nasal Spray) is currently being investigated for the rescue treatment of seizures in patients 12 years of age and older who require control of intermittent bouts of increased seizure activity (e.g., acute repetitive seizures, seizure clusters). On August 9, 2013, the sponsor requested an End-of-Phase 2 CMC meeting to discuss their proposed and ongoing development program for USL261. Background packages were received on September 10, 2013. Preliminary responses were sent to the sponsor on October 7, 2013. The sponsor provided follow-up questions the Agency's preliminary responses on October 8, 2013.

2. DISCUSSION

1. *In vitro* Bioequivalence

1.1. Does the Agency agree that the proposed approach to perform *in vitro* bioequivalence will be adequate to demonstrate equivalence between the "clinical trial" and "to-be-marketed" devices?

FDA Response: Yes, we agree. Note that if the in vitro testing fails the BE requirements, you would need to conduct an in vivo BE study comparing the two proposed products.

Sponsor Follow-up Question: Upsher-Smith would like to have additional discussion related to the planned *in vitro* bioequivalence study as well as the *in vivo* BE study comparing the two proposed products if the *in vitro* testing fails the BE requirements.

If the *in vitro* testing fails the BE requirements, Upsher-Smith proposes that a randomized single-dose crossover, pharmacokinetic study, conducted in healthy volunteers and evaluating (b) (4) would be sufficient to meet the *in vivo* BE study requirement.

Does the Agency concur with the proposed PK based BE approach?

Meeting Discussion: The sponsor stated dose proportionality studies have not been conducted with the clinical trial formulation. Therefore, the sponsor was advised to include both the high and low strengths in their PK study. The Agency stated that potential problems in measuring the moieties in plasma for the low strength could be overcome by developing a more sensitive analytical method.

Upsher-Smith has updated Table 9 (see below) of the briefing package (page 14) to summarize the proposed *in vitro* testing (b) (4)

(b) (4)

(b) (4)

(b) (4)

Additionally, Upsher-Smith would like to seek the Agency's concurrence on the proposed approach – specifically with respect to the use of a single bulk drug product batch. One bulk drug product formulation will be prepared for each dosage strength to be tested. Each bulk drug batch will be used to fill and assemble (b) (4) units. Vials will be filled and stoppered (b) (4). (b) (4)

Meeting Discussion: The Agency does not agree with (b) (4)

(b) (4)

Does the Agency agree with the use of a single bulk lot to fill and assemble our (b) (4) "clinical trial" and "to-be-marketed" batches?

Meeting Discussion: The Agency concurs.

1.2. Does the Agency agree that testing only the highest and lowest strengths will be sufficient to demonstrate equivalence for all strengths?

FDA Response: Yes we agree.

Meeting Discussion: No further discussion at the meeting.

1.3. Does the Agency agree that testing Droplet Size Distribution (DSD) and Spray Pattern (b) (4) between 2 cm and 7 cm from the laser beam will be adequate?

FDA Response: We do not agree. Perform Droplet Size Distribution (DSD) and Spray Pattern at two distances between 2 cm and 7 cm from the laser beam.

Meeting Discussion: No further discussion at the meeting.

2. Registration Stability Studies

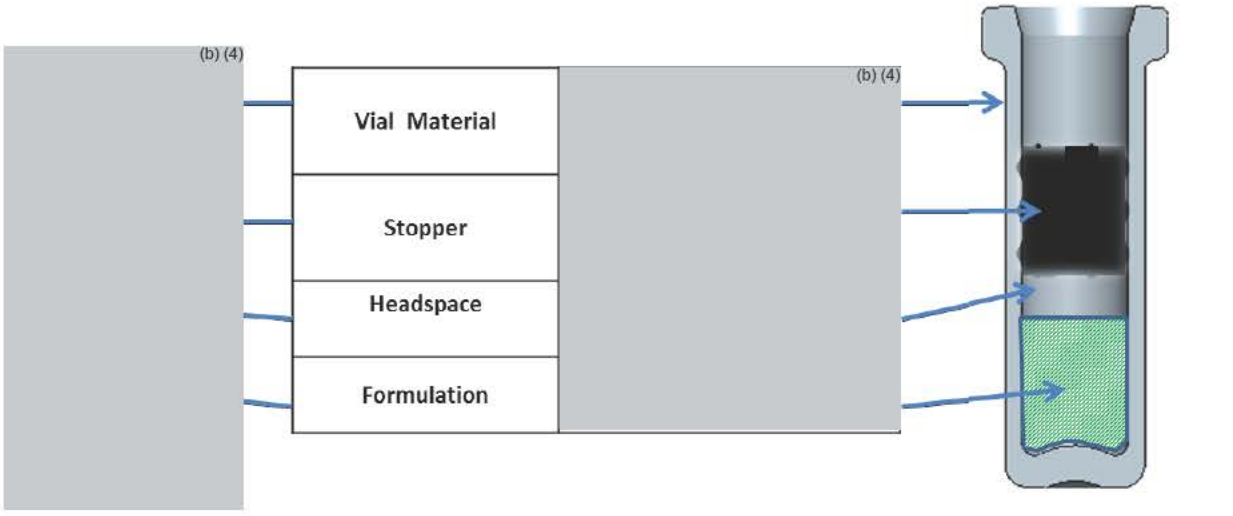
2.1. Does the Agency concur with USL's proposal to partially fill and assemble the primary stability batches?

FDA Response: We agree with your proposal to fill and assemble (b) (4) nasal spray units out of (b) (4) units of each dosage strength, and use them as the primary stability batches (three batches for each dosage strength). (b) (4) The primary stability batches should be filled into the "to-be-marketed" device.

Sponsor Follow-up Question: Upsher-Smith acknowledges the Agency's acceptance of the proposal to fill and assemble (b) (4) nasal spray units out of (b) (4) units of each dosage strength and use them as the primary stability batches (three batches for each dosage strength.)

Upsher-Smith would like to have additional discussion related to (b) (4) .

Upsher-Smith proposes that BE testing, assuming positive results, will address the equivalency in device performance between the "clinical trial" and the "to-be-marketed" devices; therefore, it is the sponsor's proposal that stability of the drug product solution in the "clinical trial" device will not be impacted by the dimensional changes in the "to-be-marketed" device. As demonstrated in the figure below, all drug product and material contact interfaces will remain the same between the two devices. In the primary component system (regardless of device), the drug product comes into direct contact with only the glass vial, rubber stopper, and sealed headspace during storage. The rubber stopper will be the same component (material composition and dimensional) used in both devices. Upsher-Smith intends to control and maintain the same headspace volume in the "to-be-marketed" device (b) (4) . Lastly, the glass type and inner diameter will remain the same in the "clinical trial" and "to-be-marketed" devices.



