CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213976Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 103173

MEETING MINUTES

Shire ViroPharma, Inc.
Attention: Ipsita Olympia Banerjee, M.S., M.B.A.
Associate Director, Global Regulatory Affairs
300 Shire Way
Lexington, MA 02421-2101

Dear Ms. Banerjee:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for budesonide oral suspension (BOS)/SHP621/TAK-721.

We also refer to the teleconference between representatives of your firm and the FDA on May 20, 2020. The purpose of the meeting was to discuss elements of the BOS/SHP621/TAK-721 program and the overall clinical and regulatory filing plan in preparation for your upcoming 505(b)(2) NDA submission.

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

If you have any questions, contact me at (301) 796-4261 or benjamin.vali@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Benjamin Vali, M.S., RAC
Regulatory Health Project Manager
Gastroenterology
Division of Regulatory Operations for
Immunology and Inflammation
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: May 20, 2020 (9:00 AM – 10:01 AM EST)
Meeting Location: Teleconference

Application Number: IND 103173
Product Name: Budesonide Oral Suspension (BOS)/SHP621/TAK-721
Indication: Treatment (b) (4) (b) (4) in Adolescent and Adult Patients with Eosinophilic Esophagitis (EoE)
Sponsor Name: Shire Viropharma, Inc.

Meeting Chair: Dr. Erica Lyons
Meeting Recorder: Mr. Benjamin Vali

FDA ATTENDEES

Office of Immunology and Inflammation (OII) / Division of Gastroenterology (DG)
Jessica J. Lee, M.D., M.M.Sc., Director (Acting)
Erica Lyons, M.D., F.A.A.P., Clinical Team Leader
Matthew Kowalik, M.D., Medical Officer
Laura Finkelstein, M.D., Medical Officer

OII / Division of Pharm/Tox for Immunology and Inflammation (DPT-II)
Yolanda Branch, Ph.D., Pharm/Tox Reviewer / Pharmacologist

Office of Regulatory Operations (ORO) / Division of Regulatory Operations for Immunology and Inflammation (DRO-II)
Benjamin Vali, M.S., RAC, Regulatory Health Project Manager, Gastroenterology

OND / Division of Clinical Outcome Assessment (DCOA)
Sarrit Kovacs, Ph.D., Team Leader
Christopher O. St. Clair, Pharm.D., Reviewer

Office of Biostatistics (OB) / Division of Biometrics III (DBIII)
David Petullo, M.S., Statistical Team Leader
Scott Komo, Dr.P.H., Patient-Focused Statistical Support Team Leader
Ling Lan, Ph.D., Statistical Reviewer
Xin Yuan, M.S., M.Ed., Patient-Focused Statistical Support Reviewer

Office of Clinical Pharmacology (OCP) / Division of Inflammation and Immune Pharmacology (DIIP)
Hyewon Kim, Ph.D., Clinical Pharmacology Reviewer

Office of Drug Evaluation Sciences (ODES) / Division of Biomedical Informatics, Research, and Biomarker Development (BIRBD)
Y. Veronica Pei, M.D., M.Ed., M.P.H., Associate Director for Biomedical Informatics (Acting) for DG

SPONSOR ATTENDEES

Shire ViroPharma Inc.
Ipsita Olympia Banerjee, M.S., M.B.A., Associate Director, Global Regulatory Affairs Lead
Nirav Desai, M.D., Director, Global Clinical Development Lead
Lan Lan, Ph.D., Associate Director, Biostatistics Program Lead
Ivy Song, Ph.D., Clinical Pharmacology Lead
Rana Ezzeddine, Dr.P.H., Senior Scientific Fellow, Statistics
Jessica Eisner, M.D., Senior Medical Director, Global Safety Lead
Bridgett Goodwin, Ph.D., Director, Outcomes Research and Epidemiology Lead
Debra Silberg, M.D., Ph.D., VP, Clinical Science Head, GI
James Williams, M.D., Senior Medical Director, Global Development Lead

1.0 BACKGROUND

On September 5, 2008, IND 103173 was activated for the investigation of budesonide oral suspension (BOS) in the treatment of patients with eosinophilic esophagitis (EoE). On May 31, 2016, BOS/SHP621 was granted Breakthrough Therapy Designation (BTD) in this proposed patient population. Under the BTD granted status (along with obtaining Orphan Drug Designation previously on December 20, 2006), the IND's Sponsor, Shire ViroPharma, Inc. (hereafter, 'the Sponsor'), engaged FDA on multiple occasions starting with the face-to-face (F2F) 'Initial Comprehensive Multidisciplinary Breakthrough Therapy Type B Meeting', which was held on November 2, 2016 (meeting minutes finalized on November 4, 2016). These multiple FDA engagements covered various aspects of BOS/SHP621's product development, i.e., clinical (including pediatrics), clinical pharmacology, biostatistics, clinical outcome assessment (COA) including patient-focused statistics, nonclinical, and product quality. The last notable meeting interaction occurred at a F2F meeting that was held on June 25, 2019 (meeting minutes finalized on June 27, 2019).

On February 14, 2020, the Sponsor requested a F2F Type B Pre-NDA meeting to discuss elements of the BOS/SHP621/TAK-721 program and the overall clinical and regulatory filing plan in preparation for their upcoming 505(b)(2) NDA submission. Due to travel and health considerations pertaining to the Coronavirus Disease 19 (COVID-

19) pandemic that was ongoing during the time frame of this meeting cycle, the requested F2F meeting was granted by the Agency as a teleconference. In order to support the Agency's review, the Sponsor submitted the meeting background information package, which was dated and received on March 17, 2020. It should be noted that a separate Chemistry, Manufacturing, and Controls (CMC)-only Type B Pre-NDA teleconference was held with the Office of Pharmaceutical Quality (OPQ) on April 20, 2020 (meeting minutes finalized on May 21, 2020).

After the Agency issued their Preliminary Comments to the Sponsor on May 15, 2020, the Sponsor sent (via email on May 19, 2020) a meeting agenda along with their full written responses to the FDA Preliminary Comments in order to help guide the overall meeting discussion (see the ATTACHMENTS AND HANDOUTS section below; Section 16.0).

It should be noted that each of the Sponsor's questions is presented below in normal font, followed by the Agency's response in **bold**. A record of the discussion that occurred during the meeting, including post-meeting comments, is presented in ***bold italics***.

2.0 DISCUSSION

OVERALL MEETING DISCUSSION
FDA acknowledged that the Sponsor intends to file the NDA during the 2020 calendar year.

Clinical

Question 1: In addition to the SHP621-301 study completed in 2019, Takeda has recently completed the SHP621-302 extension study. While the primary endpoint of relapse in the SHP621 302 study did not meet statistical significance, Takeda contends that, in subjects who achieve full clinical response after 12 weeks of initial therapy (e.g., SHP621-301 full responder group comparing BOS-BOS to BOS-PBO), the SHP621-302 study data (e.g., histology, dysphagia symptom response, and endoscopy scores) support continued treatment with BOS 2 mg BID for adolescent and adult patients with EoE. Does the Agency agree?

FDA Response:
We are unable to agree at this time. The adequacy of the data to support continued treatment with budesonide oral suspension (BOS) 2 mg BID for adolescent and adult patients with EoE who achieve full clinical response after 12 weeks will be determined at the time of NDA review.

Meeting Discussion:
No additional discussion needed.

Question 2: For subjects who do not achieve full clinical response following 12 weeks of initial therapy with BOS (SHP621-301 nonresponder group), Takeda contends that histologic and dysphagia symptom response data from the SHP621-302 extension study support additional treatment beyond 12 weeks with BOS 2 mg BID for adolescents and adults with EoE in order to obtain a full clinical response (peak eosinophil count ≤6/HPF and ≥30% reduction in dysphagia symptoms). Does the Agency agree?

FDA Response:
No, we cannot agree at this time. Ultimately, the adequacy of data to support continued treatment with BOS beyond 12 weeks for patients who do not demonstrate a response during the initial treatment period will be determined at the time of NDA review. We note that overall binary response was positioned as a secondary endpoint for study SHP621-302 and that your pre-specified plan to utilize sequential testing limited the assessment of this endpoint. Additionally, the lack of a corresponding placebo group is a significant limitation to the interpretability of the data from treatment beyond 12 weeks for those who did not achieve full clinical response with initial therapy. Given these limitations, we are concerned that your ability to support this claim may not be favorable.

Meeting Discussion:
No additional discussion needed.

Biostatistics / Informatics / Safety

Question 3: The Module 2 summary documents, Module 2.7.3 Summary of Clinical Efficacy and Module 2.7.4 Summary of Clinical Safety, will include integrated efficacy and safety data from the completed Phase 2 studies, MPI 101-01 and MPI-101-06, and the completed Phase 3 studies, SHP621-301 and SHP621-302. The data presentation and pooling methods are described further in the briefing package. Does the Agency agree with the proposed pooling methods for the integrated efficacy and safety data?

FDA Response:
We do not agree with your proposal to pool efficacy data. We remind you that the efficacy evaluation will be based on the results of the individual studies.

We have the following comments on the SAP of the ISS:

1. **Add the overall BOS safety cohort including patients who received at least one dose of BOS, including patients from SHP621-303, and specify the**

analysis plan for this cohort in the SAP of the ISS. For this cohort, you should focus safety assessments on the comparison of patients who received BOS treatment versus those who received placebo.

