

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209388Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



NDA 209388

MEETING MINUTES

Evoke Pharma, Inc.
Attention: Marilyn R. Carlson, DMD, MD
Chief Medical Officer
420 Stevens Avenue, Suite 370
Solana Beach, CA 92075

Dear Dr. Carlson:¹

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gimoti (metoclopramide nasal spray).

We also refer to the meeting between representatives of your firm and the FDA on July 25, 2019. The purpose of the meeting was to discuss your proposed plan to address deficiencies contained in FDA's Complete Response letter issued on April 1, 2019.

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

If you have any questions, call me at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Maureen Dewey, M.P.H.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

¹ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.



MEMORANDUM OF MEETING MINUTES

Meeting Type: A
Meeting Category: End of Review

Meeting Date and Time: July 25, 2019 from 9:00 AM – 10:00 AM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: NDA 209388
Product Name: Gimoti
Indication: diabetic gastroparesis in adult women
Applicant Name: Evoke Pharma Inc.

Meeting Chair: Juli A. Tomaino, M.D.
Meeting Recorder: Maureen Dewey, M.P.H.

Division of Gastroenterology and Inborn Errors Products

Joyce Korvick, M.D., Deputy Director for Safety
Juli A Tomaino, M.D., Medical Team Leader
Maureen Dewey, M.P.H., Senior Regulatory Project Manager

Office of Clinical Pharmacology (OCP)

Shirley Seo, Ph.D., Director, Division of Clinical Pharmacology (DCP) III
Sojeong Yi, Ph.D., Clinical Pharmacology Reviewer, DCP III

Office of Pharmaceutical Quality (OPQ)

Hitesh Shroff, Ph.D., Team Leader (ATL)
Caroline Strasinger, Ph.D., Quality Reviewer

Center for Devices and Radiological Health (CDRH)

Peter Petrochenko, PhD, Senior Staff Fellow

SPONSOR ATTENDEES

Dave Gonyer, PharmD, CEO
Marilyn R. Carlson, DMD, MD, RAC, Chief Medical Officer, Evoke Pharma, Inc.

(b) (4)

(b) (4)

1.0 BACKGROUND

Evoke Pharma submitted new drug application (NDA) 209388 for Gimoti (metoclopramide nasal spray) on June 1, 2018, to the Division of Gastroenterology and Inborn Errors Products (DGIEP) under the 505(b)(2) pathway based on comparative exposure to the listed drug, Reglan® Tablets 10 mg.

The proposed indication is for the relief of symptoms in adult women with acute and recurrent diabetic gastroparesis.

FDA notified the Applicant that the application was not approvable due to deficiencies related to Quality, Clinical Pharmacology and Clinical issues and consequently received a Complete Response on April 1, 2019.

Evoke submitted a type A meeting request received to discuss risk mitigation strategies to address the issues raised in the letter. The meeting was granted on July 5, 2019.

2.0 DISCUSSION

Question 1: Does the Agency agree that Evoke's root cause analysis investigation has addressed the key aspects related to the low dose subjects, that our conclusions are supported by the information collected and data generated, and that the analysis will support successful resubmission of the Gimoti NDA?

FDA Response to Question 1:

No, we do not agree. You stated that the training and behavior of the dose administrators were identified as primary contributors to the incidences of low drug exposure. However, we note that out of 14 cases from 12 subjects with the low exposure, only 6 cases from 3 subjects were dosed by the administrator who was not re-trained before the trial whereas the other cases were dosed by the administrator who was re-trained. As such, drug administration by the staff who was not re-trained cannot be considered as the exact cause of the low exposure. In addition, in the phase 3 clinical trials in which patients self-administered the drug after reviewing dosing instruction, 3 patients demonstrated low exposure (< 5 ng/mL) around T_{max} at steady state (Day 7). Thus, the 'hesitant' behavior of administrators cannot completely address the potential cause of the low exposure. Although we consider that the data suggests that administrators' behavioral variability could have contributed to the low exposure, the data are insufficient to completely rule out other possible causes. We recommend that you consider conducting a patient use/patient handling study along with PK sampling to address the potential for incomplete drug delivery that may be caused by human error.

Additionally, your root cause analysis does not completely address the “inappropriate actuation force for full dose delivery” as a potential source of error. It is unclear whether your activation force specifications are appropriate for the user population to deliver a complete dose. We recommend providing additional justification and a complete test report of the study by (b) (4) which includes a clarification of whether the (b) (4) version of the pump is the same as the device used in your clinical studies.

Additional Discussion:

The Sponsor plans to perform a comparative study between the 14 pumps implicated in the low doses and the remaining retained pumps used during the METO-IN-006 study. The Sponsor proposed performing another user study with the retained devices, however, the Agency noted that this may not accurately address the issue of an out of specification activation force, unless quantifiable data was provided. Instead, the Agency recommended establishing an activation force specification (per feedback under Question 6) with an adequate justification for the specification range and performing a bench study to determine whether the 14 devices had significantly different activation force from the other devices in the study and whether all devices in the METO-IN-006 study were outside of a reasonable activation force specification (developed per the feedback in Question 6). The Sponsor concurred and stated that they will submit the actual actuation force values with the resubmission.

The Sponsor stated that data describing the patient experience with using Gimoti during the clinical trials are available based on patient interviews conducted by an independent group. The Division recommended that the Sponsor include in the resubmission any available data on the patient experience with Gimoti in support of the medical need for this type of intranasal product.

The Division noted that, although not with the to-be-marketed product, patient use data are available from the phase 3 clinical trials (MET-IN-003 and MET-IN-004), and the patients in these clinical trials were trained on how to properly use the intranasal spray. The Division clarified that the patient use data from the clinical trials may provide reassurance that patients can properly use the device; however, the clinical trial data could not be relied upon for efficacy, safety, or PK data to support approval because the clinical trials did not include an evaluation of the to-be-marketed dose.

The Division stated that patient comprehension and use data from -003 and -004 are not directly translatable to real world use of the product (as these patients were trained and were observed by a clinical coordinator to ensure drug delivery); however, patient use and the need for education/training may be further evaluated in the post-marketing setting, if warranted. Therefore, the Division recommended the Sponsor submit labeling, including a proposal for an Instructions for Use (IFU), with the resubmission.

In addition, the resubmission should include the information obtained from the root cause analysis.

The Division stated that ultimately, the adequacy of the data provided in the resubmission (e.g., quality data, root cause analysis summary, patient use data from clinical trials, and patient experience information) would be a review issue, and the determination of whether the concerns outlined in the Complete Response Letter, dated April 1, 2019, have been adequately addressed would be based on the totality of the evidence.

The Sponsor clarified that several patients with low absorption were excluded from the original analysis of study METO-IN-006. The Sponsor referred FDA to Appendix D of the meeting background package.

Question 2: The investigation of the 14 low post-dose drug levels in 12 subjects in the comparative bioavailability study, METO-IN-006, indicates that the issue was administration and not something specific to a subject's characteristics or the pump performance. Evoke proposes removing the 14 profiles with aberrant results from the analysis. With these data removed, the study results meet the criteria for bioequivalence (BE) for all dose strengths. Evoke proposes submitting an addendum with the updated analysis to the study report for the METO-IN-006 study.

Does the Agency agree that, based on the findings and conclusions from the root cause investigation, demonstration of bioequivalence in an analysis of the data from the comparative bioavailability study with the low dose profiles removed, can provide an adequate bridge to the listed drug in the NDA?

FDA Response to Question 2:

No, we do not agree. As we stated in the response to Question 1, we determined that your root cause investigation could not find the exact cause of the low exposure. Thus, the current data do not support a retrospective, statistical analysis which excludes certain PK profiles from the analysis.

Additional Discussion: No further discussion.

See also discussion under Questions 1 and 6.

Question 3: Would an addendum to the METO-IN-006 final study report containing the analyses and the results for the overall population be adequate for the NDA?

FDA Response to Question 3:

You may submit an addendum including additional analysis to the METO-IN-006 for our formal NDA review. However, it may not address all of our concerns. Please see our responses to Question 1.

Additional Discussion: No further discussion.

Question 4: To address the product quality/device quality deficiencies, Evoke has initiated manufacturing of three batches of drug product using the defined commercial formulation (equivalent to 15 mg dose) and the commercial device at the commercial manufacturing site, manufactured by the commercial process at the planned commercial batch size, and tested using validated analytical methods at the proposed analytical sites.

