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APPLICATION NUMBER:

213976Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	213976
Priority or standard	Priority
Submit date(s)	8/22/2023
Received date(s)	8/22/2023
PDUFA goal date	2/22/2024
Division/office	Division of Gastroenterology (DG)
Review completion date	2/8/2024
Established/proper name	Budesonide
(Proposed) proprietary name	Eohilia
Pharmacologic class	Corticosteroid
Other product name(s)	TAK-721/SHP621
Applicant	Takeda Pharmaceuticals U.S.A. (Takeda)
Dosage form(s)/formulation(s)	Oral suspension
Dosing regimen	2 mg (2 mg/10 mL unit-dose packet) orally twice a day
Applicant-proposed indication(s)/population(s)	Short-term treatment of eosinophilic esophagitis (EoE), (b) (4) in adult and adolescent patients 11 years and older
SNOMED CT code for proposed indication disease term(s)^a	Eosinophilic esophagitis (235599003)
Regulatory action	Approval
Approved dosage (if applicable)	2 mg orally twice a day
Approved indication(s)/population(s) (if applicable)	For 12 weeks of treatment in adult and pediatric patients 11 years of age and older with eosinophilic esophagitis (EoE)
SNOMED CT code for approved indication disease term(s)^a	Eosinophilic esophagitis (235599003)

^a For internal tracking purposes only.

Abbreviations: NDA, New Drug Application; PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

ACTH	adrenocorticotrophic hormone
AE	adverse event
AETERM	adverse event term
ANCOVA	analysis of covariance
AUC	area under the concentration-time curve
BID	twice daily
BLA	biologics license application
BOS	budesonide oral suspension
BTD	Breakthrough Therapy Designation
CI	confidence interval
C _{max}	maximum plasma concentration
COA	clinical outcome assessment
CR	complete response
CYP	cytochrome P450 enzyme
DARRTS	Document Archiving, Reporting and Regulatory Tracking System
DSQ	Dysphagia Symptom Questionnaire
EGD	esophagogastroduodenoscopy
EoE	eosinophilic esophagitis
EREFS	EoE Endoscopic Reference Score
FAS	full analysis set
FDA	U.S. Food and Drug Administration
GERD	gastroesophageal reflux disease
GM-CSF	granulocyte macrophage colony stimulating factor
HPF	high-power field
IL	interleukin
IND	investigational new drug
IP	investigational product
ITT	intent-to-treat
LD	listed drug
MH	Mantel-Haenszel
mITT	modified intent-to-treat
NDA	new drug application
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OLE	open-label extension
OPQ	Office of Pharmaceutical Quality
P-gp	P-glycoprotein
PGIC	patient global impression of change
PGIS	patient global impression of severity
PI	prescribing information
PK	pharmacokinetic
PPI	proton pump inhibitor
PT	preferred term

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Eohilia (budesonide oral suspension)

QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
TBM	to-be-marketed
TEAE	treatment-emergent adverse event

I. Executive Summary

1. Summary of Regulatory Action

This class 2 resubmission of new drug application (NDA) 213976 for budesonide oral suspension (BOS, also known as SHP621/TAK-721; proposed trade name of Eohilia) was submitted by Takeda Pharmaceutical USA on August 22, 2023.

The original NDA submission, which sought approval of BOS for “the treatment of eosinophilic esophagitis (EoE) (b) (4) in adult and adolescent patients 11 years and older,” was received by the Food and Drug Administration for review on October 15, 2020. In the NDA, the Applicant proposed to rely, in part, upon FDA’s findings of safety as reflected in the approved product labeling for the listed drug (LD), Entocort EC (budesonide) delayed-release capsules (NDA 021324) ([Perrigo Pharma International DAC 1997](#)), as well as published literature, as permitted in Section 505(b)(2) of the Federal Food Drug and Cosmetic Act. A complete response (CR) action was issued for the original submission on December 17, 2021 due to the following reasons:

- The benefit of long-term treatment with BOS for patients with EoE was not established. The 36-week extension clinical trial, SHP621-302 (Trial 302), did not yield statistically significant results for the prespecified long-term efficacy endpoint of relapse on both histology and symptoms in the individual subject.¹
- The anchor-based analyses conducted for Trial SHP621-301 (Trial 301) did not support that the statistically significant results of the symptomatic coprimary² and key secondary efficacy endpoints tested after 12 weeks of treatment represented clinically meaningful change.
- Although a statistically significant result was observed for the histologic coprimary endpoint in Trial 301 after 12 weeks of treatment, there were inadequate data to demonstrate that short-term improvement in histologic remission³ predicts improvement in meaningful clinical outcomes. The ability of this finding to contribute to a demonstration of benefit for

¹ Relapse was defined by the Applicant as a subject meeting both the eosinophil histology relapse criterion (i.e., an eosinophil count of ≥ 15 per high power field from ≥ 2 of 3 levels of the esophagus, as determined by a central reader’s evaluation of esophagogastroduodenoscopy [EGD] biopsy tissues) and the dysphagia symptom relapse criterion (defined as a minimum of 4 days of dysphagia in the 2-week period prior to the scheduled visit, as determined by the Dysphagia Symptom Questionnaire [DSQ] Question 2) at any time during the trial.

² The symptomatic coprimary endpoint assessed in Trial 301 was a 30% reduction in the DSQ combined score after 12 weeks of treatment. Although the $\geq 30\%$ DSQ responder threshold was carried forward for use in phase 3 (based on phase 2 data) and statistically significant results were demonstrated for this analysis; 112/213 (52.6%) subjects who received BOS versus 41/105 (39.1%) subjects who received placebo, $p=0.024$; the Applicant was counseled several times regarding concerns with the $\geq 30\%$ DSQ responder threshold and that phase 3 data analyses and sensitivity analyses would be needed to confirm this responder threshold as clinically meaningful (i.e., communications under reference investigational new drug [IND] 103173: the November 12, 2014, type B end-of-phase 2 meeting; a September 3, 2015, email to the Sponsor; a September 15, 2015, advice/information request letter; a February 15, 2018, advice/information request letter; a September 17, 2018, advice/information request letter; a February 7, 2019, advice/information request letter; and the May 20, 2020, type B pre-NDA meeting).

³ In the BOS development program, histologic remission was defined as an eosinophil count of ≤ 6 per high power field.

the long-term treatment of EoE was further degraded by the lack of sustained histologic remission in Trial 302. Specifically, Trial 302 did not yield statistically significant results on the prespecified long-term efficacy endpoint of histologic remission at Week 36 in subjects that continued to receive BOS 2 mg twice daily after Trial 301, compared to those who received BOS 2 mg twice daily in Trial 301 and placebo in Trial 302.

For details related to the CR action and multidisciplinary review of the original submission, refer to the December 17, 2021 CR letter (Document Archiving, Reporting and Regulatory Tracking System [DARRTS] Reference ID: 4906609) and the December 17, 2021 integrated review of NDA 213976 (DARRTS Reference ID: 4907153).

In this resubmission, the Applicant is seeking a novel indication limited to the short-term treatment of EoE, (b) (4) in adult and adolescent patients 11 years and older. The review team acknowledges that EoE is a chronic condition for which long-term treatment is needed, and a proposal for a short-term treatment indication for a chronic condition should be carefully considered.

On May 20, 2022, dupilumab, a fully human monoclonal antibody which binds to interleukin (IL) 4 receptor alpha subunit (IL 4R α) and blocks signaling of IL 4 and IL 13, was approved for the treatment of EoE in patients who are 12 years of age or older (adolescents and adults), weighing ≥ 40 kg. On January 25, 2024, the indication for dupilumab was expanded to include adults and pediatric patients who are 1 year of age and older, weighing ≥ 15 kg, with EoE. The current standard of care for EoE also includes adherence to restricted diets, such as a full liquid diet with elemental formula or a six-food elimination diet (SFED). In addition to these therapies, clinical consensus guidelines recommend consideration for off-label therapy with proton pump inhibitors (PPIs); corticosteroid products developed as orally-inhaled drugs for the treatment of asthma; and systemically-acting corticosteroids, such as prednisone, for more severe or recalcitrant disease ([Hirano et al. 2020](#)). Due to the potential for significant toxicity, long-term use of systemic corticosteroids is generally not recommended. To provide local action on the esophageal mucosa, available orally-inhaled corticosteroid products are modified by patients and caregivers through homemade slurry preparations that are swallowed (e.g., mixing contents of inhaled products for asthma with Splenda, honey, or other sweeteners). This approach results in unstandardized dosing with products that have not been established to be safe or effective for the treatment of EoE.

Despite recent advances, patients with EoE continue to face significant challenges. For those unable or disinclined to initiate treatment with dupilumab, restricted diets remain a preferred approach. Reported response rates with full elemental diets vary from 72-97% across adult and pediatric populations ([Liacouras et al. 2005](#)) ([Peterson et al. 2013](#)). However, even short-term compliance with these diets is challenging. In the study by Peterson et al., 11/29 (38%) adult subjects failed to adhere to the diet over the 4-week assessment period. Less restrictive diets (e.g., SFED [dairy, wheat or gluten, eggs, legumes, nuts, and seafood], 4-food elimination diet [dairy, soy, egg, and wheat], 1-food elimination diet [dairy], patient-specific targeted elimination diets) can enhance compliance but can require several trial periods to identify triggers and evaluate efficacy after each elimination or adjustment. In general, patients are instructed to maintain a stable diet for a period of 6 to 8 weeks prior to each assessment, and the identification of trigger foods is most evident when patients begin trials of dietary therapy while in a state of remission ([Mayerhofer et al. 2023](#)) ([Gonsalves et al. 2012](#)). The availability of effective short-term therapy could allow patients to complete dietary trials without first needing to comply with

a highly restrictive or elemental diet to induce remission. In this way, effective short-term therapies have the potential to be used as an initial bridge to the identification and implementation of less restrictive dietary strategies that are successful for the individual patient and can be maintained long-term. Availability of effective short-term therapy could also increase patient willingness to explore targeted dietary management by providing an option to initiate treatment to relieve symptoms that develop after unsuccessful reintroduction of foods. Additionally, although few studies have assessed combined therapy with restricted diets and topical corticosteroids, available data suggest that, in addition to facilitating identification of successful restrictive dietary measures, use of a corticosteroid during initial implementation of a restricted diet could lead to an enhanced response, which could also increase compliance and patient willingness to explore long-term management strategies that rely solely upon dietary restrictions ([Reed et al. 2018](#)).

It is important to note that work is ongoing to better characterize the natural history of EoE and impact of effective interventions. A recent report described maintenance of sustained off-treatment remission in a cohort of children with EoE who achieved clinical and histologic remission with elimination diets despite re-introduction of all previously identified and eliminated food triggers ([Hoofien et al. 2020](#)). Additional studies reported sustained remission following treatment with topical corticosteroids ([Uchida et al. 2023](#)) ([Dellon and Hirano 2018](#)) ([Shaheen et al. 2018](#)) ([Assa'ad et al. 2007](#)). Among subjects randomized to receive placebo in Trial 302 after receiving BOS in Trial 301, 7/23 (30%) subjects were noted to have maintained histologic remission and 18/23 (78%) subjects met the Applicant's specified definition of "symptomatic response to Trial 301 baseline" during the Week 36 assessments. Refer to the multidisciplinary December 17, 2021 integrated review of NDA 213976 (DARRTS Reference ID: 4907153) for details. The favorable histologic findings observed in subjects following administration of placebo for 36 weeks in Trial 302 highlights the existing knowledge gap surrounding the natural history of EoE and uncertainty regarding whether intermittent treatment to quell acute flares could represent a suitable option for some patients with EoE.

Also as described in the multidisciplinary December 17, 2021 integrated review, data from Trial 302 do not support a benefit for long-term treatment with BOS in subjects with EoE. As stated above, a substantial proportion of subjects treated with BOS in Trial 301 who discontinued BOS in Trial 302 maintained favorable results on efficacy assessments conducted following 36 weeks of placebo treatment in Trial 302. Furthermore, 12/25 (48%) subjects who continued BOS in Trial 302 did not maintain histologic remission that was previously achieved in Trial 301. These findings are consistent with reports of increases in esophageal eosinophilia despite continued therapy with topical corticosteroids described in recent publications ([Collins et al. 2019](#)) ([Eluri et al. 2017](#)) ([Greuter et al. 2018](#)). The observed loss of histologic remission with corticosteroid products over time introduces concerns regarding the suitability of their use long-term.

The role of a corticosteroid product as a short-term therapy to be used in patients with EoE is further supported by experience with approved corticosteroid products for short-term use in other chronic inflammatory conditions (e.g., inflammatory bowel disease). For these chronic conditions, although long-term therapy with corticosteroids is discouraged due to the associated adverse reactions and long-term toxicity, and in favor of more specific disease-modifying therapies, the role of corticosteroids for short-term therapy has been well-established to provide rapid reduction of inflammation and induction of remission ([Lichtenstein et al. 2006](#)) ([Barrett et al. 2018](#)) ([Bruscoli et al. 2021](#)).

Accordingly, the review team determined that, in the context of NDA 213976, the combined therapeutic context; existing needs of patients with EoE; available data from both short- and long-term trials of BOS, natural history studies, and trials of other corticosteroid products presented in published literature; and mechanistic rationale provided by the substantial experience with the drug class in other chronic inflammatory gastroenterological conditions were adequate to support the suitability of a limited indication for BOS as a short-term therapy for patients with EoE. Discussions with key opinion leaders and clinicians specializing in the care of patients with EoE, following the December 17, 2021 CR action for the original submission of NDA 213976, confirmed the review team's assessment that there is a role for a corticosteroid product as a short-term therapy to be used in patients with EoE to quell acute flares and/or to function as a bridge to effective long-term management strategies.

Consideration for a short-term indication for BOS for the treatment of EoE is consistent with language included in the guidance for industry *Eosinophilic Esophagitis Developing Drugs for Treatment* (September 2020) ([FDA 2020](#)):

The trial duration and timing of efficacy assessments should be guided by the goal of therapy, the mechanism of action of the drug and its expected onset of action, and the time frame in which a clinical benefit is expected to be observed.

The resubmission of NDA 213976 is not proposing chronic administration of BOS, and the review team is recommending inclusion of the following limitation of use statement in the INDICATIONS AND USAGE section of the prescribing information (PI) based on the available data:

EOHILIA has not been shown to be safe and effective for the treatment of EoE for longer than 12 weeks [see *Dosage and Administration (2.1)*, *Clinical Studies (14)*].

To support this statement, the review team is also recommending inclusion of a description of Trial 302 in Section 14 (CLINICAL STUDIES) of the PI as an additional study.

After completing Study 1, 48 subjects from the EOHILIA 2 mg treatment arm entered a double-blind randomized withdrawal extension study. These subjects received EOHILIA 2 mg BID or placebo for up to an additional 36 weeks. Treatment with EOHILIA did not demonstrate a statistically significant difference compared to subjects re-randomized to placebo for prespecified efficacy endpoints based on eosinophil count and/or clinical symptoms measured by the DSQ at Week 36.

The short-term indication proposed in the resubmission is supported by data from two adequate and well-controlled 12-week clinical trials, MPI 101-06 (Trial 101-06) and Trial 301. Conversely, the evaluation of efficacy in the original October 15, 2020 NDA submission was based on data from a 12-week phase 3 clinical trial (Trial 301) and a 36-week extension phase 3 clinical trial (Trial 302). Although described and reported independently, Trials 301 and 302 were conducted with a shared trial population. The data from Trial 101-06 were included in the original NDA submission and contributed to the review team's evaluation of safety. However, because Trial 101-06 was limited to only 12 weeks of double-blind, placebo-controlled

treatment, these data were not adequate to inform an evaluation of efficacy for BOS for the long-term treatment indication (i.e., beyond 12 weeks) proposed by the Applicant in the original submission of the NDA. Because this resubmission is seeking a limited indication for short-term treatment only (i.e., 12 weeks of treatment), data from Trials 101-06 and 301 are both relevant and adequate to inform the benefit-risk assessment for the proposed indication.

Trials 101-06 and 301 yielded statistically significant results for their multiplicity-controlled prespecified analyses of efficacy endpoints of histologic remission (defined as a peak eosinophil count of ≤ 6 per HPF) and reduction in dysphagia symptoms (utilizing the Dysphagia Symptom Questionnaire [DSQ]). The DSQ is a clinical outcome assessment (COA) designed to be administered daily to evaluate the occurrence of dysphagia over a 14-day assessment period. However, because small but statistically significant group-level mean differences in a COA endpoint may not represent a clinically meaningful effect to patients, the guidance for industry *Eosinophilic Esophagitis: Developing Drugs for Treatment* (September 2020) ([FDA 2020](#)) recommends the use of anchor-based methods to aid in the interpretation of the clinical meaningfulness of COA endpoint results for clinical trials of drugs for the treatment of EoE.

Anchor-based methods remain the review team's preferred and recommended approach to inform clinically meaningful within-patient changes in COA endpoint scores, and these methods were utilized to interpret the clinical meaningfulness of both the $\geq 30\%$ 14-day DSQ responder threshold specified by the Applicant as the symptomatic coprimary endpoint and the prespecified alpha-controlled secondary endpoint of absolute change from baseline in DSQ combined score for Trial 301 during the original review of NDA 213976.

While data from Trial 101-06 were not adequate to inform an evaluation of BOS for the long-term treatment of EoE, as stated above, these data are adequate and informative of the evaluation of benefit for the newly proposed short-term indication. Although both Trials 101-06 and 301 reported statistically significant results for BOS compared to placebo on the common symptomatic efficacy endpoint of absolute change on the DSQ (coprimary in Trial 101-06 and key secondary in Trial 301), multiple factors precluded the use of anchor-based analyses to inform the clinical meaningfulness of the COA endpoint results in this resubmission. For example, each trial included a different anchor scale. Trial 101-06 included only a patient global impression of change (PGIC) scale with a 12-week recall period, whereas Trial 301 included only a patient global impression of severity (PGIS) scale with a 7-day recall period. The use of discordant anchors prevented an assessment of comparability across the trials. The inconsistent assessment periods between the anchor scales (12 weeks PGIC or 7 days PGIS) and the DSQ (14 days) also introduced uncertainty in the ability of the results of anchor-based analyses to support the interpretation of the COA endpoint results for either trial. Additionally, the majority of subjects in Trial 301 reported mild or moderate dysphagia symptom severity at baseline as assessed by the PGIS. The results of the anchor-based analyses indicated that, compared to subjects reporting severe or very severe dysphagia symptom severity at baseline, a larger change in DSQ combined score was necessary for subjects with mild or moderate baseline dysphagia symptom severity to experience a meaningful change of a one-category improvement on the PGIS. For full details related to the review of the anchor-based analyses based on Trial 301 data from the original NDA submission, refer to the multidisciplinary December 17, 2021 integrated review of NDA 213976 (DARRTS Reference ID: 4907153).

Due to the statistically significant results of the symptomatic efficacy endpoints, and in consideration of the existing need for short-term therapy in patients with EoE to quell acute flares and/or to function as a bridge to an effective long-term management strategies, the review team determined that it is appropriate to consider whether an alternate metric with inherent clinical meaningfulness (i.e., achieving no dysphagia or experiencing only dysphagia that “got better or cleared up on its own”) could aid in the interpretation of the available efficacy data in lieu of anchor-based analyses. To aid in the interpretation of the favorable results of the COA endpoints from these trials, the review team requested that the Applicant provide analyses of DSQ Question 2 (Q2: “Since you woke up this morning, has food gone down slowly or been stuck in your throat?”⁴) =0 (“No”) and DSQ Question 3 (Q3: “For the most difficult time you had while swallowing food today, did you have to do anything to make the food go down or to get relief?”) =0 (“No, it got better or cleared up on its own.”). Qualitative data generated during the development of the DSQ established the meaningfulness of these concepts and the representative terminology used in the items in the DSQ (i.e., Q2 and Q3), and post-development qualitative data from EoE development programs utilizing the DSQ (e.g., BOS, dupilumab) continue to support the content validity of the instrument, items, and response options. Of note, achieving Q3=0 also includes subjects who achieved no dysphagia (Q2=0), because when a subject responded “No” to Q2, they automatically received a score of 0 for Q3. The review team would not have considered the exploration of these additional assessments had either trial reported numerically nonsignificant results for the COA endpoint analyses or if the significant results had not been appropriately controlled for multiplicity.

While the Applicant conducted and submitted multiple post hoc analyses following issuance of the initial discipline review letter on March 19, 2021, and subsequent CR letter (December 17, 2021), assessments of Q3=0 were neither conducted nor proposed prior to the review team’s request. The assessment of Q3=0 was one of two analyses identified by the review team as a metric with inherent clinical meaningfulness during internal discussions; achieving no dysphagia was the other assessment. These analyses were requested by the review team without any foreknowledge of the results from either Trial 101-06 or Trial 301. Additionally, when the review team identified this alternate metric, Trial 101-06 had not been considered or positioned as an adequate and well-controlled trial by the Applicant.

While there was a trend seen on the FDA-requested assessment of no dysphagia (Q2=0), the results did not achieve the standard threshold used for defining statistical significance (i.e., $p < 0.05$). This finding is likely attributable to the small proportion of subjects meeting the stringent threshold of achieving complete resolution of all dysphagia episodes during the last 2 weeks of the 12-week treatment period. Conversely, although also limited by its lack of prespecification, analyses of DSQ Q3=0 showed that a greater proportion of subjects randomized to BOS reported no dysphagia or only experienced dysphagia that “got better or cleared up on its own” compared to placebo in both Trial 101-06 ($p = 0.0039$) and Trial 301 ($p = 0.0257$).

The demonstration of effectiveness of BOS for the short-term treatment of EoE is based on the statistically significant results for the prespecified endpoints of histologic remission and absolute change from baseline in DSQ combined score, supported by the results of the Q3=0 assessment. The strength of the evidence to support this determination is increased by the independent replication of results of efficacy assessments across the two 12-week trials (i.e., Trials 101-06

⁴ Question 2 in the version of the DSQ included in Trial 101-06 included the words “throat or chest.”

and 301). Considered collectively, the review team determined that these findings are adequate to support that treatment with BOS resulted in clinical benefit in subjects with EoE.

Regarding the evaluation of risk, BOS is an oral formulation of budesonide, a corticosteroid product with a well-established safety profile as reflected in the PI for the LD, Entocort EC (budesonide) delayed-release capsules (NDA 021324) ([Perrigo Pharma International DAC 1997](#)). Corticosteroid class effects include upper respiratory tract infection, headache, sinusitis, nausea, vomiting, dyspepsia, hypertension, increased weight, psychiatric disturbance, increased transaminases, adrenal suppression, and hypercorticism. Although the observed safety profile for BOS was largely consistent with the known safety profile of the LD and class effects of corticosteroid products, additional adverse reactions emerged during the safety review including gastrointestinal mucosal candidiasis, throat irritation, and erosive esophagitis.

Although both EoE and erosive esophagitis can present with symptoms of esophageal dysfunction (e.g., difficulty swallowing, pain, nausea, vomiting, regurgitation), in the absence of concomitant erosive esophagitis, esophageal erosions are not typically seen on endoscopic evaluation in patients with EoE. The most common endoscopic findings in patients with EoE include edema, rings, exudates, furrows, and strictures ([Kia and Hirano 2015](#)). During review of the safety data from Trial 301, esophageal erosions were found in four subjects during esophagogastroduodenoscopy (EGD) after 12 weeks of treatment with BOS. No subjects who received placebo were noted to have developed erosive esophagitis at the 12-week EGD, and none of the four BOS-treated subjects who developed erosive esophagitis had erosions at the baseline EGD. Notably, two of the four subjects had achieved histologic remission (defined as a peak eosinophil count of ≤ 6 per HPF) of their EoE at the time of erosive esophagitis diagnosis. Additionally, three of the four subjects found to have developed erosive esophagitis were receiving concomitant therapy with a PPI throughout the trial (two for the off-label treatment of EoE, and one for the treatment of symptomatic gastroesophageal reflux disease [GERD]). There is a known risk for corticosteroid products to cause or worsen acid-related disorders, such as GERD or erosive esophagitis. However, given the significant overlap in clinical symptoms of EoE, which may delay appropriate diagnosis and treatment of erosive esophagitis, as well as the development of erosive esophagitis in subjects while they were taking an established effective treatment for erosive esophagitis (i.e., concomitant PPI), the review team determined that the addition of a WARNINGS AND PRECAUTIONS section to the PI was appropriate and necessary to inform patients and prescribers of the risk for developing erosive esophagitis while taking BOS and the importance of reporting new or worsening signs or symptoms that may prompt additional endoscopic evaluation. See Section [7.7.3](#) for additional details.

Overall, the identified risks of treatment with BOS can be mitigated through labeling and monitored during routine pharmacovigilance.

As described above and in the [Benefit-Risk Framework](#), the overall benefit-risk is favorable. Therefore, the review team recommends approval of BOS for 12 weeks of treatment of adult and pediatric patients 11 years of age and older with EoE. For detailed information supporting the basis for this approval, refer to the reviews included in this multidisciplinary integrated review and the February 2, 2024 Product Quality Review (DARRTS Reference ID: 5321811).

BOS was granted Orphan Designation (ODD 06-2274) and is therefore exempt from the Pediatric Research Equity Act requirements to conduct pediatric studies. However, because EoE is a serious condition affecting younger pediatric patients as well as older pediatric and adult

patients, the review team requested the Applicant agree to a postmarketing commitment to conduct a randomized, double-blind, placebo-controlled clinical trial to evaluate the safety, efficacy, and pharmacokinetics of BOS in pediatric patients less than 11 years of age. The review team expressed the importance of the proposed pediatric trial in consideration of the need for therapies for younger patients with EoE and stated that the proposed study could have the potential to support an expanded indication for BOS. The Applicant agreed to the proposed postmarketing commitment. See Section [24](#).

Additionally, while data are available in the PI for the LD, Entocort EC (budesonide) delayed-release capsules (NDA 021324) ([Perrigo Pharma International DAC 1997](#)) from a published report of budesonide concentrations in human milk following maternal inhalation of budesonide, and adequate pharmacokinetic (PK) data are available to provide estimates of budesonide concentration in human milk following BOS administration, no lactation studies have been conducted to inform the transfer of orally-administered budesonide to human milk. Accordingly, the review team requested the Applicant agree to a postmarketing commitment to conduct a lactation study to evaluate the potential BOS exposure to the nursing child after maternal administration. This study would better inform the label and provide accurate information to counsel lactating women on the potential risks to their breast-feeding infant. The Applicant did not agree to a postmarketing commitment to conduct the requested lactation study. See Section [24](#).