2. **The proposed analysis methods included only counts and proportions of adverse events of interest (AESIs), with no measurement to quantify the uncertainty in the treatment comparison (no formal hypothesis testing required). To assist in the interpretation of different safety risks between treatment arms, we recommend that you provide additional descriptive statistics (and their corresponding 95% confidence intervals), including (but not limited to) risk difference, relative risk, risk ratio, and mean difference (continuous safety variables). The outcome(s) to be assessed should take into consideration clinical relevance and should be pre-specified. You also need to apply these recommended analyses to the overall BOS safety cohort data mentioned above.**

3. **At a minimum, include comparative analyses for adverse events (AEs) leading to discontinuation, serious adverse events (SAEs), serious infection, opportunistic infection, malignancy, and AESIs. We acknowledge that the exposure adjusted treatment-emergent adverse event (TEAE) rates will be submitted. The exposure time should generally include the time to the occurrence of the event in patients who had an event, or the time to the end of follow-up in patients who did not have an event, with a careful definition of "follow-up." This comment also applies to each individual clinical study SAP.**

4. **Section 4.7 of the ISS SAP stated that a missing severity for an AE will be imputed as 'Mild' if the AE starts prior to the date of the first dose of BOS, and be assigned as 'Severe' for an AE starting on or after the date of the first dose of BOS. The imputed values for severity assessment will be used for incidence summaries. Whether the proposed imputation method is reasonable remains a review issue. Regardless, the ISS datasets should include an indicator variable that indicates whether the value for AE severity was imputed.**

Meeting Discussion:
There was agreement that (1) the ISE datasets would not be submitted in the NDA and (2) the clinical summary of efficacy would be submitted within Module 2.7.3 of the NDA.

There was agreement that the Sponsor will include data from the SHP621-303 study in the ISS datasets. Specifically, the Sponsor agreed to submit an additional data pool in the ISS consisting of all patients exposed to at least one dose of study drug (i.e., BOS/SHP621/TAK-721) through the latest data cutoff date (i.e., May 15, 2020) from the SHP621-303 study. This additional safety data pool is

referred to as overall safety pool hereafter in this document. Furthermore, it was understood that a 90-day (under a priority review NDA) or 120-day (under a standard review NDA) safety update would be submitted to the NDA, which would include the latest pooled safety data beyond the data cutoff date for the original NDA submission.

FDA emphasized the importance of presenting an analysis of safety information from the to-be-marketed dose and agreed to provide additional clarifications regarding the recommended safety data pools as post-meeting comments.

Post-Meeting Comments:
We are providing the following table as a summary of the meeting discussion and the four agreed safety data pools for the ISS. It has been adapted from Table 1 of your Response to FDA Preliminary Meeting Comments (see the ATTACHMENTS AND HANDOUTS section below; Section 16.0). In addition, this table is reflective of FDA's recommendation to use the maximum exposure time [instead of the planned study durations (12 weeks or 52 weeks)] for the safety analysis concluding at the last dose of treatment (BOS or placebo).

Integration	Population	Studies	Treatment Groups	Maximum BOS Exposure
Induction Placebo-controlled	Adult and adolescent	MPI 101-06	BOS 2 mg BID Placebo	last dose of treatment
Adolescent Induction	Adolescent only (11-17 years, inclusive)	MPI 101-01 [1] MPI 101-06 SHP621-301	BOS 2 mg BID BOS 2 mg QD BOS 0.5 mg QD Placebo	last dose of treatment
BOS-treated Long-Term	Adult and adolescent (continuous BOS treatment)	MPI 101-06 (including open-label extension on 2 mg QD) SHP621-	BOS 2 mg BID BOS 2 mg BID/QD	Up to last dose of treatment
Overall safety	Subjects received at least one dose of BOS including healthy volunteer, adolescent and adult	All studies mentioned above Phase I study SHP621-101	Dosages mentioned above placebo in re-randomized end-of-induction responders	Up to last dose of treatment

Source: Reviewer's modification based on Table 1 of sponsor's response dated May 19, 2020.

For the safety analysis, FDA has the following recommendations:

1. ***The safety signals (AEs, etc.) should be summarized by treatment arm in three periods: a) induction period only, b) maintenance period only, and c) combined maintenance, induction, and open-label extension period post maintenance.***

2. ***During each of these analysis periods, the ISS should include results on comparison between treatment (BOS) to placebo when applicable. Specifically, these comparisons include:***

   a. ***induction only (as proposed in the ISS): BOS versus placebo in adolescent only, adult only, and pooled adolescent & adult; and***

   b. ***maintenance only: BOS-BOS versus BOS-placebo in end-of-induction responders who are exposed to BOS during the induction phase.***

3. ***For the combined induction, maintenance, and open-label extension periods, we recommend that you perform model-based analyses that address the non-randomized and complicated nature of the data. These analyses would utilize all safety data including open-label extension data and should, at a minimum, account for the following:***

   a. ***the time the patient is receiving a particular treatment (e.g., with a Poisson or Cox model); and***

   b. ***the correlation between outcomes within a patient who receives different treatments at different time periods (e.g., with a generalized estimating equation or mixed effects model).***

   It may also be important to account for important baseline prognostic factors and time in the study, given the non-randomized nature of comparisons based on such analyses.

4. ***The calculation on exposure adjusted event rate should use the actual dose received by each patient.***

5. ***We refer to the FDA guidance on "Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review" at https://www.fda.gov/media/71665/download for recommendations to support the assessment of benefit-risk in your NDA submission.***

Question 4: Given the cumulative safety data including study SHP621-302, the Sponsor contends these data support continued treatment with BOS and that the safety assessments in the integrated summary of safety (ISS) statistical analysis plan (SAP) are adequate to characterize the safety of BOS (b) (4) Does the Agency agree?

FDA Response:

We acknowledge that your proposed safety database for BOS for the treatment of EoE includes 264 patients in your proposed induction placebo-controlled safety

integration, 50 patients in your proposed adolescent induction safety integration, and 366 patients in your proposed BOS-treated long-term safety integration. Your proposed safety database appears reasonable. Ultimately, the adequacy of the safety database will be determined during the NDA review.

Meeting Discussion:
No additional discussion needed.

Regulatory

Question 5: The Sponsor has previously presented a detailed plan related to a (505)(b)(2) NDA filing, including the intent to request a rolling submission and priority review at the time of submission. Additionally, the Sponsor previously outlined those sections of the intended 505(B)(2) NDA filing which would rely on Entocort EC (Seq. 0128) and the intended nonclinical and clinical table of contents (TOC) (Seq. 0151). An updated version of the nonclinical and clinical TOC is available in the briefing package. Does the Agency agree with the eCTD placement of nonclinical and clinical information?

FDA Response:
From a technical perspective (and not content related), the organization of the nonclinical and clinical information is acceptable.

Based on your July 12, 2018 submission and subsequent discussion at the June 25, 2019 F2F meeting, we reiterate the following advice. You are proposing to reference information from FDA reviewers' public summaries for the support of safety and/or effectiveness. "Full reports of investigations" of safety and effectiveness are required to be submitted for the approval of 505(b)(1) and 505(b)(2) NDAs. The FDA reviewers' public summaries, however, do not constitute full reports of investigations. See 21 CFR 314.430(e)(2). A 505(b)(2) NDA applicant that seeks to rely upon the Agency's finding of safety and/or effectiveness for a listed drug (LD) may rely on FDA's finding of safety and effectiveness as reflected in the FDA-approved product labeling for the LD. Refer to the 505(b)(2) REGULATORY PATHWAY section below for information about submitting a 505(b)(2) NDA.

Meeting Discussion:
No additional discussion needed.

FDA ADDITIONAL COMMENTS
We have the following additional comments.

Regulatory

1. **We acknowledge your draft rolling submission request, which was included in Appendix 3 of the meeting background information package that was submitted and received on May 14, 2019, in order to support the F2F meeting held on June 25, 2019. As specified in Appendix 2 (Process for Rolling Review) of the Guidance for Industry, *Expedited Programs for Serious Conditions – Drugs and Biologics* (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics), formally submit your updated/final rolling submission request to the IND in order to obtain Agency agreement on your rolling submission proposal.**

2. **We remind you that budesonide is the active moiety/ingredient of multiple drug products that (1) have obtained NDA approval under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and (2) are currently being marketed in the United States. Consequently, budesonide is not a New Molecular Entity (NME), and thus your NDA will not be reviewed under the PDUFA VI NME Program (https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm).**

3. **We emphasize that you read all subsequent sections below (starting with Section 3.0 PREA REQUIREMENTS) as this information is critical for the preparation of your eventual NDA submission.**

Clinical Outcome Assessment (COA)

4. **Submit a patient-reported outcome (PRO) evidence dossier that includes all the evidence to support the content validity and psychometric measurement properties and performance of the latest version of the Dysphagia Symptom Questionnaire (DSQ) used in your phase 3 program. You may refer to the Appendix of the 2009 FDA Guidance for Industry, *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm193282.pdf) for the PRO-related information that should be included in an evidence dossier for review by the FDA.**

5. **Please conduct anchor-based analyses using your phase 3 data to confirm the clinically meaningful within-patient change threshold for DSQ score (absolute change and percent change). We refer you to the recommendations conveyed in our September 15, 2015 'Advice/Information Request' letter, February 15, 2018 email, September 17, 2018**

'Advice/Information Request' letter, and February 07, 2019 'Advice/Information Request' letter.