To ensure that the acceptance criteria for droplet size and spray pattern are set appropriately Evoke will be taking a statistically-based approach to determining the acceptance criteria for droplet size distribution (DSD) and spray pattern.

Evoke is planning on submitting stability data up to 24 months from its ongoing stability program (see Comment C below for further details). These data will also be assessed against the proposed commercial specifications.

Evoke believes the approach described above will provide the requisite data sets required to ensure the droplet size distribution and spray pattern acceptance criteria for quality control and on-going stability are appropriately set.
Does the Agency agree?

FDA Response to Question 4:

The approach described appears appropriate. The adequacy of the acceptance criteria will be a review issue and based on the totality of the data submitted with the resubmission.

Additional Discussion: No further discussion.

Question 5: Are there any specific data needed, beyond droplet size distribution, spray pattern or shot weight, to address any other outstanding issues?

FDA Response to Question 5:

We do not have additional recommendations beyond what was communicated in the CR Letter. Additional information, if needed, will be requested during review of the NDA.

Additional Discussion: No further discussion.

Question 6: Evoke is collaborating with (b) (4), the device manufacturer, to develop an appropriate strategy to ensure that the actuation force for the to-be-marketed product is appropriately controlled for the combination product in a consistent manner and is applicable to the intended patient population. Evoke would propose this to be a post approval commitment.

Does the Agency have any additional comments or recommendations?

FDA Response to Question 6:

We do not agree that it is appropriate to report activation force as a post approval commitment. We acknowledge your approach to develop a strategy to control activation force for the device; however, we consider activation force to be an essential performance requirement, which is critical to delivery of the drug product. We recommend you provide verification testing demonstrating that activation force performs to specifications, which ensure the device is safe and effective for its intended use. Testing should be performed on the final finished device (or include a complete justification for using any device other than the finished device you intend to market). We recommend your testing uses a statistically relevant number of samples (including consideration for total number of samples and sampled lots). Additionally, we recommend activation force to be added to release specifications, unless you have other controls in place (e.g., in-process controls that directly or indirectly ensure activation force adheres to your specifications). If you intend to refer to documentation (e.g., verification test reports) held within another submission and/or master file, provide a letter of authorization or right of reference alongside a detailed description of the location of the information within the file (i.e., volume, page number, section header, etc.). We also recommend that you provide a brief overview of how the referenced information is intended to support the review of your submission.

Additional Discussion:

The Sponsor plans to show that the actuation force from both pumps used in the METO-IN_006 study (“functioning” and “implicated”) are comparable. FDA recommends that the Sponsor develop an actuation force specification as recommended in the Division’s response above to Question 6. See also additional discussion under Question 1.

Question 7: Evoke is collaborating with (b) (4), the device manufacturer, to develop an appropriate strategy to ensure that the cap removal force will not be so high as to render it too difficult to remove by the patient population. Evoke would propose this to be a post approval commitment.

Does the Agency have any additional comments or recommendations?

FDA Response to Question 7:

Your plan to report cap removal force as a post approval commitment is reasonable. However, if information on the cap removal force is available, we recommend you include available information in the resubmission.

In the resubmission, we recommend that you 1) provide a justification for your specifications in order to ensure your testing is relevant, and 2) propose an upper bound for the acceptance criterion.

Additional Discussion: No further discussion.

Question 8: As discussed and agreed at the Type A Meeting on March 28, 2017, Evoke will be submitting additional stability data (12, 18 and 24 months at the long term storage condition of 25°C/60%RH) for the 17 mg dose strength that effectively brackets the commercial dose strength (15 mg) with the stability data already submitted in the NDA (14 mg strength data set out to (b) (4) months) to support its justification for the proposed shelf-life of the commercial product. (Type A Meeting Minutes dated March 30, 2017)

Does the Agency have any additional comments or recommendations?

FDA Response to Question 8:

We acknowledge your intent to provide additional stability data through (b) (4) months for the 17 mg strength and that it could be supportive, however, the length of the shelf-life or expiry granted at the time of approval ultimately will be determined based on the totality and adequacy of the data provided at the time of resubmission. Therefore, we reiterate our recommendation that at the time of resubmission the proposed shelf life should be supported by three batches of the drug product using the selected commercial formulation (including strength of the product) and the proposed commercial device.

In general, you may request an extension of the expiration dating period as appropriate (e.g., should a 12 month or 24-month expiry be granted at the time of approval) through annual reporting based on real-time stability data following an approved stability protocol.

Additional Discussion:

The Sponsor plans to submit additional stability data (12, 18 and 24 months at the long term storage condition of 25°C/60%RH) for the 17 mg dose strength that brackets the commercial dose strength (15 mg) with the stability data already submitted in the NDA (14 mg strength data set out to (b) (4) months) to support its justification for the proposed shelf-life of the commercial product. These additional data will be included in the resubmission.

FDA will accept the proposed bracketing data approach in the resubmission; ultimately, it will be a review issue. FDA reiterated the recommendation to submit 3 months of data with 3 batches of the to-be-marketed dose 15 mg. The sponsor agreed to submit an additional 2 batches of 15 mg stability data and include a comprehensive justification to show that the complete data set are sufficient to support the proposed shelf life.

Question 9: Evoke will be submitting the results from the comparability study and additional supporting documentation as detailed in the original NDA to support the reporting category for the additional testing facility.

Does the Agency have any additional comments or recommendations?

FDA Response to Question 9:

We do not have additional comments or recommendations at this time. The acceptability of the data will be determined upon review of the NDA submission.

Additional Discussion: No further discussion.

Question 10: Evoke is aware that the information to support this approach to dose adjustment for Specific Populations was submitted as an amendment to the NDA late in the review process. Having this opportunity to further review

(b) (4)

(b) (4)

FDA Response to Question 10:

No, we do not agree.

(b) (4) y

(b) (4)

Additional Discussion: No further discussion.

Question 11: If Evoke's proposal to decrease the frequency of dosing is not an acceptable approach to dose adjustment for specific populations, does the Agency agree with limiting the use of Gimoti to patients that do not require dose adjustment?

FDA Response to Question 11:

Yes, Gimoti would likely need to be limited to patients who do not require dose adjustment if a lower strength formulation does not exist to allow for administration of a lower dose in these specific populations. In the resubmission, you should propose an approach to limit the use of Gimoti to patients who do not require dose adjustment. We also remind you that the need

for dose adjustment in specific populations may be addressed through a post-marketing requirement(s)/commitment(s).

Additional Discussion: No further discussion.

Question 12: Does the Agency have any additional comments or recommendations regarding Gimoti use in Specific Populations?

FDA Response to Question 12:

We recommend that you develop a lower strength formulation (e.g., 7.5 mg) to address use in specific populations. In addition, a lower strength formulation could be used in the general patient population without the need for dose adjustment by indicating that patients can pump twice per dose, provided that you can demonstrate comparable exposure of the lower strength formulation after pumping once and twice to Reglan oral tablet 5 mg and 10 mg, respectively.

Additional Discussion: No further discussion.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 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 or deferred (see section 505B(a)(1)(A) of the FD C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

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 Information² and Pregnancy and Lactation Labeling Final Rule³ 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.

² <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

³ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

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

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).⁴ 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 Regulations.gov).⁵

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

⁴ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁵ <http://www.regulations.gov>

proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

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

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

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

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

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

submission.

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

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

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.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

Slides attached.

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

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

/s/

MAUREEN D DEWEY
07/31/2019 05:04:00 PM



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND025512

MEETING MINUTES

Evoke Pharma, Inc.
Attention: Marilyn R. Carlson, DMD, MD, RAC
Chief Medical Officer
420 Stevens Avenue, Suite 370
Solana Beach, CA 92075

Dear Dr. Carlson:

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

We also refer to the telecon between representatives of your firm and the FDA on March 28, 2017. The purpose of the meeting was to discuss the chemistry, manufacturing and controls of your product as well as the study design and doses to be used in the planned bioequivalence study in support of an NDA submission.

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

If you have any questions, call me, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Maureen Dewey, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: A
Meeting Category: Guidance
Meeting Date and Time: March 28, 2017
Time: 8:30 AM – 9:30 AM
Application Number: IND 25512
Product Name: Gimoti
Indication: For the relief of symptoms associated with acute and recurrent diabetic gastroparesis in adult women
Sponsor Name: Evoke Pharma, Inc.
Meeting Recorder: Maureen Dewey, M.P.H.