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Eosinophilic esophagitis (EoE) is a chronic immune- or antigen-mediated esophageal disease clinically characterized by signs and symptoms related to esophageal dysfunction and histologically characterized by eosinophil-predominant inflammation (Liacouras et al. 2011). Left untreated, EoE leads to esophageal stricture, dysphagia, and risk of food impaction (Warners et al. 2018). Environmental allergens (e.g., pollen season, cold or arid climates (Dellon and Hirano 2018)) can also lead to episodic EoE flares. Furthermore, treatment cessation can lead to a recurrence of EoE clinical symptoms and histologic activity (Dellon et al. 2020). - In patients with EoE, clinical features and histologic activity can vary independently. Patients can have a reduction or resolution in signs and symptoms despite ongoing histologic activity. Conversely, patients can have histologic remission (defined as a change in peak eosinophils per high-power field [HPF] from a count greater than or equal to 15 to less than or equal to 6) with persistent clinical symptoms (Dellon et al. 2013). - Efforts are ongoing to better characterize the natural history of EoE and impact of effective interventions. - Sustained remission has been reported after re-introduction of all eliminated foods following completion of successful elimination diets (Hoofien et al. 2020) as well as following treatment with topical corticosteroids in some patients (Uchida et al. 2023) (Dellon and Hirano 2018) (Shaheen et al. 2018) (Assa'ad et al. 2007).	EoE is a serious condition and can profoundly impact patients' health and well-being. Because the clinical features and histologic activity of EoE can vary independently, the treatment goals of EoE include resolution or reduction of the signs and symptoms of active disease to provide relief to the patient and healing or control of the esophageal inflammation and its complications. For a drug to demonstrate benefit as a therapy for EoE, efficacy should be demonstrated on both histologic remission and through clinically meaningful improvement on symptoms and/or signs. There is an existing knowledge gap surrounding the natural history of EoE, the potential durability of response following effective initial treatment, and whether intermittent treatment to quell acute flares could represent a suitable option for some patients with EoE.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	- On May 20, 2022, dupilumab, a fully human monoclonal antibody which binds to interleukin (IL)-4 receptor alpha subunit (IL-4Rα) and blocks signaling of IL-4 and IL-13, was approved by FDA for the treatment of EoE in patients who are 12 years of age or older (adolescents and adults), weighing ≥40 kg. On January 25, 2024, the indication for dupilumab was expanded to include adults and pediatric patients 1 year of age and older, weighing ≥15 kg, with eosinophilic esophagitis. - In addition to the availability of dupilumab as an effective treatment for EoE, the current standard of care for EoE includes restricted diets, such as a full liquid diet with elemental formula and a six-food elimination diet (SFED); however, long-term compliance is very challenging. - Less restrictive diets (e.g., including SFED [dairy, wheat or gluten, eggs, legumes, nuts, and seafood], 4-food elimination diet [dairy, soy, egg, and wheat], 1-food elimination diet [dairy], patient-specific targeted elimination diets) can enhance compliance but frequently require several trial periods to identify triggers and evaluate efficacy after each elimination or adjustment. - The identification of trigger foods is most evident when patients begin trials of dietary therapy while in a state of remission. - There are no approved therapies to be used after an introduced food causes a flare of active EoE. - Another standard of care therapy has been off-label use of topical corticosteroids intended for local action on the esophageal mucosa. Systemically-acting corticosteroids such as prednisone are also used but are typically reserved for more severe or recalcitrant disease. Because of the potential for significant toxicity, long-term use of systemic corticosteroids is generally not recommended. - The role of corticosteroids for short-term therapy has been well-established to provide rapid reduction of inflammation and induction of remission (Lichtenstein et al. 2006) (Barrett et al. 2018) (Bruscoli et al. 2021) in other chronic	There is one pharmacological product (dupilumab) approved by FDA for the treatment of EoE. The availability of effective short-term therapy could facilitate the evaluation and identification of triggers without patients first needing to comply with a highly restrictive or elemental diet. Effective short-term therapies have the potential to be used as an initial bridge to the identification and implementation of less restrictive dietary strategies that are successful for the individual patient and can be maintained long-term. Availability of effective short-term therapy could also increase patient willingness to explore targeted dietary management by providing an option to initiate treatment to relieve symptoms that develop after unsuccessful reintroduction of foods. Mechanistic rationale provided by the substantial experience with the drug class in other chronic inflammatory gastroenterological conditions supports the suitability of a limited indication for BOS as a short-term therapy for patients with EoE. Data to demonstrate long-term efficacy are needed to support the treatment of this chronic condition. However, there is adequate support for a potential role of a corticosteroid product for the short-term treatment of EoE to be used to quell acute flares and/or to function as a bridge to effective long-term management strategies. Although available topical corticosteroid products, developed for the treatment of asthma, are frequently used off-label as part of standard of care, their safety and efficacy have not been established for the treatment of EoE. Standardized formulations that reliably deliver the appropriate amount of drug, as well as data to inform and support the safety and efficacy of appropriate dosing regimens, are needed.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	inflammatory conditions (e.g., inflammatory bowel disease). For these chronic conditions, long-term therapy with corticosteroids is discouraged due to the associated adverse reactions and long-term toxicity, and in favor of more specific disease-modifying therapies. Although data to suggest that topically-acting corticosteroids may be beneficial for treatment of the acute clinical and pathological features of EoE when swallowed (Liacouras et al. 2011), the currently used topical formulations were not designed to have a targeted effect on the esophageal mucosa, and more information is needed to inform the appropriate dose and frequency of administration for these products. Furthermore, patient compliance with these therapies can be limited by the need to adapt currently available formulations for topical use (e.g., homemade slurry preparations for swallowing, such as mixing contents of inhaled products for asthma with Splenda, honey, or other sweeteners). This also results in unstandardized dosing and administration of products that have not been established to be safe or effective for EoE.	
Benefit	- While data from Trial 101-06 were not adequate to inform an evaluation of BOS for the long-term treatment of EoE, these data are adequate and informative of the evaluation of benefit for the newly proposed short-term indication. Accordingly, this resubmission included data from two adequate and well-controlled trials. - Trial 101-06 demonstrated statistically significant results for the coprimary efficacy endpoints of histologic remission (peak eosinophil count of ≤ 6 per high-power field across all available esophageal levels) and reduction in dysphagia symptoms (absolute change from baseline in DSQ combined score [sum of points for responses to questions 2+3]) after 12 weeks of treatment: 19/50 (38.0%) subjects who received BOS versus 1/42 (2.4%) subjects who received placebo achieved histologic remission ($p < 0.0001$) and the treatment difference in reduction in dysphagia symptoms between BOS and placebo was -8.6 (-13.7, -3.5; $p = 0.001$).	The demonstration of effectiveness of BOS for the short-term treatment of EoE is based on the statistically significant results for the prespecified endpoint of histologic remission and the statistically significant results for the prespecified endpoint of absolute change from baseline in DSQ combined score and is further supported by the results of the Q3=0 assessment. The review team would not have considered the exploration of the Q3=0 assessment to be appropriate had either trial reported numerically nonsignificant results for these analyses or if the significant results had not been appropriately controlled for multiplicity. The Q3=0 assessment showed that a greater proportion of subjects randomized to BOS reported no dysphagia or only experienced dysphagia that “got better or cleared up on its own” compared to placebo in both Trials 101-06 and 301. The strength of the evidence to support this determination is increased by the independent replication of results of efficacy

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Trial 301 demonstrated statistically significant results for the coprimary efficacy endpoint of histologic remission (peak eosinophil count of ≤ 6 per high-power field across all available esophageal levels), the symptomatic coprimary efficacy endpoint of $\geq 30\%$ reduction in DSQ combined score from baseline, and the key secondary endpoint^a of reduction in dysphagia symptoms (absolute change from baseline in the DSQ combined score) after 12 weeks of treatment: 113/213 (53.1%) subjects who received BOS versus 1/105 (1.0%) subjects who received placebo achieved histologic remission ($p < 0.0001$), 112/213 (52.6%) subjects who received BOS versus 41/105 (39.1%) subjects who received placebo achieved the $\geq 30\%$ responder threshold ($p = 0.024$), and the treatment difference in reduction in dysphagia symptoms between BOS and placebo was -3.7 (-6.8, -0.6; $p = 0.018$). These analyses were appropriately controlled for multiplicity. • The DSQ is a clinical outcome assessment (COA) designed to be administered daily to evaluate the occurrence of dysphagia over a 14-day assessment period. However, because small but statistically significant group-level mean differences in a COA endpoint may not represent a clinically meaningful effect to patients, the guidance for industry <i>Eosinophilic Esophagitis: Developing Drugs for Treatment</i> (September 2020) (FDA 2020) recommends the use of anchor-based methods to aid in the interpretation of the clinical meaningfulness of COA endpoint results for clinical trials of drugs for the treatment of EoE. • Anchor-based methods for informing clinically meaningful within-patient changes in COA endpoint scores remain the review team's preferred and recommended approach, and these methods were utilized to interpret the clinical meaningfulness of both the $\geq 30\%$ 14-day DSQ responder threshold specified by the Applicant as the symptomatic coprimary endpoint and the prespecified alpha-controlled secondary endpoint of absolute change from baseline in DSQ combined score for Trial 301 during the original review of NDA 213976.	assessments across the two 12-week trials (i.e., Trials 101-06 and 301). Considered collectively, there is adequate data to support that treatment with BOS resulted in clinical benefit in subjects with EoE.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- Multiple factors precluded the application of anchor-based analyses to aid in the interpretation of the clinical meaningfulness of the COA endpoint results from Trials 101-06 and 301 in this submission. For example, the discordant anchor scales (PGIS versus PGIC) in each trial prevented an assessment of comparability, and the assessment periods between the anchor scales (12 weeks PGIC or 7 days PGIS) and the DSQ (14 days) introduced uncertainty in the ability of the results of anchor-based analyses to support the interpretation of the COA endpoint results for either trial. - Given the existing need for short-term therapy in patients with EoE to quell acute flares and to function as a bridge to an effective long-term management strategies, the review team determined that it is appropriate to consider whether an alternate metric with inherent clinical meaningfulness (i.e., achieving no dysphagia or experiencing only dysphagia that “got better or cleared up on its own”) could aid in the interpretation of the favorable results of the COA endpoints from these trials. - The review team requested the Applicant provide analyses of DSQ Question 2 (Q2: “Since you woke up this morning, has food gone down slowly or been stuck in your throat?”^b) = 0 (“No”) and DSQ Question 3 (Q3: “For the most difficult time you had while swallowing food today, did you have to do anything to make the food go down or to get relief?”) = 0 (“No, it got better or cleared up on its own.”). Qualitative data generated during the development of the DSQ established the meaningfulness of these concepts and the representative terminology used in the items (i.e., Q2 and Q3), and post-development qualitative data from EoE development programs utilizing the DSQ (e.g., BOS, dupilumab) continue to support the content validity of the instrument, items, and response options. Of note, achieving Q3=0 also includes subjects who achieved no dysphagia (Q2=0) because when a subject responded “No” to Q2, they automatically received a score of 0 for Q3.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	While there was a trend seen on the FDA-requested assessment of no dysphagia (Q2=0), the analysis was not prespecified and the results did not achieve the standard threshold used for defining statistical significance (i.e., $p < 0.05$). This finding is likely attributable to the small proportion of subjects meeting the stringent threshold of achieving complete resolution of all dysphagia episodes during the last two weeks of the 12-week treatment period. Conversely, although also limited by its lack of prespecification, the analyses of DSQ Q3=0 achieved nominal significance and showed that a greater proportion of subjects randomized to BOS reported no dysphagia or only experienced dysphagia that “got better or cleared up on its own” compared to placebo in both Trials 101-06 ($p = 0.0039$) and 301 ($p = 0.0257$).	
Risk and risk management	- BOS is an oral formulation of budesonide, a corticosteroid product with a well-established safety profile as reflected in the prescribing information (PI) for the listed drug (LD), Entocort EC (budesonide) delayed-release capsules (NDA 021324) (Perrigo Pharma International DAC 1997). - Corticosteroid class effects include upper respiratory tract infection, headache, sinusitis, nausea, vomiting, dyspepsia, hypertension, increased weight, psychiatric disturbance, increased transaminases, adrenal suppression, and cushingoid effects. - Trial 301 included adrenocorticotrophic hormone (ACTH) stimulation testing at Baseline (Week 4) and at Week 16 (after 12 weeks of treatment); however, Trial 101-06 did not include ACTH stimulation tests. In Trial 301, the BOS and placebo treatment arms had a similar proportion of subjects noted to have adrenal suppression at Baseline (3.8% versus 5.0%). After 12 weeks of treatment, a notable imbalance was observed in the proportion of subjects treated with BOS with abnormally low cortisol values following ACTH stimulation test compared to placebo at Week 16; 18/198 (9.1%) subjects who received BOS 2 mg twice daily (BID) had abnormal ACTH stimulated serum cortisol levels versus 3/87 (3.4%) subjects in placebo group.	The observed risk profile for BOS was largely reflective of that described in the FDA-approved product labeling for the LD. Adrenal suppression occurred at a greater rate in those treated with BOS than placebo. Although noted to occur less frequently than as described with the LD, this risk should be appropriately communicated to patients and providers. Patients should be monitored during treatment with BOS for signs and symptoms of steroid withdrawal, increased risk of infection, and other corticosteroid effects. A new WARNINGS AND PRECAUTIONS section is appropriate and necessary to inform patients and prescribers of the risk for developing erosive esophagitis while taking BOS and the importance of reporting new or worsening signs or symptoms that may prompt additional endoscopic evaluation. Additionally, patients and prescribers should be informed of the risk for the adverse events potentially related to the topical administration and formulation of BOS, including throat irritation and candidiasis. If gastrointestinal mucosal candidiasis develops, patients should be treated with appropriate local or systemic antifungal therapy and discontinuation of BOS treatment should be considered.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- Review of the data presented in the PI for the LD, identified that the hypothalamic-pituitary-adrenal (HPA) axis suppression potential of BOS 2 mg appears to be lower than that observed with the use of Entocort EC (Perrigo Pharma International DAC 1997). This may be due to lower systemic exposure of budesonide in subjects treated with BOS compared to Entocort EC. However, this comparison is limited by its cross-study nature. - Although the observed adverse event profile for BOS was largely consistent with the known class effects of corticosteroid products, additional adverse events emerged during the safety review as likely or potentially related to the formulation and topical administration of BOS including gastrointestinal mucosal candidiasis, throat irritation, and erosive esophagitis. - With regard to the adverse reaction of erosive esophagitis, erosions were found at esophagogastroduodenoscopy (EGD) after 12 weeks of BOS treatment in four subjects during Trial 301. None of the four subjects had erosions at baseline EGD, and three of the four subjects were receiving concomitant therapy with a proton pump inhibitor during the trial. - There is a known risk for corticosteroid products to cause or worsen acid-related disorders such as GERD or erosive esophagitis. However, the significant overlap in clinical symptoms of erosive esophagitis and EoE may delay appropriate diagnosis and treatment of erosive esophagitis. - The Applicant conducted a two-way crossover food effect study evaluating the pharmacokinetics, safety, and tolerability of a single dose of the to-be-marketed formulation of BOS 2 mg in healthy adult subjects under fasting or fed (high-fat/high-calorie meal) conditions. For the fed condition, subjects fasted overnight for ≥ 10 hours until 30 minutes prior to BOS dosing, at which point they were given a high-fat/high-calorie breakfast that needed to be consumed entirely within 30 minutes. Subjects were then dosed with BOS, and finally subjects fasted for ≥ 4 hours post-dose. Plasma budesonide C_{max}, AUC_{last}, $AUC_{0-\infty}$, and T_{max} were	The effect of food on the pharmacokinetics, safety, and tolerability of BOS has been assessed to inform the PI on dosing instruction(s) in relation to meal intake. A high-fat/high-calorie meal is not expected to significantly change the systemic exposure to BOS compared to fasting condition. To promote contact with the mucosal surface of the esophagus, the recommended dosing instructions include not taking BOS concurrently with food or liquid, and that patients should not eat or drink for ≥ 30 minutes after taking BOS. This is consistent with how BOS was administered in Trials 101-06 and 301.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	13% lower, 26% higher, 27% higher, and 1 hour longer, respectively, following a single dose of 2 mg BOS under fed conditions compared to under fasting conditions. The delayed absorption, decreased C_{max} , and increased systemic exposure of BOS is not expected to be clinically significant. This study supports that BOS may be administered after a meal or on a full stomach.	

Source: Reviewer-generated table

^a See Section 1 for the definition of the symptomatic coprimary endpoint assessed in Trial 301.

^b Question 2 in the version of the DSQ included in Trial 101-06 included the words "throat or chest."

Abbreviations: ACTH, adrenocorticotrophic hormone; AUC_{last} , area under the concentration-time curve from time 0 to last measurable concentration; $AUC_{0-\infty}$, area under the concentration-time curve from time 0 to infinity; BOS, budesonide oral suspension; C_{max} , maximum observed plasma concentration; COA, clinical outcome assessment; DSQ, Dysphagia Symptom Questionnaire; EoE, eosinophilic esophagitis; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; HPF, high power field; IBD, inflammatory bowel disease; IL, interleukin; IND, investigational new drug; LD, listed drug; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; T_{max} , time to maximum observed plasma concentration

2.2. Conclusions Regarding Benefit-Risk

EoE is a serious chronic condition with one approved therapy, Dupixent (dupilumab, approved on May 20, 2022 under BLA 761055 for the treatment of adult and pediatric patients aged 12 years and older, weighing ≥ 40 kg, with EoE). This indication was expanded to include adults and pediatric patients aged 1 year and older, weighing ≥ 15 kg, with eosinophilic esophagitis on January 25, 2024. EoE can lead to esophageal stricture, dysphagia, and risk of food impaction. Evaluation of both histologic activity and clinical signs and symptoms is integral to diagnostic assessment and disease monitoring for this condition, but these factors can vary independently in patients with EoE. As such, candidate therapeutics should demonstrate benefit on both histologic remission and reduction or resolution in clinical signs and/or symptoms as coprimary endpoints (assessed at the population level) to support a determination of efficacy.

The Applicant is seeking a limited indication for the short-term treatment of EoE, (b) (4) in adult and adolescent patients 11 years and older. Although EoE is a chronic condition for which long-term treatment is needed, the review team determined that, in this case, consideration for a short-term treatment indication for BOS to be used in patients with EoE to quell acute flares and/or to function as a bridge to effective long-term management strategies was appropriate based on the therapeutic context and available class experience and mechanistic rationale demonstrated with corticosteroid products in other chronic inflammatory gastrointestinal conditions (e.g., IBD). For discussion of the suitability of the proposed short-term indication, see Section 1.

To support the resubmission, the Applicant provided efficacy data from two adequate and well-controlled 12-week clinical trials, Trial 101-06 and Trial 301. Because Trial 101-06 was limited to 12 weeks of double-blind, placebo-controlled evaluation, the data from Trial 101-06 were not adequate to support an evaluation of BOS for the long-term treatment of EoE. These data are, however, adequate and informative of the evaluation of benefit for the newly proposed short-term indication. As discussed in Section 6, Trials 101-06 and 301 yielded statistically significant results for their multiplicity-controlled prespecified analyses of efficacy endpoints of histologic remission (defined as a peak eosinophils/high-power field ≤ 6) and reduction in dysphagia symptoms (utilizing the DSQ).

Also, as discussed in Section 1, anchor-based methods remain the review team's preferred and recommended approach to inform clinically meaningful within-patient changes in COA endpoint scores; however, several factors precluded the application of anchor-based analyses to inform the clinical meaningfulness of the COA endpoint results from Trials 101-06 and 301. Given the statistically significant results of prespecified multiplicity-controlled efficacy analyses, and in consideration of the existing need for short-term therapy to quell acute flares and/or to function as a bridge to an effective long-term management strategies in patients with EoE, the review team determined that it is appropriate to consider an alternate metric with inherent clinical meaningfulness (i.e., achieving no dysphagia or experiencing only dysphagia that "got better or cleared up on its own") to aid in the interpretation of the favorable results of the COA endpoints from Trials 101-06 and 301. The review team requested supplementary analyses of this metric in Trials 101-06 and 301 from the Applicant without any foreknowledge of the results from either trial.

The demonstration of effectiveness for BOS for the short-term treatment of EoE is based on the statistically significant results for the prespecified endpoint of histologic remission and the statistically significant results for the prespecified endpoint of absolute change from baseline in DSQ combined score, supported by the results of the Q3=0 assessment. The Q3=0 assessment showed that a greater proportion of subjects randomized to BOS reported no dysphagia or only experienced dysphagia that “got better or cleared up on its own” compared to placebo in both Trials 101-06 and 301. The strength of the evidence to support this determination is increased by the independent replication of results of efficacy assessments across the two 12-week trials (i.e., Trials 101-06 and 301). When considered collectively, there is adequate support that treatment with BOS resulted in clinical benefit in subjects with EoE, and the results from Trials 101-06 and 301 provide substantial evidence of effectiveness.

Regarding the evaluation of risk, BOS is an oral formulation of budesonide, a corticosteroid product with a well-established safety profile as reflected in the PI for the LD, Entocort EC (budesonide) delayed-release capsules ([Perrigo Pharma International DAC 1997](#)). Corticosteroid class effects include upper respiratory tract infection, headache, sinusitis, nausea, vomiting, dyspepsia, hypertension, increased weight, psychiatric disturbance, increased transaminases, adrenal suppression, and cushingoid effects. Although the observed adverse event profile for BOS was largely consistent with the known class effects of corticosteroid products, additional adverse events emerged during the safety review as likely or potentially related to the formulation and topical administration of BOS including gastrointestinal mucosal candidiasis, throat irritation, and erosive esophagitis.

Corticosteroid products are associated with an increased risk of GERD and acid-related disorders. However, as the significant overlap in clinical symptoms of erosive esophagitis and EoE may delay appropriate diagnosis and treatment of erosive esophagitis, the review team determined that the addition of a WARNINGS AND PRECAUTIONS section to the PI was appropriate and necessary to inform patients and prescribers of the risk for developing erosive esophagitis while taking BOS and the importance of reporting new or worsening signs or symptoms that may prompt additional endoscopic evaluation. Additionally, patients and prescribers should be aware that erosive esophagitis may develop while patients are taking presumably effective therapy with PPIs. Regarding candidiasis, if gastrointestinal mucosal candidiasis develops, patients should be treated with appropriate local or systemic antifungal therapy and consideration should be made regarding discontinuing treatment with BOS. Overall, the identified risks of 12 weeks of treatment with BOS can be mitigated through labeling and monitored during routine pharmacovigilance.

Based on the data from two adequate and well-controlled trials, Trial 101-06 and Trial 301, the overall benefit-risk for BOS for the treatment of EoE in adult and pediatric patients ≥ 11 years of age is favorable.

II. Interdisciplinary Assessment

3. Introduction

Product Information

Budesonide oral suspension (BOS) is an oral formulation of budesonide, which is an anti-inflammatory corticosteroid that has a high glucocorticoid effect and a weak mineralocorticoid effect. The precise mechanism of actions of BOS in eosinophilic esophagitis (EoE) is not known. However, inflammation is an important component in the pathogenesis of EoE, and corticosteroids have a wide range of inhibitory activities against multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukocytes, and cytokines) involved in allergic and nonallergic-mediated inflammation. These anti-inflammatory actions of corticosteroids may contribute to a treatment effect in EoE.

Available Therapies

Dupilumab, a fully human monoclonal antibody which binds to interleukin (IL)-4 receptor alpha subunit (IL-4R α) and blocks signaling of IL-4 and IL-13, was approved on May 20, 2022 for the treatment of EoE in adults and adolescent patients ≥ 12 years of age, weighing ≥ 40 kg (BLA 761055 S-040). This approval was based upon the demonstration of efficacy and safety in the 52-week, phase 3 clinical trial R668-EE-1774 (Study 1774). Study 1774 assessed histologic and symptomatic coprimary endpoints and utilized anchor-based analyses to confirm that the results of the analyses of the symptomatic coprimary endpoint were representative of clinically meaningful improvement for subjects who received dupilumab 300 mg QW compared to those who received placebo. On January 25, 2024, the indication was expanded to include adults and pediatric patients aged 1 year and older, weighing ≥ 15 kg, with eosinophilic esophagitis under BLA 761055/S-057. This approval was based upon the collective data generated by the Applicant's EoE development program, including (1) extrapolation of efficacy from the adequate and well-controlled study that supported the approval of dupilumab in adults and pediatric patients aged 12 years and older weighing ≥ 40 kg (Study 1774), (2) data from the trial in younger pediatric subjects (Study R668-EE-1877), and (3) PK data from pediatric and adult subjects.

In addition to the availability of dupilumab as an effective treatment for EoE, the current standard of care for patients with EoE includes restricted diets, such as a full liquid diet with elemental formula or a SFED; however, as discussed in Section I, both short- and long-term adherence with dietary interventions is challenging. Although topically administered corticosteroid products are also considered to be an initial standard of care, none of the available products have been found to be safe or effective for the treatment for EoE. The available formulations were designed for inhaled administration for the treatment of asthma, and information is needed to inform the appropriate dose and frequency of administration for these products when they are swallowed to provide local effects on the esophageal mucosa. Furthermore, patient compliance with these products can be limited by the need to adapt currently available formulations for swallowed topical use (e.g., homemade slurry preparations

by mixing contents of inhaled products with Splenda, honey, or other sweeteners). The need to adapt products prior to administration can result in unstandardized dosing.

Current Submission

The resubmission of NDA 213976 was received by FDA on August 22, 2023. This resubmission followed the December 17, 2021 CR action for the original submission. For details of the multidisciplinary review of the original submission, refer to the December 17, 2021 integrated review of NDA 213976 (DARRTS Reference ID: 4907153).

The current submission proposes a novel indication of the short-term treatment of EoE. For discussion of the suitability of the indication and the adequacy of the available data, see Section I. To support the evaluation of safety and effectiveness of BOS related to a limited indication of short-term treatment of EoE only, the Applicant submitted data from two 12-week clinical trials (Trial 101-06 and Trial 301). The coprimary endpoints of Trial 101-06 were histologic remission (peak eosinophil count of ≤ 6 per high-power field across all available esophageal levels) and reduction in dysphagia symptoms (absolute change from baseline in the Dysphagia Symptom Questionnaire [DSQ] combined score [sum of points for responses to questions 2+3]) after 12 weeks of treatment. The coprimary endpoints of Trial 301 were histologic remission (peak eosinophil count of ≤ 6 per high-power field across all available esophageal levels) and a 30% reduction in the DSQ combined score after 12 weeks of treatment. The first-ranked secondary endpoint in Trial 301 was absolute change from baseline in DSQ combined score (sum of points for responses to questions 2+3) after 12 weeks of treatment. Because the anchor-based analysis of Trial 301 data did not support that the prespecified 30% responder threshold (included by the Applicant as the symptomatic coprimary endpoint in Trial 301²) represented clinically meaningful change to subjects with EoE, review of symptomatic efficacy for Trial 301 focuses on the first-ranked secondary endpoint of reduction in dysphagia symptoms (absolute change from baseline in DSQ combined score [sum of points for responses to questions 2+3]) after 12 weeks of treatment.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issue

3.1.1.1. Adequacy of the Available Data To Support the Demonstration of Clinical Benefit

3.1.2. Key Safety Review Issues

3.1.2.1. HPA Axis Suppression

3.1.2.2. Gastrointestinal Mucosal Candidiasis

3.1.2.3. Erosive Esophagitis

3.2. Approach to the Clinical Review

The efficacy review focused on the data generated from the two 12-week clinical trials (Trial 101-06 and Trial 301). For the evaluation of safety, data from Trials 101-06 and 301 were evaluated independently, and the following additional sources of safety information were evaluated.

- Trial SHP621-101: a phase 1 study conducted in healthy volunteers to establish bioequivalence between the MB-9 formulation used in clinical trials and the SB-10 to-be-marketed (TBM) formulation (2 mg single oral dose of BOS including (b) (4) % weight for weight)]⁵
- Trial MPI 101-01: a phase 2 dose-ranging assessment that identified 2 mg BID as the dosing regimen for future clinical trials
- Trial 302: a phase 3, 36-week extension study including a randomized withdrawal assessment in subjects who completed Trial 301
- Trial SHP621-303: an open-label extension (OLE) study for subjects who completed Trial 302

For additional description of the approach to the safety review, see Section [7.4](#).

⁵ Note that the SB-10 formulation was modified from the MB-9 formulation through the addition of sodium ascorbate and ascorbic acid. These compounds function as (b) (4)

See minutes from the April 20, 2020 Type B Pre-NDA Meeting under IND 103107 (DARRTS Reference ID: 4612777). The SB-10 TBM formulation was used in Trial TAK-721-1003, the food-effect study in healthy volunteers.