Clinical Pharmacology

6. **According to your July 12, 2018 submission, you propose to reference the FDA Clinical Pharmacology Review of the listed drug (LD) for the labeling of your product. We remind you that the FDA Clinical Pharmacology Review of the LD cannot be directly referenced for your product's labeling. Refer to our response to Question 5 above.**

7. **We recommend that you address clinical pharmacology issues that include, but are not limited to, drug-drug interaction (DDI) potential and dosing for specific populations. As you plan to rely on the labeling of the LD, you will need to provide justification on how the clinical pharmacology information for the dosage regimen of the LD (up to 9 mg QD for Entocort EC) is relevant to your proposed dosage regimen (2 mg BID) for EoE patients.**

8. **Clarify whether the to-be-marketed (TBM) formulation is the SB-10 formulation, which was included in the relative BA/BE study, SHP621-101. Based on the summary results in SHP621-101, it is unclear whether you conducted statistical analyses to compare the SB-10 formulation (TBM) and the LD. We recommend that you provide the results of the BE analysis between your TBM formulation and the LD.**

9. **It is unclear whether a food effect study was conducted with the TBM. We recommend that you conduct a food effect study with the TBM formulation.**

   For more information, refer to the FDA draft Guidance for industry, *Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations* (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-effects-food-drugs-inds-and-ndas-clinical-pharmacology-considerations). In addition, clarify how your drug was administered with respect to meals in your phase 3 trials. It is unclear whether your product was administered consistently under fed conditions, as it is stated in your protocols that the drug was administered every morning after meal and at bedtime.

10. **We remind you that electronic datasets for individual plasma concentrations and PK parameters should be submitted.**

11. **We request that a tabulated summary of *in vitro* drug-drug interaction (DDI) study results along with the prediction of *in vivo* DDI potential be provided in Module 5 with hyperlinks to the *in vitro* study reports.**

12. **We recommend that you submit the summaries of bioanalytical methods used in your clinical pharmacology studies, as well as the bioanalytical assay validation report(s). We recommend that the in-study bioanalytical assay reports clarify whether the PK samples were analyzed within the established period for long-term storage stability. Refer to the *Bioanalytical Methods Templates* Guidance for Industry Technical Specifications Document (https://www.fda.gov/media/131425/download).**

Data and Analyses

13. **Submit an annotated version of all FDA meeting minutes that request specific analyses and/or documents, and include a hyperlink, when applicable, to the analyses or documents requested. This document should be submitted in M1 Section 1.6 of the eCTD.**

14. **CDISC standards should be followed when preparing the data definition file. In addition, we encourage that you share an example data definition file with the Agency for feedback. The data definition files should include possible responses for all variables when the meaning is not obvious. Discuss the need for programs for other derived datasets with the review division. [Study Data Technical Conformance Guide (TCG) 4.1.4.5 Data Definition Files for SDTM, SEND, and ADaM; TCG Section 8.3 Study Data Traceability). General considerations include the following:**
    - **Topline summary/description of what is included in each analysis dataset (i.e., a dataset table of contents)**
    - **For each analysis dataset, document the following:**
        - **For derived or imputed variables, a description and/or algorithm of how the variable was derived or imputed from the source data**
        - **Clear definition of analysis flags**
        - **Codes and decodes of all categorical variables (e.g., 1=mild, 2=moderate, 3=severe; 0=age < 18, 1=age ≥ 18)**

15. **Submit all statistics programs/scripts and datasets used to create the analyses found in the main sections of the Summary of Clinical Efficacy, Summary of Clinical Safety, and phase 3 trial clinical study reports (CSRs). If a script contains a macro, include the macro script. The scripts and data definition files should be sufficient to facilitate the understanding of how the analyses were conducted. Footnote the tables and figures featured in the main clinical efficacy and safety sections of the NDA with the name of the script used to create the table or figure. For the principle tables and figures, include a table that contains the following:**
    - **Name of the statistical analysis code with hyperlink**
    - **Name of the table or figure with hyperlink or its location in the CSR if not hyperlinked**

- **Names of datasets used to create the table or figure (hyperlinks are helpful)**

16. **The ISS must include all deaths, SAEs, and dropouts due to AEs from all controlled trials.**

17. **For ease of navigation of the review, include a dataset that indicates those subjects for whom a case report form (CRF) and/or narrative was submitted, and the reason why it was submitted (e.g., death, SAE, AE leading to medication discontinuation, adjudication package submitted). Discuss with the review division the need for also submitting this information in tabular format with the patient identifier hyperlinked to the narrative and/or CRF.**

18. **For the pivotal trial(s), please list in one table the following:**
    - **Dates of first patient and last patient visits**
    - **Dates of database lock**
    - **Dates for each interim analysis**
    - **Dates of the initial protocol (including all revisions) with a hyperlink to the protocol and each revision; include a hyperlink to the Summary of Changes for each version**
    - **Dates of all versions of the statistical analysis plan (SAP) with a hyperlink to each SAP; include a hyperlink to the Summary of Changes for each version and specify the number of subjects enrolled in the trial at the time of each protocol change.**

19. **Please submit a table detailing all of the tables and figures featured in the main clinical efficacy and safety sections (not the Appendix) of the NDA. The table should contain the following:**
    - **Title of the table or figure in the NDA**
    - **A page number hyperlink to the location of the table or figure**
    - **A name hyperlink to the programming language (e.g., SAS) code (and/or macros) used to create the table or figure**
    - **Names of the datasets used to create the table or figure (hyperlinks are useful but not necessary)**
    - **For derived (analysis) datasets used to conduct your analyses, you should indicate the CRF pages and tabulation datasets from which the information was derived**
    - **For all derived datasets, submit all scripts/programs used to create the analysis datasets. The scripts and data definition files should be sufficient to facilitate the understanding of how the analysis datasets were created. If variables are inadequately described in the data definition files, you may need to also submit all datasets (and associated data definition files) used to derive your analysis datasets.**

20. **Submit a dataset that contains all subjects that were unblinded. The dataset should include the unique subject ID, the treatment received, who requested unblinding, the date of unblinding, and the reason for unblinding.**

21. **When creating the disposition dataset, for discontinuations due to "other," please perform a medical review to ensure appropriate categorization, e.g., discontinuation due to AE or meeting study discontinuation criteria, etc. For discontinuations due to "other" that are not appropriate for other categories, please provide the specific reason.**

22. **For each study, provide a flag in the AE dataset or a separate dataset that maps preferred terms (PTs) to the adverse events of special interest (AESIs).**

23. **You should plan to evaluate AEs based on logical groupings of PTs using standard MedDRA queries or other appropriate means. Include in your submission the procedures and rationale used for the grouping of PTs. Given the large number of relative MedDRA PTs, FDA recognized that the list of proposed PTs and findings in Sponsor submissions are not meant to be exhaustive. The intent of grouping PTs for safety analyses is to avoid the splitting of PTs to ensure that AEs are adequately captured (e.g., PTs such as "ABDOMINAL PAIN LOWER", "ABDOMINAL PAIN UPPER", "ABDOMINAL PAIN" should be grouped in the assessment for abdominal pain).**

Meeting Discussion:
Regarding FDA Additional Comment 14, FDA concurred with the Sponsor's proposal for data standardization as outlined in the Response to FDA Preliminary Meeting Comments (see the ATTACHMENTS AND HANDOUTS section below; Section 16.0) and plan to further outline the proposal in a Study Data Standardization Plan which will be submitted as a follow-up to the Pre-NDA meeting.

As related to FDA Additional Comment 10, the Sponsor clarified that raw and analyses datasets (i.e., non-CDISC compliant) for legacy study MPI 101-01 pertaining to drug concentration and PK parameters would be provided in the NDA. FDA agreed with the planned format of the datasets to be submitted for the MPI 101-01 study. Specifically, it was stated that since the MPI 101-01 study was initiated prior to December 18, 2016, it is acceptable that these datasets do not conform to CDISC data standards.

In reference to FDA Additional Comment 17, FDA expressed that the Sponsor's narrative submission proposal (see the ATTACHMENTS AND HANDOUTS section below; Section 16.0) appeared reasonable; however, the Agency notified the

Sponsor that they may request additional narratives during review of the application.

In response to FDA Additional Comment 9, the Sponsor clarified that the dosing instructions provided in the phase 3 trial were to administer the morning dose after breakfast and the evening dose at bedtime. The Sponsor explained that the evening dose at bedtime was likely administered without food. Additionally, the Sponsor said that BOS should not be taken with food and these instructions will be included in the proposed prescribing information.

FDA expressed concerns about the potential for patients to take BOS with food even if they are instructed not to take BOS with food. Additionally, FDA stated that food intake prior to dosing may increase the drug exposure and potentially cause a safety issue with BOS administration. FDA restated their recommendation that the Sponsor characterize the food effects of the to-be-marketed (TBM) formulation of BOS.

Post-Meeting Comments:
We note that the administration instructions for the phase 3 trial state that no food or liquids are permitted for 30 minutes following drug administration with the morning dose administered after breakfast and the evening dose administered at bedtime. However, there are no specific instructions regarding the timing of food intake prior to administration (e.g., at least 30 minutes after breakfast or 30 minutes after dinner).

It is unclear if you intend for patients to be in a fasted or fed state at the time of administration. We are concerned that as the instructions for the morning dose are "after meal," patients will most likely be in a fed state; however, patients will most likely be in a fasting state for the evening dose as the instructions are "at bedtime" and not in relation to a meal (i.e., dinner).

It is unknown if the systemic exposure to budesonide from the proposed product will be altered if dosed during the fed or fasted state. In addition, your proposed TBM formulation is different from the formulation used in the phase 3 trial. As the food effect may be different for different formulations, it is our general recommendation to evaluate the food effect using the TBM formulation when it is different from the clinical trial formulation.

Furthermore, as the adverse events (AEs) associated with budesonide, including hypercortisolism and adrenal axis suppression, have been shown to be concentration-dependent, the proposed timing of administration of BOS relative to food intake should be supported by the potential impact of food intake on the PK of BOS.

We continue to recommend that you characterize the effects of food intake on the PK of the TBM formulation to inform the dosing instructions, including the recommended timing of administration in relation to a meal, (e.g., 30 minutes after meal or on an empty stomach) to inform the prescribing information (PI).

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

4.0 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[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, which include:

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

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and

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

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.