FDA ATTENDEES

Division of Gastroenterology and Inborn Errors Products (DGIEP)

Donna Griebel, M.D., Division Director, DGIEP

Victor Baum, Acting Medical Team Leader

Wen-Yi Gao, M.D., Medical Reviewer

Maureen Dewey, M.P.H., Sr. Regulatory Project Manager

Hitesh Shroff, Ph.D., Chemistry and Manufacturing ADL, OPQ

Office of Clinical Pharmacology

Dilara Jappar, Ph.D., Clinical Pharmacology Reviewer, OCP

Christine Hon, Ph.D., Clinical Pharmacology Acting Team Leader, OCP

SPONSOR ATTENDEES

Evoke Pharma, Inc.

David A. Gonyer, RPh., President CEO, Evoke Pharma

Marilyn R. Carlson, DMD, MD, RAC CMO, Evoke Pharma

Wayne M. Alves, PhD VP, Clinical Operations, Evoke Pharma

Matthew D'Onofrio, MBA EVP, Chief Business Officer, Evoke Pharma

(b) (4)

(b) (4)

1.0 BACKGROUND

On August 30, 2016, a pre-NDA meeting between Evoke Pharma and FDA was held to discuss the non-clinical and chemistry content and format of a planned NDA submission for Gimoti (metoclopramide) nasal spray.

During a Type B meeting held on December 13, 2016, DGIEP and the Sponsor discussed the Gimoti clinical data and proposed regulatory pathway for a planned 505(b)2 application.

On March 1, 2017, the sponsor submitted a Type A meeting request to discuss the proposed study design and doses to be used in the planned bioequivalence study in support of an NDA submission. The meeting was granted on March 13, 2017. The background package describes the sponsor's plan to produce a series of formulations with higher concentrations of the active ingredient.

FDA sent Preliminary Comments to the Sponsor on March 24, 2017.

Additional Discussion captured during the meeting is presented in *italic* font.

2.0 DISCUSSION

2.1. CMC

Question 1

The proposed stability plan for the NDA is detailed in the CMC Section (Section 15) for Gimoti Higher Strength products. Evoke believes that the extensive data set already generated for Gimoti Current Strength, summarized in Section 15, can be considered part of the primary stability data set because there is only a minor formulation difference with respect to active content, and these data together with the data from the Gimoti Higher Strengths as described in Table 15.8 Stability Study Summary will be sufficient to support the NDA at submission. Additional stability data for the selected Gimoti commercial strength formulation will be submitted to the NDA as it becomes available. In addition, the process validation batches will also be put on a full ICH stability program.

Does the Agency agree with the proposed Gimoti stability plan for the NDA?

FDA Response to Question 1:

No. We do not agree with the proposed Gimoti stability plan. The data from the stability studies must be provided on at least three registration batches of the drug product with the same strength, formulation and packaged in the same container closure system as proposed for marketing. The registration batches must be produced using the same manufacturing process and facility. You need to submit a minimum of 1 year of stability data on three registration batches. For further details on stability of new drug products see ICH Q1A(R2) and Guidance for Nasal Spray and Inhalation Solution, Suspension and Spray drug products – Chemistry, Manufacturing and Controls Documentation.

Additional Discussion:

FDA agreed with Evoke's proposal to submit, with the initial NDA submission, three batches of the highest dose strength (17 mg) manufactured at (b) (4) with a minimum of six months accelerated data and six months controlled room temperature stability data. Additionally, the NDA submission will be supported by at least three registration batches (10 mg, 14 mg) of stability data from (b) (4). During the review, Evoke will provide further stability data as it becomes available. The shelf life will be determined at the time of NDA review.

It is permissible for the three batches (17 mg) from (b) (4) to use the same batch of API for their production.

FDA advised the sponsor that both facilities must be ready for inspection at the time of the NDA submission.

Question 2

As described in the CMC section of this briefing document Evoke plans to establish the robustness of the higher strength formulations by a series of experiments that confirm the dissolution characteristics of the drug substance do not significantly change with the proposed concentration increases and that the ensuing formulations are robust (b) (4). Based on these data Evoke believes it will have demonstrated the higher strength formulations have appropriate quality characteristics to be taken into the PK program pending release of the clinical trial batches to the current metoclopramide release specification (with modifications for drug content and pump delivery as appropriate).

Does the Agency agree these data are sufficient to support the higher dose strengths in the PK program?

FDA Response to Question 2:

The proposed release and stability drug product specification is reasonable for this stage of drug development. However, you need to add a test and acceptance limits for dose delivery in your in-use stability specification.

The pump performance will be reviewed at the time of the NDA submission. For further details on drug product specification and pump requirements see the August 30, 2016 and December 13, 2016 meetings minutes and reference ICH Q6A and Guidance for Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products – Chemistry, Manufacturing and Controls Documentation.

2.2. Clinical Pharmacology Questions

Question 3

Based on available PK data, Evoke believes the confidence intervals around the AUC of metoclopramide in a Gimoti dose of 16 mg will fall within the bioequivalence range, i.e., 80-125%, of the Listed Drug, Reglan Tablets 10 mg.

To identify the Gimoti dose, Evoke proposes conducting a single 4-period, 4-treatment, 4-sequence randomized crossover study in healthy female volunteers (Protocol No. METO-IN-006) with three doses of Gimoti and Reglan Tablets, 10 mg. The synopsis is provided in Section 16 and the draft protocol is provided in Appendix 1.

Does the Agency agree with the design of the study (Protocol No. METO-IN-006)?

FDA Response to Question 3:

We note that while the listed drug, Reglan tablet, is indicated for the relief of symptoms associated with acute and recurrent diabetic gastric stasis without any specification for sex, the proposed indication for your product, Gimoti (metoclopramide) nasal spray, is for the relief of symptoms associated with acute and recurrent diabetic gastroparesis (diabetic gastric stasis) in adult women only. You have not provided justification for limiting an indication to women only. Without further justification, your proposed relative BA study should include both male and female healthy subjects.

Additional Discussion:

Evoke agrees to include a similar number of both males and females in the BE study.

If the results from the BE study do not meet the BE criteria to the referenced listed product, Reglan tablet, Evoke may seeking guidance from FDA by requesting a Written Response Only meeting.

Evoke is considering submitting an NDA seeking an indication in diabetic women only with data to support the proposed indication.

Question 4

The Gimoti dose that most closely matches the AUC of the Reglan Tablet 10 mg will be proposed as the Gimoti dose for the 505(b)(2) NDA. This approach was presented and discussed at the pre-NDA meeting on 13 December 2016. A copy of the slide “Equivalent Exposure Pathway to a 505(b)(2) NDA” presented by Evoke at the pre-NDA meeting and included in the official meeting minutes is provided for reference in Appendix 2.

Does the Agency agree with Evoke's plan for selecting the Gimoti dose that will be acceptable for the NDA?

FDA Response to Question 4:

Yes, your proposal is reasonable. Please also refer to FDA response to Question #3.

3.0 Additional Important 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.

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

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

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.

DATA STANDARDS FOR STUDIES

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

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the

availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdcr-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

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

Additional information can be found at

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

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

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

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

SUBMISSION FORMAT REQUIREMENTS

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

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA to sponsors/applicants when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), sponsors/applicants must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the 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>.

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to

discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

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

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

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

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

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. 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).