Table 3. Pivotal Clinical Trials Submitted in Support of Efficacy and Safety Determinations for BOS

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized	Number of Centers (all U.S. only)
MPI 101-06 (NCT01642212)	Pediatric and adult subjects (11-40 years of age, inclusive) with EoE	Phase 2 R, DB, PG, PC, MC, 3-period efficacy, safety, and tolerability trial with OL extension	Dosage: BOS 2 mg BID (qAM pc and hs); PBO 2 mg BID (qAM pc and hs); Oral Number treated: 93 Duration: 12-week DB treatment period and 24-week OL extension	<u>Coprimary:</u> Histologic remission and absolute change in DSQ combined score from baseline to the final treatment period evaluation ^a <u>Secondary:</u> Absolute change in DSQ combined score over time	93	24
SHP621-301 (NCT02605837)	Pediatric and adult subjects (11-55 years of age, inclusive) with EoE	Phase 3 R, DB, PG, PC, MC, 3-period efficacy, safety, and tolerability trial	Dosage: BOS 2 mg BID (qAM pc and hs); PBO 2 mg BID (qAM pc and hs); Oral Number treated: 318 Duration: 12-week DB treatment period	<u>Coprimary:</u> Histologic remission and dysphagia symptom response ^b <u>Secondary:</u> Absolute change in DSQ combined score from baseline	322	72

Source: Reviewer-created table

^a Absolute change in DSQ combined score (sum of points for responses to questions 2+3) from baseline to Week 16 (end of 12-week double-blind treatment period)^b Dysphagia symptom response defined as $\geq 30\%$ reduction in the DSQ combined score (sum of points for responses to questions 2+3) from baseline to Week 16 (end of 12-week double-blind treatment period)

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; DB, double-blind; DSQ, Dysphagia Symptom Questionnaire; EoE, eosinophilic esophagitis; hs, at bedtime; MC, multicenter; PBO, placebo; PC, placebo-controlled; PG, parallel group; qAM pc, every morning after meals; R, randomized; U.S., United States

NDA 213976

Eohilia (budesonide oral suspension)

Table 4. Clinical Trials Submitted in Support of the Safety Determination for BOS and to Provide Additional Supportive Data^a

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized^b	Number of Centers (all U.S. only)
SHP621-101	Healthy adult subjects	Phase 1 OL, SC, single-dose, R, 2- sequence, 5- period, 5-treatment crossover, relative bioavailability study	15-day treatment period (at clinical research site): Single oral dose of each of 5 treatments, 1 every 3 days: •Treatment A: BOS MB- 9 formulation 2 mg •Treatment B: Entocort EC 9 mg •Treatment C: BOS MB- 7 formulation 2 mg •Treatment D: MB-9 formulation with (b) (4) variant (also known as SB-10) 2 mg •Treatment E: BOS MB- 9 formulation with increased (b) (4) variant 2 mg	<u>Primary:</u> Pharmacokinetics <u>Secondary:</u> Pharmacokinetics, safety, and tolerability	22	1

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized^b	Number of Centers (all U.S. only)
MPI 101-01 (NCT00762073)	Subjects ages 2 to 18 years (inclusive) with symptomatic EoE	Phase 2 R, DB, PG, PC, MC, 2- period, dose- ranging study	Dosage: Low dose group: BOS 0.05 mg/mL hs and PBO qAM pc; Medium dose group: BOS 0.2 mg/mL hs and PBO qAM pc; High dose group: BOS 0.2 mg/mL hs and qAM pc; PBO group: PBO hs and qAM pc Number treated: 82 Duration: 12-week DB treatment period and 3- week taper	<u>Primary:</u> Response to therapy (defined by both an EoE clinical symptom response and a histologic response [i.e., a peak eosinophil count of ≤6 per HPF across all available esophageal levels]) <u>Secondary:</u> Histologic response and histologic remission (i.e., peak eosinophil count of ≤1 per HPF across all available esophageal levels; note, with the exception of this trial, in this integrated review the term “histologic remission” is defined as a peak eosinophil count of ≤6 per HPF across all available esophageal levels)	82	20

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized^b	Number of Centers (all U.S. only)
SHP621-302 (NCT02736409)	Pediatric and adult subjects (11-55 years of age, inclusive) with EoE who completed the SHP621-301 trial	Phase 3 R, DB, PG, PC, MC, 3- period efficacy, safety, and tolerability extension trial to SHP621-301 A randomized withdrawal period was stratified by treatment assignment and treatment response in the SHP621-301 trial. Only subjects who were “full responders” ^b in the SHP621-301 trial were eligible to enter the randomized withdrawal period to receive either BOS 2 mg twice daily or PBO at a 1:1 ratio.	Dosage: BOS 2 mg BID (qAM pc and hs); PBO 2 mg BID (qAM pc and hs); Oral Number treated: 219 Number of subjects in randomized withdrawal period: 48 (23 PBO, 25 BOS) Duration: 36-week treatment period	<u>Primary:</u> Relapse ^c during the 36- week double-blind randomized withdrawal period (for SHP621-301 “full responders” ^d) <u>Secondary:</u> Long-term response (both histologic and symptomatic) ^e	219	70

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized^b	Number of Centers (all U.S. only)
SHP621-303 (NCT03245840)	Pediatric and adult subjects (11-55 years of age, inclusive) with EoE who completed both SHP621-301 SHP621-302 trials	Phase 3 open- label extension study to Trial SHP621-302 to provide continued access to BOS treatment	Dosage BOS 2 mg BID (qAM pc and hs); adjustments in dose regimen may be made Number treated: 131	Long-term safety and tolerability	131	44

Source: Reviewer created table

^a Includes all submitted clinical trials, even if not reviewed in-depth

^b If no randomization, then replaced with "Actual Enrolled"

^c Relapse, as a binary response (either with a relapse or not), was defined as meeting both the eosinophil histology relapse criterion (eosinophil count of ≥ 15 per HPF and the dysphagia symptom relapse criterion (a minimum of 4 days of dysphagia [with answer 'Yes' for question 2 in DSQ] in the 2-week period prior to the scheduled visit, as determined by the DSQ)

^d Defined as ≤ 6 eosinophils per HPF across all available esophageal levels and a $\geq 30\%$ reduction in DSQ at the final treatment evaluation visit

^e Defined as a binary response over the 36-week period in the Trial 301 BOS nonresponders (defined as all randomized subjects who did not respond or partially responded to assigned BOS treatment in Trial 301 and who received ≥ 1 dose of investigational product [IP] in Trial 302), where histologic remission was defined as a peak eosinophil count of ≤ 6 per HPF across all available esophageal levels at week 36 AND dysphagia symptom response was defined as $\geq 30\%$ reduction in the DSQ combined score (questions 2+3) from baseline at week 36. Two baselines were evaluated – Trial 301 baseline and Trial 302 baseline.

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; DB, double-blind; DSQ, Dysphagia Symptom Questionnaire; EoE, eosinophilic esophagitis; hs, at bedtime; HPF, high-power field; MC, multicenter; OL, open-label; PBO, placebo; PC, placebo-controlled; PG, parallel group; qAM pc, every morning after meals; R, randomized; SC, single-center; U.S. United States

4. Patient Experience Data

The Applicant included the DSQ, a patient-reported outcome instrument, as a coprimary endpoint in both of their 12-week clinical trials (Trial 101-06 and Trial 301) to assess subjects' symptom of dysphagia.

Table 5. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical Outcome Assessment Data Submitted in the Application		
☒	Patient-reported outcome	1 , 2 , 3 , 6 , 12 , 16
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

Source: Reviewer-generated table

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

Budesonide is a synthetic corticosteroid that has a high glucocorticoid effect and a weak mineralocorticoid effect. The affinity of budesonide to glucocorticoid receptors is about 200-fold higher than that of cortisol and 15-fold higher than prednisolone. The nonclinical evidence of the effectiveness of BOS in EoE comes from the PI for the LD, Entocort EC (budesonide) delayed-release capsules (NDA 021324) ([Perrigo Pharma International DAC 1997](#)), and published pharmacodynamic studies using in vitro and in vivo animal models of inflammation. Although the effectiveness of BOS has not been directly tested in models of EoE, the anti-inflammatory effects of BOS were tested in various nonclinical models of inflammation.

In an in vitro model of inflammation using cultured T-84 epithelial cell monolayers, budesonide inhibited T-84 abnormalities and prevented epithelial dysfunction by inhibiting activation of T-cells and monocytes in a dose-dependent manner ([McKay et al. 1996](#)). In cultured adherent blood monocytes and alveolar macrophages stimulated with lipopolysaccharide, budesonide caused a partial suppression of IL-1 β and IL-6. In contrast, the stimulation of granulocyte macrophage colony stimulating factor (GM-CSF) was almost completely stimulated in the culture ([Linden and Brattsand 1994](#)).

In an L2-IL5^{OXA} EoE mouse model, the role of GM-CSF in esophageal inflammation was assessed by analyses of the expression of GM-CSF mRNA and protein. Significantly increased levels of esophageal GM-CSF expression, predominantly in the esophageal eosinophils, was detected in the L2-IL5^{OXA} mouse EoE model during active inflammation. GM-CSF neutralization in L2-IL5^{OXA} EoE mice resulted in a significant diminution of epithelial eosinophilia in addition to basal cell hyperplasia and vascular remodeling ([McNamee et al. 2017](#)).

5.2. Clinical Pharmacology/Pharmacokinetics

The Applicant proposes to rely upon FDA's findings as reflected in the PI for the LD Entocort EC (budesonide) delayed-release capsules (NDA 021324) for the clinical pharmacology information for BOS ([Perrigo Pharma International DAC 1997](#)). Additionally, the Applicant evaluated the pharmacokinetics and effects of budesonide on cytochrome P450 enzymes (CYPs) and transporters after administration of BOS in healthy subjects and subjects with EoE. The results of these assessments were previously reviewed as part of the original NDA submission. Refer to the multidisciplinary December 17, 2021 integrated review of NDA 213976 in DARRTS (Reference ID: 4907153).

The in vitro drug-drug interaction studies conducted by the Applicant showed that budesonide does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 and does not induce CYP3A4, CYP1A2 or CYP2B6 at clinically relevant concentrations. In vitro, budesonide is not an inhibitor of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic

anion transporting polypeptide (OATP) 1B1, OATP1B3, organic anion transporter (OAT) 1, OAT3, or organic cation transporter (OCT) 2 at clinically relevant concentrations.

The TBM formulation (BOS SB-10) is slightly different from the formulation used in Trials 101-06 and 301 (BOS MB-9 that includes (b) (4) w/w%). Bioequivalence was demonstrated between the formulation used in the phase 3 trials (BOS MB-9) and the TBM formulation based on the results of Study SHP621-101. Refer to the multidisciplinary December 17, 2021 integrated review of NDA 213976 in DARRTS (Reference ID: 4907153) for details.

In this resubmission, results from the newly conducted food effect study TAK-721-1003 were submitted for review. In Study TAK-721-1003, concomitant high fat meal intake within 30 minutes prior to dosing increased area under the concentration-time curve (AUC) by 25% and lowered maximum plasma concentration (C_{max}) by 13% after the administration of a 2 mg single oral dose of BOS (SB-10) (Table 6). This degree of change in exposures is not considered clinically significant. Based on the findings from the food effect study, patients may consume food or drink prior to dosing. To promote contact of the product with the esophagus after administration, the PI will recommend administration of BOS without concomitant food or liquid intake. Additionally, after dosing, patients should wait for 30 minutes before consuming food or drink.

See Section 8.2 for additional details.

Table 6. Budesonide Exposure Under Fed Versus Fasting Conditions in Healthy Subjects

Food Effect (Fed/Fasted)	Geometric Least Square	
	Mean Parameter	GMR% (90% Confidence Interval)
High-fat/high-calorie meal	C_{max} (pg/mL)	87.18 (74.80-101.61)
	AUC_{last} (pg•h/mL)	125.54 (113.85-138.41)
	AUC_{∞} (pg•h/mL)	126.56 (116.60-137.36)
	T_{max}	0.472-1.285

Source: Reviewer-generated table

Abbreviations: AUC_{last} , area under the concentration-time curve from time 0 to last measurable concentration; AUC_{∞} , area under the concentration-time curve from time 0 to infinity; C_{max} , maximum observed plasma concentration; GMR, geometric mean ratio, T_{max} , time to maximum observed plasma concentration

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

The dosing regimen of 2 mg BID, administered in Trial 101-06 and Trial 301, was selected based on the results from a dose-ranging trial (Trial MPI 101-01) conducted in pediatric subjects 2 to 18 years of age with EoE. However, it should be noted that the dose-response relationship for the efficacy endpoint in Trial MPI 101-01 was driven by the histologic remission (i.e., peak eosinophil count to ≤ 6 per high-power field [HPF]), as no treatment effects were observed at any of the assessed doses compared to placebo for symptom response based on the EoE Clinical Symptom Score. For details of this assessment of this evaluation, refer to the multidisciplinary December 17, 2021 integrated review of NDA 213976 in DARRTS (Reference ID: 4907153).

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

The primary assessment of efficacy was based on two 12-week, randomized, double-blind, placebo-controlled clinical trials, Trial 101-06 and Trial 301.

6.2.1. Trial 101-06

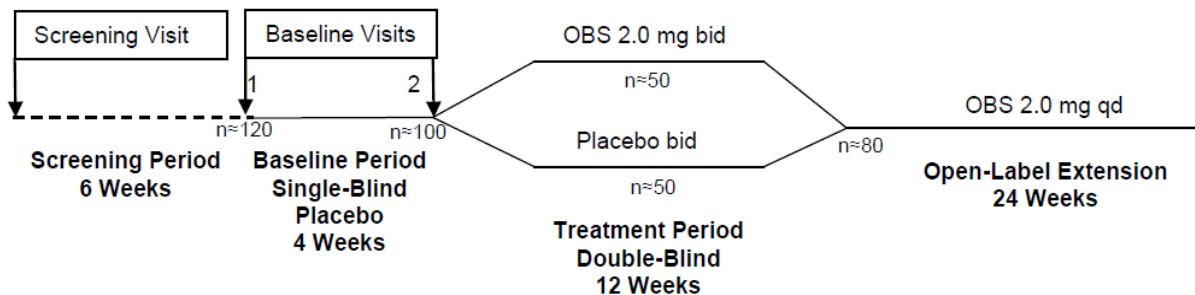
6.2.1.1. Design, Trial 101-06

Trial 101-06 was a phase 2, 12-week, randomized, double-blind, placebo-controlled, parallel group trial with an OLE. The trial evaluated the efficacy and safety of 2 mg of BOS administered BID (every morning after meals and at bedtime) for 12 weeks in pediatric and adult subjects, 11 to 40 years of age (inclusive) with EoE and symptoms of dysphagia.

As shown in [Figure 1](#), in Trial 101-06, subjects were randomized 1:1 to receive either BOS 2 mg BID or placebo BID. This trial consisted of four periods: a 6-week screening period, a 4-week single-blind placebo lead-in period, a 12-week double-blind treatment period, and a 24-week OLE period. Approximately 100 subjects were planned to be randomized 1:1 to BOS or placebo.

Trial 101-06 was designed to show superiority of BOS to placebo on two coprimary endpoints, histologic remission and change in Dysphagia Symptom Questionnaire (DSQ) combined score after 12 weeks of treatment. Histologic remission was defined as a peak eosinophil count of ≤ 6 per HPF across all available esophageal levels at the Week 16 visit (after 4 weeks of screening and 12 weeks of double-blinded treatment). The DSQ combined score was calculated using the DSQ daily diary data within a 14-day assessment period prior to the actual clinical visit at baseline or Week 16 by combining the scores from Question 2 (Q2) and Question 3 (Q3). See [Section 16.1](#).

Figure 1. Trial Design Schematic, Trial 101-06



Source: Clinical Study Report Figure 1 (Page 26)

Abbreviations: bid, twice daily; n, number of subjects in sample; OBS, oral budesonide suspension; qd, once daily

6.2.1.2. Eligibility Criteria, Trial 101-06

Selected eligibility criteria for Trial 101-06 are listed below.

Inclusion Criteria

- Male or female between the ages of 11 to 40 years, inclusive⁶
- Histologic evidence of EoE with a peak eosinophil count of ≥ 15 per HPF, from 2 or more levels of the esophagus, within 10 weeks prior to the baseline Visit 1
- History of clinical symptoms of esophageal dysfunction (e.g., eating problems, abdominal pain, heartburn, dysphagia, vomiting, food impaction, weight loss), intermittently or continuously
- Subjects must have experienced dysphagia on a minimum of 4 days in any 2 of the first 3 weeks of the Screening Period, and in the 2 weeks just prior to baseline Visit 2
- Subjects must have completed the DSQ on $\geq 70\%$ of days in the first 3-weeks of the Screening Period, and in the 2 weeks just prior to baseline Visit 2
- GERD-related and PPI-responsive esophageal eosinophilia must have been ruled out with esophageal biopsies done when the subject has been on ≥ 8 weeks of high dose PPI therapy (high dose therapy refers to the total daily dose, which may have been administered as a once or BID dosing regimen). This may occur at the time of the qualifying EGD (in which case the same PPI regimen must be continued) or this may have been done previously (in which case PPI therapy may have been stopped if there was no response to therapy based on esophageal biopsy results).
- Subjects must be willing and able to continue any dietary therapy, environmental therapy, or medical regimens (including gastric acid suppression; see exclusions below) in effect at the Screening Visit. There should be no change to these regimens within the 4 weeks prior to the qualifying EGD or between the qualifying EGD and baseline Visit 2, and no anticipated change during the Treatment Period.

Exclusion Criteria

- Use of immunomodulatory therapy within 8 weeks prior to the qualifying EGD or between the qualifying EGD and baseline Visit 2, or anticipated use of immunomodulatory therapy during the Treatment Period (except for any ongoing regimen of allergy shots). Use of long-acting immunomodulatory therapy (e.g., Rituxan) within 3 months of the qualifying EGD should be reviewed with the Medical Monitor
- Use of swallowed topical corticosteroid for EoE or systemic corticosteroid for any condition within the 4 weeks prior to the qualifying EGD, between the qualifying EGD and baseline Visit 2, or anticipated use during the Treatment Period

⁶ Although inclusion criteria specified that only subjects 11 to 40 years of age were eligible for enrollment into Trial 101-06, one subject (USUBJID [REDACTED] (b) (6)) was enrolled, randomized, and received their first dose of IP at age 9. This subject was excluded from FDA analyses.

- Initiation, discontinuation, or change in dosage regimen of PPIs, H2 antagonists, antacids, antihistamines, leukotriene inhibitors, or topical corticosteroids for any condition (such as asthma or allergic rhinitis) within the 4 weeks prior to the qualifying EGD, between the qualifying EGD and baseline Visit 2, or anticipated changes in the use of such medications during the Treatment Period
- Appearance of an esophageal stricture on qualifying EGD, as defined by the presence of a lesion that does not allow passage of a diagnostic adult upper endoscope (e.g., with an insertion tube diameter of 9.2 mm Olympus, 9 mm Pentax, or equivalent)
- Esophageal dilation within past year
- Presence of esophageal varices
- Any current disease of the gastrointestinal tract, aside from EoE, including eosinophilic gastritis, enteritis, colitis, or proctitis, inflammatory bowel disease, or celiac disease

6.2.1.3. Statistical Analysis Plan, Trial 101-06

Unless otherwise stated, the elements of the statistical analyses described in this section were prespecified.

Clinical Outcome Assessments

Dysphagia was measured in Trial 101-06 with the DSQ. For details of the administration, scoring, and content of the DSQ, see Section [16.1](#).

Endpoints

The coprimary endpoints in Trial 101-06 were (i) histologic remission at Week 16, defined as a peak eosinophil count of ≤ 6 per HPF across all levels of the esophagus in a subject, and (ii) absolute change from baseline in DSQ combined score at Week 16.

Analysis Populations

The intent-to-treat (ITT) population was defined in the protocol and statistical analysis plan (SAP) to include all randomized subjects. The modified intent-to-treat (mITT) population was defined in the protocol and SAP to include all randomized subjects who received at least one dose of a double-blind investigational product (IP) and had both an evaluable postbaseline biopsy in the treatment period and a postbaseline DSQ combined score. The safety population, or full analysis set (FAS), was defined in the protocol and SAP to include all subjects who received at least one dose of any double-blind IP. The FAS was identical to the ITT population. However, the review team determined that the mITT and FAS populations utilized for efficacy and safety analyses would be modified to exclude a 9-year-old subject enrolled into the BOS treatment group, as this subject did not meet the inclusion criteria specified in the protocol and SAP (i.e., 11 to 40 years of age). The prespecified primary analyses of the coprimary endpoints were initially conducted in the mITT population. However, because the mITT population conditioned on post-randomization variables, the review team's preferred analyses of the symptomatic endpoint of change from baseline in total DSQ combined score was conducted in the FAS

population. The primary analysis of the coprimary histologic endpoint was repeated in the FAS population, and this analysis is presented in Section [6.2.1.4](#).

Efficacy Analysis

The analysis of the coprimary histologic endpoint used Pearson's chi-square test or, if the frequency count was less than five in any cell, used Fisher's exact test. Of note, the method for testing the histologic endpoint did not account for covariates due to the low response rate expected in the placebo group. Although not a prespecified analysis, the adjusted treatment difference was reported by averaging the treatment difference across strata defined by age group and diet restriction using Mantel-Haenszel (MH) weights. The analysis of the coprimary DSQ endpoint used an analysis of covariance (ANCOVA) model with treatment group as a factor and the baseline DSQ combined score as a covariate. The FDA-preferred analysis used ANCOVA with treatment group, age group, and diet restriction as factors and baseline DSQ combined score as a covariate.

Missing Data

For the coprimary histologic endpoint using either the mITT or FAS population, subjects with missing data were classified as nonresponders. For the coprimary DSQ endpoint, the prespecified primary analysis excluded subjects with missing data. Because excluding subjects from an analysis may introduce bias, the review team also considered analyses that used multiple imputation to handle the missing data for the coprimary DSQ endpoint. This analysis first used the Markov Chain Monte Carlo (MCMC) method to fill in intermittent missing values so that a monotone pattern was formed and then imputed the remaining missing values using a regression method that includes treatment group, prior DSQ combined scores, age group, and diet restriction as covariates. This imputation method assumed the DSQ combined score at Week 16 was missing at random conditional on the model covariates and DSQ combined score at prior weeks. Additional sensitivity analyses were performed using a more conservative placebo-based imputation to handle missing values due to dropout. For the symptomatic outcome, subjects with missing data were classified as nonresponders.

Multiplicity Adjustment

The trial would be considered successful if both coprimary efficacy endpoints demonstrated a statistically significant difference ($p < 0.05$) between the two treatment groups.

Algorithms for Calculating DSQ Endpoints

The DSQ combined score for the coprimary endpoint was calculated by summing the points from Questions 2 and 3 from each reported daily diary with nonmissing data and dividing this by the number of reported daily diaries with nonmissing data in the selected 14-day period. This quotient was then multiplied by 14. For the DSQ combined score, data for a given day was set to missing if the diary was not reported or the answer to Q1 (i.e., did you eat solid food) was "no." These endpoints were then set to missing if fewer than 8 of the 14 days were available during the

assessment period. For the DSQ combined score, a window-shift rule⁷ was applied in the prespecified analysis. The review team does not agree with the use of the window-shift rule because the “Week 16” DSQ combined score would not measure symptoms during the same timeframe for all subjects. Additional analyses performed by the review team did not use the window-shift rule.

In the multidisciplinary December 17, 2021 integrated review of NDA 213976 in DARRTS (Reference ID: 4907153), the review team’s preferred analysis used an alternative approach for calculating the DSQ combined score with two differences from the current approach presented in this review.

First, in the review of the original submission, the DSQ combined score was set to 6 (i.e., worst possible value) if the answer to Q1 was “No” (i.e., no solid food was eaten that day). However, because it is unclear whether avoidance of solid food (i.e., a response to Q1 of “No”) was due to a subject’s EoE, the review team determined that using the original prespecified approach based on multiple imputation for missing values due to a response to Q1 of “No” was a more suitable approach than assigning a value of 6 for responses to Q1 of “No.” (b) (4), (b) (5)



Second, in the review of the original submission, values were set to missing if fewer than four out of seven daily DSQ diaries were available in either week of the assessment period. The use of four out of seven days was originally recommended to ensure that subjects’ observed DSQ combined scores reflected their symptom severity during the entire 2-week period. This review will use the Applicant’s prespecified approach of requiring 8 out of 14 days in the assessment period for a total score to be considered nonmissing. The review team decided that this approach was reasonable because the DSQ was developed as a 14-day assessment. Additionally, sensitivity analyses showed both methods resulted in similar DSQ combined scores. Furthermore, the requirement for 8 out of 14 completed diary days in the assessment period is consistent with the approach used during the clinical trial that supported the May 2022 approval of Dupixent (dupilumab injection, BLA 761055) for the treatment of EoE.

⁷ If diary entries were available for fewer than 8 of the 14 days, the Applicant searched for an earlier 14-day window with 8 diary entries. Such 14-day periods cannot be shifted for more than 7 days (not including the trial visit day) when calculating DSQ combined score at baseline Visit 2, Week 8, and Week 12, and cannot be shifted for more than 14 days prior to the Week 16/Termination Visit (not including the visit day of Week 16/Termination Visit) for the DSQ combined score at the Final Treatment Period Evaluation.

6.2.1.4. Results of Analyses, Trial 101-06

Baseline Demographics and Clinical Characteristics

Among the safety population, most subjects were male (68%), White (95%), and adults (63%). The median age was 21 years with a range of 11 to 42 years of age. Over 65% of the subjects were on concomitant PPIs. The mean standard deviation DSQ combined scores at baseline were 30.7 (16.0) and 29.0 (13.5) in the BOS and placebo groups, respectively. Demographic factors and baseline disease characteristics and concomitant PPI use were generally balanced between the two treatment groups, as summarized in [Table 7](#) and [Table 8](#), respectively. Note that, as stated [above](#), all reported results exclude the subject who did not meet trial eligibility criteria for age at the time of randomization.⁸

Table 7. Baseline Demographic and Clinical Characteristics, Safety Population,^a Trial 101-06

Demographic and Clinical Characteristics	BOS 2 mg BID (N=50)	Placebo (N=42)	Total (N=92)
Sex, n (%)			
Female	16 (32.0)	13 (31.0)	29 (31.5)
Male	34 (68.0)	29 (69.0)	63 (68.5)
Age (years)			
Mean (SD)	23.0 (7.7)	21.3 (7.5)	22.2 (7.6)
Median	22.2	20.5	21.3
Min, max	12.2, 42.1	11.0, 39.3	11.0, 42.1
Age groups, n (%)			
<18 years	17 (34.0)	17 (40.5)	34 (37.0)
≥18 years	33 (66.0)	25 (59.5)	58 (63.0)
Race, n (%)			
Black or African American	3 (6.0)	0	3 (3.3)
White	47 (94.0)	40 (95.2)	87 (94.6)
Other	0	2 (4.8)	2 (2.2)
Months Since EoE Diagnosis			
Mean (SD)	385 (34.4)	36.5 (42.6)	37.6 (38.2)
Median	33.5	19.5	26.3
Min, max	0.0, 135.0	-0.1, 164.2	-0.1, 164.2
Baseline DSQ combined score			
N	50	41	91
Mean (SD)	30.7 (16.0)	29.0 (13.5)	29.9 (14.9)
Median	27.0	28.0	28.0
Min, max	6.5, 61.1	8.0, 50.4	6.5, 61.1
Baseline peak eosinophil count			
N	50	42	92
Mean (SD)	158.9 (96.7)	133.0 (81.6)	147.0 (90.6)
Median	134.0	135.0	134.0
Min, max	37.0, 426.0	22.0, 303.0	22.0, 426.0

Source: Based on Clinical Study Report Table 6 (page 62) and Table 7 (page 63). Verified by reviewer using ADSL.xpt and ADMH.xpt

^a One subject (USUBJID (b) (6)) was excluded from summary statistics due to not meeting trial eligibility criteria for age. Abbreviations: BID, twice daily; BOS, budesonide oral suspension; DSQ, Dysphagia Symptom Questionnaire; EoE, eosinophilic esophagitis; N, number of subjects; n, number of subjects in sample; SD, Standard Deviation

⁸ One subject (USUBJID (b) (6)) was excluded from summary statistics due to not meeting trial eligibility criteria for age.

Table 8. Concomitant PPI Use, Safety Population,^a Trial 101-06

Concomitant PPI Use	BOS 2 mg BID N=50 ^a n (%)	Placebo N=42 n (%)	Total N=92 n (%)
Any concomitant PPI use ^b	36 (72.0)	28 (66.7)	64 (69.6)
Dexlansoprazole ^c	1 (2.0)	1 (2.4)	2 (2.2)
Esomeprazole ^d	3 (6.0)	1 (2.4)	4 (4.3)
Lansoprazole ^e	7 (14.0)	4 (9.5)	11 (12.0)
Omeprazole ^f	21 (42.0)	19 (45.2)	40 (43.5)
Pantoprazole ^g	4 (8.0)	2 (4.8)	6 (6.5)
Omeprazole/sodium bicarbonate ^h	0	1 (2.4)	1 (1.1)

Source: Applicant-submitted table in response to an FDA information request

^a One subject (USUBJID (b) (6)) was excluded from summary statistics due to not meeting trial eligibility criteria for age^b One subject (USUBJID (b) (6)) had a dose decrease from omeprazole 20 mg BID to 20 mg QD^c Dexlansoprazole includes dexlansoprazole and Dexilant^d Esomeprazole includes esomeprazole and Nexium^e Lansoprazole includes lansoprazole and Prevacid^f Omeprazole includes omeprazole and Prilosec^g Pantoprazole includes pantoprazole and Protonix^h Omeprazole/sodium bicarbonate was recoded from Zegerid

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; N, number of subjects; n, number of subjects in sample; PPI, proton pump inhibitor; QD, once daily

Disposition

Subject disposition is summarized in [Table 9](#). Of the 92 subjects in the safety population, 87 (94.6%) subjects completed the double-blind treatment period and 86 (93.5%) of those 87 subjects were included in the mITT population. All subjects excluded from the mITT population were excluded because they did not have an evaluable postbaseline biopsy.