5.0 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.[3]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[4] 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.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

[3] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[4] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

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 started on or 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 FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.
If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[5]

6.0 DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

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

[5] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the Pre-NDA meeting.

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

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

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

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

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

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

7.0 LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources[6] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[7]

[6] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[7] https://www.fda.gov/media/109533/download

8.0 SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[8]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification, *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[9]

9.0 SECURE EMAIL COMMUNICATIONS

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

10.0 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.

[8] http://www.fda.gov/ectd
[9] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

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)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[10] and the Guidance for Industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[11]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

11.0 505(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).[12] 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-

[10] https://www.fda.gov/media/84223/download
[11] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[12] 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.

2003-P-0274-0015, available at Regulations.gov.[13]

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

[13] http://www.regulations.gov

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.

12.0 OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018), and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[14]

13.0 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.*

14.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

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

15.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Finalized Meeting Minutes	FDA	June 19, 2020 (however, will be finalized as soon as feasible)
Rolling Submission Request	Shire	As soon as feasible

16.0 ATTACHMENTS AND HANDOUTS

On May 19, 2020, the Sponsor via email provided the Agency with a meeting agenda along with their full written responses to the FDA Preliminary Comments (dated May 15, 2020) in order to help guide the overall meeting discussion. All provided material is attached herein.

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

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

/s/

BENJAMIN P VALI
06/02/2020 11:59:47 PM

IND 103173

MEETING MINUTES

Shire ViroPharma Inc.
Attention: Ipsita Olympia Banerjee, M.S., M.B.A.
Associate Director, Global Regulatory Affairs
300 Shire Way
Lexington, MA 02421-2101

Dear Ms. Banerjee:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for budesonide oral suspension (BOS)/SHP621.

We also refer to the meeting between representatives of your firm and the FDA on June 25, 2019. The purpose of the meeting was to discuss your planned overall 505(b)(2) NDA submission package and strategy.

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

If you have any questions, contact me at (301) 796-4261 or benjamin.vali@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Benjamin Vali, M.S.
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: June 25, 2019; 8:59 AM – 9:25 AM EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room 1417
Silver Spring, Maryland 20903

Application Number: IND 103173
Product Name: Budesonide Oral Suspension (BOS)/SHP621
Indication: Treatment (b) (4) (b) (4) in Patients with Eosinophilic Esophagitis (EoE)
Sponsor Name: Shire Viropharma, Inc.

Meeting Chair: Dr. Erica Lyons
Meeting Recorder: Mr. Benjamin Vali

FDA ATTENDEES

Office of New Drugs (OND) / Office of Drug Evaluation III (ODEIII)/Immediate Office (IO)
Julie Beitz, M.D., OND Deputy Director (Acting) and ODEIII Office Director

Division of Gastroenterology and Inborn Errors Products (DGIEP)
Jessica J. Lee, M.D., M.M.Sc., Associate Director
Erica Lyons, M.D., F.A.A.P., Medical Officer Team Leader
Elizabeth (Betsy) Mannick, M.D., Medical Officer
Jackye Peretz, Ph.D., Toxicologist
Benjamin Vali, M.S., Regulatory Project Manager

Office of Biostatistics (OB) / Division of Biometrics III (DBIII)
Xin Yuan, M.S., M.Ed., Clinical Outcome Assessments (COA) Statistical Reviewer

Office of Clinical Pharmacology (OCP) / Division of Clinical Pharmacology III (DCPIII)
Jie (Jack) Wang, Ph.D., Clinical Pharmacology Team Leader
Xiaohui (Michelle) Li, Ph.D., Clinical Pharmacology Reviewer

Eastern Research Group Attendee
Sraavya Polisetti, Independent Assessor

SPONSOR ATTENDEES

Shire ViroPharma Inc.
Ipsita Olympia Banerjee, M.S., M.B.A., Global Regulatory Affairs Lead
Nirav Desai, M.D., Global Clinical Development Lead
Richard Finkelman, D.D.S., Ph.D., Senior Clinical Pharmacology Medical Director
Heng (Ivy) Song, Ph.D., Clinical Pharmacology & Pharmacokinetics Lead *(on the phone/WebEx)*
Lan Lan, Ph.D., Biostatistics Program Lead
Robin Morey, M.P.H., Clinical Programs Lead
Bridgett Goodwin, Ph.D., Outcomes Research and Epidemiology Lead
Debra Silberg, M.D., Ph.D., Clinical Science Head, GI
Joerg Pfeifer, Ph.D., Global Regulatory Affairs
James Williams, M.D., Global Development Lead

External Consultants

(b) (4)

1.0 BACKGROUND

On September 5, 2008, IND 103173 was activated for the investigation of budesonide oral suspension (BOS) in the treatment of patients with eosinophilic esophagitis (EoE). On May 31, 2016, BOS/SHP621 was granted a Breakthrough Therapy Designation (BTD) in the proposed patient population. Under the BTD granted status (along with obtaining Orphan Drug Designation previously on December 20, 2006), the IND's Sponsor, Shire ViroPharma Inc. (hereafter, 'the Sponsor'), engaged FDA on multiple occasions starting with the 'Initial Comprehensive Multidisciplinary Breakthrough Therapy Type B Meeting', which was held on November 2, 2016 (meeting minutes finalized on November 4, 2016). These multiple FDA engagements covered various aspects of BOS/SHP621's product development, i.e., clinical (including pediatrics), clinical pharmacology, biostatistics, clinical outcome assessments (COA), nonclinical, and product quality.

On April 18, 2019, the Sponsor requested a face-to-face (F2F) Type B pre-NDA meeting to discuss their planned overall 505(b)(2) NDA submission package and strategy. FDA granted this F2F meeting request, and the Sponsor subsequently submitted their meeting background information package on May 14, 2019. During its review, FDA sent two information requests (via email) on June 5, 2019 and June 10, 2019. The Sponsor responded to these requests on June 10, 2019 and June 11, 2019, respectively.

After the Agency issued their Preliminary Comments to the Sponsor on June 13, 2019, the Sponsor sent (via email on June 21, 2019) their full written responses to the FDA

Preliminary Comments, which included the meeting agenda, in order to help guide the overall meeting discussion (see the ATTACHMENTS AND HANDOUTS section below; Section 12.0).

It should be noted that each of the Sponsor's questions is presented below in normal font, followed by the Agency's response in **bold**. A record of the discussion that occurred during the meeting is presented in ***bold italics***.

2.0 DISCUSSION

Clinical / Regulatory

Question 1: The Sponsor intends to submit an initial NDA registration package based on the SHP621-301 Induction study data only. Does the Agency agree?

FDA Response:
No, we do not agree. We have concerns regarding your proposal to pursue initial NDA registration based only on the SHP621-301 Induction study data. Clinical experience, including current practice guidelines (Dellon, Gonsalves, et al., 2013), suggests that chronic dosing with topical corticosteroids is necessary to achieve and maintain the resolution of eosinophilic inflammation and clinical symptoms in patients with eosinophilic esophagitis. As such, safety and efficacy data from long-term treatment use are necessary to (1) inform dosing and labeling, and (2) support the successful filing of an NDA as outlined in the Draft Guidance for Industry, *Eosinophilic Esophagitis: Developing Drugs for Treatment*, which is available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/eosinophilic-esophagitis-developing-drugs-treatment-guidance-industry. We additionally remind you of the November 2, 2016 'Initial Comprehensive Multidisciplinary Breakthrough Therapy Type B Meeting' (meeting minutes finalized on November 4, 2016), during which we stated that we could not agree with submission of an initial NDA based solely on induction data from SHP621-301. The reasons cited were the need for (1) information to inform chronic dosing at the time of NDA approval, (2) information regarding the retreatment of patients who relapse when no longer receiving steroids, and (3) long-term safety data.

Meeting Discussion:
The Sponsor stated that they agreed with FDA's position regarding the need for the submission of maintenance data but reiterated their desire to pursue an initial NDA submission with induction data alone (i.e., without maintenance data) in order to provide earlier treatment access to EoE patients. FDA thanked the Sponsor for their commitment to EoE patients and stated that due to (1) evidence suggesting that EoE patients require chronic therapy, (2) evidence suggesting relapse if treatment is withdrawn from EoE patients, and (3) the need to further

characterize the longer-term safety profile of BOS/SHP621, maintenance data would be necessary to support the initial NDA submission. The Sponsor clarified that if maintenance data are required for the initial NDA, the NDA submission would be targeted for July 2020. If maintenance data are not required, the Sponsor stated that the NDA submission would instead be targeted for November 2019.

The Sponsor agreed with FDA that they would submit the initial NDA (1) with both induction and maintenance data, (2) as a rolling submission, and (3) with the plan to request for a priority review. The Sponsor also stated that the initial NDA submission would likely still be based on the MB-9 formulation; however, they plan to continue their collaboration with the Agency on the development of the SB-10 formulation.

Question 2: Shire intends to submit an ISS and ISE as part of the proposed initial induction only NDA. The Module 2 summary documents, ISS and ISE will include efficacy and safety data from the completed Phase 2 studies MPI 101-01 and MPI-101-06 and the completed Phase 3 study SHP621-301. Phase 3 studies SHP621-302 and SHP621-303 will be reported as ongoing in the initial induction only NDA. The data presentation and pooling methods will be described further in Section 10.2. Does the Agency agree?

FDA Response:

No, we do not agree. See our response to Question 1 above. As stated above, chronic use is anticipated should BOS/SHP621 become an approved therapy. The ISS and ISE for an NDA should include data from both the induction trial (SHP621-301) and the maintenance trial (SHP621-302) in order to be considered sufficient for filing. We remind you that the efficacy evaluation will be based on the results of the individual studies. Additionally, we recommend that data from all phase 2 and phase 3 trials be included in your ISS. With respect to your planned submission, please provide the rationale or justification for excluding data from the extension phase of study MPI-101-06 and the taper period of study MPI-101-01.