Upsher-Smith proposes to fill the stability batches manufactured at the alternate site in the "to-be-marketed" device and a minimum of 6 months of accelerated and long term stability data will be available at the time of the original application. The proposed registration stability data that will be included in the original NDA submission is summarized in the table below.

Summary of Available Stability Data in Original NDA Submission

Drug Product Strength	Primary Manufacturing Site "Clinical Trial" Device			Alternate Manufacturing Site "To-be-marketed" Device		
	Number of Batches	Available Data		Number of Batches	Available Data	
		Storage Condition	Months		Storage Condition	Months
7.5 mg	3	40°C/75% RH	6	(b) (4)	40°C/75% RH	6
		25°C/60% RH	12		25°C/60% RH	6

5 mg	3	40˚C/75% RH	6	1	40˚C/75% RH	6
		25˚C/60% RH	12		25˚C/60% RH	6
2.5 mg	3	40˚C/75% RH	6	1	40˚C/75% RH	6
		25˚C/60% RH	12		25˚C/60% RH	6
1.25 mg	3	40˚C/75% RH	6	(b) (4)	40˚C/75% RH	6
		25˚C/60% RH	12		25˚C/60% RH	6

In addition, Upsher-Smith intends to perform the following product characterization studies with the "to-be-marketed" device and submit the data in the original NDA application: Temperature cycling, device robustness, effect of dosing orientation, and plume geometry. These data, as well as the "sameness" of the primary component systems of the "clinical trial" and "to-be-marketed" devices, support the proposal to fill the primary stability batches into the "clinical trial" device.

Does the Agency concur that stability data generated in the "clinical trial" and "to-be-marketed" devices are adequate to support the proposed commercial drug product packaged in the "to-be-marketed" device, assuming acceptable data?

Meeting Discussion: Provided the BE study is acceptable, a bracketing approach for the amount of the stability data on the "To-be-marketed" device is recommended to include 3 batches of the highest dosage strength (7.5 mg), 3 batches of the lowest strength (1.25 mg), and 1 batch for each middle strengths (2.5 mg and 5 mg). The sponsor concurred.
After Meeting Discussion: Regarding the alternate manufacturing site for the "To-be-marketed" device, you will need to provided the comparability of the entire process at the alternate site vs. that at the primary manufacturing site: process of filling vials, assembling the device, and the identity of the equipment used. The release test at both facilities should be comparable as well.

2.2. Does the Agency agree that the planned stability studies are adequate to support the proposed commercial drug product packaged in the "to-be-marketed" device, assuming acceptable data?

FDA Response: Your proposal to incorporate a minimum of one additional distinct lot of each excipient during the manufacture of the registration stability batches is reasonable however final determination will be a review issue. **At least three primary batches of each dosage strength of the drug product should be placed on stability, and these batches should be packaged in the to-be-marketed device.**

Regarding the registration stability protocol, the tests for microbial limits and particulate matter should include testing of the vials in upright position at long term storage conditions as well as the inverted orientation. (b) (4) . A temperature cycling study should be performed to evaluate the effects of high and low temperature variations that may be encountered during shipping and handling on the quality and performance of the drug product.

Meeting Discussion: No further discussion at the meeting. Refer also to the meeting discussion for question 2.1.

3. Alternate Manufacturing Site

3.1. Does the Agency agree that the planned approach, with batch release and 3 months accelerated and controlled room temperature stability data for one batch of each strength and placebo, is adequate to support the proposed addition of an alternate manufacturing site, assuming acceptable data?

FDA Response: We agree with your approach to provide the batch release and 3 months accelerated and controlled room temperature stability data for one batch of each strength and placebo, to support the alternate drug product manufacturing sites.

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 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.				

Meeting Discussion: No further discussion at the meeting.

4. Alternate Drug Substance Manufacturer

4.1. Does the Agency agree that the planned approach to utilize two (2) distinct lots of Midazolam USP/EP supplied by (b) (4) in the manufacture of the primary stability batches is adequate to support the addition of an alternate drug substance manufacturer, assuming acceptable data?

FDA Response: We will evaluate (b) (4) as an alternate drug substance manufacturer at the time of NDA submission. That evaluation will include review of the manufacturing process used at (b) (4) as well as batch data. To support the addition of an alternate drug substance manufacturer, you will need to provide a direct comparison of the release and stability data for drug product batches manufactured with the drug substance from both sources (for example, a comparison of the clinical product manufactured with the (b) (4) drug substance to the primary stability batches manufactured by (b) (4) and filled in the to-be-marketed device). The plan to manufacture drug product primary stability batches utilizing two distinct lots of Midazolam from (b) (4) appears reasonable.

Meeting Discussion: No further discussion at the meeting.

4.2. Does the Agency agree that the data from the clinical batches manufactured with Midazolam USP/EP supplied by (b) (4) is adequate to support approval of (b) (4) as a drug substance manufacturer in the NDA, assuming acceptable data?

FDA Response: The data from the drug product clinical batches manufactured with Midazolam USP/EP supplied by (b) (4) will be reviewed at the time of the NDA submission along with the registration batches. Likewise, the acceptance of the (b) (4) as a drug substance manufacturer, will be a review issue based on the quality of the drug product data.

Meeting Discussion: No further discussion at the meeting.

Additional FDA Comments

The proposed design changes from the clinical device to the "to-be-marketed" device may potentially impact Agency conclusions regarding the safety, efficacy, and usability of the commercial product. We note that you intend to request feedback regarding Human Factors and Usability Engineering in the future. It is important that you identify all design changes between the clinical and "to-be-marketed" devices when you submit your protocol for comment.

The "to-be-marketed" device requires (b) (4), the amount of residual drug remaining in the device after use would (b) (4). For safety reasons, we recommend that you minimize the amount of residual drug to the lowest possible level.

We anticipate that we will consult the Center for Devices and Radiological Health (CDRH) Office of Device Evaluation regarding device quality aspects during review of your NDA. If you need additional feedback regarding submission of supporting information for the device, we recommend that you request a follow-up meeting with ONDQA and CDRH prior to the pre-NDA meeting.

Sponsor Follow-up Question: Upsher-Smith would like to have discussion related to FDA's additional comments.

Upsher-Smith Laboratories, Inc. is committed to performing a formal Human Factors and Usability Engineering program for USL261. Through the course of development, USL has conducted preliminary safety and use risk assessments on the "clinical trial" device. The output of these initial assessments, along with additional design input from key stakeholders (physicians, caregivers, patients), have provided the basis of the additional safety features and design modifications incorporated into the "to-be-marketed" device.