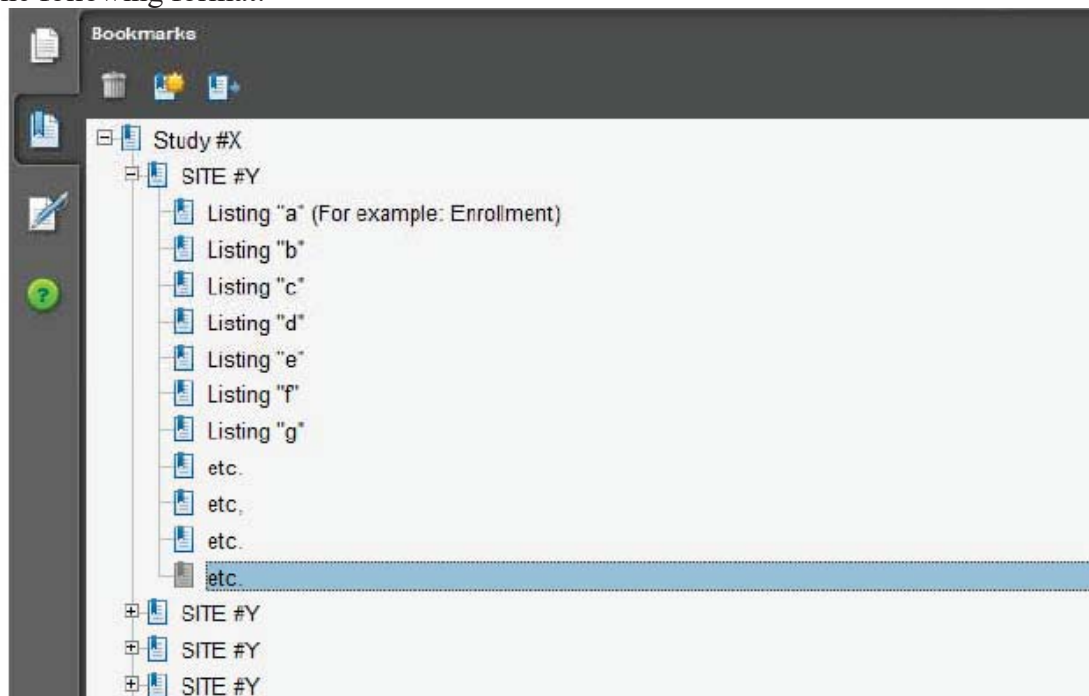
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

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 Item¹	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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ATTACHMENTS AND HANDOUTS

Sponsor's slides

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

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

/s/

MAUREEN D DEWEY
03/30/2017



IND25512

MEETING MINUTES

Evoke Pharma, Inc.
Attention: Marilyn R. Carlson, DMD, MD, RAC
505 Lomas Santa Fe Drive
Suite 270
Solana Beach, CA 92075

Dear Dr. Carlson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for EVK-001 (metoclopramide) nasal spray.

We also refer to the meeting between representatives of your firm and the FDA on August 30, 2016. The purpose of the meeting was to discuss the content and format of your planned NDA submission.

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 me, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Maureen Dewey, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA
Meeting Date and Time: August 30, 2016
Time: 9:00 AM – 10:00 AM
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903
Application Number: IND 25512
Product Name: EVK-001 (Gimoti)
Indication: For the relief of symptoms associated with acute and recurrent
diabetic gastroparesis in adult women
Applicant Name: Evoke Pharma, Inc.
Meeting Chair: Stephanie O. Omokaro
Meeting Recorder: Maureen Dewey

FDA ATTENDEES

Division of Gastroenterology and Inborn Errors Products (DGIEP)

Donna Griebel, M.D., Division Director
Stephanie O. Omokaro, M.D., Medical Team Leader
Patroula Smpokou, M.D., Medical Reviewer
Sushanta Chakder, Ph.D., Supervisory Pharmacologist
Jackye Peretz, Ph.D., Pharmacology Reviewer
Kevin Bugin, M.S., RAC, Chief, Project Management Staff
Maureen Dewey, M.P.H., Sr. Regulatory Project Manager

Donna Christner, Ph.D., Chemistry and Manufacturing Branch Chief, OPQ
Danuta Gromek-Woods, Ph.D., CMC Lead, OPQ
Lawrence Perez, Ph.D., CMC Reviewer, OPQ
Sue Chih Lee, Ph.D., Clinical Pharmacology Team Leader, OCP
Dilara Jappar, Ph.D., Clinical Pharmacology Reviewer, OCP
Yeh-Fong Chen, Ph.D., Biostatistics Team Leader, OB
Wen Jen Chen, Ph.D., Biostatistics Reviewer, OB
Vasant Malshet, Ph.D., Toxicologist, Division of Ophthalmologic ENT Devices, CDRH

SPONSOR ATTENDEES

David A. Gonyer, RPh., President CEO, Evoke Pharma
Marilyn R. Carlson, DMD, MD, RAC CMO, Evoke Pharma
Wayne M. Alves, PhD VP, Clinical Operations, Evoke Pharma

(b) (4)

1.0 BACKGROUND

On June 3, 2016, the Agency received a pre-NDA meeting request for IND 25512 metoclopramide nasal spray. The proposed indication is for the relief of symptoms associated with acute and recurrent diabetic gastroparesis in adult women. The meeting purpose is to discuss the content and format of a planned 505(b)2 NDA submission. The meeting was granted on June 23, 2016, and a background package was received on July 26, 2016. FDA sent Preliminary Comments to Evoke on August 19, 2016.

2.0 DISCUSSION

Introductory Comments

If you intend to rely, in part, on information required for approval that comes from studies not conducted by you or for you and for which you have not obtained a right of reference (e.g., FDA's finding of safety and/or effectiveness for a listed drug(s), published literature) 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. You also must establish that reliance on studies described in the literature or on other studies is scientifically appropriate. Please be aware that if the published literature necessary for approval describes a listed drug that constitutes reliance on FDA's finding of safety and effectiveness for that listed drug.

You state in your meeting package that you intend to rely on FDA's finding of safety and/or effectiveness for Reglan Tablets (NDA 017854) and on published literature. Clarify what information and sections of your NDA, including the labeling, you intend to support through such reliance and how you will establish the bridge between your proposed drug product and Reglan Tablets and the published literature.

For further information about submitting a 505(b)(2) NDA, see the 505(b)(2) Regulatory Pathway section below.

Regulatory Question

Question 1:

Safety information from the “legacy” studies conducted from 1984 through 1995 by previous sponsors with different metoclopramide nasal formulations in support of other indications will be provided in tabular format as a safety synopsis in the Summary of Clinical Safety (SCS) section of the NDA. No datasets and no clinical study reports for these “legacy” studies will be included in the NDA. Does the Agency agree with the plan for presentation of the “legacy” studies in the Gimoti 505(b)(2) NDA?

FDA Response:

No, we do not agree with your plan for presentation of “legacy” studies safety information. Available safety information from all previously conducted studies should be submitted as part of the NDA in the format of summary tables, datasets, and CRFs for deaths, serious adverse events, and discontinuations. The data should be organized by categories such as study population (i.e. healthy subjects vs. patients), drug dose, treatment duration/exposure, gender, etc. Additionally, clarify the format of “legacy” datasets.

Additional Discussion:

Evoked agreed to submit the following:

- a) Summary tables of adverse events (AEs) classified by body system, grouped by subject type (i.e., healthy volunteers vs. patients), drug dose, treatment duration/exposure, gender, more common/less common AEs, AEs of special interest such as extrapyramidal symptoms, sub-groups with predisposing risk factors (i.e. neurological history, abnormal nasal conditions such as trauma, chronic sinusitis, etc.). (Excel Format also requested).**
- b) Verbatim terms in addition to categorization by body system (e.g., grouped by nasal abnormalities, CNS)**
- c) Copies of CRFs for deaths, serious adverse events, and discontinuations will be submitted, where available.**

Question 2:

For the 505(b)(2) NDA, Evoked plans to prepare the draft product label based on the label for the listed product, Reglan Tablets. Because the Reglan Tablet label is not prepared in accordance with the Physician Labeling Rule (PLR), we plan modernize the format of the label to be consistent with the PLR and will include relevant safety that is included in labeling for other metoclopramide products. This would include specific warnings and precautions, drug interaction information and adverse reactions data from these labels. In addition, adverse event information from the literature and Evoked-sponsored controlled clinical trials with Gimoti will be included. Does the Agency agree that this approach acceptable?

FDA Response:

We agree with your approach to modernize the format of the prescribing information (PI), as described above. 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 in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances, and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Chemistry Manufacturing and Controls Questions

Question 3:

Gimoti is a drug/device product using a commercially available (b) (4) nasal spray pump. A draft table of contents is presented for Sections 3.2.P.2.4 and 3.2.P.7 of Module 3 of the NDA that provides all of the relevant container closure information. Does the Agency agree with the proposal for the organization of these sections of Module 3?

FDA Response:

The proposed location with regard to the container closure system information in the NDA submission is acceptable.

Question 4:

Based on the information provided, does the Agency agree with the specifications and limits proposed for the drug substance?