As per the Draft Guidance for Industry, *Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products* (available at https://www.fda.gov/media/117976/download), combining data across all patients in the trials by treatment group can produce misleading results, especially when there are large sample size disparities between trials with different randomization ratios. The overall comparative measure should be based on combining the comparative measure from each individual trial.

The comparability of treatment groups with respect to safety outcomes can be affected if the average treatment duration substantially differs by treatment

group. Simple adjustments for exposure may be appropriate when the assumption of constant hazards is reasonable, but may not sufficiently correct for non-comparability when that assumption is violated.

Meeting Discussion:
No additional discussion needed.

Question 3: The Sponsor herein confirms that as part of the registration process, it will:

a) Submit a 505(b)(2) NDA package with cross-references to Entocort EC as outlined to FDA in July 2018 (Seq. 0128).

b) Request Priority Review in consideration of the unmet medical need for patients with EoE.

c) Submit the 505(b)(2) NDA package on a rolling basis, with the intent to provide the agency with three separate sequences over the course of the initial filing.

Does the Agency agree?

FDA Response:
No, we do not agree. If you intend to cross-reference NDA 021324 for Entocort EC (budesonide) capsules, then you will need to obtain a letter of authorization (LoA) from the applicant of the Entocort EC NDA. However, if you intend to rely, in part, on information required for approval that comes from studies not conducted by you or for you, or for which you have not obtained a right of reference (e.g., reliance on FDA's finding of safety and/or effectiveness for a listed drug or published literature), then your marketing application will be a 505(b)(2) application.

You are proposing to reference information from FDA reviewers' public summaries for the support of safety and/or effectiveness. "Full reports of investigations" of safety and effectiveness are required to be submitted for the approval of 505(b)(1) and 505(b)(2) NDAs. The FDA reviewers' public summaries, however, do not constitute full reports of investigations. See 21 CFR 314.430(e)(2). A 505(b)(2) NDA applicant that seeks to rely upon the Agency's finding of safety and/or effectiveness for a listed drug may rely on FDA's finding of safety and effectiveness as reflected in the FDA-approved labeling for the listed drug.

You 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)).

Refer to the 505(b)(2) REGULATORY PATHWAY section below for information about submitting a 505(b)(2) NDA.

Your proposal to request priority review along with a rolling submission appears reasonable; however, we remind you that the review clock will not begin until a complete NDA (i.e., including all efficacy and safety data from SHP621-301 and SHP621-302) is submitted. After submission of the complete NDA, we will make a filing determination within the usual timeframe.

Meeting Discussion:
No additional discussion needed.

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

4.0 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 https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM624623.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start 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 on or 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.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content. The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

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

5.0 LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

6.0 SUBMISSION FORMAT REQUIREMENTS

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

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

7.0 SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA to sponsors 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 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).

8.0 505(b)(2) REGULATORY PATHWAY

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

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

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

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

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must

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

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

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

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

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

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

9.0 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 Labeling Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

10.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

11.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Finalized Meeting Minutes	FDA	July 25, 2019 (however, will be finalized as soon as feasible)

12.0 ATTACHMENTS AND HANDOUTS

On June 21, 2019, the Sponsor via email provided the Agency with full written responses to the FDA Preliminary Comments (dated June 13, 2019), which included the meeting agenda, in order to help guide the overall meeting discussion. All provided material is attached herein.

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

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

/s/

BENJAMIN P VALI
06/27/2019 03:39:48 PM

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	IND 103173
Request Receipt Date	3/30/2016
Product	Budesonide Oral Suspension (BOS)/SHP621
Indication	Eosinophilic Esophagitis
Drug Class/Mechanism of Action	Glucocorticosteroid
Sponsor	Shire ViroPharma Incorporated (Shire)
ODE/Division	ODE III/DGIEP
Breakthrough Therapy Request Goal Date (within 60 days of receipt)	6/1/2016

Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). ***Note:*** *Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.*Section I to be completed within 14 days of receipt for all BTDRs*

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

   For the treatment of eosinophilic esophagitis.

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequeate and sufficiently complete to permit a substantive review?
      - ☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
      - ☐ Undetermined
      - ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked "No", BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If 3b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

- *Information regarding the disease and intended population for the proposed indication.*
- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

Eosinophilic esophagitis (EoE) is a clinicopathologic disease characterized histologically by eosinophil-predominant inflammation and clinically by symptoms related to esophageal dysfunction. Left untreated, it leads to an increase in esophageal stricture rate, dysphagia, and risk of food impaction. EoE is designated as a rare disease with a prevalence of approximately 0.5-1 cases/1000. Three phenotypes of EoE have been described based on endoscopic findings: inflammatory, mixed, and fibrostenotic EoE. EoE is considered to be a progressive condition from the inflammatory to fibrostenotic phenotype, with remodelling and deposition of fibrosis as key pathogenic features. Clinical symptoms vary by age; infants and toddlers present with feeding difficulties, school-aged children are more likely to present with vomiting or pain, and adolescents and adults present with dysphagia and food impaction. It has been hypothesized that in children, eosinophilic inflammation

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

in the esophagus manifests with white plaques or exudates, decreased vascularity or mucosa edema, and linear furrows, but without esophageal rings or strictures, and causes symptoms such as pain, heartburn, and failure to thrive. With ongoing inflammation, however, subepithelial collagen is deposited, esophageal rings, narrowing, and strictures develop, and symptoms become dysphagia predominant. The standards of care are diet therapies, use of non-Food and Drug Administration (FDA) approved pharmacologics, "off-label" swallowed use of aerosolized or nebulized corticosteroids, and esophageal dilation which temporarily relieves symptoms, but without effect on the underlying inflammation. The ACG Clinical Guideline for the diagnosis and management of EoE[3] states that topical steroids are a first-line pharmacologic therapy for treatment of EoE.

BOS is being developed to be a (b) (4) ready-to-use suspension of (b) (4) budesonide. It is believed to interrupt the inflammatory response in EoE. Several formulations of the glucocorticosteroid budesonide have been approved by the FDA to treat inflammatory disease affecting the respiratory system delivered by the inhalation route, and inflammatory bowel disease of the lower GI tract by oral or rectal administration. These products include Pulmicort® Respules for inhalation (1999; for asthma), Rhinocort® Aqua nasal spray (1999; for rhinitis), Entocort® EC capsules for oral use (2001; for Crohn's disease), and Uceris® tablets (2013; for ulcerative colitis). FDA-approved budesonide product labeling does not address the appropriate information to ensure safe and effective use for EoE.

An orphan drug designation (ODD 06-2274) for the use of budesonide in the treatment of pediatric EoE was granted by the FDA in December 2006. In June 2011, the orphan designation was expanded to include treatment of both adults and pediatrics with EoE.

7. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The endpoints used to support breakthrough therapy designation include improvement in histologic response (≤6 eos/HPF), and improvement in dysphagia as measured by the Dysphagia Symptom Questionnaire (decrease in DSQ score by at least 30% from baseline). The above histologic and symptomatic endpoints were designated as co-primary endpoints in the sponsor's ongoing phase 3 induction trial. Two phase 2 trials assessing histology with physician-administered symptom assessment scale (MPI-101-01) and histology with PRO measures as co-primary endpoints (MPI-101-06) have been completed, and comprise the sponsor's submission in support of BTDR. These clinical trials are described and discussed in Section 10 below.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
- *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
- *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit*.

[3] Dellon, E, Gonsalves, N, et.al. ACG Clinical Guideline: Evidenced Based Approach to the Diagnosis and Management of Esophageal Eosinophilia and Eosinophilic Esophagitis (EoE). Am J Gastroenterol 2013; 108:679–692.

There is limited experience with endpoints in EoE clinical trials. No medication is currently approved by the FDA for treatment of eosinophilic esophagitis. The following comments represent the current thinking of the Division:

EoE is a clinicopathologic disorder, and resolution of symptoms cannot accurately predict histologic remission. Similarly, histologic response alone is not sufficient to demonstrate a clinically meaningful outcome in EoE as reduction in eosinophils per HPF do not necessarily correlate with a symptomatic response (dysphagia is a principal clinical symptom of the disease in adolescents and adults). As such, the Division currently recommends a co-primary endpoint approach, with the two endpoints comprising the proportion of subjects who are symptomatic responders and the proportion of subjects with a histologic response. The Sponsor has proposed a ≥30% change in the DSQ score (Figure 1 depicts the DSQ below) as a symptomatic responder definition for their phase 3 studies. This has been found acceptable by both the Division and COA staff as long as it is supported by sensitivity analyses looking at absolute point changes.

Figure 1. Dysphagia Symptom Questionnaire (v.4) used in Study MPI 101-06

1. Since you woke up this morning, did you eat solid food?
   - No
   - Yes
2. Since you woke up this morning, has food gone down slowly or been stuck in your throat?
   - No
   - Yes
3. For the most difficult time you had swallowing food today (during the past 24 hours), did you have to do anything to make the food go down or to get relief?
   - No, it got better or cleared up on its own
   - Yes, I had to drink liquid to get relief
   - Yes, I had to cough and/or gag to get relief
   - Yes, I had to vomit to get relief
   - Yes, I had to seek medical attention to get relief
4. The following question concerns the amount of pain you have experienced when swallowing food. What was the worst pain you had while swallowing food over the past 24 hours?
   - None, I had no pain
   - Mild
   - Moderate
   - Severe
   - Very Severe

Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

None.