As part of our commitment to a formal Human Factors and Usability Engineering program, Upsher-Smith has engaged the services of (b) (4) to develop a comprehensive plan for the "to-be-marketed" device. The final outputs of the plan will include a Usability Engineering report, a summative study report, and a safety risk management report, all of which are intended to be incorporated into the original NDA filing. Upsher-Smith acknowledges the recommendation to request a follow-up meeting with ONDQA and CDRH prior to the pre-NDA meeting to get feedback regarding submission of supporting information for the device.

Upsher-Smith acknowledges FDA's recommendation to minimize the amount of residual drug to the lowest possible level and to identify all design changes between the "clinical trial" and "to-be-marketed" devices when we submit the draft summative validation protocol for comment.

What is the typical review time of a Human Factors and Usability testing protocol submitted to CDRH for feedback?

Meeting Discussion: The Office of New Drug Quality Assessment does not review Human Factors submissions. The Division of Neurology Products will consult the appropriate disciplines once the application is submitted. The sponsor asked which modules (Module 3 or Module 5) to include the Human Factors data. The Agency responded that this can be discussed during the pre-NDA meeting. The Agency advised the sponsor to be aware of possible changes by the Consumer Safety Product Commission regarding a lock-out device for children.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

4.0 ACTION ITEMS

None.

5.0 ATTACHMENTS AND HANDOUTS

None.

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/s/

TESHARA G BOUIE
11/07/2013

OLEN M STEPHENS
11/07/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 077421

MEETING MINUTES

Upsher-Smith Laboratories, Inc.
Attention: Sandra Croak-Brossman, Ph.D.
Senior Director, Regulatory Affairs
6701 Evenstad Drive
Maple Grove, MN 55369-6026

Dear Dr. Croak-Brossman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for midazolam nasal spray (USL261).

We also refer to the meeting between representatives of your firm and the FDA on January 28, 2013. The purpose of the meeting was to discuss the on-going development program for midazolam nasal spray.

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

If you have any questions, contact Fannie Choy, Regulatory Project Manager, by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Russell G. Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2 (EOP2) Meeting

Meeting Date and Time: Jan 28, 2013 2:00 p.m. EST
Meeting Location: FDA White Oak Campus, Building 22, Rm 1313

Application Number: IND 077421
Product Name: Midazolam nasal spray (USL261)
Indication: Rescue treatment of seizures
Sponsor/Applicant Name: Upsher-Smith Laboratories, Inc.

Meeting Chair: Russell Katz, M.D.

FDA ATTENDEES

Division of Neurology Products
Russell Katz, MD, Director
Eric Bastings, MD, Deputy Director
Norman Hershkowitz, MD, PhD, Clinical Team Leader
Phil Sheridan, MD, Clinical Reviewer
Lois Freed, PhD, Supervisory Pharmacologist, DNP
Ed Fisher, PhD, Nonclinical Reviewer
Fannie Choy, RPh, Regulatory Project Manager

Office of Clinical Pharmacology (OCP)
Angela Men, MD, PhD, Clinical Pharmacology Team Leader
Jagan Parepally, PhD, Clinical Pharmacology Reviewer
Atul Bhattaram, PhD, Pharmacometric Reviewer

Division of Biometrics I
Ohidul Siddiqui, PhD, Statistical Reviewer

Pediatric and Maternal Health Staff (PMHS)
Erica Radden, MD, Medical Officer
Courtney Suggs, PharmD, MPH, Regulatory Project Manager

Division of Medication Error and Analysis
Irene Z. Chan, PharmD, BCPS, Team Leader
Julie Neshiewat, PharmD, Safety Reviewer

SPONSOR ATTENDEES

Upsher-Smith Laboratories, Inc.
Harvey Altman, PhD, Director, Clinical Development, USL261
Sandra Croak-Brossman, PhD, Sr. Director, Regulatory Affairs
Heather Dworak, PhD, Sr. Clinical Research Scientist, Clinical Development
Leslie Helou, PharmD, Project Leader, USL261
William Pullman, MB, BS, PhD, FRACP, Chief Scientific Officer
Richard Ridgewell, PhD, Director, Preclinical Development
Encarnacion Suarez, PharmD, Director, Regulatory Affairs
W. Mark Todd, MD, Sr. Director, Chief Safety Officer

(b) (4)
, Regulatory Lead, Consultant

(b) (4)
, Regulatory and Development Advisor

1.0 BACKGROUND

Upsher-Smith Laboratories has requested the EOP2 meeting to obtain the Division's concurrence on the development plans and address the remaining aspects of the USL261 (midazolam intranasal) development program.

USL261, a new formulation for intranasal administration, is being developed for the rescue treatment of seizures in patients (ages 14 - 65 years) who require control of intermittent bouts of increased seizure activity (e.g. acute repetitive seizures and seizure clusters). Sponsor is proposing to submit a new drug application (NDA) under section 505(b)(2) for USL261. The 505(b)(2) application is expected to rely upon the full prescribing information of the listed drug, ANDA 075484, midazolam hydrochloride injection 5 mg (base)/mL.

Summary of Regulatory Background	
July 17, 2007	PIND meeting: Ikano Therapeutic, Inc. (previous sponsor)
September 26, 2007	Ikano submitted IND
October 1, 2008	Agency granted Fast Track Designation
November 25, 2008	Type B meeting: to discuss pivotal Phase 3 clinical study
October 20, 2009	FDA Orphan Designation
January 29, 2010	SPA Agreement (Protocol P261-401)
September 13, 2010	Transfer of IND Sponsorship to Upsher-Smith Laboratories, Inc.
October 29, 2012	SPA Modification Agreement (Protocol P261-401)

2.0 DISCUSSION

Note: Questions are numbered according to sponsor's briefing document.

NONCLINICAL PROGRAM

Question 8.1.1:

USL would like to confirm that FDA agrees that the nonclinical package is complete to support the active product, midazolam, for proposed IN administration registration?

FDA Preliminary Response to Question 8.1.1:

The nonclinical package appears sufficient to support an NDA for IN midazolam; however, the adequacy of the data will be a matter of review.

Meeting Discussion:

None.

Question 8.1.2:

Does FDA agree that the nonclinical data supports higher doses of IN midazolam including the clinical dose up to 15 mg per administration?

FDA Preliminary Response to Question 8.1.2:

Yes.

Meeting Discussion:

None.

Question 8.1.3:

Based on this completed nonclinical package for the active product, USL believes that this supports the continuation of clinical studies beyond 1 year. Does FDA agree?