FDA Response:

Your proposed quality tests in the specification for metoclopramide HCl appear reasonable for submission of the NDA application, but please clarify why (b) (4) is not included in the specification. The proposed acceptance criteria for the quality tests will be evaluated during the NDA review.

Additional Discussion:

Evoked clarified that although Related Compound (b) (4) is not named as an identified impurity, it is controlled as an unidentified impurity at a level NMT (b) (4) % by (b) (4) specific validated HPLC assay.

Evoked stated that additional information is contained in (b) (4) Drug Master File (DMF) (b) (4). Evoked will provide a letter of authorization to access the DMF in Section 1.4.1 of the NDA and will cross reference the relevant section of the DMF that illustrates the separation of Related Compound (b) (4).

Question 5:

Gimoti has been assessed for elemental trace impurities. The data developed support the drug substance and excipient specifications and the suitability of the manufacturing equipment for Gimoti production. The container closure data support the suitability of the (b) (4) pump manufactured by (b) (4) over the proposed shelf-life of the product. Based on this assessment routine testing of the drug product for elemental impurities is not required. Does the Agency agree with this assessment?

FDA Response:

No, we do not agree at this time. You will need to conduct routine testing of elemental impurities for your drug product until sufficient product history is established, and submit a change in specification as a Prior Approval supplement. Alternatively, in your NDA submission you may provide data, along with a detailed justification, for not including elemental impurities in your drug product specification. Acceptability of your justification will be a review issue.

As per the meeting background package, elemental impurities have been assessed in accordance with the recommendations detailed in ICH Q3D and USP General Chapter <232> Elemental Impurities. The assessment includes the drug substance, excipients, manufacturing equipment and container closure system. Using the guidance detailed in ICH Q3D (b) (4), you propose an elemental concentration limit of (b) (4).

For additional information, please refer to the ICH Guideline for Elemental Impurities available at:

[http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3D/Q3D \(b\) \(4\).pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3D/Q3D (b) (4).pdf)

Additional Discussion:

Evoked plans to conduct extensive elemental analysis as part of the testing of the process validation batches (3 full scale batches) and will conduct additional testing on the recently manufactured full scale engineering batch currently on a long term ICH stability program. FDA agrees with this proposal.

Based on the expectation that the test results will demonstrate the product has elemental concentrations significantly lower than the (b) (4) limit, Evoke proposes submitting these data during the NDA review (within 6 months of the NDA submission) as the basis for the justification for not including elemental impurities in the drug product specification.

FDA does not agree and recommends submitting the elemental impurities results for the process batches within 3 months of the NDA submission.

FDA requests that additional information on the type of elemental impurities and analytical methodologies used for testing be submitted with the NDA.

If Evoke is unable to provide the data within 3 months of NDA submission, Evoke agrees to include elemental impurities as part of the final product release specification in line with the ICH Q3D guideline.

A full extractables and leachables report will be submitted at the time of the NDA.

Question 6:

Gimoti is a drug/device product using a commercially available (b) (4) nasal spray pump. Evoke has conducted a human factors assessment based on a critical task assessment in the proposed patient population using experience from the clinical studies and a risk assessment of the critical user tasks identified. Does the Agency agree this assessment is adequate to support the 505(b)(2) NDA?

FDA Response:

We do not agree that your submitted human factors assessment is adequate to support the 505(b)(2) NDA. We are unable to determine the following from your background package:

- 1. The specific use tasks for this proposed product. Your proposed Instructions for Use contains subtasks that were not evaluated in your use-related risk analysis (e.g., turn bottle away from face, (b) (4) etc.).**
- 2. Risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies. Additionally, we note that this device is novel for this specific indication by this patient population. Therefore, we recommend that you perform a comprehensive use-related risk analysis of your proposed product to determine whether your product identifies any new or unique risks.**
- 3. Your conclusion, based on this risk assessment, whether you need to perform a human factors (HF) validation study under simulated use conditions with representative users performing necessary tasks to demonstrate safe and effective use of the product.**

Please note that a comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your

product (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform (consider known problems for similar products), and the potential negative clinical consequences of use errors and task failures. Your risk analysis should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable.

Based on this risk analysis, you will need to determine whether you need to perform a HF validation study under simulated use conditions with representative users performing necessary tasks to demonstrate safe and effective use of the product. The risk analysis can be used to inform the design of a human factors validation study protocol for your product. If you determine that an HF validation study is not needed for your product, submit your risk analysis and justification for not conducting the HF validation study to the Agency for review under the IND. The Agency will notify you if we concur with your determination. If you determine that a HF validation study is needed for your product, we recommend you submit your study protocol for feedback from the Agency. Please note we will need 90 days to review and provide comments on the HF validation study protocol. Plan your development program timeline accordingly.

The following items are needed to inform the review of your HF study protocol:

- A summary of preliminary analyses and evaluations, including formative studies;
 - Include in your summary a discussion of key findings and any changes made to your product or labeling, including how the findings were used to update the user interface and risk analysis
- An updated risk analysis for your product;
- Detailed HF validation study protocol to include the following elements:
 - Description of intended product users, uses, use environments, and training (if applicable) for commercial product
 - Graphical depiction and written description of product user interface
 - Summary of known use problems with previous models or similar products
 - User task selection, categorization (e.g., critical) and prioritization
 - Validation testing details
 - Objective(s)
 - Type of testing (simulated or actual use)
 - Test environment and conditions of use
 - Training provided to participants and rationale for how it corresponds to real-world training (if applicable)
 - Distinct user groups broken out by number and type of test participants and rationale for how they represent the intended user populations
 - User tasks and use scenarios that will be studied

- Description of data to be collected and methods for documenting observations and interview responses
- Methods for root cause analysis of all use errors, difficulties, close calls
- Definition of performance success and performance failure
- Moderator transcript
- Intend-to-market labels and labeling (including an editable word version of the IFU if an IFU is proposed) that will be tested in the HF validation study
- Five intend-to-market samples of product that will be tested in the HF validation study

The requested information should be placed in eCTD section 5.3.5.4 – Other Study reports and related information.

Guidance on human factors procedures to follow can be found in: Applying Human Factors and Usability Engineering to Medical Devices, available online at:
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf>

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

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development and can be found online at:
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf>

Safety Considerations for Product Design to Minimize Medication Errors and can be found online at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf>

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors and can be found online at:
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>

Additional Discussion:

Evoked plans on completing a risk analysis. If upon completion, the sponsor concludes that a HF validation study is not needed, Evoked proposed to submit the risk analysis and justification for not conducting the HF validation study to the IND for the Agency's review.

Post-Meeting Comment:

FDA will review Evoked's use-related risk analysis and justification within a 60 day review period after receiving Evoked's risk analysis and justification. FDA will notify Evoked if we concur with their determination.

Question 7:

Does the Agency agree with the specifications and limits proposed for the drug product?

FDA Response:

From a mechanical engineering view, the Agency agrees with the specifications and limits proposed for the device portion of the drug/device combination product.

In addition to the proposed testing, in your specification you will need to include the Spray Pattern and Plume Geometry testing to ensure that every time the same dose is delivered to the patient. The acceptance criteria for spray pattern should include the shape as well as the size of the pattern along with justification for these parameters. Please refer to the FDA Guidance *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products - Chemistry, Manufacturing, and Controls Documentation*, available at:

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070575.pdf>

Additional Discussion:

Evoked agrees to include Spray Pattern testing in the finished product specification.

Evoked has generated plume geometry data as part of the registration stability program testing at T-0, T-6 months and annually (to 36 months) to build a database. Evoked will repeat this program for the process validation batches.

Evoked does not intend to do further plume geometry testing unless there is a significant change to the pump or formulation that would impact its performance characteristics. FDA stated that final determination with regard to the plume geometry testing as part of drug product release would be made during the review process based on the totality of data provided in the NDA.

Question 8:

Based on the information provided in this briefing document on extractables, leachables, and impurities for the drug product, no additional qualification is planned. Does the Agency agree?

FDA Response:

Although your extractables/leachables summary provided in the Pharmaceutical Development section of your background package indicates an adequate and systematic approach while conducting your extractables/leachables studies, we are unable to provide you with a definitive response at this point based on the limited information. In your NDA, provide the leachables and extractables data from the Gimoti container closure system. The decision on whether or not additional qualification is required will be made upon review of data provided in your NDA.