Table 9. Summary of Analysis Sets: Safety Population,^a Trial 101-06

Disposition Outcome	BOS 2 mg BID	Placebo	All Subjects
Safety set, n	50	42	92
Complete double blind treatment period, n (%)	48 (96.0%)	39 (92.9%)	87 (94.6%)
Did not complete double blind treatment period	2 (4.0%)	3 (7.1%)	5 (5.4%)
Primary reason for not completing trial, n (%)			
Adverse event	1 (2.0%)	0	1 (1.1%)
Lack of efficacy	0	1 (2.4%)	1 (1.1%)
Noncompliance with IP/visits	0	1 (2.4%)	1 (1.1%)
Physician decision	1 (2.0%)	0	1 (1.1%)
Pregnancy	0	1 (2.4%)	1 (1.1%)
mITT population	48 (96.0%)	38 (90.5%)	86 (93.5%)

Source: Based on Clinical Study Report Table 3 (page 57). Verified by reviewer using ADSL.xpt

^a One subject (USUBJID (b) (6)) was excluded from the analysis due to not meeting trial eligibility criteria for age.

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; mITT, modified intent-to-treat; n, total number of subjects in sample

Treatment Compliance

The SAP defined treatment compliance as a compliance rate within a range of 70% to 130% inclusive. In the safety population, the compliance rate during the double-blind treatment period ranged from 26.4% to 125.4% with a mean rate of 86.7% (median: 87.5%). In this population, 90.2% of subjects satisfied the Applicant's definition of treatment compliance.

Efficacy Results

Histologic Remission (Coprimary Endpoint)

The BOS treatment group had a statistically significantly higher proportion of histologic responders (38.0%) compared to those who received placebo (2.4%), $p < 0.001$ for the FAS population ([Table 10](#)). Results for the prespecified mITT population were similar.

Table 10. Histologic Responders at the Final Treatment Evaluation: mITT/FAS Population,^a Trial 101-06

Parameter	BOS 2 mg BID	Placebo
Prespecified analysis in the mITT population ^b		
Subjects with a histologic remission, n/N (%)	19/48 (39.6)	1/38 (2.6)
Adjusted treatment difference (95% CI)		36.4 (17.0, 51.0)
p-value		<0.0001
FDA preferred analysis in the FAS population ^b		
Subjects with a histologic remission, n/N (%)	19/50 (38.0)	1/42 (2.4)
Adjusted treatment difference (95% CI)		35.8 (17.2, 50.0)
p-value		<0.0001

Source: Based on Clinical Study Report Table 9 (page 68) and Table 2 of the IR response submitted on 12/15/23; verified by reviewer using XEFF.xpt

^a One subject (USUBJID (b) (6)) was excluded from the analysis due to not meeting trial eligibility criteria for age.

^b The adjusted treatment difference is the average treatment difference across strata defined by age group and diet restriction using MH weights. The 95% CI used the Newcombe method. p-value is based on Fisher's exact test.

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; FAS, full analysis set; MH, Mantel-Haenszel; mITT, modified intent-to-treat

Reduction in Dysphagia Symptoms Based on Absolute Change From Baseline in DSQ Combined Score (Coprimary Endpoint)

A statistically significant treatment difference in absolute change from baseline in DSQ combined score between BOS and placebo treatment groups was observed with a mean difference of -8.60 (95% confidence interval [CI]: -13.74, -3.46) and a p-value of 0.001 based on the FDA-recommended analysis in the FAS population. The Applicant's prespecified analysis in the mITT population produced similar results ([Table 11](#)).

Table 11. DSQ Endpoint: mITT/FAS Population,^a Trial 101-06

Statistic	BOS 2 mg BID	Placebo
Absolute change in DSQ combined score from baseline at Week 16 (prespecified analysis in mITT population) ^b		
N	48	38
LS Mean (95% CI)	-14.2 (-17.6, -10.8)	-7.6 (-11.4, -3.7)
LS Mean Difference (95% CI)		-6.6 (-11.7, -1.5)
p-value		0.0118
Absolute change in DSQ combined score from baseline at Week 16 (FDA preferred analysis in FAS population) ^c		
N	50	42
LS Mean (95% CI)	-14.5 (-18.0, -11.0)	-5.9 (-10.0, -1.8)
LS Mean Difference (95% CI)		-8.6 (-13.7, -3.5)
p-value		0.001

Source: Based on Clinical Study Report Table 10 (page 70) and Table 3 of the IR response submitted on 11/30/2023; verified or generated by reviewer using XEFF.xpt, and ADDSQ4.xpt

^a One subject (USUBJID (b) (6)) was excluded from the analyses due to not meeting trial eligibility criteria for age.

^b Results were based on an ANCOVA model with treatment group as a factor and baseline score as a covariate. Missing subjects were excluded from the analysis and the window-shift-rule was applied. Subjects were considered missing if they had fewer than 8 nonmissing daily DSQ combined scores during the 14-day period. Daily scores were considered missing on days where no solid was eaten (i.e., DSQ-Q1 = 'No').

^c FDA preferred analysis using ANCOVA model with treatment group, age group and diet restriction as factors and baseline score as a covariate using multiple imputation. Subjects were considered missing if they had fewer than 8 nonmissing daily DSQ combined scores during the 14-day period. Daily scores were considered missing on days where no solid was eaten (i.e., DSQ-Q1 = 'No').

^d Treatment difference was averaged across strata defined by age group and diet restriction using MH weights. Confidence interval was calculated using the Newcombe score method and the p-value was based on the CMH statistic. Missing data were handled using nonresponder imputation. Subjects were considered missing if they had fewer than 8 nonmissing daily DSQ combined scores during the 14-day period. Daily scores were considered missing on days where no solid was eaten (i.e., DSQ-Q1 = 'No').

Abbreviations: ANCOVA, analysis of covariance; BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; CMH, Cochran Mantel Haenszel; DSQ, Dysphagia Symptom Questionnaire; FAS, full analysis set; FDA, U.S. Food and Drug Administration; LS Mean, least squares mean; MH, Mantel-Haenszel; mITT, modified intent-to-treat; N, number of subjects

As a sensitivity analysis, the analysis of the absolute change from baseline in DSQ combined score was repeated using a more conservative placebo-based imputation to handle missing values due to dropout. The results of this analysis were similar to those presented above.

Subgroup Analyses

An analysis of histologic remission was performed in subgroups defined by sex, age, race, ethnicity, and diet restriction ([Table 12](#)). In all evaluable subgroups, the response rate was larger in the BOS treatment group, as compared to the placebo treatment group.

Table 12. Histologic Responders at the Final Treatment Evaluation by Subgroup: FAS Population,^a Trial 101-06

Demographic	BOS 2 mg BID n/N (%)	Placebo n/N (%)	Difference ^b (95% CI)
Sex			
Female	8/16 (50.0)	0/13 (0.0)	50.0 (25.5, 74.5)
Male	11/34 (32.4)	1/29 (3.4)	28.9 (11.8, 46.0)
Age group			
<18 years	8/17 (47.1)	1/17 (5.9)	41.2 (15.0, 67.4)
≥18 years	11/33 (33.3)	0/25 (0.0)	33.3 (17.3, 49.4)
Race			
Black or African American	3/3 (100)	0/0 (--)	--
White	16/47 (34.0)	1/40 (2.5)	31.5 (17.2, 45.9)
Other	0/0 (--)	0/2 (0.0)	--
Ethnicity			
Hispanic or Latino	0/0 (--)	0/1 (0.0)	--
Not Hispanic or Latino	19/50 (38.0)	1/41 (2.4)	35.6 (21.3, 49.8)
Diet restriction			
Yes	8/18 (44.4)	0/9 (0.0)	44.4 (21.5, 67.4)
No	11/32 (34.4)	1/33 (3.0)	31.3 (13.9, 48.8)

Source: Reviewer-generated results using XEFF.xpt

^a One subject (USUBJID (b) (6)) was excluded from the analysis due to not meeting trial eligibility criteria for age.^b The difference is the unadjusted difference in proportions and the CI is based on the Wald method.

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; FAS, full analysis set, N, number of subjects; n, total number of subjects in sample

An analysis of the absolute change from baseline in DSQ combined score was also performed in subgroups defined by sex, age, race, ethnicity, and diet restriction ([Table 13](#)). With the exception of the pediatric subgroup, the absolute change from baseline in DSQ combined score was more pronounced in the BOS treatment group when compared to the placebo group. In the pediatric subgroup, the absolute change from baseline in DSQ combined score was similar in both treatment arms. Of note, these exploratory subgroup analyses are based on observed DSQ combined scores.

Table 13. Absolute Change From Baseline in DSQ Combined Score at Week 16 by Subgroup: FAS Population,^a Trial 101-06

Demographic	BOS 2 mg BID		Placebo		
	N	Mean (95% CI)	N	Mean (95% CI)	Difference ^b (95% CI)
Sex					
Female	16	-12.6 (-17, -8.1)	13	-5.3 (-10.2, -0.4)	-7.3 (-13.9, -0.6)
Male	34	-16.1 (-20.9, -11.2)	29	-8.2 (-13.6, -2.7)	-7.9 (-15.2, -0.6)
Age groups					
<18 years	17	-10.0 (-16.8, -3.2)	17	-10.8 (-17.3, -4.3)	0.8 (-8.7, 10.2)
≥18 years	33	-17.2 (-21.4, -13.1)	25	-4.7 (-9.7, 0.3)	-12.5 (-19.0, -6.0)
Race					
Black or African American	3	-18.0 (-243.0, 207.1)	0	--	--
White	47	-14.7 (-18.3, -11.2)	40	-7.2 (-11.1, -3.4)	-7.5 (-12.8, -2.3)
Ethnicity					
Hispanic or Latino	0	--	1	-6.5 (--)	--
Not Hispanic or Latino	51	-14.9 (-18.5, -11.3)	41	-7.3 (-11.4, -3.3)	-7.6 (-13.0, -2.2)
Diet Restriction					
Yes	18	-14.9 (-22.4, -7.5)	9	-2.4 (-12.2, 7.4)	-12.5 (-24.8, -0.2)
No	32	-15.1 (-19.1, -11.1)	33	-8.6 (-12.8, -4.5)	-6.4 (-12.2, -0.6)

Source: Reviewer-generated results using ADDSQ4

^a One subject (USUBJID (b) (6)) was excluded from the analysis due to not meeting trial eligibility criteria for age.^b The difference is the unadjusted difference in means and the CI is based on the Wald method. Subjects with missing data were excluded from the analysis.

Abbreviations: ANCOVA, analysis of covariance; BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; DSQ, Dysphagia Symptom Questionnaire; FAS, full analysis set; MH, Mantel-Haenszel; N, number of subjects

6.2.2. Trial 301

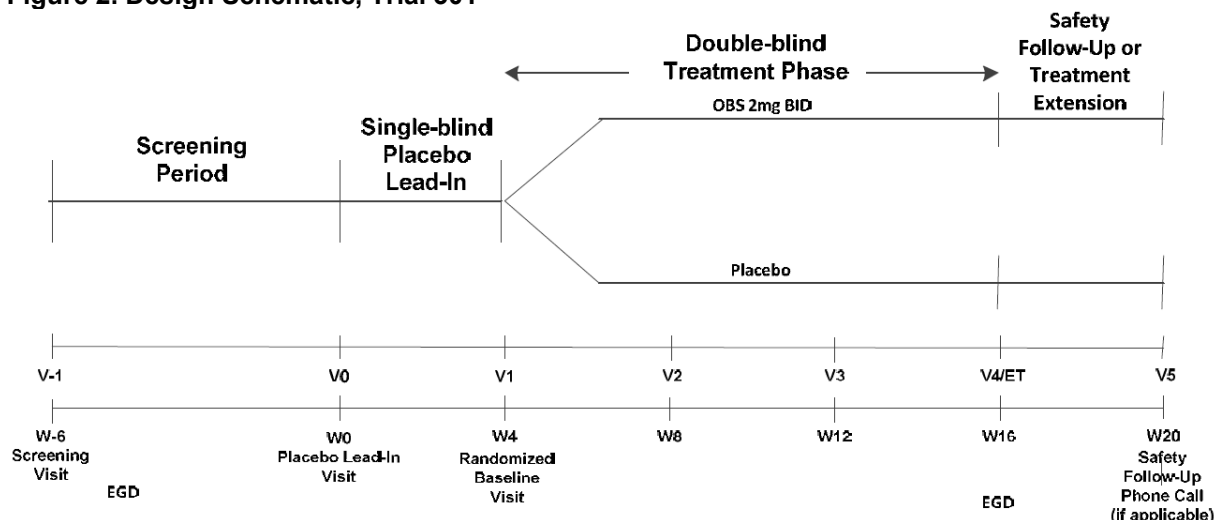
Trial 301 was previously reviewed as presented in the multidisciplinary December 17, 2021 integrated review of NDA 213976 in DARRTS (Reference ID: 4907153). This review will only include key details of the trial, key analyses to support the evaluation of benefit-risk, and new analyses not included in the original review.

6.2.2.1. Design, Trial 301

Trial 301 was a phase 3, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy and safety of BOS treatment administered BID (every morning after meals and at bedtime) for 12 weeks in pediatric and adult subjects, 11 to 55 years of age (inclusive) with EoE and symptoms of dysphagia.

As shown in [Figure 2](#), subjects in Trial 301 were randomized 2:1 to receive either BOS 2 mg or placebo. This trial consisted of three periods: a 3- to 6-week screening period, a 4-week single-blind placebo lead-in period, and a 12-week double-blind treatment period. At least 306 subjects were planned to be randomized 2:1 to budesonide or placebo.

Figure 2. Design Schematic, Trial 301



Source: Applicant-submitted Summary of Clinical Efficacy Figure 2, p. 30

Abbreviations: BID, twice daily; OBS, oral budesonide suspension; EGD, esophagogastroduodenoscopy; ET, end of treatment; V, visit; W, Week

Trial 301 was designed to show superiority of BOS to placebo on the two coprimary endpoints of histologic remission and dysphagia symptom response. Histologic remission was defined as a peak eosinophil count of ≤ 6 per HPF across all available esophageal levels at Week 16 visit (after 4 weeks of screening and 12-week double-blinded treatment). Dysphagia symptom response was defined as $\geq 30\%$ reduction in the DSQ combined score (sum of questions 2+3) from baseline. The DSQ combined score was calculated using the DSQ daily diary data within a 14-day analysis window prior to the actual clinical visit at baseline or Week 16.

Although the $\geq 30\%$ 14-day DSQ responder threshold was prespecified by the Applicant based on phase 2 data, FDA cautioned the Applicant several times during communications issued under IND 103173 that further evidence would be needed to support the $\geq 30\%$ 14-day DSQ responder threshold reflects a clinically meaningful benefit to patients based on phase 3 data and anchor-based analyses. These communications include:

- November 12, 2014 type B end-of-phase 2 meeting
- July 13, 2015 type C guidance meeting
- September 15, 2015 advice/information request letter
- September 17, 2018 advice/information request letter
- February 7, 2019 advice/information request letter
- May 20, 2020 type B pre-NDA meeting

Although statistically significant results were reported, the clinical meaningfulness of the Applicant's prespecified symptomatic coprimary endpoint of a $\geq 30\%$ reduction in the DSQ combined score after 12 weeks of treatment for Trial 301 could not be confirmed. For more details, refer to the multidisciplinary December 17, 2021 integrated review of NDA 213976 in DARRTS (Reference ID: 4907153). The first-ranked secondary endpoint of absolute change from baseline in DSQ combined score was identified by the review team as informative of the

symptomatic treatment effect of BOS. This endpoint was also evaluated as the symptomatic coprimary endpoint in Trial 101-06.

6.2.2.2. Eligibility Criteria, Trial 301

Eligibility criteria for Trial 301 were similar to those for Trial 101-06 shown in Section [6.2.1.2](#). For full details, refer to the multidisciplinary December 17, 2021 integrated review of NDA 213976 in DARRTS (Reference ID: 4907153).

6.2.2.3. Statistical Analysis Plan, Trial 301

For details of the SAP for Trial 301, refer to the multidisciplinary December 17, 2021 integrated review of NDA 213976 in DARRTS (Reference ID: 4907153).

Endpoints

The two coprimary endpoints for Trial 301 were (i) histologic remission at Week 16 and (ii) dysphagia symptom response, defined as $\geq 30\%$ reduction in the DSQ combined score from baseline to Week 16. The first-ranked secondary endpoint was absolute change from baseline in DSQ combined score at Week 16. As stated above, for additional discussion on the clinical meaningfulness of the Applicant's definition of dysphagia symptom response, refer to the multidisciplinary December 17, 2021 integrated review of NDA 213976 in DARRTS (Reference ID: 4907153). Trial 301 also included the EoE Endoscopic Reference Score (EREFS) as a secondary endpoint. (b) (4)

FDA encourages the prospective and systematic collection of data on endoscopic findings (e.g., EREFS), as well as histologic features of EoE, as exploratory endpoints during clinical trials. Data collected using these assessments in development programs of drugs for the treatment of EoE may support the future identification and subsequent verification of thresholds based on EREFS, or similar instruments, that correlate with clinical improvement and/or worsening.

Analysis Populations

The definitions of the analysis populations were similar to the definitions used in Trial 101-06. The FDA-preferred analysis population for the coprimary and key secondary efficacy endpoints was defined as the FAS, which consisted of all randomized subjects who received at least one dose of IP.

Efficacy Analysis

The coprimary histologic endpoint was analyzed using a Cochran-Mantel-Haenszel test with histologic remission as the dependent variable, stratified by baseline age group and diet restriction. The adjusted treatment differences were reported by averaging the treatment difference across strata defined by age group and diet restriction using MH weights along with the corresponding Newcombe 95% confidence intervals. The prespecified analysis for the first-ranked secondary efficacy endpoint, absolute change from baseline in DSQ combined score at Week 16, was an ANCOVA model with treatment group and age group as factors and the baseline DSQ combined score as a continuous covariate. The FDA-preferred analysis used an ANCOVA model with treatment group, age group, and diet restriction as factors and baseline score as a covariate.

Missing Data

For the coprimary histology endpoint, subjects with missing data were classified as nonresponders. For the first-ranked secondary DSQ endpoint, the prespecified analysis excluded subjects with missing data. Because excluding subjects from an analysis may introduce bias, the review team also considered analyses that used multiple imputation to handle the missing data for the coprimary DSQ endpoint. This analysis first used the MCMC method to fill in intermittent missing values so that a monotone pattern was formed and then imputed the remaining missing values using a regression method that includes treatment group, prior DSQ combined scores, age group, and diet restriction as covariates. This imputation method assumed the DSQ combined score at Week 16 (i.e., after 12 weeks of treatment) was missing at random conditional on the model covariates and DSQ combined score at prior weeks. In the multidisciplinary December 17, 2021 integrated review of NDA 213976 (DARRTS Reference ID: 4907153), missing data was handled using a pattern mixture model with a control-based imputation method for the preferred FDA analysis. Missing data due to drop out in the BOS group were imputed assuming missing not at random while intermittent missing data in the BOS group and all missing data in the placebo group were imputed assuming missing at random. This approach is more conservative than the missing at random imputation; however, most sensitivity analyses based on the pattern mixture model demonstrated statistically significant results (refer to Table 43 in the multidisciplinary December 17, 2021 integrated review of NDA 213976 [DARRTS Reference ID: 4907153]) and the efficacy results were considered robust with respect to missing data assumptions. The missing at random imputation approach was chosen to maintain consistency with the approach used during the clinical trial that supported the May 2022 approval of Dupixent (dupilumab injection, BLA 761055) for the treatment of EoE.

Multiplicity Adjustment

A hierarchical testing procedure was used to control the Type I error with the first-ranked secondary endpoint only tested if the trial first succeeded with its coprimary endpoints.

Algorithms for Calculating DSQ Endpoints

The algorithm for calculating the DSQ endpoints for Trial 301 is the same algorithm used for Trial 101-06. See *Algorithms for Calculating DSQ Endpoints* in Section [6.2.1.3](#) for details and a description of the differences between the approach in this resubmission compared to the

preferred approach used in the multidisciplinary December 17, 2021 integrated review of NDA 213976 (DARRTS Reference ID: 4907153).

6.2.2.4. Results of Analyses, Trial 301

Results from analyses of the histologic coprimary endpoint and the first-ranked secondary endpoint (i.e., absolute change from baseline in DSQ combined score) are presented below. Refer to the multidisciplinary December 17, 2021 integrated review of NDA 213976 in DARRTS (Reference ID: 4907153) for additional analyses and results including: demographic information, disposition, analyses of the coprimary symptomatic endpoint, missing data sensitivity analyses, and subgroup analyses for the coprimary and first-ranked secondary endpoints.

Among the safety population, most subjects were male (60%), White (95%), and adults (87%). The median age was 34 years with a range of 11 to 56 years of age. Over 80% of the subjects were on concomitant PPI. The mean standard deviation DSQ combined scores at baseline were 30.3 (13.9) and 30.4 (13.1) in the BOS and placebo groups, respectively. Demographic factors, baseline disease characteristics, and concomitant PPI use were generally balanced between the two treatment groups. [Table 14](#) summarizes the concomitant PPI use in the trial.

Table 14. Concomitant PPI Use, Safety Population, Trial 301

Concomitant PPI Use ^a	BOS 2 mg BID N=213, n (%)	Placebo N=105, n (%)	Total N=318, n (%)
Any concomitant PPI use	176 (82.6)	92 (87.6)	268 (84.3)
Dexlansoprazole	2 (0.9)	2 (1.9)	4 (1.3)
Esomeprazole ^b	16 (7.5)	3 (2.9)	19 (6.0)
Lansoprazole	10 (4.7)	5 (4.8)	15 (4.7)
Omeprazole	105 (49.3)	57 (54.3)	162 (50.9)
Pantoprazole ^c	43 (20.2)	25 (23.8)	68 (21.4)

Source: Applicant-submitted table in response to an FDA information request

^a Although six subjects had more than one PPI, or more than one dose of the same PPI listed as concomitant during the double-blind treatment period, only the first PPI taken by the subject during the trial has been included in the table above. Of note, USUBJID (b) (6) switched from lansoprazole 30 mg QD oral for GERD to pantoprazole 40 mg QD oral for GERD; USUBJID (b) (6) was listed in the ADCM.xpt dataset as being on both esomeprazole 20 mg QD oral for EoE and dexlansoprazole 60 mg QD oral for EoE concurrently with no end date (in response to an FDA information request, the Applicant stated that the subject switched from esomeprazole to dexlansoprazole during the trial); and USUBJID (b) (6) switched from omeprazole 40 mg QD oral for EoE to pantoprazole 40 mg QD IV for three days for an acute illness). These subjects are accounted for in the table as having used lansoprazole, esomeprazole, and omeprazole, respectively.

^b Esomeprazole includes esomeprazole and esomeprazole magnesium

^c Pantoprazole includes pantoprazole and pantoprazole sodium sesquihydrate

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; GERD, gastroesophageal reflux disease; N, number of subjects; n, total number of subjects in sample, PPI, proton pump inhibitor; QD, once daily

Efficacy Results

Histologic Remission and Dysphagia Symptoms Response (Coprimary Endpoints)

As shown in [Table 15](#), the BOS treatment group had a statistically significantly higher proportion of histologic responders compared to the placebo group (53.1% versus 1.0%, p-value <0.001) and subjects achieving $\geq 30\%$ improvement in absolute change from baseline in DSQ combined score (52.6% versus 39.1%, p=0.024).

Table 15. Coprimary Efficacy Results at Week 16, FAS, Trial 301

Coprimary Endpoint	BOS 2.0 mg BID N=213 n (%)	Placebo N=105 n (%)	Treatment Difference^a (95% CI)	P-Value
Histologic remission	113 (53.1)	1 (1.0)	52 (43.3, 59.1)	<0.001
Dysphagia symptom response				
≥30% improvement	112 (52.6)	41 (39.1)	13 (1.6, 24.3)	0.024

Source: FDA review team's Analysis

^a The adjusted treatment difference is the average treatment difference across strata defined by age group and diet restriction using MH weights. The 95% CI used the Newcombe method.^b p-value is based on the CMH test.

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; FAS, full analysis set; MH, Mantel-Haenszel; N, number of subjects; n, total number of subjects in sample

As stated above (Section [I](#)), although the ≥30% DSQ responder threshold was carried forward for use as the symptomatic coprimary endpoint in Trial 301, and statistically significant results were demonstrated for this analysis (112/213 [52.6%] subjects who received BOS versus 41/105 [39.1%] subjects who received placebo, p=0.024), the available data do not confirm this threshold as clinically meaningful. Therefore, to support the evaluation of the effect of BOS on clinical symptoms of dysphagia in Trial 301, the review team focused on the first-ranked secondary endpoint (i.e., absolute change from baseline in DSQ combined score). As absolute change from baseline in DSQ combined score was evaluated as the symptomatic coprimary endpoint in Trial 101-06 (see Section [6.2.1](#)), the review team was able to assess the reproducibility of the results of analyses of this endpoint across the two adequate and well-controlled trials. See Section [6.3.1](#) for additional discussion.

First-Ranked Secondary Endpoint - Absolute Change from Baseline in DSQ Combined Score

A statistically significant treatment difference in absolute change from baseline in DSQ combined score between BOS and placebo treatment groups was observed with a mean difference of -3.70 (95% CI: -6.78, -0.62) and a p-value of 0.018 based on the FDA-preferred analysis in the FAS population ([Table 16](#)).

Table 16. Absolute Change From Baseline in DSQ Combined Score Endpoint: FAS Population, Trial 301

Statistic	BOS 2 mg BID	Placebo
Absolute change in DSQ combined score from baseline to Week 16 (prespecified analysis) ^a		
N	213	105
LS mean (95% CI)	-13.0 (-15.4, -10.6)	-9.1 (-12.1, -6.1)
LS mean difference (95% CI)		-3.9 (-7.1, -0.8)
p-value		0.015
Absolute change in DSQ combined score from baseline to Week 16 (FDA preferred analysis) ^b		
N	213	105
LS mean (95% CI)	-10.2 (-13.2, -7.3)	-6.5 (-10.1, -3.1)
LS mean difference (95% CI)		-3.7 (-6.8, -0.6)
p-value		0.018

Source: Based on Clinical Study Report Table 12 (page 102) and Table 1 of the IR response submitted on 12/15/2023; verified by reviewer using ADDSQ.xpt and ADDSQ7.xpt

^a Results were based on an ANCOVA model with treatment group and age group as factors and baseline score as a covariate. Missing subjects were excluded from the analysis and the window-shift-rule was applied. Subjects were considered missing if they had fewer than 8 nonmissing daily DSQ combined scores during the 14-day period. Daily scores were considered missing on days where no solid was eaten (i.e., DSQ-Q1 = 'No').

^b FDA preferred analysis using ANCOVA model with treatment group, age group, and diet restriction as factors and baseline score as a covariate using multiple imputation. Subjects were considered missing if they had fewer than 8 nonmissing daily DSQ combined scores during the 14-day period. Daily scores were considered missing on days where no solid was eaten (i.e., DSQ-Q1 = 'No').

Abbreviations: ANCOVA, analysis of covariance; BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; CMH, Cochran Mantel Haenszel; DSQ, Dysphagia Symptom Questionnaire; FAS, full analysis set; LS mean, least squares mean; MH, Mantel-Haenszel; N, number of subjects

Subgroup Analyses

Subgroup analyses for the prespecified primary and secondary endpoints are available in the multidisciplinary December 17, 2021 integrated review of NDA 213976 in DARRTS (Reference ID: 4907153).

6.2.3. Trial 302

Although not positioned to support the determination of substantial evidence of effectiveness for BOS for the short-term treatment of EoE, it is important to note that Trial 302 (36-week extension trial following Trial 301) did not yield statistically significant results on the prespecified long-term primary efficacy endpoint of relapse, or the prespecified secondary endpoints of histologic remission or symptomatic response, in subjects who were considered “Trial 301 BOS full responders”⁹ and who continued to receive BOS 2 mg twice daily in Trial 302, compared to “Trial 301 BOS full responders” who received placebo in Trial 302 (these subjects switched from having received BOS 2 mg twice daily in Trial 301).¹⁰ See [Table 17](#) for the results of the prespecified efficacy endpoints from Trial 302.

⁹ “Trial 301 full responders” were defined by the Applicant as having both ≤ 6 eosinophils per HPF across all available esophageal levels and $\geq 30\%$ reduction in DSQ combined scores at the final treatment evaluation for Trial 301.

¹⁰ Relapse was defined by the Applicant as a subject meeting both the eosinophil histology relapse criterion (i.e., an eosinophil count of ≥ 15 per high power field from ≥ 2 of 3 levels of the esophagus, as determined by a central reader’s valuation of EGD biopsy tissues) and the dysphagia symptom relapse criterion (defined as a minimum of 4 days of dysphagia in the 2-week period prior to the scheduled visit, as determined by the DSQ Question 2) at any time during the trial.