FDA Preliminary Response to Question 8.1.3:

The nonclinical package appears sufficient to support clinical studies in adults beyond 1 year; however, the adequacy of the data will be a matter of review.

Meeting Discussion:

(b) (4)

Question 8.1.4:

Based on the nonclinical studies completed to date for the excipient MPEG-(b) (4), and assuming the remainder of genotoxicity is negative, does the agency agree that further studies, including a carcinogenicity program, are not needed?

FDA Preliminary Response to Question 8.1.4:

The adequacy of the nonclinical data, including the genotoxicity studies, for MPEG (b) (4) will be a matter of review.

Additional comment: The pregnancy labeling for the class of benzodiazepines is currently undergoing reevaluation. It is likely that your drug would be assigned a Pregnancy Category C rather than Category D as previously indicated.

Sponsor submitted discussion question (Jan 28, 2013):

Nonclinical - Question 8.1.4

Discussion on potential need and timing for additional nonclinical studies, specifically DART and carcinogenicity to qualify MPEG (b) (4).

Meeting Discussion:

The Division agreed to provide the sponsor with comments on the adequacy of the nonclinical data supporting the use of MPEG (b) (4) as soon as possible following submission of the data.

ADULT PROGRAM

Question 8.2.2:

Does the agency concur with amending the protocol from 4 visits to 3 by combining the randomization visit with the test-dose visit?

FDA Preliminary Response to Question 8.2.2:

Yes, Visit 2 (test-dose visit) can be combined with Visit 3 (randomization visit) provided that the patient is not treated for a qualifying seizure until three days after this combined visit.

Meeting Discussion:

None.

Question 8.2.3:

Does the agency concur that Protocol P261-401 can be amended to collect PK data on 25% of subjects enrolled (approximately 35 subjects)? If not, on what percentage of subjects would the agency recommend PK data is collected during the P261-401 study?

FDA Preliminary Response to Question 8.2.3:

OCP Response: Yes, the proposal is acceptable.

Clinical Response: The proposed sample of about 35 patients should be apportioned to give adequate representation of the full age range of 14 to 65 years.

Meeting Discussion:

At the meeting, the Agency asked the sponsor to clarify the selection of 5 mg as an effective dose in adults. The sponsor stated that literature suggests that 5 mg is an effective dose in adults.

Question 8.3.1:

The treatment decision criteria require at least 2 seizures in a 6 hour period prior to study drug administration and therefore model the acute repetitive seizure condition. Does the agency agree that the treatment criteria provide an acceptable confirmatory model (b) (4)?

FDA Preliminary Response to Question 8.3.1:

In proposed (b) (4) study P261-301 (Synopsis in Appendix 13), (b) (4) In this proposed open-label study P261-301, all patients who have had at least 2 seizures during the 6 hour Control Observation period (COP) would be treated with 5 mg. Historical data (references 17 and 28 on p103) suggest that 65% of untreated patients who have had at least 2 seizures during the 6 hour COP will have one or more seizures during the 6-hour Treatment Observation Phase (TOP). (b) (4)

[redacted]

Given the difficulty in recruiting a sufficient number of outpatients with ARS [redacted], the Agency would agree an alternative approach may be reasonable. Assuming that Study P261-401 is successfully concluded in the patient population corresponding to the proposed indication (outpatient treatment of ARS), [redacted] is not acceptable. A contemporaneous placebo control would be required. One approach would be to randomization 2:1 :: USL261:PBO for those patients having one or 2 seizures in the COP. Randomized patients in either arm would exit after one on-treatment seizure and then receive standard care. It is noted that you propose to exclude patients in the COP whose seizure activity appears consistent with status epilepticus and who could not tolerate a delay of standard therapy for status epilepticus. The secondary endpoints outlined in the P261-301synopsis appear appropriate.

As currently proposed in the synopsis of Study P261-301 (a complete protocol has not been presented as yet), even patients down to age [redacted] years would be treated with the same dose of 5 mg USL261 as the adults would receive (despite [redacted] and 40 kg. being the 50%ile for 12 year-olds). Will PK Study P261-202 be done prior to Study P261-301 to inform appropriate dosage?

A DSMB would probably be required for this study.

The Agency would need to review the full protocol for P261-301 as an SPA before approving it [redacted].

PMHS comment: PEG is associated with pediatric case reports of metabolic acidosis (with and without increased anion gap), and neuropsychiatric adverse events such as seizures, headache, anxiety, lethargy, sedation, aggression, rages and mood swings. [redacted]

Sponsor submitted discussion question (Jan 28, 2013):

Adult Program - Questions 8.3.1 and 8.3.6

Upsher-Smith appreciates the Division's responses regarding the proposed [redacted] Study P261-301. Upsher-Smith would like to discuss with the Division design options for an acceptable placebo-controlled trial, as well as the need to conduct the study under a SPA.

Meeting Discussion:

The sponsor proposed a different placebo-controlled study design for the proposed (b) (4) *Study P261-301 in the EMU patient population.* (b) (4)

The Agency agreed with the overall design concept. However, the Agency requested that the protocol be submitted for review as an SPA and an SAP. The Agency also requested that the published and unpublished data used to generate the historical untreated rate (65%) be presented in the SPA submission. The sponsor stated that they will try to submit this SPA protocol within the next several weeks and requested prompt review.

To address concerns of systemic exposure of an IN drug containing the excipient PEG, the sponsor could potentially provide data from the published clinical literature on other PEG-containing products.

Question 8.3.2:

Does the agency agree that patients enrolled will have the diagnosis of epilepsy but not necessarily the diagnosis of intermittent bouts of increased seizure activity (e.g. acute repetitive seizures, seizure clusters)?

FDA Preliminary Response to Question 8.3.2:

See preliminary response to 8.3.1.

Meeting Discussion:

See 8.3.1 discussion.

Question 8.3.3:

The primary efficacy endpoint is (b) (4) **in the Treatment Observation Phase. For any patient,** (b) **in the 6-hour Treatment Observation Phase. Is the primary endpoint acceptable?**

FDA Preliminary Response to Question 8.3.3:

As we recommend that the study include a placebo, we find it tentatively acceptable. Our final decision should await a more detailed description provided in an SPA.

Meeting Discussion:

See 8.3.1 discussion.

Question 8.3.4:

The key secondary endpoints are: 1) separate estimates of Time to First Seizure during the Treatment Observation Phase vs Control Observation Phase, and 2) (b) (4) Are these endpoints acceptable?