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s)

used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

There are no available therapies for EoE. Aerosolized and nebulized corticosteroids approved for other inflammatory conditions are used off-label as a swallowed preparation, though dose and dosing regimens are not standardized. Prednisone is also used if topical steroids are not effective or in patients who require rapid improvement in symptoms. Dietary elimination therapies (e.g., six food elimination diet) are considered as initial therapy in the treatment of EoE. Esophageal dilation may be used in symptomatic patients with strictures that persist despite medical or dietary therapy.

Budesonide is recommended to be used off-label as first-line therapy in patients with EoE. However, without any standardized dose or dosing regimens, it is imperative that this product be studied in a controlled environment to inform product usage in this population.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[4].

None.

10. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[5], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

The sponsor has provided data from two completed phase 2 clinical studies to demonstrate preliminary clinical efficacy: MPI-101-01 and MPI-101-06. Additional data are provided from the long-term extension period of MPI-101-06. An overview of the clinical trials is summarized in Table 1.

[4] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[5] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

Table 1: Overview of Clinical Development Plan

	MPI-101-01	MPI-101-06
Phase	2 (completed)	2 (completed)
Trial Design	12 Week Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging evaluating low, medium, and high dose BOS	12 Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Dose-Ranging, with a 24 Week Open Label Extension(OLE)
Treatment Group/Population	M/F pts. aged 2-18y with EoE and baseline symptoms based on Physician Administered EoE Symptom Score (PAESS)[1]	M/F pts. aged 11-40y with EoE and symptoms of dysphagia based on the Dysphagia Symptom Questionnaire (DSQ) (see Figure 1 above)
N	82 randomized	93 randomized (BOS n=51, placebo n=42) 82 entered the OLE
Primary Endpoint	≥50% reduction in clinical symptom score from baseline and a reduction in peak esophageal eosinophil count to ≤6/HPF	Co-primary endpoints were histologic response (peak eosinophil count ≤6/HPF) and symptom response as measured by DSQ
Trial Results	52.6% medium dose (10 of 19), 47.1% high dose (8 of 17) compared to 5.6% placebo subjects (1 of 18; p<0.02 for both pairwise comparisons)[2]. Low dose BOS group was 11.8% (2 of 17; p=0.5282)	Co-primary endpoint – histologic response: BOS 38.8% vs. placebo 2.6% (p<0.0001) Co-primary endpoint – DSQ score LS mean change from baseline: BOS -14.27 vs. placebo -6.75 (-11.8, -1.7; p=0.0096) Overall responders – histologic + symptoms(≥30% reduction in DSQ score): BOS 26.5% vs. placebo 2.6% (p=0.0206)

Source: reviewer's table.

[1]ObsRO/ClinRO

[2]Driven by histologic response. There were no statistically significant differences among the treatment groups on the clinical symptom response variables using the physician reported EoE clinical symptom score assessment.

b. Include any additional relevant information. Consider the following in your response:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness .*
- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*

MPI-101-01 was a proof of principle study for the treatment of EoE, using a commercially viable formulation of budesonide oral suspension in children 2 to 18 years of age. The medium dose of BOS was 1.4 mg and 2 mg daily in subjects 2 to 9 years of age and 10 to 18 years of age, respectively, and the high dose was 2.8 mg and 4 mg daily in subjects 2 to 9 years of age and 10 to 18 years of age, respectively. For subjects to be eligible, esophageal mucosal biopsy specimens, obtained in the 6 weeks prior to the Baseline Visit, must have shown a peak eosinophil count of ≥20 per high-power field (HPF) from at least 2 levels in the esophagus. At the Baseline Visit, subjects were evaluated by a physician investigator using a 6 category, 18-point EoE Clinical Symptom Score in which symptoms were rated by severity using coping behaviors, and were to have a total symptom score of ≥3 in the two weeks prior to dosing.

The primary efficacy endpoint was Response to Therapy, defined as a ≥50% reduction in clinical symptom score from baseline and a reduction in peak esophageal eosinophil count to ≤6/HPF from proximal, mid, and distal esophageal biopsies, at the Final Treatment Evaluation for the Full Analysis Set (FAS) population. Response to therapy was achieved in 52.6% of medium dose BOS subjects (10 of 19) and 47.1% of high dose BOS subjects (8 of 17) compared to 5.6% of placebo subjects (1 of 18; $p<0.02$ for both pairwise comparisons). The response to therapy in the low dose BOS group was 11.8% (2 of 17) and was not distinguishable from placebo ($p=0.5282$). The percentage of responders in the medium and high dose BOS groups was comparable.

At the Final Treatment Evaluation, histologic response (i.e., peak esophageal eosinophil count ≤6/HPF) was achieved in 5.6%, 23.5%, 52.6% and 94.1% of subjects in the placebo, low, medium, and high BOS dose groups, respectively. Histologic response in the medium and high dose BOS groups was greater than the response observed in the low dose BOS and placebo groups. A dose-related effect was also observed on the histologic remission endpoint (i.e., peak esophageal eosinophil count ≤1/HPF) with the percentage of subjects meeting the remission criterion of 0%, 11.8%, 42.1% and 76.5%, respectively, across the four treatment groups. These remission percentages were reported to be statistically significant for the medium and high dose groups versus placebo (both $p<0.005$). The percent reductions in peak eosinophil counts at all esophageal levels and improvement in endoscopy scores were reported to be statistically significant for all doses of BOS compared to placebo.

Clinical symptoms improved in all treatment groups and across all symptom domains as assessed by the physician-reported EoE Clinical Symptom Score (PAESS). Clinical response (i.e., a ≥50% reduction in symptom scores from baseline) occurred in 77.8%, 64.7%, 78.9% and 52.9% of subjects in the placebo, low, medium and high BOS dose groups, respectively. There were no statistically significant differences among the treatment groups on the clinical symptom response variables. However, the PAESS utilizes scores of children, parents, and physicians into the domain scores, thereby combining multiple concepts (signs/symptoms, coping behaviors/impact) in the same domain. Multiple issues were identified by the COA staff with the use of this instrument, and may have been problematic in assessing symptoms of EoE in a well-defined and reliable way. Advice was given regarding development of an instrument that enables caregiver assessment and self-assessment of core signs and symptoms, among other recommendations. The sponsor then modified their plan by using an agreed upon PRO measure (DSQ) to assess symptoms in MPI-101-06 and the phase 3 program.

MPI-101-06 was a phase 2, randomized, double-blind, placebo-controlled parallel group study to evaluate the efficacy, safety, and tolerability of BOS 2 mg (budesonide 0.2mg/mL) administered twice daily (bid) for up to 12 weeks in adolescent and adult subjects 11 to 40 years of age with EoE and symptoms of dysphasia. The study also included an evaluation of the safety and tolerability of BOS 2 mg once daily during 24 weeks of open label extension (OLE) treatment. For subjects to be eligible, histological evidence of EoE defined as a peak eosinophil count of ≥15 per high power field (HPF) from at least 2 levels of the esophagus had to be present within 10 weeks of the placebo baseline period. Subjects also had to have a history of clinical symptoms of esophageal dysfunction intermittently or continuously, dysphagia on a minimum of 4 days within any 2 of the first 3 weeks during screening and within 2 weeks of randomization.

The co-primary endpoint was a histologic response (Peak eosinophils ≤6/HPF) and a symptom response (change in the 2-week DSQ score from baseline to the final treatment period). At the final treatment evaluation, a statistically significantly greater proportion of subjects in the BOS group vs. placebo was reported to have a peak

eosinophil count ≤6/HPF; 38.8% subjects in the BOS group vs. 2.6% in the placebo group attained a histologic response. BOS was reported to be statistically significantly more effective than placebo in decreasing the mean DSQ score, indicating a reduction in the frequency and severity of dysphasia symptoms.

Secondary efficacy endpoints appeared supportive of the co-primary endpoint results; in particular, the sponsor performed responder analyses with the DSQ as secondary endpoints where a responder was defined as a ≥30% and ≥50% reduction in DSQ score, and both were reported to show a statistically significant difference. While there are no approved therapies using the DSQ, this approach is what the Division has found acceptable as a model to assess efficacy in the sponsor's phase 3 program.

The table below summarizes the results of the efficacy measures obtained in the 12-week blinded therapy of MPI-101-06.

Efficacy Endpoints	Placebo (N=38)	BOS 2 mg bid (N=49)	p-value
Co-primary endpoint (Pathologist reported) **Histologic response** - Peak eosinophils ≤6/HPF [n (%)]	1 (2.6)	19 (38.8)	<.0001
Co-primary endpoint (Subject recorded) **Dysphagia Symptom Questionnaire (DSQ) score** LS mean change from baseline LS mean difference from placebo (95% CI)	-7.53	-14.27 -6.75 (-11.8, -1.7)	0.0096
Histologic response - Peak eosinophils ≤1/HPF [n (%)]	0	15 (30.6)	<.0001
Symptom responders - % reduction in DSQ score ≥30% reduction in DSQ score [n (%)] ≥50% reduction in DSQ score [n (%)]	17 (44.7) 15 (39.5)	34 (69.4) 31 (63.3)	0.0206[c] 0.0275[c]
Overall responders - Histologic + symptoms (dysphagia) Peak eos ≤6/HPF+ ≥30% reduction in DSQ score [n (%)] Peak eos ≤6/HPF+ ≥50% reduction in DSQ score [n (%)]	1 (2.6) 1 (2.6)	13 (26.5) 10 (20.4)	0.0026 0.0199
Histopathology epithelial features (Pathologist reported) LS mean change from baseline LS mean difference from placebo (95% CI)	-1.41	-23.75 -22.34 (-30.3, -14.3)	<.0001
Endoscopy score (Physician reported) LS mean change from baseline LS mean difference from placebo (95% CI)	0.19	-3.58 -3.76 (-5.2, -2.4)	<.0001
Physician Global Assessment (0 to 100 mm) LS mean change from baseline LS mean difference from placebo (95% CI)	-10.16	-28.61 -18.44 (-29.6, -7.3)	0.0015

Source: Sponsor's table reproduced from BTDR submission dated 3/25/2016, pg. 17.