Table 17. Primary and Secondary Efficacy Results, “Trial 301 BOS Full Responders” FAS, Trial 302

Endpoints	BOS 2 mg BID N=25 n (%)	Placebo N=23 n (%)	Treatment Difference BOS-Placebo (95% CI^[1])	p-Value^[2]
Primary endpoint over 36-week period				
Relapse (both histology and DSQ)	6 (24)	10 (43)	-19 (-0.45, 0.08)	0.13
Secondary endpoints at week 36				
Histology response	7 (30)	13 (52)	22 (-0.07, 0.49)	0.11
Symptomatic (DSQ) response to SHP621-301 baseline	18 (78)	21 (84)	6 (-0.18, 0)	0.44
Symptomatic (DSQ) response to SHP621-302 baseline	9 (39)	10 (40)	1 (-0.27, 0.29)	0.59

Source: Review team's adaptation of Study 302 CSR Tables 8, 10, 15

^[1] The 95% confidence interval (CI) used the exact CI.

^[2] P-value was based on the Fisher's exact test

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; DSQ, Dysphagia Symptom Questionnaire; FAS, full analysis set; PBO, placebo

For review and discussion of the lack of demonstration of long-term efficacy in Trial 302, refer to the multidisciplinary December 17, 2021 integrated review of NDA 213976 in DARRTS (Reference ID: 4907153).

As efficacy beyond 12 weeks of treatment was not demonstrated for BOS for the treatment of EoE, the review team is recommending inclusion of the following limitation of use statement in the INDICATIONS AND USAGE section of the PI to appropriately communicate the limited indication supported by the available data.

EOHILIA has not been shown to be safe and effective for the treatment of EoE for longer than 12 weeks [see *Dosage and Administration (2.1)*, *Clinical Studies (14)*].

To support this statement, the review team is also recommending inclusion of the following description of Trial 302 in the Section 14 CLINICAL STUDIES of the PI.

Additional Study

After completing Study 1, 48 subjects from the EOHILIA 2 mg treatment arm entered a double-blind randomized withdrawal extension study. These subjects received EOHILIA 2 mg twice daily or placebo for up to an additional 36 weeks. Treatment with EOHILIA did not demonstrate a statistically significant difference compared to subjects re-randomized to placebo for prespecified efficacy endpoints based on eosinophil count and/or clinical symptoms measured by the DSQ at Week 36.

6.3. Key Efficacy Review Issue

6.3.1. Adequacy of the Available Data To Support the Demonstration of Clinical Benefit

Issue

Statistically significant results were obtained for the evaluation of the symptomatic endpoint (absolute change from baseline in DSQ combined score) in both Trial 101-06 and Trial 301. However, as described in Section I, multiple factors precluded utilization of FDA's preferred approach of using anchor-based analyses to aid in interpretation of whether the statistically significant results of the symptomatic endpoint analyses represented clinically meaningful change in this resubmission.

Background

In patients with EoE, clinical features and histologic activity can vary independently. Trial 101-06 and Trial 301 both yielded statistically significant results for their histologic coprimary endpoint of remission, defined as a peak eosinophil count of ≤ 6 per HPF. Because this definition has been adequately characterized and supported to represent improvement, the results of these analyses are both interpretable and consistent with improvement. These two trials also yielded statistically significant results for their respective symptomatic coprimary endpoints of $\geq 30\%$ reduction in absolute DSQ combined score (Trial 301) and absolute change from baseline in DSQ combined score (Trial 101-06). Trial 301 also achieved statistically significant results for the prespecified first-ranked secondary endpoint of absolute change from baseline in DSQ combined score. However, because small but statistically significant group-level mean differences in a clinical outcome assessment endpoint may not establish whether an effect is clinically meaningful to patients, the guidance for industry *Eosinophilic Esophagitis: Developing Drugs for Treatment* (September 2020) ([FDA 2020](#)) recommends the use of anchor-based methods to aid in the interpretation of the clinical meaningfulness of clinical outcome assessment endpoint results. As described in Section I, multiple factors precluded utilization of FDA's preferred approach of anchor-based analyses to aid in interpretation of whether the statistically significant results of the symptomatic endpoint analyses represented clinically meaningful change.

Given the favorable results on the prespecified COA endpoints across two adequate and well-controlled trials and the existing need for short-term therapy to quell acute flares and/or to function as a bridge to an effective long-term management strategies in patients with EoE (see Section I), the review team determined that it is appropriate to consider whether an alternate metric with inherent clinical meaningfulness (i.e., achieving no dysphagia or experiencing only dysphagia that "got better or cleared up on its own") could provide additional information and context to inform the evaluation of the statistically significant results of the symptomatic endpoint in lieu of anchor-based analyses.

As described in Section I, the review team requested the Applicant provide analyses to evaluate DSQ Question 2 (Q2: "Since you woke up this morning, has food gone down slowly or been stuck in your throat?") =0 ("No") and DSQ Question 3 (Q3: "For the most difficult time you had while swallowing food today, did you have to do anything to make the food go down or to get

relief?”) =0 (“No, it got better or cleared up on its own.”). The additional assessments of Q2=0 and Q3=0 were identified and requested by the review team independent of the Applicant’s submitted post-hoc analyses and prior to the positioning of Trial 101-06 as an adequate and well-controlled trial to support the proposed indication. The relevance and clinical meaningfulness of achieving no dysphagia or only dysphagia that “got better or cleared up on its own” to patients with EoE was established based on qualitative data supporting the terminology, as well as its contribution to the DSQ combined score, during development of the DSQ and has been confirmed by qualitative data from development programs that have utilized the DSQ subsequently. While there was a trend seen on the FDA-requested assessment of no dysphagia (Q2=0), the results did not achieve the standard threshold used for defining statistical significance (i.e., $p < 0.05$). This finding is likely attributable to the small proportion of subjects meeting the stringent threshold of achieving complete resolution of all dysphagia episodes during the last 2 weeks of the 12-week treatment period. Therefore, the review team focused on the assessment of Q3=0 (no dysphagia or dysphagia that “got better or cleared up on its own”) to evaluate the clinical meaningfulness of the symptomatic treatment effect. Of note, achieving Q3=0 also includes subjects who achieved no dysphagia (Q2=0), given that when a subject responded no to Q2, they automatically received a score of 0 for Q3.

In addition to the assessments of Q3=0 for Trials 101-06 and 301, exploratory analyses based on the observed DSQ combined score and the Q3=0 assessment over the 12-week treatment duration were conducted to evaluate when observable treatment effects were demonstrated and how observable treatment effects progressed throughout the trials. Results of these assessments are shown for Trial 101-06 and Trial 301 below.

Assessment

Trial 101-06

Assessment of Q3=0

The results of the evaluation of the outcome of having no dysphagia or only dysphagia that got better or cleared up on its own are presented in [Table 17](#). This post hoc outcome is representative of an interpretable symptomatic response and is defined as having either answered “No” to DSQ Q2 or answered “No, it got better or cleared up on its own” to DSQ Q3 for all diary entries reported during the Week 16 assessment period (i.e., no score greater than 0 on DSQ Q3 at Week 15 or Week 16). This outcome is equivalent to not having dysphagia that required adaptive behaviors or interventions during the evaluated timepoint.

During Trial 101-06, a greater proportion of subjects randomized to BOS achieved the outcome of Q3=0 during Weeks 15 and 16 (45.1%) compared to placebo (21.4%). Although this analysis was not prespecified, the results ($p = 0.0039$) met the standard threshold used for defining statistical significance (i.e., $p < 0.05$) ([Table 18](#)). The estimated treatment difference was computed by averaging the treatment difference across strata defined by age group and diet restriction using MH weights. The 95% CI was estimated using the stratified Newcombe score method and the p-value was calculated based on the Cochran-Mantel-Haenszel test.

Table 18. DSQ Outcome of Q3=0: FAS Population,^a Trial 101-06

Statistic	BOS 2 mg BID	Placebo
No daily score >0 for DSQ Q3 at Week 16 in FAS population ^b		
N	50	42
Responders, n (%)	22 (44.0)	9 (21.4)
Difference in response rates (95% CI)		28.2 (7.7, 44.9)
p-value		0.0039

Source: Based on Table 1420.2.2.3.1.2.2 of the IR response submitted on 10/26/2023; verified or generated by reviewer using ADDSQ4.xpt

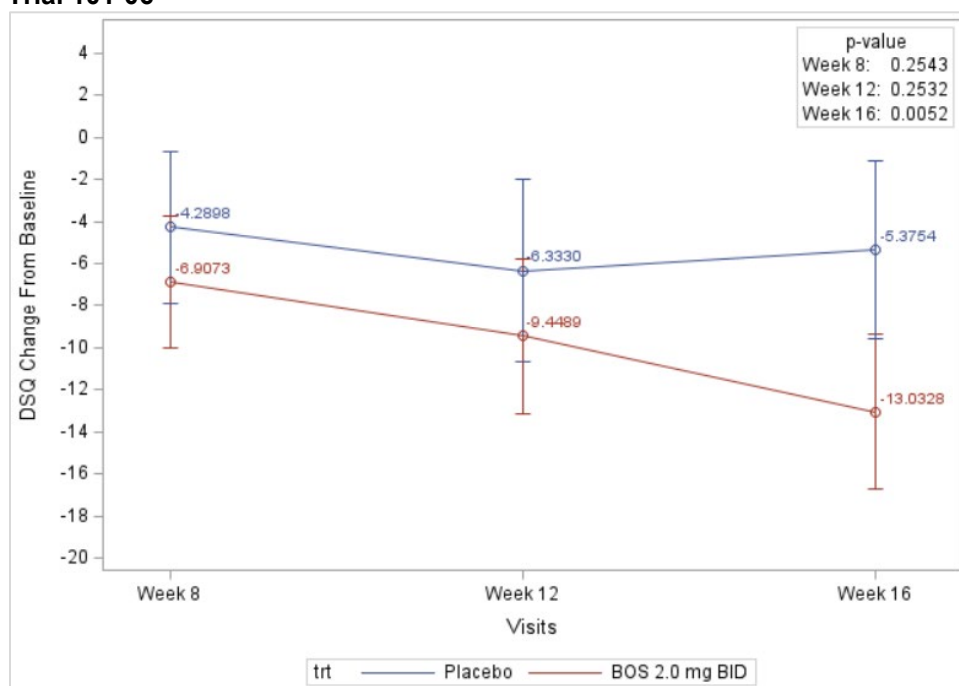
^a One subject (USUBJID [REDACTED] (b) (6)) received BOS and was excluded from summary statistics due to not meeting trial eligibility criteria for age.

^b Treatment difference was averaged across strata defined by age group and diet restriction using MH weights. Confidence interval was calculated using the Newcombe score method and the p-value was based on the CMH statistic. Missing data were handled using nonresponder imputation. Subjects were considered missing if they had fewer than 8 nonmissing daily DSQ combined scores during the 14-day period. Daily scores were considered missing on days where no solid was eaten (i.e., DSQ Q1 = 'No').

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; CMH, Cochran Mantel Haenszel; DSQ, Dysphagia Symptom Questionnaire; FAS, full analysis set; MH, Mantel-Haenszel; N, number of subjects; n, total number of subjects in sample

Change in DSQ Combined Score Over Time

In addition to the additional assessment of the DSQ outcome of Q3=0, the review team conducted exploratory analyses based on the observed DSQ combined score to explore change in the score over time. Although separation between treatment groups was observed at Week 8 (i.e., after 4 weeks of treatment) and Week 12 (i.e., after 8 weeks of treatment), the between-arm difference in the change was not nominally significant until Week 16 (i.e., after 12 weeks of treatment). These results are shown in [Figure 3](#) and are supportive of identifiable treatment effects of BOS within the 12-week treatment period.

Figure 3. Absolute Change^a in DSQ Combined Score From Baseline Over Time: FAS Population,^b Trial 101-06

Source: Reviewer-generated analysis using XEFF.xpt

^a Results are based on ANCOVA model with treatment group, age group and diet restriction as factors and baseline score as a covariate in the FAS population. Subjects with missing data were excluded from the analysis. Points represent LS means and vertical lines indicate 95% CIs.

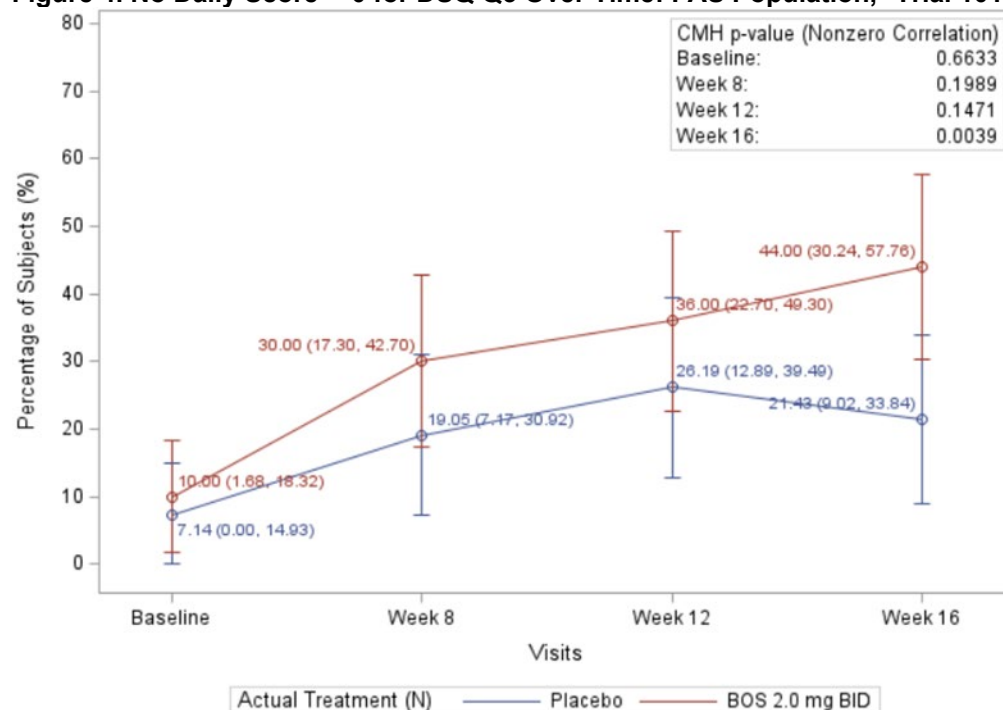
^b One subject (USUBJID (b) (6)) received BOS and was excluded from summary statistics due to not meeting trial eligibility criteria for age.

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; DSQ, Dysphagia Symptom Questionnaire; FAS, full analysis set; OBS, oral budesonide suspension; trt, treatment

Assessment of Q3=0 Over Time

Additional exploratory analyses were conducted for the assessment of Q3=0 over the course of Trial 101-06. As shown in [Figure 4](#), the proportion of subjects with no daily score greater than 0 for Q3 (i.e., Q3=0) was larger in the BOS treatment group as compared to the placebo group starting after 4 weeks of treatment at Week 8. As with absolute change in DSQ combined score over time, the difference between treatment groups was not nominally significant until Week 16.

Figure 4. No Daily Score^a >0 for DSQ Q3 Over Time: FAS Population,^b Trial 101-06



Source: Reviewer-generated analysis using ADDSQ4.xpt

^a The points indicate percentage of subjects with no daily score >0 for Q3 and the vertical lines indicate the 95% CIs. Subjects with missing data are considered nonresponders.

^b One subject (USUBJID [REDACTED] (b) (6)) received BOS and was excluded from summary statistics due to not meeting trial eligibility criteria for age.

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; CI, Confidence Interval; CMH, Cochran Mantel Haenszel; DSQ, Dysphagia Symptom Questionnaire; FAS, full analysis set; N, number of subjects

Trial 301

Assessment of Q3=0

Similar to Trial 101-06, a greater proportion of subjects randomized to BOS achieved the outcome of Q3=0 during Weeks 15 and 16 (30.1%) compared to placebo (18.1%). Although this analysis was not prespecified, the results ($p=0.0257$) met the standard threshold used for defining statistical significance (i.e., $p<0.05$) (Table 19). The estimated treatment difference was computed by averaging the treatment difference across strata defined by age group and diet restriction using MH weights. The 95% CI was estimated using the stratified Newcombe score method and the p-value was calculated based on the Cochran-Mantel-Haenszel test.

Table 19. DSQ Outcome of Q3=0: FAS Population, Trial 301

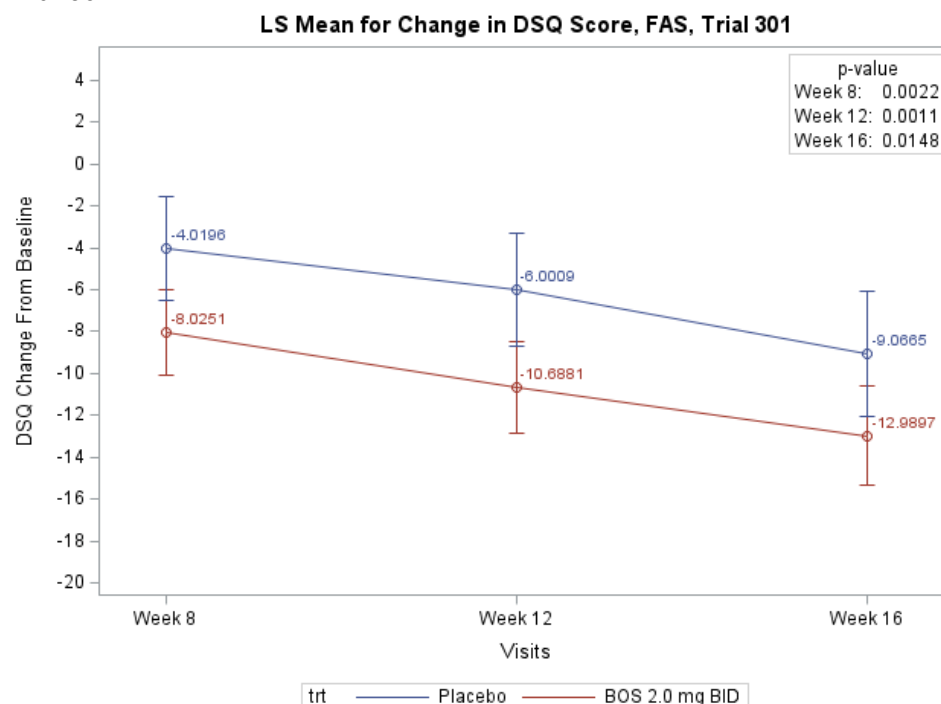
Statistic	BOS 2 mg BID	Placebo
No daily score >0 for DSQ Q3 at Week 16 ^a		
N	213	105
Responders, n (%)	64 (30.0)	19 (18.1)
Difference in response rates (95% CI)		11.9 (1.5, 20.9)
p-value		0.0257

Source: Based on Summary of Clinical Efficacy Figure 19 (page 86) submitted on 8/22/2023; verified by reviewer using ADDSQ7.xpt

^a Treatment difference was averaged across strata defined by age group and diet restriction using MH weights. Confidence interval was calculated using the Newcombe score method and the p-value was based on the CMH statistic. Missing data were handled using nonresponder imputation. Subjects were considered missing if they had fewer than 8 nonmissing daily DSQ combined scores during the 14-day period. Daily scores were considered missing on days where no solid was eaten (i.e., DSQ-Q1 = 'No'). Abbreviations: BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; CMH, Cochran Mantel Haenszel; DSQ, Dysphagia Symptom Questionnaire; FAS, full analysis set; MH, Mantel-Haenszel; N, number of subjects; n, number of subjects in sample

Absolute Change in DSQ Combined Score Over Time

As with the exploratory analyses based on the observed DSQ combined score to explore absolute change in the score over time for Trial 101-06, separation between treatment groups was observed for this analysis for Trial 301 at Week 8 (i.e., after 4 weeks of treatment) and Week 12 (i.e., after 8 weeks of treatment). However, unlike Trial 101-06, the differences were nominally significant for all analyzed trial weeks ([Figure 5](#)).

Figure 5. Absolute Change^a in DSQ Combined Score From Baseline Over Time: FAS Population, Trial 301

Source: Reviewer-generated analysis using ADDSQ.xpt

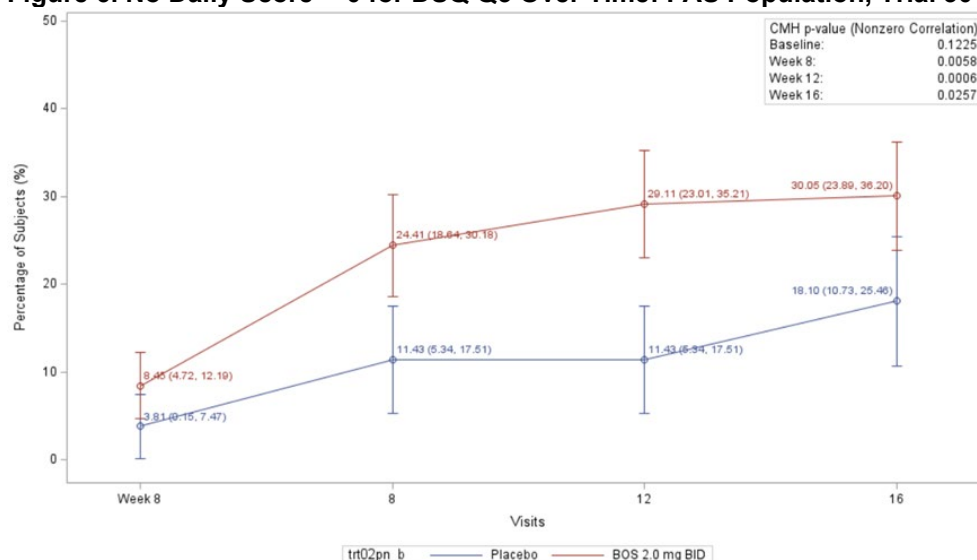
^a Results are based on ANCOVA model with treatment group, age group and diet restriction as factors and baseline score as a covariate in the FAS population. Subjects with missing data were excluded from the analysis. Points represent LS means and vertical lines indicate 95% CI.

Abbreviations: ANCOVA, analysis of covariance; BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; DSQ, Dysphagia Symptom Questionnaire; FAS, full analysis set; LS Mean, least squares mean

Assessment of Q3=0 Over Time

As with the analysis of absolute change from baseline in DSQ combined score over time, the difference between treatment groups for the analysis of the outcome of Q3=0 was nominally significant at Week 8, Week 12, and Week 16 (Figure 6).

Figure 6. No Daily Score^a >0 for DSQ Q3 Over Time: FAS Population, Trial 301



Source: Reviewer-generated analysis using ADDSQ7.xpt

^a The points indicate percentage of subjects with no daily score >0 for Q3 and the vertical lines indicate the 95% CI for the point estimates. Subjects with missing data are considered nonresponders.

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; CMH, Cochran Mantel Haenszel; DSQ, Dysphagia Symptom Questionnaire; FAS, full analysis set

Conclusions

The demonstration of effectiveness for BOS for the short-term treatment of EoE is based on the statistically significant results for the multiplicity-controlled prespecified endpoints of histologic remission and symptomatic improvement (i.e., $\geq 30\%$ reduction in DSQ combined score [Trial 301] and absolute change from baseline in DSQ combined score [Trials 101-06 and 301]). The demonstration of effectiveness is supported by the nominally significant results for the post-hoc analysis of DSQ Q3=0 and the results of the exploratory analyses of the DSQ-based endpoints over time. The strength of the evidence to support the determination of clinical benefit for 12 weeks of treatment of BOS in subjects 11 years of age and older with EoE is bolstered by the independent replication of results of these efficacy assessments across the two 12-week trials (i.e., Trials 101-06 and 301). Considered collectively, the review team determined that available data from histologic and symptomatic efficacy assessments were adequate to support that treatment with BOS resulted in clinical benefit in subjects with EoE.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The nonclinical safety profile of budesonide has been extensively evaluated in comprehensive pharmacology, PK, and toxicology studies to support the approval of currently marketed budesonide-containing products. It has also been widely documented in the published literature. In addition, supplemental studies were conducted with the new formulation of BOS to support the EoE indication in the proposed patient population. The nonclinical studies submitted in NDA 213976 for BOS consisted of juvenile animal toxicity studies in rats and dogs to support dosing in pediatric patients and a series of genotoxicity studies to qualify the impurity

(b) (4) The toxicity of BOS was evaluated in juvenile rats and dogs for 91 days following oral administration. All observed effects were expected pharmacological effects following administration of a glucocorticoid, with no novel toxicities identified. The degradation impurity (b) (4) was mutagenic in the Ames assay; however, it did not induce mutagenicity in the 28-day rat *Pig-A* assay. There were no significant safety concerns identified in the toxicology studies conducted following oral administration of BOS in rats and dogs.

In the 91-day toxicity study in juvenile rats (PND22), daily administration of BOS at doses of 0.05, 0.2, 0.6, and 1.5 mg/kg/day was generally well tolerated. Seven unscheduled deaths were observed in this study. The deaths were attributed to urogenital inflammation secondary to immunosuppression and dosing error. Significant reductions in body weight and food consumption occurred in a dose-dependent manner. Classic effects of glucocorticoids were noted, including (i) lymphocyte and leukocytic changes, (ii) clinical chemistry changes consistent with glucocorticoid administration, (iii) adrenal atrophy, (iv) lymphoid depletion in the thymus, lymph nodes, Peyer's patch, and spleen, (v) decreased cellularity in bone marrow, (vi) hyperostosis and physeal atrophy, (vii) atrophy of the stomach, and (viii) decreased bone length of the tibia and femur. The effects observed following BOS administration were consistent with the pharmacological effects of glucocorticoids. The no observed adverse effect levels following daily administration of BOS for 91 days in juvenile rats was 0.05 mg/kg/day.

In the 91-day toxicity study in juvenile dogs (6 weeks old), BOS was administered at 0.05, 0.2, and 0.6 mg/kg/day. Gross and histopathology assessments showed expected glucocorticoid-related changes. There were 10 unscheduled deaths following BOS administration, which were attributed to pharmacologically-mediated immunosuppression or inguinal hernias. Cushing disease-like changes and steroid hepatopathy were noted at doses of ≥ 0.2 mg/kg/day. The observed test article-related effects included decreased body weight gain, decreased food consumption, leukocytic/lymphocyte changes, adrenal cortical atrophy, lymphoid depletion in lymphoid organs, decreased cellularity in bone marrow, hyperostosis and physeal atrophy, and suppression of long bone growth. Apart from the expected pharmacologic actions of this class of compound, no apparent unexpected or adverse toxicity was observed with BOS at the doses tested.

In the Segment I fertility and early embryonic developmental toxicity study in rats, there was a significant reduction in maternal body weight gain, prenatal viability, and the viability of the pups at birth and during lactation at a dose of 20 μ g/kg/day. These findings were more

pronounced at the high dose of 80 µg/kg/day. Budesonide had no effect on fertility in rats at doses up to 80 µg/kg/day.

In the embryofetal developmental toxicity study in pregnant rats, there was a decrease in food consumption and body weight gain in the budesonide-treated animals. At a dose of 100 µg/kg/day, there was increased fetal loss and fetal abnormalities. Fetal abnormalities including umbilical eventration and reduced ossification of skull bones along with sternal or vertebral defects were observed at a dose of 500 µg/kg/day. In the embryofetal developmental toxicity study in rabbits, there was a decrease in food consumption and body weight gains at doses of 25 and 125 µg/kg/day following subcutaneous administration of budesonide. There was an increase in visceral abnormalities at doses of 2 and 25 µg/kg/day. Skeletal anomalies (skull and vertebral defects) were increased at a dose of 25 µg/kg/day. There was an increase in maternal abortion, effects on fetal development, and a reduction in litter weights at doses up to approximately 25 µg/kg/day.

In the Segment III pre- and postnatal development study in rats, a slight prolongation of gestational period was noted. There was no test article related effects on parturition, nursing, and lactation. In the mid- and high-dose dams, there was a decrease in body weight gain. At a dose of ≥ 20 µg/kg/day, maternal toxicity was observed, offspring survival was reduced, and surviving offspring had decreased mean body weights at birth and during lactation.

Budesonide was not mutagenic in the standard in vitro and in vivo genotoxicity tests. The degradation impurity (b) (4) was mutagenic in the Ames assay up to 1500 µg/plate and was negative in the *Pig-A* gene mutation assay at doses up to and including 0.50 mg/kg/day in males and 0.20 mg/kg/day in females.

In the 2-year oral carcinogenicity study in rats, there was a statistically significant increase in the incidences of gliomas in males dosed with 50 µg/kg/day and primary hepatocellular tumors in the males dosed with ≥ 25 µg/kg/day. There were no tumor findings in the female rats. In an additional 2-year carcinogenicity study in rats, the only tumor findings were increased incidences of hepatocellular tumors at an oral dose of 50 µg/kg. Budesonide was not carcinogenic in mice at doses up to 200 µg/kg/day.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

The safety profile of corticosteroid drugs is well-characterized due to their widespread use as therapeutics for multiple inflammatory conditions. This is reflected in the PI for the application's LD, Entocort EC (budesonide) delayed-release capsules (NDA 021324) ([Perrigo Pharma International DAC 1997](#)), which, in addition to a contraindication related to hypersensitivity to budesonide or any of the ingredients in Entocort EC, includes warnings and precautions related to hypercorticism and adrenal axis suppression, symptoms of steroid withdrawal in patients transferred from other systemic corticosteroids, increased risk of infections including serious and fatal chicken pox and measles, and other established corticosteroid-associated adverse effects.