FDA Preliminary Response to Question 8.3.4:

As these endpoints are applied to a placebo comparison, we find them to be tentatively acceptable. Our final decision should await a more detailed description provided in an SPA. Labeling of such a secondary endpoint is a separate issue that will require negotiation. There are a number of criteria for the allowance of such labeling. Three of which include: 1) the endpoint must describe a different domain than that of the primary endpoint, 2) the endpoint results require replication, 3) the endpoint must be validated for measuring a significant clinical outcome.

Meeting Discussion:

See 8.3.1 discussion.

Question 8.3.5:

Does the agency agree that the EMU setting and proposed study entry criteria provide acceptable safety monitoring and appropriate subject selection to allow adolescents (b) (4) to take part in the study provided they have a body mass of 40 kg or heavier?

FDA Preliminary Response to Question 8.3.5:

Considering that your protocol recruits down to (b) (4) years of age (b) (4)

(b) (4)

OCP Response: The proposed dose is acceptable.

PMHS Comment: (b) (4) 40 kg is the 50th percentile for 12 year old males and 11.7 year old females according to CDC's weight for age tables. (See http://www.cdc.gov/growthcharts/html_charts/wtage.htm)

Meeting Discussion:

See 8.3.1 discussion.

Question 8.3.6:

(b) (4)

Does the agency agree that the difference of a 50% reduction in seizure rate (.65 reduced to .30) is clinically meaningful?

FDA Preliminary Response to Question 8.3.6:

The statistical considerations will require revision given the required protocol changes in the preliminary response to 8.3.1.

Meeting Discussion:

See 8.3.1 discussion.

Question 8.3.7:

Does the agency agree that both the EMU setting and proposed study design are acceptable? If not, what additional data is required?

FDA Preliminary Response to Question 8.3.7:

See preliminary response to 8.3.1.

PMHS comment: The EMU setting must be equipped to ensure appropriate safety monitoring and emergency care for pediatric patients (i.e., involve immediate availability of resuscitative drugs and age- and size-appropriate equipment for bag/valve/mask ventilation and intubation as well as skilled personnel able to respond to respiratory depression).

Meeting Discussion:

See 8.3.1 discussion.

PEDIATRIC PROGRAM

Sponsor submitted discussion question (Jan 28, 2013):

Pediatric Program – Questions 8.4.1, 8.4.4, 8.4.6, and 8.4.8 (and related Nonclinical Question 8.1.3)

Upsher-Smith would like to confirm the acceptability of submitting the adult indication for USL261 (b) (4) pediatric data (b) (4).

In addition, Upsher-Smith would like to discuss certain concerns raised by the Division including:

- (b) (4)
- Agency concerns over variable nasal absorption and local toxicity in pediatric patients
- PEG toxicity (Adult Program - Question 8.3.1)
- Need for a juvenile toxicology study (Nonclinical – Question 8.1.3)
- Review of Study P261-202 results (b) (4)

Question 8.4.1:

Does the agency concur with the overall study design and age range (6 to ≤ 13 years of age) for Study P261-202, entitled *"An Open-Label, Phase I, Pharmacokinetic and Pharmacodynamic Study of Single Doses of Intranasal Midazolam (USL261) in Pediatric Subjects with Epilepsy in the Epilepsy Monitoring Unit (EMU)"*?

FDA Preliminary Response to Question 8.4.1:

Yes, provided that the Agency and sponsor agree on how to address efficacy and safety in the pediatric population below age 14 years (b) (4). See preliminary response to 8.4.9.

PMHS comment: Due to concern for variable nasal absorption and possible increased local toxicity in all pediatric patients, PK and local toxicity data are necessary for all pediatric populations to be studied unless sufficient data are available from other sources.

(b) (4)

Meeting Discussion:

(b) (4)

(b) (4)

Therefore, pediatric efficacy studies will be required to establish efficacy and a pediatric indication for IN midazolam.

The Agency clarified that pediatric patients may be more sensitive to adverse events related to epistaxis and local irritation.

Question 8.4.2:

(b) (4)

Sponsor submitted Clarification (Jan 28, 2013):

Pediatric Program – Question 8.4.2

The assumption in our PK model that the metabolism of midazolam is similar in adults and children > 2 years of age is based on the literature as well as information in the product labeling for i.v. midazolam (Appendix 6 in our Briefing Document). The proposed pediatric PK Study P261-202 is intended to test this assumption, (b) (4).

Meeting Discussion:

See discussion for 8.4.5

Question 8.4.3:

Does the agency agree with the selection of doses?

FDA Preliminary Response to Question 8.4.3:

OCP Response: The dose selection is acceptable.

Meeting Discussion:

See discussion for 8.4.5.

Question 8.4.4:

Does the agency agree that pediatric patients enrolled will have the diagnosis of epilepsy but not necessarily the diagnosis of intermittent bouts of increased seizure activity (e.g., acute repetitive seizures, seizure clusters)?

FDA Preliminary Response to Question 8.4.4:

See preliminary response to 8.3.1

Pediatric patients with epilepsy but not ARS would be acceptable subjects for the PK/tolerability conclusions for study P261-202, (b) (4).

PMHS comment: (b) (4)

Meeting Discussion:

See discussion for 8.3.1.

Question 8.4.5:

USL261 pediatric data at the time of NDA filing will include the following unique exposures: 30 subjects age 12-17 years (Study MZ0815), 36 subjects age 6 to ≤ 13 years (Study P261-202), and an additional number of pediatric subjects enrolled in studies P261-401(14 to < 18 years of age) and P261-407. Does the agency agree that this is adequate for initial NDA filing?

FDA Preliminary Response to Question 8.4.5:

Does the sponsor mean P261-407 or (b) (4)

This requires further discussion and will be decided at the time of NDA submission.

Sponsor-submitted clarification (January 28, 2013)

Pediatric Program – Question 8.4.5

Upsher-Smith apologizes for the typographical error in the text of this question. Reference to Study P261-407 should have read "Study P261-301."

Meeting Discussion:

"P261-407"in question 8.4.5 was clarified as a typo which should have read "P261-301".

The Agency agreed with the sponsor that the initial NDA application for ages 14 years and above could be submitted based on (b) (4) *studies in patients age 14-65 years (ongoing Study 261-401 and* (b) (4) *as discussed under question 8.3.1) before the completion of Study 261-202 (a PK tolerability study in patients age 6 to 13 years).* (b) (4)

Study 261-202 will provide dosing guidance (b) (4) *(see discussion for 8.4.6).*

Question 8.4.6:

Will the ISMC review be sufficient (b) (4) **?**

FDA Preliminary Response to Question 8.4.6:

(b) (4)

Meeting Discussion:

(b) (4)

Question 8.4.7:

(b) (4)

FDA Preliminary Response to Question 8.4.7:

(b) (4)

PMHS comment: See the answer to question 8.4.1 - 8.4.5.