Division assessment: The Divison agrees that the results of MPI-101-01 and MPI-101-06 provide evidence of improvements in EoE symptoms, which represent a clinical benefit to EoE patients. The overall trial results for MPI-101-01 showed statistically significant improvement of the primary endpoint. This finding appears to have been driven by the histologic response as there were no statistically significant differences among the treatment groups on the clinical symptom response variables using the physician reported EoE clinical symptom score assessment. However, the EoE assessment score utilized in this study combined scores of children, parents, and physicians into the domain scores, thereby combining multiple concepts (signs/symptoms, coping behaviors/impact) in the same domain. Therefore, the use of this scale may have been problematic in assessing symptoms of EoE. Regardless, positive trends were reported in clinical symptoms in all treatment groups.

For MPI-101-06, the sponsor claims statistical significance for the changes in score of the DSQ, including responder analyses assessing ≥30% and ≥50% reductions in the DSQ score. Although there are no approved therapies using the DSQ instrument, the Division and COA Staff have accepted that a ≥30% reduction in DSQ score is clinically meaningful.

It appears that BOS has shown effectiveness in reducing eosinophils/HPF in EoE, and some improvements in dysphagia as measured by the DSQ were reported in MPI-101-06. Secondary endpoints, including endoscopy, histopathology, and global assessment of symptoms, appear to be supportive. Therefore the Division agrees that

preliminary clinical evidence indicates that BOS may demonstrate substantial improvement on a clinically significant endpoint, and supports breakthrough therapy designation.

- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

Specific safety of long-term use of steroids (e.g., effects on growth, HPA axis suppression) in a pediatric population has been of concern in this program. Safety and monitoring of potential adverse reactions from chronic glucocorticoid exposure in pediatrics is being assessed in the ongoing phase 3 induction and maintenance trial.

In MPI-101-01, the individual TEAEs most commonly reported in all BOS subjects during the treatment period were pyrexia and cough. Potentially corticosteroid-related TEAEs included two subjects who received BOS (1 subject in the medium dose BOS group, and 1 subject in the high dose BOS group) had a TEAE of candidiasis. Other possible corticosteroid-related events were evenly distributed across the four treatment groups. There were no reported clinically meaningful or dose-related changes in basal cortisol levels throughout the study. In MPI-101-06, during the treatment period, a similar percentage of subjects across the groups experienced a TEAE, the most common event in the BOS group being upper respiratory infection. Overall, 12 subjects experienced 13 potential corticosteroid-related TEAEs (1 subject [placebo/BOS] experienced 2 events, esophageal candidiasis and acne during OLE). No clinically meaningful changes in mean growth velocity value or the gender matched height-for-age Z score were reported during the study (treatment period and OLE), as measured for subjects <18 years of age.

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT :

Provide brief summary of rationale for granting:

Based on review of the clinical data provided, Division recommends that a breakthrough therapy designation be granted for BOS for the treatment of EoE. We agree with the sponsor that BOS is intended to treat a serious or life-threatening disease or condition. There are no available approved therapies for this indication, and preliminary clinical data have demonstrated substantial improvement over existing therapies on 1 or more clinically significant endpoints.

The sponsor has demonstrated that BOS reduces the number of eosinophils/HPF in patients with EoE. While histology alone can not be relied on as a measure of clinical improvement in EoE, there appears to be some improvement in dysphagia as measured by the DSQ; subjects with ≥30% and ≥50% improvement in the DSQ score in the BOS group vs. placebo was shown. Therefore, preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies.

Based on the above outlined reasons, the Division recommends that the breakthrough designation request be granted.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for

traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

12. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The Division has provided guidance to the sponsor regarding their phase 3 induction and maintenance studies. Both protocols have been reviewed and comments communicated, and the induction study is currently ongoing.

For the induction study, the sponsor has proposed a ≥30% change in the DSQ score as a responder definition. This has been found acceptable by both the Division and COA staff as long as it is supported by sensitivity analyses looking at absolute point changes.

Since EoE is a chronic disease that often requires long-term treatment, it is important to evaluate BOS as a maintenance therapy. Understanding the role of BOS in maintenance treatment for this disease is currently unknown and needs to be a component of further study. The proposed maintenance study is designed to inform dosing BOS over long periods (beyond 12 weeks), including whether continued vs. intermittent dosing is needed, particularly in light of concerns over the safety of long-term corticosteroid use.

We intend to continue to work with the sponsor as they conduct their phase 3 trial(s).

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

13. List references, if any: Dellon, E, Gonsalves, N, et.al. ACG Clinical Guideline: Evidenced Based Approach to the Diagnosis and Management of Esophageal Eosinophilia and Eosinophilic Esophagitis (EoE). Am J Gastroenterol 2013; 108:679–692.

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

5-7-15/M. Raggio

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

/s/

PREETI VENKATARAMAN
05/27/2016

LAURIE B MULDOWNEY
05/27/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 103173

MEETING MINUTES

Meritage Pharma, Inc.
Attention: Elaine Phillips, Ph.D.
President & CEO
12555 High Bluff Drive, Suite 385
San Diego, CA 92130

Dear Dr. Phillips:

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

We also refer to the end of Phase 2 meeting between representatives of your firm and the FDA on November 12, 2014. The purpose of the meeting was to review the clinical efficacy findings from study MPI 101-06, a 2-arm placebo-controlled efficacy/safety study with 4 week blinded placebo run-in, 12 week treatment period and 24 week open label extension.

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) 796-1008.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., MBA
Chief, Project Management Staff
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: Type B
Meeting Category: End-of-Phase 2

Meeting Date and Time: November 12, 2014; 4PM – 5PM
Meeting Location: White Oak Bulding #22, Conference Room 1309

Application Number: IND 103173
Product Name: Budesonide Oral Suspension
Indication: Eosinophilic Esophagitis (EoE)
Sponsor/Applicant Name: Meritage Pharma, Inc.

FDA ATTENDEES (tentative)

Donna Griebel, M.D.	Director	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Andrew Mulberg, M.D.	Deputy Director	DGIEP
Robert Fiorentino, M.D.	Medical Team Leader	DGIEP
Preeti Venkataraman, M.D.	Medical Officer	DGIEP
Brian Strongin, R.Ph., MBA	Chief, Project Management Staff	DGIEP
Robert Temple, M.D.	Deputy Director for Clinical Science; Office of the Center Director	
Sue Chih Lee, Ph.D.	Clinical Pharmacology Team Leader Division of Clinical Pharmacology III (DCP III)	
Insook Kim, Ph.D.	Clinical Pharmacology Reviewer	DCP III
Freda Cooner, Ph.D.	Biometrics Team Leader	Division of Biometrics III

SPONSOR ATTENDEES

(b) (4)

Malcolm Hill, PharmD (Chief Scientific Officer, Meritage)
Elaine Phillips, PhD (President and Chief Executive Officer, Meritage)

(b) (4)

BACKGROUND

IND 103173 for Budesonide Oral Suspension (OBS), was submitted August 4, 2008 by Meritage Pharma, Inc. The following meetings have been held between Meritage and the Agency concerning this IND:

End of Phase 2 meeting	11/8/10
Type C Meeting	7/17/12
Type C Meeting	8/17/13

Meritage has completed the treatment period of the phase 2 study MPI-101-06, a 2 arm, placebo-controlled, efficacy/safety study with a 4 week blinded placebo run-in, 12 week treatment period and a 24 week open labeled extension. The study endpoints are:

- Change in the two-week Dysphagia Symptom Questionnaire (DSQ) score from the Baseline period to the Final Treatment Evaluation
- Proportion of subjects who are histologic responders. For each subject histologic response will be defined as a peak eosinophil count of less than or equal to 6HPF across all esophageal levels at the Final Treatment Evaluation.

Meritage has requested this meeting to discuss the clinical efficacy findings from Study MPI-101-06 and to request FDA concurrence with the clinical development program.

DISCUSSION

Question 1a: Does the Agency agree with the use of the DSQ instrument to measure the clinical endpoint in the phase 3 study?

FDA Response:

Yes. You are progressing in the right direction with your continued improvement and revision to the DSQ.

We have the following comments regarding the content validity of the DSQv5:

1. (b) (4) **question "Since you woke up this morning, did you eat solid food?" from version 5. Our understanding was that this question would be included in the DSQ, but not in the co-primary endpoint score.**
2. **It is our understanding that you propose the passing slowly/difficulty swallowing domain as a co-primary endpoint. Please confirm.**
3. **Please provide your rationale for designating the pain on swallowing domain as exploratory, rather than as a key secondary endpoint.**
4. **We are concerned that because there is no recall period stated for the pain on swallowing question in version 5, as compared with the difficulty**

swallowing question, patients may interpret the recall period differently (e.g., the worst pain they have ever had) which would add variability into the assessment.

Discussion:

Sponsor:

Item#1: (b) (4)

FDA recommended assessing for this question even if not used in the primary analysis. The sponsor agreed.

Item #2: Sponsor confirmed that the "passing slowly/difficulty swallowing domain" will be a co-primary endpoint for the planned phase 3 trial.

Item #3: Sponsor stated that based on previous data, pain is not a key symptom in their study populations and that they are not seeking labeling claims for pain on swallowing.

Item #4: Sponsor acknowledged FDA's concern and proposed to reword this question (to "while swallowing food today").

Question 1b: Does the Agency agree with the proposed co-primary endpoints for the phase 3 study?