In consideration of the known class effects and FDA's evaluation of the Applicant's submitted safety data, several potential signals were identified for additional consideration during the review. The following grouped queries were conducted in addition to the evaluation of safety data using the individual preferred terms (PTs):

- Adrenal suppression (adrenal insufficiency, adrenal suppression, adrenocorticotrophic hormone [ACTH] stimulation test abnormal, blood cortisol abnormal, blood cortisol decreased)
- Candidiasis (esophageal and oropharyngeal)
- Respiratory infection (upper respiratory tract infection, respiratory tract infection, sinusitis, nasopharyngitis, rhinitis)
- Mucosal irritation (erosive duodenitis, gastrointestinal ulcer, esophageal ulcer, gastritis)

See Sections [7.6.1.8](#) and [7.6.2.8](#) for additional description of the grouped queries that were examined.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Not applicable. BOS is not yet commercially available in any country.

7.4. FDA Approach to the Safety Review

The safety review of this 505(b)(2) application focused primarily on the data from the treatment periods of Trials 101-06 and 301, the two 12-week, randomized, double-blind, placebo-controlled trials. Analyses of data from these trials represent events that occurred through Week 16 (end of the 12-week double-blind treatment period) of each trial.

Additionally, the Applicant submitted data from a phase 1 study in healthy adult subjects (SHP621-101), a phase 2 dose-ranging trial in children and adolescents with EoE (MPI 101-01), a phase 2 trial in pediatric and adult subjects with EoE (Trial 101-06), and the extension phase 3 trial in pediatric and adult subjects with EoE (SHP621-303). Summaries of the clinical trials that contributed data to inform the clinical safety evaluation for BOS as a candidate therapeutic for patients with EoE are located in [Table 3](#) and [Table 4](#). For review and discussion of the additional safety data, refer to the multidisciplinary December 17, 2021 integrated review of NDA 213976 in DARRTS (Reference ID: 4907153). Unless otherwise specified, the safety analyses presented in this review represent the evaluation of data from Trials 101-06 and 301.

Clinical trial data were independently analyzed using Python, R, SAS, JMP, and JMP Clinical software. All safety assessments and conclusions are those of the review team unless otherwise specified. The review team did not identify any major data quality or integrity issues that precluded performing a thorough safety review.

The Applicant's proposed adverse event (AE) definitions including severity, relatedness, outcome, treatment-emergence (i.e., whether an AE is considered to be a treatment-emergent AE), and classification as serious were reviewed and found to be acceptable.

Treatment-emergent adverse events (TEAEs) were defined as AEs that first occurred or worsened on or after the first dose of double-blind (or OLE, if applicable) IP. Serious AEs were defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or results in a congenital anomaly or birth defect.

The Applicant translated verbatim AE terms to MedDRA PTs for the AEs reported in phase 2 Trial MPI 101-01 using version 12.0, phase 2 Trial 101-06 using version 15.0, and in phase 3 Trials 301, SHP621-302, and SHP621-303 using version 18.0. The translations were reviewed and generally found acceptable, except for where FDA PT recoding is noted in this review. See Sections [17.1](#) and [17.2](#) for the Agency's PT recoding for phase 2 Trial 101-06 and phase 3 Trial 301.

7.5. Adequacy of the Clinical Safety Database

The safety database was adequate for a comprehensive safety assessment of BOS 2 mg BID for the proposed indication, subject population, dosage regimen, and duration.

The two phase 2 trials (Trials MPI 101-01 and 101-06) and two phase 3 trials (Trials 301 and 302) included 426 unique subjects who were exposed to BOS 2 mg BID. An additional 131 subjects received at least one dose of BOS 2 mg BID in the completed phase 3 OLE study (SHP621-303).

[Table 20](#) and [Table 21](#) summarize the exposure periods for Trial 101-06 and Trial 301, respectively, and include the treatment arm assignment to provide an estimated duration of exposure to the assigned IP. The duration of BOS exposure was equivalent between the two groups of subjects who received BOS in both Trials 101-06 and 301, with a mean duration of treatment of 11.8 weeks in both trials, respectively.

Table 20. Duration of Exposure, Double-Blind Treatment Period, Safety Population, Trial 101-06

Parameter	BOS 2 mg BID N=50 ^a n (%)	Placebo N=42 n (%)
Duration of treatment, weeks ^b		
Mean (SD)	11.8 (1.9)	12 (1.7)
Median (min, max)	12 (0.3, 13.3)	12 (6, 18)
Subjects treated, by duration, n (%)		
≥1 dose	50 (100)	42 (100)
≥4 weeks	49 (98.0)	42 (100)
≥8 weeks	49 (98.0)	41 (97.6)
≥12 weeks	35 (70.0)	30 (71.4)

Source: adsl.xpt; Software: R

Duration of double-blind treatment is 12 weeks.

^a One subject (USUBJID (b) (6)) received BOS and was excluded from summary statistics due to not meeting trial eligibility criteria for age.

^b Duration of treatment reflects the start and end dates of IP administration. Treatment interruptions were included in the durations; however, subjects received only the protocol-specified 12 weeks of treatment.

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

Table 21. Duration of Exposure, Double-Blind Treatment Period, Safety Population, Trial 301

Variable	BOS 2 mg BID N=213, n (%)	Placebo N=105, n (%)
Duration of treatment (weeks)		
Mean (SD)	11.8 (1.8)	11.3 (2.6)
Median (min, max)	12.0 (2.1, 15.9)	12.0 (0.1, 15.0)
Subjects treated, by duration, n (%)		
≥1 dose	213 (100)	105 (100)
≥4 weeks	212 (99.5)	100 (95.2)
≥8 weeks	203 (95.3)	97 (92.4)
≥12 weeks	188 (88.3)	80 (76.2)

Source: adex.xpt; Software: Python

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; SD, standard deviation

7.6. Safety Results

The following subsections include safety findings and concerns identified during the review of data from phase 2 Trial 101-06 and phase 3 Trial 301. For review and discussion of the additional safety results, refer to the multidisciplinary December 17, 2021 integrated review of NDA 213976 in DARRTS (Reference ID: 4907153).

7.6.1. Safety Results, Trial 101-06

7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, Trial 101-06

[Table 22](#) provides a summary of TEAEs reported for Trial 101-06. Upon review of the TEAEs in Trial 101-06, the percentage of subjects receiving BOS versus placebo who experienced at least one TEAE was equivalent across the treatment arms. In the BOS treatment arm, one subject experienced TEAEs of chest discomfort, dyspnea, nausea, and vomiting that led to discontinuation of IP (Section [7.6.1.4](#)). A greater proportion of subjects treated with BOS than those who received placebo reported mild TEAEs, and a greater proportion of subjects who received placebo than those treated with BOS reported moderate TEAEs. Compared to placebo, one additional subject in the BOS arm reported a TEAE leading to interruption of IP. There were no predictable trends observed related to this summary of overall TEAEs reported in Trial 101-06.

Table 22. Overview of Treatment-Emergent Adverse Events During 12-Week Treatment Period, Trial 101-06

Event Category	BOS 2 mg BID N=50^a, n (%)	Placebo N=42, n (%)
Any TEAE	25 (50.0)	21 (50.0)
Severe and worse	1 (2.0)	0
Moderate	7 (14.0)	8 (19.0)
Mild	17 (34.0)	13 (31.0)
Any SAE	1 (2.0)	0
SAE with fatal outcome	0	0
TEAE leading to discontinuation of IP	1 (2.0)	0
TEAE leading to dose modification of IP	3 (6.0)	2 (4.8)
TEAE leading to interruption of IP	3 (6.0)	2 (4.8)
TEAE leading to reduction of IP	0	0
TEAE leading to delay of IP	0	0

Source: Reviewer analysis using Applicant-submitted data, ADAE.xpt

Note: Grading Scale: The severity (intensity) of AEs was assessed as mild, moderate, and severe.

^a One subject (USUBJID (b) (6)) received BOS and was excluded from summary statistics due to not meeting trial eligibility criteria for age.

Abbreviations: BOS, budesonide oral suspension; CI, confidence interval; IP, investigational product; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event; TEAE, treatment-emergent adverse event

7.6.1.2. Deaths, Trial 101-06

No deaths were reported in Trial 101-06.

7.6.1.3. Serious Treatment-Emergent Adverse Events, Trial 101-06

The only serious adverse event (SAE) reported for Trial 101-06 was food poisoning, which was unrelated to the IP and resolved without sequelae. The subject subsequently completed the treatment period and entered the OLE period of the trial.

7.6.1.4. Treatment-Emergent Adverse Events Leading to Treatment Discontinuation, Trial 101-06

In Trial 101-06, one subject (2%) receiving BOS and zero subjects receiving placebo discontinued the trial due to TEAE ([Table 23](#)). The one subject (USUBJID (b) (6)) receiving BOS who discontinued the trial was a 19-year-old male reported to have experienced moderate chest tightness, mild exacerbations of nausea and vomiting, and mild shortness of breath on Study Day 1. All four TEAEs were considered by the investigator to be possibly related to the IP and all four TEAEs resolved without sequelae on Study Day 2. The subject withdrew from the trial on Study Day 2.

Table 23. Treatment-Emergent Adverse Events Leading to Discontinuation of IP, Trial 101-06

System Organ Class Preferred Term	BOS 2.0 mg BID N=50 ^a , n (%)	Placebo N=42, n (%)
Subjects reporting ≥1 TEAE leading to discontinuation of IP	1 (2.0)	0
Chest discomfort	1 (2.0)	0
Dyspnea	1 (2.0)	0
Nausea	1 (2.0)	0
Vomiting	1 (2.0)	0

Source: Reviewer analysis using Applicant-submitted data, ADAE.xpt

Treatment-emergent adverse events defined as events that started or worsened after the first dose of the IP during double-blind treatment period. Duration of double-blind treatment is 12 weeks.

^a One subject (USUBJID (b) (6)) received BOS and was excluded from summary statistics due to not meeting trial eligibility criteria for age.

Abbreviations: AE, adverse event; BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; NA, not applicable; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event; TEAE, treatment-emergent adverse event

7.6.1.5. Treatment-Emergent Adverse Events, Trial 101-06

Table 24 displays the TEAEs in Trial 101-06 that occurred in greater than 2% of subjects treated with BOS that occurred at a higher rate than placebo. On review, the most common TEAEs observed in subjects treated with BOS were headache, sinusitis, throat irritation, and upper respiratory tract infection. The threshold of greater than 2% of subjects treated with BOS was selected because multiple individual TEAEs occurred in only one subject. Because there were only 50 subjects receiving BOS in Trial 101-06, 2% of subjects in the BOS arm equals only one subject.

Although occurring in ≤2% of subjects in the BOS arm, it should be noted that there were two subjects who were treated with BOS who reported one TEAE each of esophageal candidiasis or oropharyngeal candidiasis; neither PT was reported as a TEAE among subjects who received placebo.

Table 24. Treatment-Emergent Adverse Events Occurring at >2% in BOS Arm and Greater Than Placebo During 12-Week Treatment Period, Trial 101-06

Preferred Term	BOS 2 mg BID N=50 ^a , n (%)	Placebo N=42, n (%)
Any AE	25 (50.0)	21 (50.0)
Headache	3 (6.0)	1 (2.4)
Upper respiratory tract infection	3 (6.0)	2 (4.8)
Food poisoning	2 (4.0)	0
Sinusitis	2 (4.0)	1 (2.4)
Throat irritation	2 (4.0)	1 (2.4)

Source: Reviewer analysis using Applicant-submitted data, ADAE.xpt

Coded as MedDRA15.0 preferred terms. See Section 17.1 for the Agency's PT recoding for Trial 101-06.

^a One subject (USUBJID (b) (6)) received BOS and was excluded from summary statistics due to not meeting trial eligibility criteria for age.

Abbreviations: AE, adverse event; BOS, budesonide oral suspension; BID, twice daily; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; TEAE, treatment-emergent adverse event

7.6.1.6. Laboratory Findings and Vital Sign Analyses, Trial 101-06

No clinically meaningful trends or changes were identified upon review of hematology and chemistry laboratory data or vital signs when comparing subjects who received BOS versus placebo in Trial 101-06.

7.6.1.7. Assessment of Drug-Induced Liver Injury, Trial 101-06

Upon review of the safety data for potential drug-induced liver injury, there were no Hy's law cases and no imbalances across treatment arms noted in Trial 101-06 that would warrant further investigation. There were four cases noted of either isolated elevated bilirubin or transaminases (two subjects treated with BOS and two subjects who received placebo in Trial 101-06). None of these elevations were pronounced (greater than 5x upper limit of normal for alanine aminotransferase or aspartate aminotransferase, or greater than 3x upper limit of normal for bilirubin) or prolonged. All elevations were noted to resolve without intervention or discontinuation of the IP.

7.6.1.8. FDA Grouped Queries, Trial 101-06

In consideration of the known class effects of budesonide, the review team identified several potential signals for additional consideration. Unlike in Trial 301, ACTH stimulation testing was not conducted in Trial 101-06 (see Section [15](#)). Additionally, no TEAEs related to mucosal irritation were reported. Therefore, the review team was unable to replicate the grouped query analyses related to adrenal suppression/insufficiency and mucosal irritation that were conducted for Trial 301.

The following two grouped queries were conducted in addition to the evaluation of safety data based on the individual TEAE PTs identified in Trial 101-06.

- Candidiasis (esophageal and oropharyngeal)
- Upper respiratory tract infection (nasopharyngitis, sinusitis, upper respiratory tract infection)

Upon review of the data from these queries as shown in [Table 25](#), the risks for both candidiasis and respiratory infections were greater for BOS versus placebo in Trial 101-06.

Table 25. FDA Grouped Queries by Preferred Term, Trial 101-06

Grouped Query Preferred Term	BOS 2.0 mg BID N=50^a, n (%)	Placebo N=42, n (%)
Candidiasis (GQ)	2 (4.0)	0
Esophageal candidiasis	1 (2.0)	0
Oropharyngeal candidiasis	1 (2.0)	0
Upper respiratory tract infection (GQ)	8 (16.0)	6 (14.3)
Nasopharyngitis	4 (8.0)	4 (9.5)
Upper respiratory tract infection	3 (6.0)	2 (4.8)
Sinusitis	2 (4.0)	1 (2.4)

Source: Reviewer analysis using Applicant-submitted data, ADAE.xpt

Coded as MedDRA15.0 preferred terms. See Section 17.1 for the Agency's PT recoding for Trial 101-06.

^a One subject (USUBJID (b) (6)) received BOS and was excluded from summary statistics due to not meeting trial eligibility criteria for age.

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; GQ, grouped query; N, number of subjects in treatment arm; n, number of subjects with adverse event

7.6.1.9. Subgroup Analyses, Trial 101-06

Subgroup safety analyses were performed for the reported age, sex, race, and ethnicity demographic characteristics. However, there were no notable trends observed and the limited number of subjects in each subgroup precluded the identification of clinically relevant differences in safety due to sex, race, or ethnicities.

7.6.2. Safety Results, Trial 301

7.6.2.1. Overview of Treatment-Emergent Adverse Events Summary, Trial 301

[Table 26](#) provides a summary of TEAEs reported for Trial 301. Upon review of the TEAEs in Trial 301, there were no notable differences in the percentage of subjects receiving BOS versus placebo who experienced any TEAEs, SAEs, or TEAEs leading to IP modification or interruption. A greater proportion of subjects treated with BOS than those that received placebo reported moderate or severe TEAEs, and a greater proportion of subjects who received placebo than those treated with BOS had TEAEs leading to IP discontinuation.

Table 26. Overview of Treatment-Emergent Adverse Events During 12-Week Treatment Period, Trial 301

Event Category	BOS 2 mg BID N=213, n (%)	Placebo N=105, n (%)
Any TEAE	130 (61.0)	64 (61.0)
Moderate or severe TEAEs	61 (28.6)	26 (24.8)
Any SAE	2 (0.9)	1 (1.0)
SAE with fatal outcome	0	0
TEAE leading to discontinuation of IP	3 (1.4)	5 (4.8)
TEAE leading to dose modification of IP	4 (1.9)	1 (1.0)
TEAE leading to interruption of IP	4 (1.9)	1 (1.0)
TEAE leading to reduction of IP	0	0
TEAE leading to delay of IP	0	0

Source: adae.xpt; Software: Python

Grading scale: The severity (intensity) of AEs was assessed as mild, moderate, and severe.

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; IP, investigational product; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event; TEAE, treatment-emergent adverse event

7.6.2.2. Deaths, Trial 301

No deaths were reported in Trial 301.

7.6.2.3. Serious Treatment-Emergent Adverse Events, Trial 301

[Table 27](#) provides a summary of SAEs reported for Trial 301. Although more subjects that received BOS reported SAEs compared to placebo, the number of subjects was too small to inform definitive conclusions.

Table 27. Serious Adverse Events During 12-Week Treatment Period, Trial 301

Preferred Term	BOS 2 mg BID N=213, n (%)	Placebo N=105, n (%)
Subjects reporting ≥1 SAE	2 (0.9)	1 (1.0)
Gastroenteritis	1 (0.5)	0
Localized intraabdominal fluid collection	1 (0.5)	0
Sepsis	1 (0.5)	0
Ovarian cyst	0	1 (1.0)

Source: Reviewer analysis using Applicant-submitted data, ADAE.xpt

See Section [17.2](#) for FDA PT recoding for Trial 301

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SAE, serious adverse event

7.6.2.4. Treatment-Emergent Adverse Events Leading to Treatment Discontinuation, Trial 301

In Trial 301, three subjects (1.4%) in the BOS group and five subjects (4.8%) in the placebo group discontinued IP due to TEAEs ([Table 28](#)) but completed the trial. Of the 12 TEAEs leading to discontinuation of IP, 9 were observed in the placebo group (5 of which were considered to be related to the IP: esophageal candidiasis, mood swings, mouth ulceration, dizziness, headache, and adrenal insufficiency). The three TEAEs leading to discontinuation in the BOS group (i.e., adrenal insufficiency, esophageal candidiasis, and esophageal stenosis) were all considered to be related to the IP. Of note, one subject in the BOS group (reporting esophageal stenosis) and three subjects in the placebo group (reporting mood swings [one subject]; dizziness and headache [one subject]; and mouth ulceration [one subject]) discontinued the trial in addition to discontinuing the IP.

Table 28. Treatment-Emergent Adverse Events Leading to Discontinuation of IP, Trial 301

Preferred Term	BOS 2 mg BID N=213, n (%)	Placebo N=105, n (%)
Subjects reporting ≥1 TEAE leading to discontinuation of IP	3 (1.4)	5 (4.8)
Adrenal insufficiency	1 (0.5)	0
Esophageal candidiasis	1 (0.5)	0
Esophageal stenosis	1 (0.5)	0
Diarrhea	0	1 (1.0)
Dizziness	0	1 (1.0)
GERD	0	1 (1.0)
Headache	0	1 (1.0)
Mood swings	0	1 (1.0)
Mouth ulceration	0	1 (1.0)
Nausea	0	1 (1.0)
Psoriatic arthropathy	0	1 (1.0)
Vomiting	0	1 (1.0)

Source: Reviewer analysis using Applicant-submitted data, ADAE.xpt

See Section [17.2](#) for the Agency's PT recoding for Trial 301

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; IP, investigational product; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; TEAE, treatment-emergent adverse event

7.6.2.5. Treatment-Emergent Adverse Events, Trial 301

[Table 29](#) displays the TEAEs in Trial 301 by individual preferred term that occurred in greater than or equal to 2% of subjects treated with BOS and occurred at a higher rate than placebo. It was noted that the same percentage of subjects across the treatment groups experienced at least one TEAE (61.0% BOS and 61.0% placebo). On review, the most common TEAEs observed in subjects treated with BOS were oropharyngeal candidiasis and headache, both of which were reported in 10/213 subjects (4.7%). Although occurring in <2% of subjects in the BOS arm, the following TEAEs occurred at a higher rate than placebo: arthralgia, adrenal suppression,¹¹ fatigue, hirsutism, hypertension, and transaminases increased.

¹¹ Note that “adrenal suppression” does not include the PTs of “adrenal insufficiency,” “ACTH stimulation test abnormal,” or blood cortisol related preferred terms. See Section 7.6.2.8 for the “Adrenal suppression” FDA grouped query results.

Table 29. Treatment-Emergent Adverse Events Occurring at $\geq 2\%$ in BOS Arm and Greater Than Placebo During 12-Week Treatment Period, Trial 301

Preferred Term	BOS 2 mg BID N=213, n (%)	Placebo N=105, n (%)
Subjects with ≥ 1 TEAE	130 (61.0)	64 (61.0)
Nasopharyngitis	11 (5.2)	4 (3.8)
Oropharyngeal candidiasis	10 (4.7)	0
Headache	10 (4.7)	2 (1.9)
Sinusitis	10 (4.7)	3 (2.9)
Esophageal candidiasis	8 (3.8)	2 (1.9)
Gastroenteritis	7 (3.3)	1 (1.0)
Throat irritation	6 (2.8)	2 (1.9)
Procedural pain	5 (2.3)	1 (1.0)
Erosive esophagitis	4 (1.9)	0

Source: Reviewer analysis using Applicant-submitted data, ADAE.xpt

Coded as MedDRA 18.0 preferred terms. See Section 17.2 for the Agency's PT recoding for Trial 301.

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; TEAE, treatment-emergent adverse event

During review of TEAEs by PT, several events were noted to represent the same or a similar clinical condition. These events were further explored through the conduct of grouped queries. See Section 7.6.2.8 for additional details. To provide patients and prescribers with the most informative and relevant descriptions of the adverse reactions observed during Trial 301, the review team elected to include a combination of both individual PTs and grouped queries, as appropriate, in the table of common adverse reactions in the PI, shown in Table 30 below. The review and assessment of the findings of erosive esophagitis are discussed further in Section 7.7.3.

Table 30. Common Adverse Reactions in Trial 301 by PT and FDA Grouped Queries

Preferred Term	BOS 2 mg BID N=213, n (%)	Placebo N=105, n (%)
Respiratory tract infection ^b	13%	11%
Gastrointestinal mucosal candidiasis ^c	8%	2%
Headache ^d	5%	2%
Gastroenteritis	3%	1%
Throat irritation ^e	3%	2%
Adrenal suppression ^f	2%	0
Erosive esophagitis ^g	2%	0

Source: Reviewer-created table

Coded as MedDRA 18.0 preferred terms. See Section 17.2 for the Agency's PT recoding for Trial 301.

^a Reported in $\geq 2\%$ of subjects in the Eohilia group and at a rate greater than placebo.^b Includes: acute sinusitis, sinusitis, nasopharyngitis, respiratory tract infection, respiratory tract infection viral, upper respiratory tract infection, viral upper respiratory tract infection, rhinitis^c Includes: esophageal candidiasis, oropharyngeal candidiasis^d Includes headache, migraine^e Includes throat irritation, oropharyngeal pain (only when verbatim term was "sore throat")^f Includes: adrenal suppression, adrenal insufficiency^g Includes esophagitis only where erosions were present at the EGD conducted after 12 weeks of treatment

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; EGD, esophagogastroduodenoscopy; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term

7.6.2.6. Laboratory Findings and Vital Sign Analyses, Trial 301

A notable imbalance was observed in the proportion of subjects in the BOS treatment arm with abnormally low cortisol values following an ACTH stimulation test compared to subjects in the placebo treatment arm in Trial 301 at Week 16 as shown in [Table 31](#). This finding is consistent with the known class effect of corticosteroids such as BOS.

Table 31. ACTH Stimulation Test Values, Safety Population, Trial 301

Variable	BOS 2 mg BID n (%)	Placebo n (%)
Week 4 screening maximum cortisol post-dose ACTH		
n	211	100
Subjects with abnormal peak cortisol levels ≤ 18 $\mu\text{g/dL}$	8 (3.8)	5 (5.0)
Very low unstimulated AM cortisol < 1 $\mu\text{g/dL}$ (baseline)	0	1 (1.0)
Week 16 maximum cortisol post-dose ACTH		
n	198	87
Subjects with abnormal peak cortisol levels ≤ 18 $\mu\text{g/dL}$	18 (9.1)	3 (3.4)
Very low unstimulated AM cortisol < 1 $\mu\text{g/dL}$ (baseline)	4 (2.0)	0

Source: adlb.xpt; Software: R

Abbreviations: ACTH, adrenocorticotropic hormone; AM, morning; BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; n, number of subjects

With the exception of ACTH stimulation test values, no clinically meaningful trends or changes were identified upon review of hematology and chemistry laboratory data or vital signs when comparing subjects who received BOS versus placebo in Trial 301.

7.6.2.7. Assessment of Drug-Induced Liver Injury, Trial 301

Upon review of the safety data for potential drug-induced liver injury, there were no Hy's law cases and no imbalances across treatment arms noted in Trial 301 that would warrant further investigation. There were four cases of either isolated elevated bilirubin or transaminases (two subjects treated with BOS and two subjects who received placebo); however, none of these elevations appeared to be prolonged and they all were noted to resolve without intervention or discontinuation of the IP. Additionally, an alternative potential etiology for the identified elevated laboratory values was provided by the Applicant for all subjects.

7.6.2.8. FDA Grouped Queries, Trial 301

In consideration of the known class effects of budesonide, the review team identified several potential signals for additional consideration. To further characterize these issues, the following grouped queries were conducted in addition to the evaluation of safety data using the individual PTs:

- Adrenal suppression (adrenal insufficiency, adrenal suppression, ACTH stimulation test abnormal, blood cortisol abnormal, blood cortisol decreased)
- Candidiasis (esophageal and oropharyngeal)

- Respiratory tract infection (upper respiratory tract infection, respiratory tract infection, sinusitis, nasopharyngitis, rhinitis)
- Mucosal irritation (erosive duodenitis, gastrointestinal ulcer, esophageal ulcer, gastritis)

Upon review of the data from these queries, as shown in [Table 32](#), a significant risk of candidiasis with BOS versus placebo was observed in Trial 301. The data from these queries also show that the risk was greater for subjects receiving BOS versus placebo for respiratory tract infection and adrenal effects. Gastrointestinal mucosal candidiasis (i.e., oropharyngeal candidiasis or esophageal candidiasis), respiratory tract infection, and adrenal suppression were added to the ADVERSE REACTIONS section of the PI (Note: The PTs of esophageal candidiasis and oral candidiasis were already included in this section of the Applicant-submitted PI). Details related to concerns with oropharyngeal candidiasis and esophageal candidiasis were already included in the existing subsection “Increased Risk of Infection” and details related to adrenal effects were already included in the existing subsection “Hypercorticism and Adrenal Axis Suppression” of the WARNINGS AND PRECAUTIONS section of the PI. These adverse reactions are discussed further in the Section [7.7](#) below.

Table 32. FDA Grouped Queries by Preferred Term, Safety Population, Trial 301

Grouped Query Preferred Term	BOS 2 mg BID N=213, n (%)	Placebo N=105, n (%)
Candidiasis	16 (7.5)	2 (1.9)
Oropharyngeal candidiasis	10 (4.7)	0
Esophageal candidiasis	8 (3.8)	2 (1.9)
Respiratory tract infection	28 (13.1)	11 (10.5)
Nasopharyngitis	11 (5.2)	4 (3.8)
Sinusitis	10 (4.7)	3 (2.9)
Upper respiratory tract infection	5 (2.3)	3 (2.9)
Respiratory tract infection	2 (0.9)	0
Rhinitis	0	1 (1.0)
Adrenal suppression	14 (6.6)	6 (5.7)
ACTH stimulation test abnormal ^a	8 (3.8)	3 (2.9)
Adrenal suppression	3 (1.4)	0
Adrenal insufficiency	2 (0.9)	0
Blood cortisol decreased	1 (0.5)	2 (1.9)
Blood cortisol abnormal	0	2 (1.9)
Mucosal irritation	3 (1.4)	3 (2.9)
Gastritis	2 (0.9)	1 (1.0)
Erosive duodenitis	1 (0.5)	0
Esophageal ulcer	1 (0.5)	0
Gastrointestinal ulcer	0	2 (1.9)

Source: adae.xpt; Software: Python

^a Note that not all subjects with an abnormal ACTH stimulation test (see [Table 31](#)) were identified as an AE using a corresponding AE Preferred Term. See Section [17.2](#) for FDA PT recoding for Trial 301

Abbreviations: ACTH, adrenocorticotrophic hormone; BOS, budesonide oral suspension; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event

7.6.2.9. Subgroup Analyses, Trial 301

Subgroup safety analyses were performed for the reported age, sex, race, and ethnicity demographic characteristics. However, there were no notable trends observed and the number of

subjects in each subgroup was too small to draw conclusions regarding the safety of BOS among sex, race, and ethnicities.