Meeting Discussion:

See discussion for 8.4.6 (b) (4).

Question 8.4.8:

(b) (4) **after completion of Study P261-202, including review of the PK and safety data and pharmacometric confirmation of appropriate dosing. The P261-202 study will provide in-clinic monitoring, including monitoring for respiratory adverse effects after USL261 administration. Further, it is anticipated that at the time of study start, P261-401 will have completed a test dose on at least 155 patients. Assuming this data supports the safety of USL261, USL proposes that** (b) (4) **Does FDA concur with this proposal?**

FDA Preliminary Response to Question 8.4.8:

See the preliminary response to 8.4.7.

Although Study P261-401 will have test-dosed 155 patients, these patients range in age from 14 to 65 years. [(b) (4)] P261-202 (open label PK study of 36 patients 6-13 years) will provide some data for the younger children, [(b) (4)].

Given the possible variation of nasal absorption in younger patients, [(b) (4)]. In addition, higher doses may be needed in younger patients (see response to question 8.4.2).

Meeting Discussion:

The necessity for a test dose was not discussed and will be addressed at the time of [(b) (4)] *. See also discussion for 8.4.6.*

Question 8.4.9:

[(b) (4)]

FDA Preliminary Response to Question 8.4.9:

[(b) (4)]

Meeting Discussion:

The [(b) (4)] *was not discussed.*

SAFETY EXPOSURES

Question 8.5.1:

Does the agency agree with the above plan and will the total number of exposures to the 5.0 mg dose of intranasal midazolam be sufficient to support the NDA?

FDA Preliminary Response to Question 8.5.1:

This will require further discussion.

In PK study (P261-202), the subjects will only receive a single dose, and modeling will be used to support the PK of repeat-dosing in the pediatric population. P261-402 will provide actual safety data from multiple exposures in ages 14-65 years. In summary (page 79) about 400 individual subjects age 6 to 65 will have received at least one dose of USL261 $\geq$ 5 mg.

Sponsor submitted discussion question (Jan 28, 2013):

Safety Exposures – Question 8.5.1

We look forward to discussion with the Agency regarding Safety exposure.

Meeting Discussion:

The sponsor proposed safety exposure from efficacy, PK, and safety studies (Tables 19-21 in the meeting package).

The Agency stated that 400 patients exposed to one or more doses of the 5 mg dose (or greater) of IN midazolam may be adequate if each patient receives multiple doses (has multiple exposures) during the time period of the study. Since IN midazolam is a chronic intermittent drug, the usual criteria (for 6 and 12 month continuous exposures at a therapeutic level) do not apply.

Study 261-402 will be a two year open-label outpatient study in patients 14-65 years of age. The sponsor stated that their experts estimated that patients in the two year study would experience an average of 3 to 6 ARS episodes each year. The Agency stated that a principal safety concern is adverse effects from multiple doses. The data should be collected and presented in a manner that clearly indicates the dosing intervals between multiple doses so as to allow assessment of exposure-response for adverse effects. According to the proposed protocol and anticipated labeling, a second dose is allowed at least 10 minutes after the first dose but subsequent doses must not be given until a three day interval has elapsed. More frequent dosing could lead to a loss of effect from tachyphylaxis or to withdrawal seizures when the midazolam was stopped.

ELDERLY

Question 8.6.1:

Does the Agency agree with our proposal?

FDA Preliminary Response to Question 8.6.1:

This will require further discussion.

Sponsor submitted discussion question (Jan 28, 2013):

Elderly – Question 8.6.1

We look forward to discussion with the Agency regarding this population.

Meeting Discussion:

The sponsor indicated that having dosing adjustments for the elderly in labeling would not be feasible since the intranasal dose is a fixed metered dose.

The sponsor further stated that they don't anticipate having a significant number of patients above age 60 years in their studies. To date, in ongoing study 261-401, about one third of the total n of 155 has been enrolled and none of the patients are above age 60. The possibility of PK and tolerability studies in normal volunteers above age 60 was raised. However, these normal volunteers will not be on the concomitant drugs commonly used in the elderly population. Another possibility is to study patients in the EMU where an estimated 5-10% of patients are over 60 years of age.

The sponsor asked whether the absence of data would lead to a contraindication in the elderly. The Agency responded that it would not lead to a contraindication in the elderly.

TEST DOSE

Question 8.7.1:

Does the agency concur that based on the proposed development program and controlled safety studies, the test dose will not be required in marketed use? If not, what additional data is required to ensure the test dose will not be required?

FDA Preliminary Response to Question 8.7.1:

Potentially yes, depending on the safety data to be presented to the Agency.

Review of the meta-analysis would be required.

Sponsor submitted Clarification (Jan 28, 2013):

Test-Dose – Question 8.7.1

Upsher-Smith would like to confirm that the "meta-analysis" mentioned to in the preliminary response refers to an integrated summary of USL261 safety data and not an update to the literature review previously provided.

Meeting Discussion:

The necessity for a test dose in marketed use was not discussed and remains an open issue.

CARDIAC CONDUCTION SAFETY (QT/QTc)

Question 8.8.1:

Does FDA agree that a thorough QT/QTc study is not required?

FDA Preliminary Response to Question 8.8.1:

Yes, we agree.

Meeting Discussion:

None.

DRUG INTERACTIONS

Question 8.9.1:

Does FDA agree that (b) (4) **for use of USL261 with any known inducers and inhibitors of CYP 3A4 drugs?**

FDA Preliminary Response to Question 8.9.1:

OCP Response: No. We do not agree that (b) (4) when USL261 is combined with known CYP3A4 inducer and inhibitors.

- CYP 3A4 inducers: In study MZ0815 when repeat dose of midazolam was given there was 30 to 40% difference in Cmax for adult subjects in the presence of CYP 3A4 inducers and in the absence of inducers. However, adolescent subjects (n=2 on inducers) had lower PK profile on inducers for the initial dose but this was not seen with second dose. Please provide justification for this discrepancy.

- CYP 3A4 inhibitors: The magnitude of change in the exposure of IV midazolam when administered concomitantly with strong CYP3A4 inhibitors is not described in IV midazolam PI. Saari et al., showed that voriconazole increased the Cmax and AUC of oral midazolam by 3.8- and 10.3-fold, respectively. Due to the potential safety concern, we recommend that strong CYP 3A4 inhibitors should be contraindicated with the use of IN midazolam. Mild and moderate CYP 3A4 inhibitors should be used with caution to support the use of IN midazolam in the target population.