Please refer to the FDA Guidance for Industry, *Container Closure Systems for Packaging Human Drugs and Biologics, Chemistry, Manufacturing, And Controls Documentation* available at the following website:

<http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070551.pdf>

Question 9:

Evolve intends to produce a Physician Sample product that will be identical in all respects to the proposed commercial product except the fill volume will be reduced to provide only one week of supply. It is anticipated that one batch in this configuration will be produced and it will be labeled appropriately. It will also have supporting stability based on the commercial specifications (except fill volume). These data and information will be submitted in the NDA. Is the plan for the Physician Sample product acceptable to the Agency?

FDA Response:

Your plans regarding your physician sample appear acceptable.

Question 10:

Does the Agency agree that the registration stability program for the drug product is sufficient to support the 505(b)(2) NDA?

FDA Response:

Overall, your stability program appears to be acceptable. Data from stability studies should be provided on at least three primary batches of the drug product; please refer to the ICH Guideline *Stability Testing Of New Drug Substances And Products Q1A(R2)* dated 2003 available at:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1A_R2/Step4/Q1A_R2_Guideline.pdf

Final acceptability of your stability data in support of the proposed expiration dating period will be determined during the NDA review.

NONCLINICAL

Question 11:

At the EOP2 meeting, the Agency agreed that the completed nonclinical data package, in addition to information in the published literature, are adequate to support this 505(b)(2) NDA for the proposed indication. Evoke will rely on the FDA's previous findings of safety and efficacy for Reglan tablets for this 505(b)(2) NDA and literature will be summarized in the NDA. Does the Agency agree?

FDA Response:

In addition to your completed nonclinical studies, we agree with your proposal to rely on FDA's finding of safety and effectiveness for Reglan Tablets and on published literature, provided that you establish an adequate bridge to Reglan Tablets and establish that reliance on the studies described in the published literature is scientifically appropriate. See Introductory Comments.

Question 12:

For the nonclinical portions of the product label, Evoke will use language for mutagenicity and carcinogenicity that is used in other metoclopramide labels. Pregnancy labeling regulations have changed with the finalization of the Pregnancy and Lactation Labeling Rule (PLLR). Should Evoke mimic the approved product labeling for pregnancy, lactation and fertility information, or follow the PLLR?

FDA Response:

It is required that you follow PLLR for the labeling of your product. See response to Regulatory Question 2. The language that is used for mutagenicity and carcinogenicity in the labeling for Reglan tablets can be supplemented with information from the published literature. If you use language for mutagenicity and carcinogenicity from metoclopramide labels, other than Reglan tablets, this constitutes reliance on FDA's findings of safety and/or effectiveness for those additional products and would require building an adequate bridge to those products.

Additional Comments:

- 1. In response to the additional information submitted on July 29, 2016:**
 - a. You have provided adequate references to the FDA cleared device with the same materials from the same manufacturer and for similar intended use. Therefore, the patient-contacting materials are biocompatible during the intended use of this device.**
- 2. A review issue will be whether you have adequate data to determine whether there is an increase in CNS effects with intranasal compared to oral routes of administration. Please describe the adequacy of your safety database to address this issue.**

3.0 PREA REQUIREMENTS

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

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

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

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. Beginning **May 5, 2017**, the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** 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>.

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, in part, 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, in part, 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., trade name(s)).

If you intend to rely, in part, 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 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 relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. 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 in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing 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 efficacy 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 X
3. Example: NDA YYYYYY “TRADENAME”	Previous finding of safety for Carcinogenicity, labeling section XXX
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.

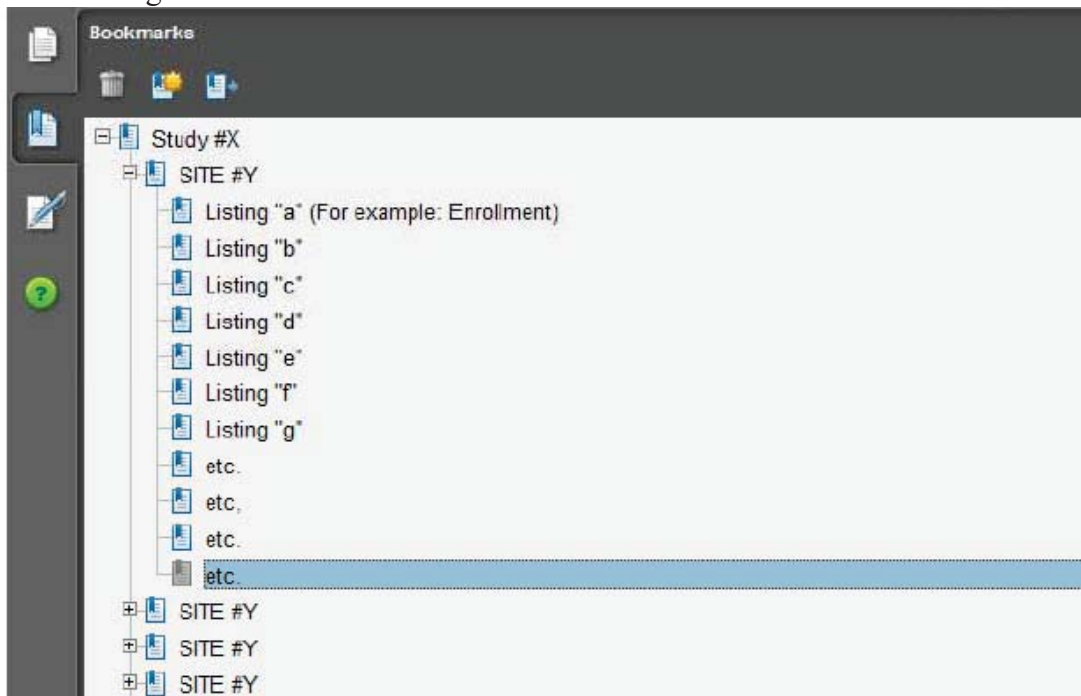
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

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.

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

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

4.0 ATTACHMENTS AND HANDOUTS

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

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

/s/

MAUREEN D DEWEY
09/01/2016



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING MINUTES

IND 25512

Evoked Pharmaceuticals, Inc.
Attention: David Gonyer, R.Ph.
President CEO
12671 High Bluff Drive, Suite 200
San Diego, CA 92130

Dear Dr. Gonyer:

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

We also refer to the End of Phase 2 meeting between representatives of your firm and the FDA on September 27, 2011.

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

If you have any questions, please call me at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Maureen Dewey, M.P.H.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes/Sponsor Slides

MEMORANDUM OF MEETING MINUTES

Meeting Type: B'
Meeting Category: End of Phase 2'
Meeting Date and Time: September 27, 2011'
Meeting Location: Silver Spring, MD'
Application Number: 25512
Product Name: (b) (4) (metoclopramide) Nasal Spray
Indication: For the relief of symptoms associated with acute and recurrent diabetic gastric stasis (gastroparesis) in women with diabetes mellitus
Sponsor/Applicant Name: Evoke
Meeting Chair: Ruyi He, M.D.
Meeting Recorder: Maureen Dewey, M.P.H.

FDA ATTENDEES

Division of Gastroenterology and Inborn Errors Products

Donna Griebel, M.D., Director
Ruyi He, M.D., Medical Team Leader
Nancy Snow, M.D., Clinical Reviewer
Sandhya Apparaju, Ph.D., Clinical Pharmacology Reviewer
Sushanta Chakder, Ph.D., Supervisory Pharmacologist
Mike Welch, Ph.D., Deputy Director, Division of Biometrics 3
Freda Cooner, Ph.D., Biometrics Reviewer
Kevin Bugin, Regulatory Project Manager
Maureen Dewey, Regulatory Project Manager

Study Endpoints and Labeling Division

Paivi Miskala, M.S.P.H., Ph.D., Study Endpoints Reviewer

SPONSOR ATTENDEES

Evoke Pharma, Inc'

David Gonyer, R.Ph., President CEO'
Matt D'Onofrio, Executive Vice President'

(b) (4)

Bill Kramer, Evoke Pharma
Charles S. Davis, Evoke Pharma

(b) (4)

1.0 BACKGROUND

On June 8, 2011, Evoke submitted a meeting request to the Division of Gastroenterology and Inborn Errors Products. The meeting request was granted on June 28, 2011.