7.7. Key Safety Review Issues

7.7.1. HPA Axis Suppression

Issue

An imbalance was observed in the proportion of subjects treated with BOS with abnormally low cortisol values following an ACTH stimulation test compared to placebo in Trial 301 at Week 16.

Background

Hypothalamic-pituitary-adrenal axis suppression is a known class effect of corticosteroid use, and dedicated ACTH stimulation testing was conducted in Trial 301. Because ACTH stimulation testing is considered a more reliable assessment of hypothalamic-pituitary-adrenal axis suppression compared to the evaluation of morning cortisol levels, the review primarily focused on the results of ACTH stimulation test in Trial 301. Of note, ACTH stimulation tests were not conducted in Trial 101-06 (see Section [15](#)).

Assessment

ACTH stimulation testing was conducted at baseline and after respective treatment periods in Trial 301. Blood samples were collected just prior to and approximately 30 to 60 minutes following injection (intramuscular or intravenous) of synthetic ACTH (250 µg) to measure the stimulated level of cortisol. Adrenal suppression or abnormal ACTH stimulated serum cortisol levels were defined as peak ACTH stimulated serum cortisol of ≤ 18 µg/dL after synthetic ACTH injection.

In Trial 301, the BOS and placebo treatment arms had a similar proportion of subjects noted to have adrenal suppression at baseline (i.e., Week 4; 3.8% versus 5.0%). After 12 weeks of treatment (at Week 16), a higher percentage of subjects who received BOS 2 mg BID had abnormal ACTH stimulated serum cortisol levels (9.1%) when compared to subjects in the placebo group (3.4%). See Section [7.6.2.6](#).

HPA Suppression Comparison Pediatric and Adult Subjects

As shown in [Table 33](#), upon comparative analysis of ACTH stimulation testing between pediatric and adult subjects, abnormal ACTH-stimulated peak cortisol levels (≤ 18 µg/dL) were more common among pediatric subjects compared to adult subjects both at baseline (i.e., Week 4) and Week 16 (after 12 weeks of treatment). Both pediatric and adult subjects treated with BOS had a higher proportion of abnormal ACTH-stimulated peak cortisol levels at the end of the treatment period (Week 16) than those receiving placebo. Additionally, the increase in percentage of subjects who developed abnormal ACTH stimulation testing based on a peak value of ≤ 18 µg/dL was larger for pediatric subjects than adult subjects treated with BOS (8% versus 4.8%) or placebo (6.6% versus -3.2%) when comparing baseline to Week 16. This suggests that pediatric

patients may be more likely to have abnormal ACTH stimulation testing than adults at baseline and may be more likely to develop abnormal ACTH stimulation testing after exposure to BOS; however, the interpretability of this finding is limited by the small number of pediatric subjects assessed.

Table 33. ACTH Stimulation Test Values by Age, Safety Population, Trial 301

Variable	BOS 2 mg BID n (%)		Placebo n (%)	
	<18 Years	≥18 Years	<18 Years	≥18 Years
Week 4 screening maximum cortisol post-dose ACTH				
n	27	184	13	87
Subjects with abnormal peak cortisol levels ≤18 µg/dL	2 (7.4)	6 (3.3)	1 (7.7)	4 (4.6)
Very low unstimulated AM cortisol <1 µg/dL (baseline)	0	0	0	1 (1.1)
Week 16 maximum cortisol post-dose ACTH				
n	26	172	14	73
Subjects with abnormal peak cortisol levels ≤18 µg/dL	4 (15.4)	14 (8.1)	2 (14.3)	1 (1.4)
Very low unstimulated AM cortisol <1 µg/dL (baseline)	1 (3.8)	3 (1.7)	0	0

Source: adlb.xpt; Software: R

Abbreviations: ACTH, adrenocorticotrophic hormone; AM, morning; BID, twice daily; BOS, budesonide oral suspension; n, number of subjects in sample

Conclusion

The percentage of subjects with abnormal ACTH stimulated serum cortisol was higher in the BOS group than in the placebo group after 12 weeks of treatment in Trial 301. Adrenal suppression is a known corticosteroid class effect for this product and should be appropriately communicated to patients and providers. The WARNINGS AND PRECAUTIONS section of the PI includes recommendations to monitor patients during treatment with BOS for signs and symptoms of hypercorticism and adrenal axis suppression, as well as considerations regarding patients with hepatic impairment. Specifically, patients with moderate to severe hepatic impairment (Child-Pugh Class B and C, respectively) could be at increased risk of hypercorticism and adrenal axis suppression due to an increased systemic exposure of oral budesonide. Use is not recommended in patients with severe hepatic impairment (Child-Pugh Class C) and monitoring for signs and/or symptoms of hypercorticism is recommended in patients with moderate hepatic impairment (Child-Pugh Class B). See Section [8.1](#).

7.7.2. Gastrointestinal Mucosal Candidiasis

Issue

BOS is a corticosteroid product formulated for topical effect on the esophagus. Although the observed AE profile for BOS was largely consistent with the known class effects of corticosteroid products, additional AEs emerged during the safety review as likely or potentially related to the formulation and topical administration of BOS, including gastrointestinal mucosal candidiasis.

Assessment

As discussed [above](#), in Trials 101-06 and 301, esophageal candidiasis and oropharyngeal candidiasis were seen at higher rates in subjects treated with BOS compared to those who received placebo. The risk for the development of gastrointestinal mucosal candidiasis emerged as a prominent safety signal during the review.

Conclusion

Patients that develop gastrointestinal mucosal candidiasis should receive appropriate local or systemic antifungal therapy and consider discontinuing treatment with BOS. These recommendations are already included in the Applicant-submitted version of the proposed PI.

7.7.3. Erosive Esophagitis

Issue

An imbalance in the occurrence of erosive esophagitis was observed between BOS-treated subjects and subjects who received placebo in Trial 301.

Assessment

Although both EoE and erosive esophagitis can present with symptoms of esophageal dysfunction (e.g., difficulty swallowing, pain, nausea, vomiting, regurgitation), in the absence of concomitant erosive esophagitis, esophageal erosions are not typically seen on endoscopic evaluation in patients with EoE. Common endoscopic findings in patients with EoE include edema, rings, exudates, furrows, and strictures ([Kia and Hirano 2015](#)). As shown in [Table 30](#), erosive esophagitis was found in 4/213 (1.9%) subjects after 12 weeks of treatment with BOS during the Week 16 EGD, compared to no subjects who received placebo. None of the four BOS-treated subjects who developed erosive esophagitis had erosions at the baseline EGD, and three of the four subjects found to have developed erosive esophagitis were receiving concomitant therapy with a PPI throughout the trial (two for the off-label treatment of EoE and one for the treatment of symptomatic GERD) ([Table 34](#)).

Table 34. Subjects Receiving BOS 2 mg BID and Findings of Erosive Esophagitis, Trial 301

USUBJID	(b) (6)			
Finding of erosive esophagitis at baseline EGD?	No	No	No	No
Finding of erosive esophagitis at Week 16 EGD	Yes, considered a moderate TEAE. LA Classification Grade A esophageal erosion noted at both proximal and distal parts of the esophagus	Yes, considered a moderate TEAE. LA Classification Grade C esophageal erosion was noted in the distal part of the esophagus; however, no esophageal erosion was noted at the proximal part of the esophagus	Yes, considered a mild TEAE. LA Classification Grade B esophageal erosion was noted in the distal part of the esophagus; however, no esophageal erosion was noted at the proximal part of the esophagus	Yes, considered a mild TEAE. LA Classification Grade A esophageal erosion was noted in the distal part of the esophagus; however, no esophageal erosion was noted at the proximal part of the esophagus
Relevant past medical history:	GERD, esophagitis, gastritis	GERD, heartburn	Severe esophagitis, chronic gastritis	GERD, non-erosive gastritis
Concomitant PPI:	Omeprazole 40 mg QD for EoE	None	Pantoprazole 40 mg BID for EoE	Omeprazole 40 mg BID for GERD
Baseline (Week 4) peak eosinophil count/HPF	77	31	76	27
Week 16 peak eosinophil count/HPF	38	1	0	15

Source: Source: Reviewer-created table based on data submitted to NDA 213976 and the Applicant's December 12, 2023 response to FDA information requests containing endoscopy reports for the subjects listed above.

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; LA, Los Angeles; PPI, proton pump inhibitor; QD, once daily; TEAE, treatment-emergent adverse event; USUBJID, unique subject identification number

Two of the four subjects with erosive esophagitis were noted to have achieved histologic remission (i.e., a peak eosinophil count of ≤ 6 per high power field) at the time of erosive esophagitis diagnosis, and these two subjects were observed to have the most severe erosive esophagitis based on Los Angeles Classification (i.e., Grade C and Grade B versus Grade A in the other two subjects). Although limited by the small number of subjects affected, this finding supports that the development of erosive esophagitis was unrelated to persistent inflammation due to EoE.

Conclusion

It is important for patients, caregivers, and providers to be aware of the potential for the development of erosive esophagitis with BOS treatment because there is significant overlap between clinical symptoms of erosive esophagitis and EoE (e.g., chest pain, dyspepsia, dysphagia) that may lead to attribution of new symptoms to EoE and delay diagnosis and appropriate treatment of erosive esophagitis. Thus, the review team recommends the addition of a new WARNINGS AND PRECAUTIONS section to the PI to describe the occurrence of erosive esophagitis in subjects who received BOS in the 12-week clinical trial (Trial 301), including that none of the subjects had erosions at baseline EGD and that most were receiving

concomitant therapy with a PPI during the trial. This statement advises patients or caregivers to report new onset or worsening signs or symptoms of erosive esophagitis to their healthcare provider and includes a recommendation for providers to consider endoscopic evaluation as appropriate.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Details on therapeutic individualization based on hepatic impairment, renal impairment, and body weight are available in the clinical pharmacology supplementary review that was signed into DARRTS on December 17, 2021 (Reference ID: 4907153).

Hepatic Impairment

Use of Eohilia is not recommended in patients with severe HI based on the lack of information to support dosing. This recommendation is consistent with the PI for the LD, Entocort EC (budesonide) delayed-released capsules (NDA 021324) ([Perrigo Pharma International DAC 1997](#)).

In patients with moderate hepatic impairment (Child-Pugh B), the budesonide systemic exposure AUC was 3.5-fold higher compared to subjects with normal hepatic function based on the information in the PI for the LD.

Considering the relative contribution of local action and systemic action of BOS in the esophagus is unknown, a dose reduction could compromise efficacy by reducing local drug availability in the esophagus; therefore, dosage adjustment is not recommended.

Doses higher than the proposed 2 mg BID have not been studied in patients with EoE; however, based on the 60% lower AUC of budesonide after BOS administration compared to the LD (Entocort EC), the systemic exposure in patients with moderate HI after BOS administration is unlikely to be substantially higher than that after administration of approved dose of the LD (9 mg). Refer to the multidisciplinary December 17, 2021 integrated review for the relative BA study results (DARRTS Reference ID: 4907153).

Therefore, the review team recommends no changes to the recommended dosing regimen for patients with moderate HI with close monitoring for signs/symptoms of adrenal suppression and hypercorticism.

8.2. Extrinsic Factors

Food Effect

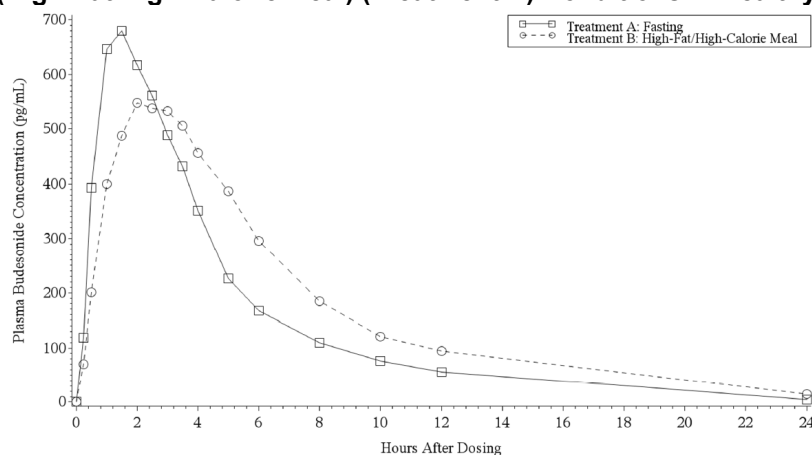
The Applicant's proposed dosing instruction in the label is to not take the proposed product with food or liquid and to not eat or drink for 30 minutes after taking it. The proposal for not eating or drinking for 30 minutes after dosing is consistent with the dosing instructions provided to subjects in Trial 301. The Applicant's provided rationale for the administration instructions is to maximize the contact between the proposed product, a viscous suspension, and the esophagus.

The Applicant conducted a food effect study (TAK-721-1003) to evaluate the effects of a high-fat/high-calorie meal consumed before dosing on pharmacokinetics of a single 2-mg dose of BOS compared to the dosing under fasting conditions. The TBM formulation SB-10 was used in this food effect study. Study TAK-721-1003 was open-label, single-dose, randomized, two-period, two-sequence, two-way crossover study in 20 healthy adult subjects. For fasting conditions, subjects fasted overnight for ≥ 10 hours prior to dosing and continued to fast for ≥ 4 hours post-dose. For fed condition, subjects fasted overnight for ≥ 10 hours until 30 minutes prior to scheduled morning dose, when they were given a high-fat breakfast (800 to 1000 calories and approximately 50% fat) which was entirely consumed within 30 minutes. Subjects fasted for ≥ 4 hours post-dose.

The mean plasma concentration-time profile of budesonide after the oral administration of 2 mg BOS under fasting and fed condition is shown in [Figure 7](#). The geometric mean plasma budesonide C_{max} , AUC_{last} , and AUC_{inf} were approximately 13% lower, 26% higher, and 27% higher, respectively, following a single dose of 2 mg BOS under fed (high-fat/high-calorie meal) conditions compared to under fasting conditions ([Table 35](#)). Under fed conditions, T_{max} was delayed by about one hour when compared to fasting condition. Due to the small variations observed, the delayed absorption, decreased C_{max} , and increased AUC of BOS after administration under fed conditions are not expected to be clinically significant. This study supports that administration of BOS under fed conditions is acceptable.

However, to maximize local availability of budesonide at the esophagus after swallowing, BOS should be taken without concomitant food or liquid. Patients should wait 30 minutes after dosing before consuming food or drinks. This administration regimen is consistent with the dosing instructions in Trials 101-06 and 301.

Figure 7. Arithmetic Mean Plasma Budesonide Concentration Versus Time Profiles Following a Single Dose of 2 mg Budesonide Oral Suspension Under Fasting (Treatment A) and Fed (High-Fat/High-Calorie Meal) (Treatment B) Conditions in Healthy Subjects (Linear Scale)



Source: Study TAK-721-1003 Report, Page 49

Note: The SB-10 formulation was used in the food effect study TAK-721-1003.

Table 35. Statistical Comparison of Plasma Budesonide Pharmacokinetic Parameters Following a Single Dose of 2 mg Budesonide Oral Suspension Under Fed (High-Fat/High-Calorie Meal) (Treatment B) Versus Fasting (Treatment A) Conditions in Healthy Subjects

	Treatment B (Test)		Treatment A (Reference)				
Pharmacokinetic Parameter (Unit)	n	Geometric LSMs	n	Geometric LSMs	GMR (%)	90% Confidence Interval	Intra- participant CV%
C _{max} (pg/mL)	20	604.1	20	692.9	87.18	74.80 - 101.61	28.5
AUC _{last} (pg•h/mL)	20	3529	20	2811	125.54	113.85 - 138.41	18.0
AUC _∞ (pg•h/mL)	20	3892	20	3075	126.56	116.60 - 137.36	15.0

Source: Study TAK-721-1003 Report, Page 52

Abbreviations: AUC_{last}, area under the concentration-time curve from time 0 to last measurable concentration; AUC_∞, area under the concentration-time curve from time 0 to infinity; C_{max}, maximum observed plasma concentration; CV%, coefficient of variation; GMR, geometric mean ratio; LSM, least squares mean; n, number of subjects in sample

8.3. Plans for Pediatric Drug Development

Although this development program received Orphan Drug Designation in December 2006, and is therefore exempt from Pediatric Research Equity Act requirements, the Applicant included pediatric subjects ages 11 years and older in both the phase 2 Trial 101-06 and phase 3 Trial 301. Additionally, the application includes a request for an indication for pediatric patients ages 11 years and older. Given that EoE is a serious condition affecting both younger and older pediatric patients as well as adult patients, the review team requested the Applicant agree to a postmarketing commitment to conduct of a randomized, double-blind, placebo-controlled clinical trial to evaluate the safety, efficacy, and pharmacokinetics of BOS in pediatric patients less than 11 years of age. See Section [24](#).

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

The Division of Pediatric and Maternal Health revised the Applicant's proposed draft labeling during review of the original submission of NDA 213976 to comply with the Pregnancy and Lactation Labeling Rule. For more detail, refer to the March 15, 2021, Maternal Health Labeling Review by Jane Liedtka (DARRTS Reference ID: 4760638). In this current resubmission review cycle, Division of Pediatric and Maternal Health has updated labeling for the lactation section of the USPI. An information request was sent to the Applicant asking for further information about a publication by Fält and colleagues ([Falt et al. 2007](#)), which described a lactation study in eight mothers receiving inhaled budesonide. Despite contacting the investigators, the Applicant was unable to obtain any additional information. The review team agreed to keep most of the current labeling language in Section 8.2 (*Lactation*) regarding the publication except for correcting the dosage and calculated relative infant dose for use of BOS compared to the inhaled budesonide dose. The review team requested the Applicant agree to a postmarketing commitment to conduct a clinical lactation study with BOS to obtain more accurate estimation of the potential exposure to budesonide to an infant through breast milk following maternal administration. However, the Applicant did not agree to this postmarketing commitment. See Section [24](#).

8.5. Drug Interaction

Budesonide is CYP3A4 and P-gp substrate. The concomitant administration of budesonide with inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin, cyclosporine, and grapefruit juice) or inhibitors of P-gp (e.g., ketoconazole) should be avoided because they may increase plasma concentrations of budesonide several-fold.

In vitro studies conducted by the Applicant indicated the following and will be included in the PI:

Budesonide is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6 in vitro. Budesonide is not an inducer of CYP3A4, CYP1A2 or CYP2B6 at clinically relevant concentrations.

In vitro, budesonide is not an inhibitor of P-gp, breast cancer resistance protein (BCRP), OATP1B1, OATP1B3, OAT1, OAT3, or organic cation transporter (OCT) 2 at clinically relevant concentrations.

For details of the review and evaluation of budesonide drug interactions, refer to the April 15, 2021 Clinical Pharmacology Supplementary Review in DARRTS (Reference ID: 4780092).

9. Product Quality

Approval

The Office of Pharmaceutical Quality (OPQ) review team has determined that the Applicant has provided sufficient chemistry, manufacturing, and controls (CMC) information to assure the identity, strength, purity, and quality of the drug substance, budesonide, and drug product for BOS 2 mg/10mL (0.2 mg/mL) in the resubmission of NDA 213976.

The Office of Pharmaceutical Manufacturing Assessment (OPMA) has made the overall recommendation of “adequate” for the facilities involved in this application.

The CMC-related revisions to the labels/labeling have been communicated to the Applicant and the recommended CMC-related revisions have been accepted by the Applicant. However, to ensure this drug will be available to the patients with no further delays, some of the editorial changes have been deferred to post-approval. For example, the Agency recommended revision of the dosage and packaging description be changed from “single-dose stick packs” to “unit-dose packets,” which will be adopted post-approval.

The Applicant intends to submit a prior approval supplement post-approval to adopt all remaining revisions recommended by the Agency within 1 month of the action date. This will allow patients to receive the drug while changes to labeling are made. Therefore, based on the Applicant’s commitment to adopt the Agency’s recommended revisions post-approval, the current PI labeling as well as container closure and carton labels are considered adequate to support the approval of this applicant from the labeling perspective.

The Applicant’s request for categorical exclusion from preparation of an environmental assessment has been found adequate and was granted.

Therefore, the OPQ review team has recommended approval of BOS with an expiration dating period of 36 months pending the submission of the final PI labeling and container and carton labels to the NDA. Refer to the February 2, 2024 Product Quality Review (DARRTS Reference ID: 5321811).

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

Clinical site inspections were conducted during the review of the original submission of NDA 213976. Refer to the multidisciplinary December 17, 2021 integrated review of NDA 213976 in DARRTS (Reference ID: 4907153) for the prior assessment. In summary:

Three clinical site inspections were conducted to support the review of this application. The conclusion is that the studies were conducted adequately, and the data generated are suitable to evaluate the proposed indication. Review of the financial disclosures did not raise any concerns about the validity or reliability of the data.

Although Trial 101-06 was not considered adequate to contribute to the evaluation of effectiveness for the indication sought in the original submission of NDA 213976 (i.e., the treatment of EoE in patients 11 years of age and older), the data from this 12-week trial are adequate to contribute to the evaluation of effectiveness for the indication proposed in the resubmission (i.e., for 12 weeks of treatment in adult and pediatric patients 11 years of age and older with EoE).

Review of the data submitted across clinical sites from Trial 101-06 was not concerning for imbalances in the results of efficacy analyses, protocol violations, or adverse event reporting across the sites. Additionally, there was substantial overlap between the clinical sites and investigators participating in Trials 101-06 and 301, and the clinical study site with the highest enrollment in Trial 101-06 was inspected during the review of the original submission. The review team determined that no additional site inspections were needed during the review of this resubmission.

11. Advisory Committee Summary

An advisory committee meeting was not held during the review of this NDA resubmission, as the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

III. Additional Analyses and Information

12. Summary of Regulatory History

On December 20, 2006, Meritage Pharma, Inc. (hereafter “Meritage”) obtained Orphan Drug Designation for the treatment of pediatric eosinophilic esophagitis (EoE). The FDA received IND 103173 on August 5, 2008, for the evaluation of budesonide oral suspension (BOS; referred to as oral budesonide suspension [OBS] by Meritage) for the treatment of patients with EoE. The Sponsor for the new IND was Meritage, and the IND was subsequently activated on September 4, 2008. Meritage did not hold a pre-IND meeting with the FDA. There were multiple follow-up type C meeting interactions between FDA and Meritage, which were used to discuss the Sponsor’s phase 2 clinical trials (i.e., trials MPI 101-01 and MPI 101-06) along with their patient-reported outcome instrument (i.e., the Dysphagia Symptom Questionnaire [DSQ]). During this time and specifically on June 29, 2011, Meritage broadened their Orphan Drug Designation to the treatment of EoE. The multiple meetings between FDA and Meritage culminated in a face-to-face (F2F) type B end-of-phase 2 meeting on November 12, 2014 (meeting minutes finalized on November 30, 2014), in which FDA provisionally agreed to the Sponsor’s proposed coprimary endpoint approach for their phase 3 program (i.e., separately evaluating histology through biopsy and symptomatology using the DSQ).

On March 18, 2015, the IND was transferred to Shire Viropharma Inc. (hereafter “Shire”). Shire referred to the product as “SHP621,” and they continued to engage the Agency with a follow-up type C meeting on July 13, 2015 (meeting minutes finalized on July 15, 2015), which was used to gain alignment on their phase 3 trials (i.e., induction trial SHP621-301 and maintenance trial SHP621-302) in EoE subjects 11 to 55 years of age. On May 31, 2016, BOS/SHP621 was granted Breakthrough Therapy Designation (BTD) for the treatment of patients with EoE, which was based on the histology and symptomatology data obtained from the noted phase 2 trials MPI 101-01 and MPI 101-06. Under the BTD granted status, Shire engaged FDA on multiple occasions starting with the 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 pediatric] development, clinical pharmacology, biostatistics, clinical outcome assessment, patient-focused statistics, statistics, nonclinical, and product quality). A point of disagreement at the “Initial Comprehensive Multidisciplinary Breakthrough Therapy Type B Meeting” was regarding whether the results from the induction trial alone (i.e., Trial SHP621-301) would be sufficient to file an NDA. Shire and FDA agreed to discuss this issue at a future meeting. This future F2F meeting ultimately occurred on June 25, 2019 (meeting minutes finalized on June 27, 2019), in which FDA firmly stated that the induction data from Trial SHP621-301 alone would not be sufficient to file an NDA and that longer-term maintenance data (specifically from Trial SHP621-302) would be needed to support chronic administration. The Agency’s position was based on FDA guidance for industry *Eosinophilic Esophagitis: Developing Drugs for Treatment* (September 2020) ([FDA 2020](#)), which was issued as a draft guidance earlier that calendar year on February 6, 2019. This guidance was finalized on September 16, 2020.

FDA on multiple occasions reiterated their concerns to the Sponsor regarding their proposed 30% DSQ responder threshold for the symptomatic coprimary endpoint for the phase 3 program under IND 103173. Specifically, the FDA emphasized that the Sponsor needed to confirm that their chosen percent responder threshold represented a clinically meaningful within-patient change using the phase 3 data. This was communicated via advice letters and formal emails sent to the Sponsor on September 15, 2015, February 15, 2018, September 17, 2018, and February 7, 2019. This was also communicated at the previously noted type C F2F meeting on July 13, 2015, and in minutes from the type B pre-NDA meeting on May 20, 2020. (b) (4)

On May 20, 2020, the Sponsor held a type B pre-NDA teleconference with FDA to discuss all elements of their program along with the overall clinical and regulatory filing plan in preparation for their 505(b)(2) NDA submission, which was planned during the latter half of calendar year 2020. The minutes for this meeting were finalized on June 2, 2020. The notable outcome from this meeting was that the Sponsor's maintenance trial, SHP621-302, did not show clinical benefit for EoE subjects treated with BOS with respect to histology and symptomatology. FDA communicated to the Sponsor that this would ultimately be an NDA review issue. FDA used the opportunity to again communicate to the Sponsor that they would need to establish a clinically meaningful within-patient change for the responder threshold that was prespecified for the symptomatic (using the DSQ) coprimary endpoint (specifically for induction trial SHP621-301). A separate Chemistry, Manufacturing, and Controls-only type B pre-NDA teleconference was held with the Office of Pharmaceutical Quality on April 20, 2020 (meeting minutes finalized on May 21, 2020). A follow-up Chemistry, Manufacturing, and Controls-only type A teleconference was held on July 28, 2020 (meeting minutes finalized on July 30, 2020) to align on a contingency plan for the future NDA with respect to current Good Manufacturing Practice compliance issues associated with the future Applicant's planned commercial drug substance manufacturing site.

On August 20, 2020, the IND was transferred to Takeda Development Center Americas, Inc. (hereafter "Takeda"). Takeda subsequently recoded the drug name to "TAK-721," and they continued engaging the FDA under the product's BTD-granted status. FDA granted Takeda's rolling review request for their NDA on August 28, 2020. The Applicant for the NDA was specifically Takeda Pharmaceuticals USA, Inc., which is a wholly owned subsidiary of Takeda. On August 31, 2020, Takeda submitted the first agreed-upon piece of the NDA, which covered electronic common technical document module 4 and associated nonclinical module 2 elements along with all pertinent regulatory information included in module 1.

The original submission of NDA 213976 for Eohilia (BOS, also known as SHP621/TAK-721, 2 mg/10 mL) was submitted to the FDA on October 15, 2020 via a rolling NDA submission "for the treatment of eosinophilic esophagitis (EoE), (b) (4) in adult and adolescent patients 11 years and older." The Applicant pursued the 505(b)(2) regulatory pathway for a new formulation and dosage form of budesonide formulated as a white to yellow viscous oral suspension with cherry flavoring supplied in 2 mg/10 mL child-resistant unit-dose packets taken twice daily. The Applicant proposed to rely on FDA's findings of safety as reflected in the approved product labeling for the listed drug

NDA 213976

Eohilia (budesonide oral suspension)

Entocort EC (budesonide) delayed-release capsules (NDA 021324)

([Perrigo Pharma International DAC 1997](#)), as well as published literature, as permitted in Section 505(b)(2) of the Federal Food Drug and Cosmetic Act. The Applicant's proposed proprietary name of "Eohilia" was also deemed conditionally acceptable shortly before filing on November 25, 2020, which was consistent with the conditional acceptability of the same name that was previously proposed under the reference IND (deemed conditionally acceptable under the IND on December 10, 2019, after the initially proposed "(b) (4)" was deemed unacceptable under the IND on August 6, 2019).