Sponsor submitted Clarification (Jan 28, 2013):

Drug Interactions – Question 8.9.1

As requested, we believe the discrepancy between adolescent and adult data in MZ0815 is due to the limited number of subjects and the variability. We intend to have adequate population PK data to characterize IN midazolam used concomitantly with CYP3A4 inducers.

Meeting Discussion:

None.

Question 8.9.2:

Does FDA agree that no additional drug interaction studies are required to support the use of IN midazolam in the target population?

FDA Preliminary Response to Question 8.9.2:

OCP Response: See response to 8.9.1.

Meeting Discussion:

None.

Question 8.9.3:

Does FDA concur the use of (b) (4) drug interaction information will be reflected in the USL261 label?

FDA Preliminary Response to Question 8.9.3:

OCP Response: No. [redacted] (b) (4) [redacted] (b) (4) [redacted]. You need to update the DDI section per the response to 8.9.1.

Meeting Discussion:

None.

ABUSE LIABILITY

Question 8.10.1:

To address the concerns expressed by CSS, USL proposes to conduct the Abuse Liability Study. Does the agency agree that this study addresses the identified concern? If not, what other data will be required?

FDA Preliminary Response to Question 8.10.1:

CSS input is pending.

Sponsor submitted Clarification (Jan 28, 2013):

Abuse Liability – Question 8.10.1

Upsher-Smith looks forward to receiving input from the CSS on this question.

Post-Meeting Comment:

No, the human abuse potential study alone does not address identified concern.

The objective of the study is to evaluate the abuse potential of new formulation of midazolam relative to that of currently marketed oral formulations of midazolam. The sponsor needs to submit a full protocol of abuse potential study to CSS for review.

However, in addition to the protocol for human abuse potential study the sponsor should provide the following information and data related to abuse potential from all clinical studies, including raw data and adverse events coded with the most recent MedDRA terminology, that includes:

1. *Tables of Adverse Events related to abuse potential that summarize all studies submitted, broken down by population, patients or healthy volunteers, age and gender.*

2. *For MedDRA coding of AEs, the sponsor should provide their coding convention, as MedDRA SOC terms may not capture unusual signs and symptoms that may be related to abuse liability if verbatim terms were used.*

3. *Descriptions and details of all reports in all clinical studies, including narratives of all incidents of abuse, misuse, overuse, or overdose (intentional or unintentional), or drug that is lost, stolen, missing or unaccounted for, and related to drug withdrawal and withdrawal symptoms, and any other indication of dependence.*

4. *Case narratives of patients in clinical trials who are discontinued from studies for lack of compliance to study medication or procedures, or who discontinue participation without returning the study medication.*

5. *Tabulation of patients who were discontinued from the study, or dropped out for reasons related to potential abuse and diversion, including narratives describing reasons and follow-up information.*

6. *All post-marketing safety reports of AEs related to potential abuse.*

The details of abuse potential evaluation are described in the FDA draft Guidance for Industry Assessment of Abuse Potential of Drugs, January 2010: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

LABEL

Question 8.12.1:

Does FDA concur that key safety sections of the Full Prescribing Information (labeling) for Intranasal Midazolam will differ in content from the labeling for midazolam injection (the reference drug) given that the reference drug contains data that are specific to the intravenous route of administration and the indication for sedation for the following sections:

a. Boxed warning
b. Contraindications
a. Warnings and precautions

FDA Preliminary Response to Question 8.12.1:

Although some changes in labeling will be required given the differences in route of administration, indication, dosing and administration including the home setting, and the findings of the studies in progress or planned, it is not possible to determine

at this time whether such label components as the boxed warning, contraindications, or warnings and precautions will be required in the label of P261. Such decisions will need to be deferred to as a review issue.

The need for test-dosing is currently an unresolved issue.

Meeting Discussion:

None.

Question 8.12.2:

While we recognize this is a review issue, the critical elements reflected in the label drive the development program, as such we are seeking the benefit of the Division's guidance early regarding potential text for an appropriate "indication and usage" for USL IN midazolam program which we propose reflects the population and age range studied in the clinical development program. Does FDA agree with the proposed indication and usage text?

FDA Preliminary Response to Question 8.12.2:

This will need to be deferred to as a review issue.

Meeting Discussion:

None.

Question 8.12.3:

While we recognize this is a review issue, the critical elements reflected in the label drive the development program, as such we are seeking the benefit of the Division's guidance early regarding potential text for an appropriate "dosage and administration" for USL IN midazolam program where there is no requirement of a test dose. This is based on the proposed development program. Does the FDA agree with the proposed dosage and administration text?

FDA Preliminary Response to Question 8.12.3:

This will have to remain a review issue.

Meeting Discussion:

None. See 8.7.3.

3.0 ADDITIONAL COMMENTS

3.1 HUMAN FACTORS AND USABILITY ENGINEERING

We note that your proposed nasal spray appears to be identical to the design of the Imitrex (sumatriptan) nasal spray. Although the device itself is similar between the two products, there are differences in the medication (differences in medication viscosity and other solution characteristics can change the functioning of the device), indication of use (acute treatment of migraine attacks vs. rescue treatment of acute seizures), patient population (migraine patients vs. seizure patients), and who administers the medication (self-administration of Imitrex vs. caregiver administration of midazolam nasal spray). Based on these differences, we require you to conduct a usability study to demonstrate that the proposed product can be used safely and correctly in the intended population. Please submit your study protocol for FDA's review prior to implementation.

Please provide a comprehensive use-related risk analysis for your proposed product. This analysis should include a comprehensive evaluation of all the steps involved in using your device (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform, the potential negative clinical consequences of use errors and task failures, the risk-mitigation strategies you employed to reduce any moderate or high risks to acceptable levels, and the method of validating the risk-mitigation strategies. We need this information to ensure that all potential risks involved in using your device have been considered and adequately mitigated and the residual risks are acceptable (i.e., not easily reduced further and outweighed by the benefits of the device).

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm.

The Agency published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm

Meeting Discussion:

During meeting discussion, the sponsor proposed postponing the discussion regarding usability to a future CMC meeting.

3.2 505(b)(2) APPLICATION

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate. We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature.

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

A 505(b)(2) application contains "full reports of investigations" of safety and effectiveness where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use. Reliance on an approved ANDA is not acceptable to support your proposed 505(b)(2) application. You need to identify the

NDA that was the basis for submission for the ANDA you have incorrectly proposed to rely upon to support your proposed 505(b)(2) application. You must also provide a patent certification or statement with respect to each patent listed in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book) for the listed drug upon which you rely (see 21 CFR 314.54(a)(1)(vi)).