On August 25, 2011, the sponsor submitted a background package which included a Patient-Reported Outcome Measures (PRO) evidence dossier. Preliminary Responses were sent to the sponsor on September 23, 2011.

The purpose of the meeting is to review the results of the Phase 2 dose-ranging study in patients with diabetic gastroparesis and the endpoint validation for Phase 3, the Phase 3 study design, and to discuss the clinical, nonclinical, quality (CMC), and regulatory strategies for this product and the proposed indication.

2. DISCUSSION

Regulatory

- 1.&Metoclopramide Nasal Spray represents a change in dosage form and route of administration from the Listed Drug (LD); Reglan[®] Tablets (metoclopramide tablets, USP). The planned New Drug Application (NDA) for Metoclopramide Nasal Spray will contain full reports of investigations of safety and effectiveness, but some of the information required for approval will come from studies not conducted by or for Evoke and for which Evoke has not obtained a right of reference (section 505(b)(2)).

Given the well-characterized safety and efficacy profile of metoclopramide and the efficacy and safety demonstrated in Evoke's Phase 2 study (Protocol Number METO-IN-002), does the Division concur that, if positive, the single proposed adequate and well-controlled confirmatory Phase 3 clinical study of Metoclopramide Nasal Spray versus placebo in women with diabetic gastroparesis would be adequate for filing an NDA under section 505(b)(2)?

FDA Response:

A single study may not be adequate.

Please justify why the mean change from baseline to week 4 in individual symptoms (as listed in Table 19) is clinically meaningful. We have concerns that the small changes depicted in the table, although statistically significant, may not be clinically meaningful.

Further, we do not agree with your proposal to conduct a study in women only. Males should be included in your Phase 3 studies in order to obtain safety and efficacy data and to confirm the findings from your Phase 2 study.

Presentation: Sponsor slides

Additional Discussion

The sponsor will submit a new proposal for hypothesis testing and justification of their Phase 3 study. The Agency will review the proposal and provide a response as part of the official meeting minutes.

FDA comments pursuant to sponsor follow-up from Type B meeting:

We have reviewed your proposal and are willing to further discuss it at the November 7, 2011 meeting.

- 2.&Evoke plans to seek approval for the use of Metoclopramide Nasal Spray in female patients with symptoms associated with acute and recurrent diabetic gastroparesis. The planned NDA for the single indication; for the relief of symptoms associated with acute and recurrent diabetic gastroparesis in women with diabetes mellitus is planned.

Although Evoke understands that prior to the conduct of the pivotal Phase 3 study (Protocol Number METO-IN-003), the phrasing of an indication cannot be determined precisely; does the Division agree generally with the proposed indication?

FDA Response:

We cannot agree on the indication at this time. Your final indication will depend upon the clinical data you obtain from your Phase 3 trials.

Clinical

- 3.&Based on results of the PK study (Protocol Number METO-IN-001) with the current formulation of Metoclopramide Nasal Spray and spray pump, and results of the completed Phase 2 study (Protocol Number METO-IN-002) with the same nasal spray formulation and spray pump, Evoke proposes (b) (4) (one spray) IN (intranasal) 30 minutes before meals and at bedtime (q.i.d.) as the proposed dose of Metoclopramide Nasal Spray.

Does the Division agree with the proposed dose and regimen of Metoclopramide Nasal Spray ((b) (4) mg IN q.i.d.) to be studied in the Phase 3 study (Protocol Number METO-IN-003)?

FDA Response:

Yes, we agree with the proposed dose and regimen.

- 4.&Evoke characterized the single dose pharmacokinetics (PK) of the current formulation of Metoclopramide Nasal Spray and spray pump in a single dose PK study (Protocol Number METO-IN-001) in 39 healthy volunteers. Evoke further examined the plasma concentration of metoclopramide 30 minutes after the first dose and the last dose after q.i.d. dosing for 28 days with the current formulation of Metoclopramide Nasal Spray

with the same spray pump in 190 patients with diabetic gastroparesis in the completed Phase 2 study (Protocol Number METO-IN-002). Evoke plans to include sparse PK sampling (population PK) in the proposed Phase 3 study (Protocol Number METO-IN-003).

Does the Division agree no further PK characterization is needed other than population PK?

FDA Response:

Yes, we agree. During Phase 3, the time of dosing (on the day before and on the day of PK sampling), as well as the sampling times relative to dosing should be properly documented.

Population PK analyses should explore the effect of covariates including age, race, BMI, renal impairment, hepatic impairment, CYP2D6 status, as well as concomitant medications (e.g. CYP2D6 inhibitors) etc on systemic exposure. You should attempt to include a sufficient number of patients ≥ 65 years of age.

5. & Evoke plans to use the Gastroparesis Symptom Assessment (GSA), a patient-reported assessment of severity of gastroparesis symptoms, as the instrument to measure efficacy in the Phase 3 study.

Does the Division agree with use of the GSA for the primary endpoint for the Phase 3 study?

FDA Response:

We agree with the use of an instrument to measure gastroparesis that captures the cardinal symptoms of the disease. Although these appear to be nausea, early satiety, bloating, and upper abdominal pain or discomfort, the SEALD division requires more time to fully review the materials you provided. They will complete their review within the next few weeks and we will provide additional comments, if any, at that time.

With regard to the inclusion criteria, you do not indicate upon what the diagnosis of gastroparesis is based. As you are aware, gastroparesis is diagnosed by a combination of symptoms and delayed gastric emptying. Please expound upon this inclusion criteria.

Presentation: Sponsor slides

Additional Discussion:

With respect to the inclusion criteria, the sponsor will submit additional data demonstrating that there is a high correlation of other diabetic complications with diabetic gastroparesis (e.g., retinopathy, peripheral neuropathy, peripheral neuropathy) as documented by a gastric emptying study. The inclusion criteria could

be modified to include previously documented gastric emptying study. The Agency will review the proposal.

The Agency will grant a face-to-face meeting with the sponsor once the comments on the GSA have been finalized.

FDA comments pursuant to sponsor follow-up from Type B meeting:

We believe it is important to have an objective measure of delayed gastric emptying during your PRO development process and clinical trials in order to ensure that patients participating in the qualitative interviews and drug development actually have diabetic gastroparesis.

SEALD Response:

We applaud your use of Rasch statistics to explain the qualitative research results. The instrument looks promising and we agree with the use of the GSA if the following concerns are adequately addressed:

- a) The eligibility criteria for qualitative research were unclear as to how gastroparesis diagnosis was made and if these patients had comorbidities. In what proportion of patients was scintigraphy used as part of the diagnosis? How was gastroparesis severity determined? Did these patients have comorbidities?**
- b) The 4 symptom scale as drafted does not capture symptoms in patients with severe disease (i.e., scale to population targeting appeared inadequate). Your qualitative research indicated, for example, that vomiting was a frequent and bothersome aspect of gastroparesis, but was not included in the final instrument. We suggest that you review your qualitative research findings again, particularly as it relates to symptom experience by disease severity, and rerun Rasch analysis with additional symptoms to see if better scale-to-population targeting can be achieved with an improvement in ability to differentiate people according to gastroparesis severity.**
- c) We are uncertain at this time whether a summary score can be developed or not (i.e., is it a unidimensional scale or not). We note that an unweighted average summary score may not be appropriate when the instrument items and response categories are not equally spaced along the gastroparesis severity continuum.**
- d) You should evaluate response categories further. Evaluation of category probability curves may provide additional useful information whether revision is warranted (e.g., should very mild category be deleted?).**
- e) Instrument recall period should be made clearer in the instrument. Your qualitative research suggested that 32% of patients interviewed did not use the 24-hour recall period when answering the questions. It is also unclear how this instrument is read to the patients during the voice-prompted telephone interview since it is not in an interview format.**
- f) You should use both anchor- and distribution-based methods to determine what might be a clinically important change in the instrument. $\frac{1}{2}$ SD benchmark is insufficient to determine clinically important changes in the instrument.**

Quality (CMC)

6. Evoke has conducted an extractables and leachables program on the container-closure system (the glass vial and spray pump) with the drug product and tracked the performance of the system with respect to leachable compounds for the duration of the registration stability program. Evoke believes these data, along with data from the spray pump manufacturer, (b) (4), satisfactorily demonstrate the suitability of the container-closure system for use with Evoke's Metoclopramide Nasal Spray formulation.