FDA Response:

We agree that the study should be designed to show statistically significant differences vs. placebo in the proportion of responders based on both the DSQ score and number of eosinophils on histology. However, given the new phase 2 data presented and revisions to the DSQ during development, please provide your rationale that a ≥30% reduction in DSQ from baseline (e.g., as opposed to ≥50%) is still clinically meaningful for a phase 3 trial. We note that the proportion of responders who had a ≥50% reduction in DSQ from baseline was similar to those who had a ≥30% reduction compared to placebo.

We would also note that the data presented in Figure 5 (page 40) of the meeting package suggest that some subjects may benefit from receiving OBS beyond 12 weeks of treatment since the size of the observed treatment effect was still increasing out to the Week 16 assessment. Consider designing your study to evaluate whether continued treatment should be given to subjects who are not responders after 12 weeks of treatment.

In addition, as recommended in our meeting on July 17, 2012, since EoE is a chronic disease that often requires long-term treatment, it is important to evaluate OBS as a maintenance therapy. The open-label phase will not

provide robust data to inform dosing OBS over long periods (beyond 12 weeks), including whether continued vs. intermittent dosing is needed, particularly in light of concerns over the safety of long-term corticosteroid use. Further, the open-label phase isn't designed to provide data on how or when to re-dose patients if their EoE clinically relapses upon discontinuation of OBS treatment. A randomized, controlled withdrawal phase in those subjects who are responders could assess persistence of effect, as well as characterize the incidence of relapse and need for re-dosing.

In your phase 3 protocol synopsis you note that during the open label extension, the dose of OBS may be increased from qhs dosing to BID dosing at the investigator's discretion. However, for purposes of providing informative data (or labeling) on such a dose escalation regimen, it would be useful to evaluate dose escalation in a well-designed manner (e.g., in a blinded fashion with re-randomization to qhs vs. BID).

Discussion:

Sponsor reiterated their primary endpoint model; they plan to test the histologic endpoint first and the DSQ endpoint next, in a sequential fashion. Study success will require that both of these endpoints are statistically significant vs. placebo. The sponsor reiterated their plan to perform a secondary endpoint analysis using a ≥50% reduction in DSQ and the FDA noted that this endpoint could represent a more persuasive clinical benefit, (b) (4) (b) (4)

FDA expressed concern that the open-label portion of the proposed trial would not definitively support the need for maintenance therapy beyond 12 weeks, as also noted in FDA's preliminary comments. With regard to withdrawing subjects from active treatment, the sponsor stated that they have preliminary data from the completed phase 2 trial (Study 06) that indicates that subjects predictably lose response if they are withdrawn from treatment. FDA indicated that they would need to review these data to provide more definitive comment on the proposed phase 3 trial design but expressed concern that loss of response appeared to be based on a "physician global assessment" rather than the DSQ. FDA mentioned that it may be helpful to administer the DSQ for a week at specified time points during the open label extension period with the possibility of using reminders to maximize patient compliance with completion of the DSQ. In addition, these data may inform whether or not the phase 3 trial should incorporate a randomized withdrawal design to placebo or alternatively a randomized dose-reduction design (e.g., 2mg BID to qD).

A number of trial designs were discussed; the FDA requested that the sponsor consider whether proposed trials are designed to determine that continued, chronic corticosteroid treatment is warranted, including what is the most

appropriate maintenance dose. FDA requested that the phase 2 study results be submitted to the FDA for review prior to initiation of the phase 3 trial; further discussion on revised phase 3 trial designs or protocols may be warranted.

Towards the end of the meeting, the sponsor offered a study design in which subjects who were randomized to OBS 2 mg bid in the 12 week treatment period (and are responders) are re-randomized to the two arms OBS 2 mg bid vs. placebo ((b) (4)) in the 36 week extension period. FDA acknowledged that in general this could represent an acceptable approach, however the protocol would need to be reviewed internally.

Question 2: Does the Agency agree that the size of the proposed safety database is adequate to support registration of OBS in the treatment of this orphan population?

FDA Response:

The size of the safety database in your proposed development program (including the planned phase 3 trial) could be adequate to support efficacy. However, since the safety of OBS may be dependent on the duration of therapy, you would have to submit data that characterizes the safety of the proposed dosing regimen over the anticipated duration of use (see our response to Question 1b). It is not clear at this time if data from other referenced budesonide products will be sufficient if the referenced budesonide exposures and disease indications are different than your product. The adequacy of the safety database submitted for supporting approval will be determined when the application is reviewed. We also recommend that you give the FDA sufficient time to review your planned phase 3 study protocol prior to initiation so that we can provide more definitive feedback.

Discussion: See discussion following questions 1a and 1b

Question 3: Does the Agency agree that the proposed relative bioavailability study, MPI 101-02, supports registration based on a 505(b)(2) submission?

FDA Response:

We note that comparison of PK of budesonide in OBS is planned with that of Entocort EC (b) (4) mg, although Entocort is approved for either 9 mg once daily or 6 mg once daily. We do not agree that the proposed relative BA study can be used to bridge the safety information in Entocort EC. We recommend that in the relative BA study Entocort EC be used at the approved dose. We note that due to the differences in target population and the age of patients

between OBS and Entocort EC, reliance on the safety of Entocort EC based on a relative BA study may be limited. Please see our response to Question 2.

According to the backgrounder, the formulation MB-7, which is different from the to-be-marketed formulation, was used for both the 28-day nonclinical studies and the MPI 101-01 study. You should address how the formulation difference between MB-7 and the to-be-marketed formulation affect the interpretation of the 28-day nonclinical studies and the PK study in pediatric patients done in Study MPI 101-01.

We recommend that PK be characterized in adult patients with EoE in the proposed study and that elderly patients be enrolled in the trial if the proposed product is likely to be used by the elderly patients. Your rationale to exclude the elderly patients in the clinical trials is unclear.

We recommend that the potential effects of budesonide on concomitant drugs via inhibition of various CYP enzymes and transporters be addressed.

We recommend that drug interaction potential via induction of CYP enzymes be addressed as glucocorticoids have been reported to induce CYP enzymes. The potential effects of budesonide on induction of transporters should also be addressed.

Discussion: none

Question 4: Does the Agency agree that the planned OBS development program, including the data from the 2 completed studies, will support registration with the proposed indication?

FDA Response:

A confirmatory phase 3 trial will be needed to support approval of OBS for EoE. If the co-primary endpoints are successfully achieved in the proposed phase 3 study, the data could be used to support approval. However, see our response to previous questions regarding the design of your phase 3 trial.

Discussion: See discussion following questions 1a and 1b

Questions 5. Based on the results of the 2 completed studies and the favorable benefit-risk assessment of OBS, would the Agency be amenable to granting a pre-NDA meeting upon completion of the open label portion of MPI 101-06?

FDA Response:

No, we do not agree. Although the findings of Study MPI 101-06 could be used to support efficacy, a confirmatory phase 3 trial will be needed. The clinical outcome of Study MPI 101-06 was not highly statistically persuasive (e.g., p-value <0.001) and reproducibility of these findings will be needed. Further, we are still in the process of understanding the use of the DSQ as a measure of dysphagia in EoE, a disease in which lack of correlation between histologic findings and clinical response remains vexing, as is an incomplete understanding of the natural history of the disease (and expectations regarding what constitutes treatment response). In addition, understanding the role of budesonide in maintenance treatment for this disease is currently unknown and will be a component of further study.

Additional FDA Comments:

(b) (4)

d. In the phase 2 trial MPI 101-06, please clarify how many patients ingested solid foods on a daily basis during the diary period (i.e., Question 1 of the DSQ), as well as if missing data originated from subjects who had food avoidance. Also, as future trials may involve pediatric patients, please provide data regarding how children versus adolescents responded to the DSQ question regarding pain (Question 4 of the DSQ).

e. The effects of puberty may artificially increase or decrease BMD (i.e., a child with delayed puberty would appear to have an artificially low BMD Z-score for chronological age.). BMD Z-scores should be adjusted for height z-scores, to correct for the effects of growth. These can be calculated at the BMDCS website: http://www.bmdcspublic.com/zscore.htm.

The following comments concern the growth assessment. For further information, please also refer to Guidance for Industry: Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071968.pdf

- **The interpretation of growth data can be limited by a child's growth velocity undergoing normal physiological acceleration associated with puberty.** (b) (4) **to account for pubertal timing, you would also need to use alternative growth charts (e.g., Bayer and Bailey).**

- **The first measurable sign of puberty in girls can be the beginning of the growth spurt, and it can precede the onset of secondary sexual characteristics by as much as 1 year (Kaplan and Love 2001; Kulin 1996). In addition, in post-menarchal females, linear growth is negligible (1-2 inches/yr). Therefore, it would be important to ensure that pre-menarchal females are identified and included in the growth assessments.**

- **There are conflicting statements in the literature about the timing of the growth spurt in boys relative to the onset of secondary sexual characteristics. Nevertheless, we recommend Tanner staging, including breast and testicular exams, be documented by an experienced investigator in all patients during**

physical exam visits. In addition, stratified randomization based on age and sex is recommended to help balance the percentage of patients whose pubertal growth spurt may have already begun during the baseline period or will begin during the treatment period.

- **We recommend that a stadiometry measurement is taken at the open label extension (OLE) 24 week visit to avoid "skewing" of the results secondary to too short (i.e. at Final Treatment Evaluation) or too long intervals (i.e., at Final OLE Evaluation).**

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.

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. 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.

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.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

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

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.

ISSUES REQUIRING FURTHER DISCUSSION

None

ACTION ITEMS

FDA requested that Meritage submit the phase 2 study results for review prior to initiation of the phase 3 trial; further discussion on revised phase 3 trial designs or protocols may be warranted.

ATTACHMENTS AND HANDOUTS

Sponsor slides

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

/s/

BRIAN K STRONGIN
11/30/2014