If you choose to rely on FDA's finding of safety and/or effectiveness for a discontinued listed drug(s) and intend to support the scientific appropriateness of reliance through a comparative bioavailability study, you should use the ANDA product designated as the RLD in the Orange Book as the comparator in a comparative clinical trial to establish a bridge between your proposed drug product and the specified listed drug(s). Note also that reliance on FDA's finding of safety and/or effectiveness for a discontinued listed drug(s) is contingent on FDA's finding that the drug was not discontinued for reasons of safety or effectiveness.

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

3.3 DATA STANDARDS FOR STUDIES

The *PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013 THROUGH 2017* guidance provides specific requirements for electronic submissions and standardization of electronic drug application data. The sponsor should design and implement data standardization in all research protocols to be included in regulatory submissions, as required based on the timing for implementation of the research. The non-clinical and clinical research study designs should include concise and complete explanation for implementation of data standardization in the data collection section of the protocol. The sponsor should use the Clinical Data Interchange Standards Consortium (CDISC) Technical Road Map to design end-to-end harmonized data standardization, including the Clinical Data Acquisition Standards Harmonization (*CDASH*) standard for design and implementation of data collection instruments.

The Agency's methodology and submission structure supports research study design, as indicated in the *Guidance to Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* and the *Study Data Specifications*. The Agency's methodology and submission structure also supports integrating study

data collection for Safety and Efficacy study submission. Each study should be complete and evaluated on its own merits. The sponsor should maintain study data independently in the SEND datasets for non-clinical tabulations, SDTM datasets for clinical tabulations, and ADaM datasets for analyses tabulations. (See *SEND*, *SDTM* and *ADaM* as referenced in *Study Data Specifications)*. Study analyses datasets should be traceable to the tabulations datasets.

The *Study Data Specifications* provide the current specifications for submissions. The specifications provide the most conducive data content definition and structure for the review team, although this may vary based on the submission and reviewing division (pg. 4). The review team assigned to the submission determines the acceptability. Therefore, you are encouraged to follow this best practice noted in the *Study Data Specifications*, "prior to submission, sponsors should discuss with the review division the datasets that should be provided, the data elements that should be included in each dataset and the organization of the data within the file" (p. 4).

In addition, please reference the *CDER Common Data Standards Issues Document* for further information on data standardization in submissions.

Additional Links:

Electronic Regulatory Submissions and Review Helpful Links
Electronic Common Technical Document (eCTD)

3.4 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.

3.5 PREA PEDIATRIC STUDY PLAN

The Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 made the pediatric study requirements under the Pediatric Research Equity Act (PREA) permanent; however, PREA does not apply as your product received Orphan Designation. You will need to submit a Proposed Pediatric Study Request (PPSR) for FDA consideration if you plan to seek a Written Request for studies in

the pediatric population. Although you are not required to do so, you may also submit a Pediatric Study Plan (PSP) for FDA review.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

- Sponsor submitted document, dated January 28, 2013, containing comments and proposed meeting agenda.
- Table 19. USL 261 Studies at Time of NDA Submission, from volume 1 (page 76) of the sponsor submitted Type B Briefing Document, dated December 3, 2012.

Upsher-Smith is in receipt of FDA's preliminary written responses to the questions posed in our Type B Meeting Briefing Document dated December 3, 2012.

We appreciate the Division's time in reviewing the Briefing Document and providing these preliminary responses. We understand and have no need for further discussion at the meeting on the following questions and responses:

- Nonclinical - Questions 8.1.1 and 8.1.2
- Adult Program (Study P261-401) - Question 8.2.2 and 8.2.3
- Adult Program (Study P261-301) - Questions 8.3.2, 8.3.3, 8.3.4, 8.3.5, and 8.3.7
- Pediatric Program (Studies P261-202 and (b) (4)) – Question 8.4.3, 8.4.7, and 8.4.9
- Cardiac Conduction Safety – Question 8.8.1
- Drug Interactions – Question 8.9.2 and 8.9.3
- Labeling – Questions 8.12.1, 8.12.2, and 8.12.3

PROPOSED MEETING AGENDA

Upsher-Smith would like to have further discussion with the Division regarding the following questions:

Nonclinical - Question 8.1.4

Discussion on potential need and timing for additional nonclinical studies, specifically DART and carcinogenicity to qualify MPEG (b) (4).

Adult Program - Questions 8.3.1 and 8.3.6

Upsher-Smith appreciates the Division's responses regarding the proposed (b) (4) Study P261-301. Upsher-Smith would like to discuss with the Division design options for an acceptable placebo-controlled trial, as well as the need to conduct the study under a SPA.

Pediatric Program – Questions 8.4.1, 8.4.4, 8.4.6, and 8.4.8 (and related Nonclinical Question 8.1.3)

Upsher-Smith would like to confirm the acceptability of submitting the adult indication for USL261 (b) (4) pediatric data (b) (4).

In addition, Upsher-Smith would like to discuss certain concerns raised by the Division including:

- (b) (4)

- Agency concerns over variable nasal absorption and local toxicity in pediatric patients
- PEG toxicity (Adult Program - Question 8.3.1)
- Need for a juvenile toxicology study (Nonclinical – Question 8.1.3)
- Review of Study P261-202 results (b) (4)

Safety Exposures – Question 8.5.1

We look forward to discussion with the Agency regarding Safety exposure.

Elderly – Question 8.6.1

We look forward to discussion with the Agency regarding this population.

In addition, we do not believe that further discussion is required at the meeting with regards to the following questions; however, we offer the following clarifications:

Pediatric Program – Questions 8.4.2

The assumption in our PK model that the metabolism of midazolam is similar in adults and children > 2 years of age is based on the literature as well as information in the product labeling for i.v. midazolam (Appendix 6 in our Briefing Document). The proposed pediatric PK Study P261-202 is intended to test this assumption, (b) (4) .

Pediatric Program – Question 8.4.5

Upsher-Smith apologizes for the typographical error in the text of this question. Reference to Study P261-407 should have read "Study P261-301."

Test-Dose – Question 8.7.1

Upsher-Smith would like to confirm that the "meta-analysis" mentioned to in the preliminary response refers to an integrated summary of USL261 safety data and not an update to the literature review previously provided.

Drug Interactions – Question 8.9.1

As requested, we believe the discrepancy between adolescent and adult data in MZ0815 is due to the limited number of subjects and the variability. We intend to have adequate population PK data to characterize IN midazolam used concomitantly with CYP3A4 inducers.

Abuse Liability – Question 8.10.1

Upsher-Smith looks forward to receiving input from the CSS on this question.

(b) (4)

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/s/

RUSSELL G KATZ
02/26/2013