Does the Division agree that no further extractables or leachables-related studies are required to support the NDA filing?

FDA Response:

Your approach to determining the extractables and leachables for the container-closure system is reasonable and additional extractables/leachables data will likely not be required if the complete data that you submit for these studies hold up to closer scrutiny during our review of the NDA.

Questions Based on September 30, 2008 End of Phase 2 Meeting

7. Non-Clinical

In response to pharmacology and toxicology questions from Evoke at the 30 September 2008 End of Phase 2 Meeting, the Division asked Evoke to submit full reports on the intranasal toxicology studies in rabbits (Study 6988-102) and monkeys (Studies 6988-101 and 011/994-219) and stated no additional nonclinical studies were needed for Phase 3 or the NDA. Evoke plans to submit the full study reports (Please see **Appendix 11.6** for tabulated summaries) prior to Phase 3.

Does the Division confirm there is no change in their position with respect to the nonclinical responses?

FDA Response:

Yes, we agree.

8. Quality (CMC)

At the 30 September 2008 End of Phase 2 Meeting, the Division reviewed Evoke's CMC proposals. The summary of extractables and leachables is provided in

Does the Division confirm there is no change in their position with respect to the CMC responses?

FDA Response:

Our responses regarding the CMC issues raised in the 2008 meeting remain unchanged.

9. CYP2D6

At the 30 September 2008 End of Phase 2 Meeting, Evoke was asked to address the in vivo drug interaction potential of metoclopramide based on an in vitro study of CYP2D6 using human liver microsome (Desta et al., 2002). Since there is no plan to prescribe Metoclopramide Nasal Spray as part of any multidrug regimen containing CYP2D6 inhibitors, there is no obvious target for a new drug-drug interaction study. A study with metoclopramide and fluoxetine, a potent CYP2D6 inhibitor has already been completed. The known impact of fluoxetine, and the predicted impact of the CYP2D6 genetic polymorphism on systemic exposure to metoclopramide, are comparable to the two-fold decrease in metoclopramide clearance observed in patients with renal impairment. Since it is currently recommended that the metoclopramide dosage be halved for renally-impaired patients, it is reasonable to assume that the same dosage adjustment is applicable to genetically determined CYP2D6 poor metabolizers (PMs) and patients co-medicated with fluoxetine, paroxetine and any other strong CYP2D6 inhibitors. Since the worst case scenario for CYP2D6 inhibition is the PM (no CYP2D6 activity), and the recommended dosage adjustment for PMs is a 50% reduction, it should not be necessary to reduce the dose further for any inhibitor that might be used by patients taking Metoclopramide Nasal Spray.

Therefore, Evoke proposes that

(b) (4)

(b) (4)

(b) (4)

interaction studies are unlikely to change this dosage recommendation and should not be needed.

Does the proposed plan, together with the information provided, address the Division's request to evaluate the in vivo drug interaction potential of metoclopramide?

Does the Division agree that no additional drug-drug interactions studies are required for the 505(b)(2) NDA for Metoclopramide Nasal Spray?

FDA Response:

Yes, we agree based on the information available at this time. To render the population PK analyses more meaningful and to facilitate exposure-response analyses we recommend genotyping for CYP2D6 in the planned Phase 3 study(ies).

Sponsor Slide Presentation

Additional Discussion regarding Question #4 and Question #9:

The Sponsor agreed to collect blood samples from all patients in phase 3 but will only genotype those patients whose clearance values appear smaller than the

majority and those who experience serious adverse events in the trial. The Sponsor also noted that they do not plan to include CYP2D6 status as covariate in the planned population PK analyses, citing low frequency of its occurrence in the study population (< 7 %). The Agency stated that they would need to discuss this proposal further internally, to determine the potential implications of not having CYP2D6 genotype information for all patients during the planned population PK and exposure-response analyses. The sponsor will submit any additional information to justify their proposal in this regard to the Agency for review.

FDA comments pursuant to sponsor follow-up from Type B meeting:
Your proposal regarding CYP2D6 genotyping in phase 3 is acceptable.

If the authors provide access to the full data for their fluoxetine-metoclopramide study (Vlase et al, 2006), please include it in the NDA submission for the Agency's review, along with the final publication.

10. Cardiovascular Risk

At the 30 September 2008 End of Phase 2 Meeting, the Division asked Evoke to address the effect of Metoclopramide Nasal Spray on QT prolongation. In response to this request, Evoke has provided an initial summary of cardiac safety as reported in the literature and as observed in the Metoclopramide Nasal Spray clinical studies (Please see the Cardiovascular Risk Assessment for Metoclopramide Nasal Spray, in **Section 10.3**).

For the 505 (b)(2) NDA for Metoclopramide Nasal Spray, Evoke will summarize the cardiac safety literature relevant to metoclopramide and analyze the aggregate cardiac safety data from clinical studies (Phases 1, 2 and 3) conducted under IND 25,512.

Does this proposal adequately address the Division's request to evaluate the QT' prolongation potential of Metoclopramide Nasal Spray?'

Does the Division agree that no study other than further ECG and cardiac safety' evaluation in the Phase 3 study is required?'

FDA Response:

You will need to conduct a thorough QT study for the metoclopramide nasal spray formulation.

Sponsor Slide Presentation

Additional Discussion:

The sponsor will submit their proposal for alternative cardiac safety monitoring to the Agency for review.

FDA comments pursuant to sponsor follow-up from Type B meeting:

We have sought the advice of the QT interdisciplinary review team on the matter of a thorough QT study, and have the following comments. A tQT study will be needed. Even though the systemic exposure following inhalation can be lower than that following oral and IV administration, it is likely that the intra-cardiac concentration is higher following inhalation (usually cannot be directly measured in human subjects). As a result, an increased QT interval prolongation risk can be anticipated.

ADDITIONAL COMMENTS:

CLINICAL PHARMACOLOGY:

For the NDA submission, we recommend that you submit PK profile simulations in renal impairment patients with a CrCl value of 40 mL/min and for those with total renal failure following the proposed reduced dosing frequency, in comparison with healthy controls at the recommended dosing regimen.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

505(b)(2) APPLICATIONS

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 October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf>. 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 challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://inside.fda.gov:9003/downloads/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027521.pdf>)).

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.

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), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 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.

Statistical Comments on the Proposed Phase 3 Study(ies):

- 1. The Statistical Analysis Plan (SAP) should be finalized and submitted to the Agency for review before the start of study. You should note that all principal components of the statistical analysis plan should be pre-specified in the protocol and not introduced in the SAP at a later date.**
- 2. Your proposed ITT population definition should be considered as a modified ITT (mITT) population for supportive purposes. A true ITT population should be defined as all patients randomized. Any patient who is randomized but has no efficacy assessment should be considered as a treatment failure (non-responder).**
- 3. You have not specified any multiplicity adjustment for the treatment comparisons on the secondary endpoints. These comparisons would be considered exploratory and would not adequately support secondary efficacy claims in the labeling.**
- 4. You have not provided any missing data handling strategy for the analyses of primary and secondary endpoints. We would advise you to consider an approach that assigns values that represent treatment failure. You should plan multiple sensitivity analyses on the primary efficacy endpoint to investigate the impact of missing data on the efficacy conclusions. These could include observed-case, completed-case, worst-case, and multiple imputation methods.**
- 5. You indicated that the primary endpoint will be analyzed using an analysis of covariance (ANCOVA) model with effects for treatment group and baseline**

mean GSA score. However, the primary endpoint follows an ordered categorical scale and the normality assumption for the model residuals may not be valid. You should investigate the validity of the model using the phase 2 study data. Moreover, we recommended you also pre-specify a non-parametric rank-based linear regression method to compare the treatment effects assessed by the primary endpoint. In order for your data to provide substantial evidence to support the proposed indication, both ANCOVA and the non-parametric rank-based linear regression methods are expected to show positive results in favor of the study drug. In addition, the non-parametric approach would be the principal analysis if the ANCOVA assumptions are not supported by the data.

Sponsor Slide Presentation

Additional Discussion:

The Agency agrees in theory that the use of ANCOVA is appropriate for the primary efficacy analysis, however, we recommend that the model assumptions be assessed.

ATTACHMENTS AND HANDOUTS

Sponsor Slides

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

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

/s/

MAUREEN D DEWEY
11/04/2011