In the absence of a determination of substantial evidence of effectiveness during review of the original NDA submission, the overall benefit-risk assessment was not favorable to support the approval of BOS for the long-term treatment of EoE, "(b) (4)" in adult and pediatric patients 11 years and older. The multidisciplinary review team did not recommend approval and the signatory authority concurred with the review team's recommendation to take a complete response (CR) action. A CR letter was sent to the Applicant on December 17, 2021. The CR letter indicated that approval of the NDA will require design of a new adequate and well-controlled clinical trial including pediatric and adult subjects with EoE to support chronic administration of BOS. For additional details, refer to the multidisciplinary December 17, 2021 integrated review (DARRTS Reference ID: 4907153).

A resubmission of the application was received on August 22, 2023, in response to the December 17, 2021 CR letter from FDA. The resubmission sought a revised indication of "the short-term treatment of EoE, "(b) (4)" in adult and adolescent patients 11 years and older" to support the determination of substantial evidence of effectiveness related only to a short-term treatment indication of 12 weeks of BOS administration.

For a description of additional regulatory interactions with the Applicant during the review of the NDA resubmission, see Section [1](#).

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

No nonclinical toxicology studies were submitted in the IND (103173). Only references to nonclinical safety assessment from approved budesonide products were submitted to the IND.

13.2. Individual Reviews of Studies Submitted With the New Drug Application

Refer to the nonclinical supplementary review of the original submission signed into DARRTS on March 18, 2021 (Reference ID: 4764652).

14. Clinical Pharmacology

14.1. In Vitro Studies

There were no new drug-drug interaction studies provided in this resubmission. The in vitro drug-drug interaction studies were previously reviewed and signed in DARRTS on December 17, 2021 (Reference ID: 4907153), and on April 15, 2021 (Reference ID: 4780092). Importantly, budesonide is a substrate of cytochrome P450 enzyme (CYP) 3A4, and the label will recommend avoiding the concomitant administration of budesonide with CYP3A4 inhibitors as they may increase the plasma concentration of budesonide by several folds.

Note that potential of budesonide being a substrate for CYP enzymes was relied on the labeling for the listed drug, Entocort EC (budesonide) delayed-release capsules (NDA 021234), and that budesonide is extensively metabolized by CYP3A4 according to the PI for the LD, Entocort EC ([Perrigo Pharma International DAC 1997](#)).

14.2. In Vivo Studies

Refer to the April 15, 2021 Clinical Pharmacology Supplementary Review in DARRTS (Reference ID: 4780092) and the multidisciplinary December 17, 2021 integrated review in DARRTS (Reference ID: 4907153).

In this resubmission, the Applicant conducted a food effect study (TAK-721-1003) to evaluate the impact of food on the systemic exposure to budesonide after the administration of BOS 2 mg.

Food Effect Study TAK-721-1003

Study Design

This was an open-label, single-dose, randomized, two-period, two-sequence, two-way crossover phase 1 study in 20 healthy adult subjects to assess the relative bioavailability, pharmacokinetics, safety, tolerability of a single dose of BOS administered under fasting and fed (high-fat/high-calorie meal) conditions.

Treatment

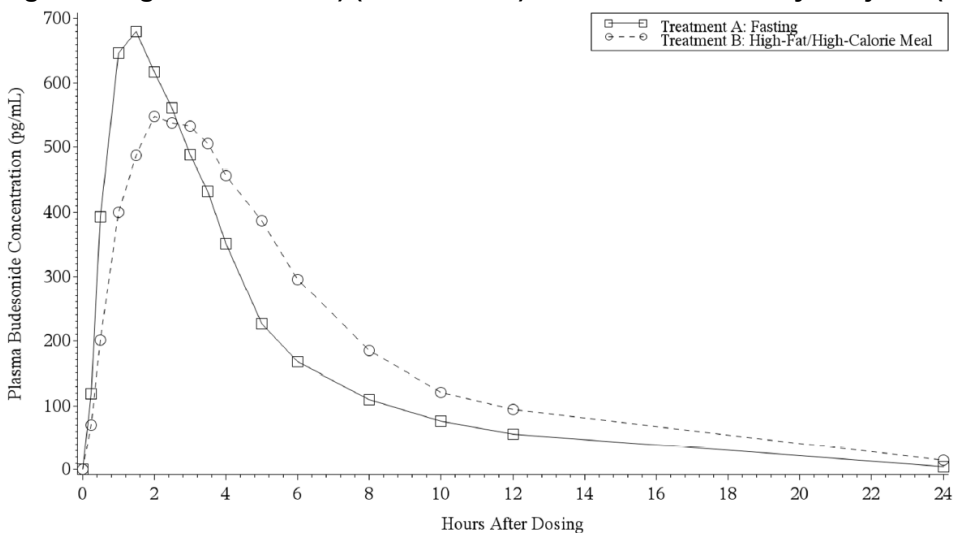
On Day 1 of each period, a 2 mg single oral dose of BOS (SB-10 formulation, to-be-marketed) was administered under fasting (Treatment A) or fed (Treatment B) conditions with a washout period of ≥ 2 days between doses. For Treatment A, subjects fasted overnight for ≥ 10 hours prior to dosing and continued to fast for ≥ 4 hours post-dose. For Treatment B, subjects fasted overnight for ≥ 10 hours until 30 minutes prior to scheduled morning dose, at which point they were given a high-fat/high-calorie breakfast (800 to 1000 calories and approximately 50% fat) which was entirely consumed within 30 minutes before dosing with BOS, after which subjects fasted for ≥ 4 hours post-dose.

Blood samples for assessment of budesonide pharmacokinetics were collected pre-dose and up to 24 hours in each period.

Results

The mean plasma concentration-time profile of budesonide after the oral administration of 2 mg BOS under fasting (Treatment A) and fed (Treatment B) conditions ([Figure 8](#)). A summary of budesonide PK parameters following a single dose of 2 mg BOS during fasting and fed conditions in healthy subjects is provided in [Table 36](#).

Figure 8. Arithmetic Mean Plasma Budesonide Concentration Versus Time Profiles Following a Single Dose of 2 mg Budesonide Oral Suspension Under Fasting (Treatment A) and Fed (High-Fat/High-Calorie Meal) (Treatment B) Conditions in Healthy Subjects (Linear Scale)



Source: Study TAK-721-1003 Report, Page 49

Table 36. Summary of Plasma Budesonide Pharmacokinetic Parameters Following a Single Dose of 2 mg Budesonide Oral Suspension Under Fasting (Treatment A) and Fed (High-Fat/High-Calorie Meal) (Treatment B) Conditions in Healthy Subjects

Pharmacokinetic Parameter (Unit)	Treatment A	Treatment B
t_{lag} (h)	0.328 (0.26, 0.56) [n=20]	0.308 (0.25, 0.53) [n=20]
t_{max} (h)	1.286 (0.55, 2.57) [n=20]	2.516 (1.01, 6.03) [n=20]
C_{max} (pg/mL)	692.9 (54.4) [n=20]	604.1 (46.6) [n=20]
AUC_{last} (pg•h/mL)	2811 (57.5) [n=20]	3529 (52.1) [n=20]
AUC_{∞} (pg•h/mL)	3075 (57.0) [n=20]	3892 (47.1) [n=20]
AUC_{0-12} (pg•h/mL)	2728 (53.0) [n=20]	3208 (42.2) [n=20]
$AUC_{extrap\%}$ (%)	8.455 ± 4.7335 [n=20]	9.006 ± 7.2717 [n=20]
$t_{1/2z}$ (h)	4.457 ± 1.4349 [n=20]	4.933 ± 1.3879 [n=20]
CL/F (L/h)	744.2 ± 405.98 [n=20]	565.8 ± 261.96 [n=20]
Vz/F (L)	4358 ± 2155.0 [n=20]	3686 ± 1174.6 [n=20]

Source: Study TAK-721-1003 Report, Page 51

Note: t_{lag} and t_{max} values are presented as median (minimum, maximum). C_{max} , AUC_{last} , AUC_{∞} and AUC_{0-12} are presented as geometric mean (geometric percent coefficient of variation). $AUC_{extrap\%}$, $t_{1/2z}$, CL/F and Vz/F values are presented as arithmetic mean ± standard deviation.

Abbreviations: t_{lag} , lag time to first quantifiable concentration; t_{max} , time to reach maximum concentration; C_{max} , maximum drug concentration; AUC_{last} , area under the concentration-time curve from time 0 to the last quantifiable concentration; AUC_{∞} , area under the concentration-time curve from time 0 to infinity calculated using the observed value of the last quantifiable concentration; AUC_{0-12} , area under the concentration-time curve from time 0 to 12 hours; $AUC_{extrap\%}$, area under the concentration-time curve from the last quantifiable concentration to infinity; $t_{1/2z}$, terminal disposition phase half-life; CL/F, apparent clearance after extravascular administration; Vz/F, apparent volume of distribution during the terminal disposition phase after extravascular administration

The geometric mean plasma budesonide maximum plasma concentration (C_{max}), area under the concentration-time curve (AUC)_{last}, and AUC_{inf} were approximately 13% lower, 26% higher, and 27% higher, respectively, following a single dose of 2 mg BOS under fed (high-fat/high-calorie meal) conditions (Treatment B) compared to fasting conditions (Treatment A) (Table 37). Moreover, food delayed the absorption of budesonide by 0.884 hour when compared to fasting condition.

Table 37. Statistical Comparison of Plasma Budesonide Pharmacokinetic Parameters Following a Single Dose of 2 mg Budesonide Oral Suspension Under Fed (High-Fat/High-Calorie Meal) (Treatment B) Versus Fasting (Treatment A) Conditions in Healthy Subjects

Pharmacokinetic Parameter (Unit)	Treatment B (Test)		Treatment A (Reference)				
	n	Geometric LSMs	n	Geometric LSMs	GMR (%)	90% Confidence Interval	Intra-participant CV%
C_{max} (pg/mL)	20	604.1	20	692.9	87.18	74.80 - 101.61	28.5
AUC_{last} (pg•h/mL)	20	3529	20	2811	125.54	113.85 - 138.41	18.0
AUC_{∞} (pg•h/mL)	20	3892	20	3075	126.56	116.60 - 137.36	15.0

Source: Study TAK-721-1003 Report, Page 52

Abbreviations: AUC_{last} , area under the concentration-time curve from time 0 to last measurable concentration; AUC_{∞} , area under the concentration-time curve from time 0 to infinity; C_{max} , maximum observed plasma concentration; CV%, coefficient of variation; GMR, geometric mean ratio; LSM, Least Squares Mean; n, number of subjects in sample

Conclusion

Plasma budesonide C_{max} , AUC_{last} , AUC_{∞} , and time to maximum concentration were 13% lower, 26% higher, 27% higher, and 1 hour longer, respectively, following a single dose of 2 mg BOS under fed (high-fat/high-calorie meal) conditions compared to under fasting conditions. Due to the small differences from the fasting state, the delayed absorption, decreased C_{max} , and increased systemic exposure of BOS observed after administration in the fed state are not expected to be clinically significant.

14.3. Bioanalytical Method Validation and Performance

The review team assessed the bioanalytical method validation reports and sample analysis reports for the quantitation of budesonide in human plasma. Method validation and sample analysis were acceptable. Validation results for bioanalytical methods are summarized in [Table 38](#). A complete assessment of the bioanalytical method validation and performance is available in the original Clinical Pharmacology Review (DARRTS, NDA 213976, 04/15/2021).

Table 38. Bioanalytical Method Validation for the Determination of Budesonide in Human Plasma

Table 36: Bioanalytical method validation for the Determination of Budesonide in Human Plasma			
Parameter	(b) (4) Study 42-1709	(b) (4) Study CN51830PLVAL	
Bioanalytical method validation report name, study number supported, and hyperlinks	(b) (4) Study 42-1709 (for SHP621-101 [pivotal BA/BE study], SHP621-301 studies, and TAK-721-1003) 42-1709-SHP621 meth val rep	(b) (4) Study CN51830PLVAL (for MPI 101-01 study, dose ranging Phase 2 study) CN51830plval-shp621 meth val rep	
	Method 1	Method 2	Method 3
Method description	Liquid-liquid extraction followed by LC-MS/MS	Solid phase extraction followed by LC-MS/MS	Solid phase extraction followed by LC-MS/MS
Stability in human plasma	189 Days at -20°C 370 Days at -70C 20 Hours at Ambient Temperature	33 days at -20°C 129 days at -70°C 6 hrs. at room temp	129 days at -20°C 425 days at -70°C
Processed extract stability			
Standard calibration curve performance during accuracy and precision runs			
LLOQ	20 pg/mL	50 pg/mL	50 pg/mL
Validated range	20–5000 pg/mL	50–2000 pg/mL	50–3000 pg/mL
Within-run precision (%CV)	≤15%	≤15%	≤15%
Between-run precision (%CV)	≤15%	≤15%	≤15%

Source: FDA Reviewer's table

Abbreviations: CV, coefficient of variation; LLOQ, lower limit of quantitation; LC-MS/MS, Liquid chromatography–mass spectrometry;

(b) (4) Clinical Research Organization

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Not applicable.

14.5. Pharmacometrics Assessment

A complete pharmacometrics assessment is available in the clinical pharmacology review signed to DARRTS on December 17, 2021 (Reference ID: 4907153), and on April 15, 2021 (Reference ID: 4780092).

14.6. Pharmacogenetics

Not applicable.

15. Trial Design

15.1. Trial Design (Trial 101-06)

[Table 39](#) displays the schedule of procedures and assessments for Trial 101-06.

Table 39. Schedule of Assessments During Screening, Baseline, and Double-Blind Treatment Periods, Trial 101-06

Procedures	Screening	Baseline Visit 1 Week 0 ^a	Baseline Visit 2 (±2 days)	Week 8 (±2 days)	Week 12 (±2 days)	Final Evaluation (OLE Baseline) Week 16 ^j (±2 days)
Informed consent/assent	X					
Medical history review	X	X	X			
Inclusion/exclusion criteria review	X	X	X			
EGD with endoscopy score and biopsy ^b	X					X
DSQ training & issue of handset	X ^c					
Retrieval of DSQ handset						X
DSQ compliance assessment ^d		X	X	X	X	X
Physician Global Assessment (VAS)			X			X
EoE symptom survey			X			X
Patient Global Impression of Change						X
Physical examination	X	X	X	X	X	X
Clinical laboratory tests ^e	X		X	X		X
Serum pregnancy test ^f	X					X
Morning cortisol (target 6:00 to 9:00 am)	X			X		X ^k
Vital signs ^g , height, and weight	X	X	X	X	X	X
Randomization ^h			X			
Study medication supplied		X	X	X	X	X
Study medication compliance assessment			X	X	X	X
Concomitant medications recorded	X	X	X	X	X	X
Review of adverse events ⁱ			X	X	X	X

^a Baseline Visit 1 occurred within 6 weeks after obtaining informed consent for study participation.

^b EGD and biopsies were performed at the study center or by a referring physician prior to or during screening, but within 10 weeks of Baseline Visit 1. Pre-treatment endoscopy included esophageal, gastric and duodenal biopsies. Final evaluation EGD included esophageal biopsies (gastric and duodenal biopsies were obtained at the discretion of the Investigator).

^c DSQ ePRO may be issued at any time during the screening, but at least 3 weeks prior to Baseline Visit 1.

^d Compliance data available to the study site prior to each visit.

^e Clinical laboratory tests were to be obtained with the subject in a fasted state.

^f Serum pregnancy test was performed for all female subjects.

^g Vital signs included blood pressure (systolic and diastolic), heart rate, respirations, and temperature.

^h Randomization occurred at Week 4 (Baseline Visit 2) once the subject's eligibility for study entry was confirmed.

ⁱ Adverse events review and physical examinations included specific assessments for signs of glucocorticoid excess (eg, moon face, acne, hirsutism, mood swings, insomnia, and depression).

^j Final treatment evaluation was performed at Week 16, or earlier for subjects who prematurely withdraw from the study. For subjects who withdraw prematurely or who do not enter the OLE, a safety follow-up telephone call was to be performed 4 weeks after the last dose of study drug.

^k If a clinically significantly low value was observed at the final evaluation for subjects who were not continuing to the OLE period, the subject was to have a repeat morning cortisol within 4 weeks, and during this visit, the subject was questioned about any serious adverse events experienced (therefore, the follow-up safety call was not required).

Source: Applicant's Clinical Study Report Table 1 (pages 35-36)

Abbreviations: am, morning; DSQ, Dysphagia Symptom Questionnaire; EGD, esophagogastroduodenoscopy; EoE, eosinophilic esophagitis; OLE, open label extension; VAS, Visual Analogue Scale

15.2. Trial Design (Trial 301)

[Table 40](#) displays the schedule of procedures and assessments for Trial 301.

Table 40. Schedule of Assessments During Screening, Baseline, and Double-Blind Treatment Periods, Trial 301

Procedures	Screening	Placebo Lead-in	Treatment Phase				Safety Follow-up Telephone Contact ^f
	Visit -1	Visit 0	Randomization Baseline/Visit 1	Visit 2	Visit 3	Visit 4 or ET ^q	Visit 5
Week	-6	0	4	8	12	16	20
Window	≤6 weeks	--	±3 days	±3 days	±3 days	±3 days	±3 days
Informed consent/assent	X						
Medical history review	X						
Inclusion/exclusion criteria review	X	X	X				
Vital signs ^a , height ^b and weight ^c assessment	X	X	X	X	X	X	
EGD with endoscopy score (EREFS) and biopsy ^d	X					X	
DSQ training and issue of handset	X						
Retrieval of DSQ handset						X	
DSQ completion			Once daily completion				
DSQ compliance assessment ^e		X	X	X	X	X	
EQ-5D ^f			X			X	
PedsQL-EoE (subjects 11-17 years of age, inclusive)			X			X	
EoE-QoL-A (subjects ≥18 years of age)			X			X	
PGI-S			X	X	X	X	
Physical examination	X	X	X	X	X	X	
Tanner Staging Assessment ^g	X					X	
Clinical laboratory tests ^h	X	X	X	X	X	X	
Urinalysis ⁱ	X	X	X	X	X	X	
Pregnancy test ^j	X	X	X	X	X	X	
Morning cortisol (target 6:00-9:00 AM)			X	X	X	X	
ACTH stimulation testing			X			X	
Blood pharmacokinetic sampling (subjects ≥18 years of age) ^k				X	X	X	
DXA Scan		X				X	

Procedures	Screening	Placebo Lead-in	Treatment Phase				Safety Follow-up Telephone Contact ^f
	Visit -1	Visit 0	Randomization Baseline/Visit 1	Visit 2	Visit 3	Visit 4 or ET ^q	Visit 5
Week	-6	0	4	8	12	16	20
Window	≤6 weeks	--	±3 days	±3 days	±3 days	±3 days	±3 days
(subjects 11-17 years of age, inclusive) ^l							
Randomization ^m			X				
IP supplied ⁿ		X	X	X	X	X ^l	
IP administration ^o			Twice-daily administration of IP				
IP compliance assessment			X	X	X	X	
Concomitant medications and procedures recorded	X	X	X	X	X	X	X
Review of adverse events ^p		X	X	X	X	X	X

ACTH=adrenocorticotrophic hormone; DSQ=Dysphagia Symptom Questionnaire; DXA=dual-energy X-ray absorptiometry; EGD=esophagogastroduodenoscopy; EoE-QoL-A=Adult Eosinophilic Esophagitis Quality of Life; EQ-5D=EuroQol; EQ-5D-3L=EuroQol-5 Dimension 3-level; EQ-5D-Y=EuroQol-5 Dimensions Youth; EREFS=EoE Endoscopic Reference Score; hs=at bedtime; IWRS=interactive web-based response system; PedsQL-EoE=Pediatric Quality of Life Inventory – EoE; pc=after meals; PGI-S=Patient Global Impression of Severity; qAM=every morning

^a Vital signs were assessed after the subject has been in a supine position for at least 5 minutes immediately prior to the assessment and included blood pressure (systolic and diastolic), heart rate, respirations, and temperature.

^b Height was collected at screening visit (Visit -1) and Visit 4 for all subjects. Stadiometers were required for subjects 11-17 years of age, inclusive, and were used at Visit -1 and 4. Height measurements for adolescent subjects (11-17 years of age, inclusive) were measured in triplicate.

^c Weight measurements for adolescent subjects (11-17 years, inclusive) were measured in duplicate.

^d Pretreatment endoscopy was performed during the screening phase (at least 2 weeks prior to placebo lead-in visit [Visit 0] to allow adequate time for processing and central review). Endoscopy was to include esophageal (proximal, mid-, and/or distal), gastric, and duodenal biopsies. Final treatment evaluation EGD was to include esophageal biopsies; gastric and duodenal biopsies could be done at the discretion of the investigator. Final treatment evaluation EGD was to occur at or within (±) 7 days of the scheduled visit.

^e DSQ assessment included completion of reports on DSQ handset (ie, eligibility reports and visit confirmations).

^f Subjects 11-17 years of age, inclusive, completed the EQ-5D-Y; subjects ≥18 years of age completed the EQ-5D-3L.

^g Tanner staging assessments was performed for all subjects aged ≥11 years until investigator confirmed subject was post-puberty.

Source: Applicant's Clinical Study Report Table 2 (pages 46-47)

16. Efficacy

16.1. The Dysphagia Symptom Questionnaire

The DSQ version 4 was administered to all subjects in Trial 101-06 and version 5 was administered to all subjects in Trial 301. The DSQ is a well-defined and reliable patient-reported outcome instrument for measuring dysphagia in adult and pediatric patients with EoE based on evidence of content validity from participant interviews and evidence of measurement properties using data from Trial 301. Refer to the supplementary review finalized in DARRTS by the Division of Clinical Outcome Assessment on March 29, 2021 (Reference ID: 4768072), for more information.

The DSQ versions 4 and 5 consist of four questions assessing avoidance of solid food, symptoms of dysphagia, and painful swallowing ([Table 41](#)). The differences between the two versions of the DSQ were related to the terminology “throat or chest” and “today (during the past 24 hours)” used in version 4 and “throat” and “today” in version 5.

Table 41. DSQ (Version 5) Items, Response Options, and Item Scoring, Trial 301

DSQ Questions (Version 5)	Response Options	Scoring
1. Since you woke up this morning, did you eat solid food?	Yes	Patient continues Not scored
	No	Patient stops Questions 2 through 4 are set to missing
2. Since you woke up this morning, has food gone down slowly or been stuck in your throat?	Yes	2 points
	No	0 points, scores for Questions 3 and 4 are each set to “0”
3. For the most difficult time you had while swallowing food today, 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	0 points
	Yes, I had to drink liquid to get relief	1 point
	Yes, I had to cough and/or gag to get relief	2 points
	Yes, I had to vomit to get relief	3 points
	Yes, I had to seek medical attention to get relief	4 points
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 today?	None, I had no pain	0 points
	Mild	1 point
	Moderate	2 points
	Severe	3 points
	Very severe	4 points

Source: DSQ version 5, Trial SHP621-301 clinical study report, dated July 31, 2019 (version 1.0), page 50; and Statistical Analysis Plan for Integrated Summary of Efficacy, dated February 27, 2020, Appendix 1, pages 34-35
Abbreviation: DSQ, Dysphagia Symptom Questionnaire

The DSQ scoring method used to support the symptomatic coprimary endpoints in Trials 101-06 and 301 is defined as the sum of scores of questions 2 and 3 prorated for a 14-day period (i.e., the “DSQ combined score”):

$$\text{DSQ combined score} = ((\text{Sum of daily DSQ question 2 and question 3 responses}) \times 14 \text{ days}) / (\text{Number of daily diaries with nonmissing data in the selected 14-day period})$$

The possible range of daily scores for question 2 + question 3 is 0 to 6. Therefore, over a 14-day period, the range of possible DSQ combined scores is 0 to 84.

17. Clinical Safety

17.1. FDA’s Preferred Term Recoding for Phase 2 Trial 101-06

Some of the preferred terms were recoded for phase 2 Trial 101-06 as follows to aid in capturing any potential safety signals:

- Fracture (recoded) includes clavicle fracture, hand fracture, wrist fracture
- Gastroenteritis (recoded) includes gastroenteritis, gastroenteritis viral
- Headache (recoded) includes headache, migraine, sinus headache, tension headache
- Hypersensitivity (recoded) includes allergy to arthropod sting, food allergy, hypersensitivity
- Oropharyngeal candidiasis (recoded) includes oral candidiasis, oropharyngeal candidiasis
- Physical thyroid examination abnormal (recoded) includes goiter
- Sinusitis (recoded) includes acute sinusitis, sinusitis
- Skin abrasion (recoded) includes excoriation
- Sleep disorder (recoded) includes insomnia
- Throat irritation (recoded) includes oropharyngeal, throat irritation
- Upper respiratory tract infection (recoded) includes upper respiratory tract infection, viral upper respiratory tract infection

17.2. FDA’s Preferred Term Recoding for Phase 3 Trial 301

Some of the preferred terms were recoded for phase 3 Trial 301 as follows to aid in capturing any potential safety signals:

- Abdominal pain (recoded) includes abdominal pain, abdominal pain upper

- Adrenocorticotrophic hormone stimulation test abnormal (recoded) includes adrenocorticotrophic hormone stimulation test abnormal, blood cortisol decreased (only when the AETERM stated that it was in relation to a stimulation test)
- Dermal cyst (recoded) includes dermoid cyst
- Disturbance in attention (recoded) includes disturbance in attention, feeling abnormal (only when the AETERM stated “mental foggiess”)
- Diverticulum (recoded) includes diverticulum, diverticulum intestinal
- Dyslipidemia (recoded) includes dyslipidaemia, hyperlipidaemia
- Esophageal discomfort (recoded) includes sensation of foreign body (only when the AETERM stated “feeling of a lump in esophagus”)
- Fracture (recoded) includes foot fracture, upper limb fracture
- Gastroenteritis (recoded) includes gastroenteritis, gastroenteritis viral
- Gastrointestinal ulcer (recoded) includes duodenal ulcer, gastric ulcer
- Headache (recoded) includes headache, migraine
- Hiatus hernia (recoded) includes diaphragmatic hernia, hiatus hernia
- Hyperbilirubinemia (recoded) includes blood bilirubin increased, hyperbilirubinaemia
- Hyperkalemia (recoded) includes blood potassium increased, hyperkalaemia
- Hypersensitivity (recoded) includes anaphylactic reaction, hypersensitivity
- Intestinal polyp (recoded) includes duodenal polyp, large intestine polyp
- Lymphadenopathy (recoded) includes lymphadenopathy, lymphadenopathy mediastinal
- Myalgia (recoded) includes myalgia, pain (only when the AETERM stated “body aches”)
- Oropharyngeal candidiasis (recoded) includes candida infection (only when the AETERM stated “thrush”), oral candidiasis, oropharyngeal candidiasis, tongue fungal infection
- Osteosclerosis (recoded) includes myosclerosis
- Pain in extremity (recoded) includes metatarsalgia (only when the AETERM stated “metatarsalgia right foot”), pain in extremity
- Paraesthesia (recoded) includes genital paraesthesia
- Pneumonia (recoded) includes pneumonia bacterial
- Protein urine present (recoded) includes protein urine present, proteinuria
- Rash (recoded) includes rash, rash macular, rash pruritic
- Respiratory tract infection (recoded) includes respiratory tract infection, respiratory tract infection viral
- Sinusitis (recoded) includes acute sinusitis, sinusitis

- Sleep disorder (recoded) includes insomnia, sleep disorder
- Throat irritation (recoded) includes oropharyngeal pain, throat irritation
- Transaminases increased (recoded) includes alanine aminotransferase increased, aspartate aminotransferase increased
- Upper respiratory tract infection (recoded) includes upper respiratory tract infection, viral upper respiratory tract infection
- Urine ketone body present (recoded) includes ketonuria, urine ketone body present
- Vaginitis bacterial (recoded) includes *Gardnerella vaginitis*

18. Clinical Virology

Not Applicable.

19. Clinical Microbiology

Not Applicable.

20. Mechanism of Action/Drug Resistance

For mechanism of action, see *Product Information* in Section [3](#).

21. Other Drug Development Considerations

Not applicable.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

Refer to the multidisciplinary December 17, 2021 integrated review of NDA 213976 in DARRTS (Reference ID: 4907153).

23. Labeling: Key Changes and Considerations

This PI review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft PI ([Table 42](#)). The PI was reviewed to ensure it meets regulatory/statutory requirements, is consistent with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Of note, the trial identifiers have been updated to Study 1 (referring to Trial 301) and Study 2 (referring to Trial 101-06) throughout the PI.

Table 42. Key Labeling Changes and Considerations

Full Prescribing Information Sections ^a	Rationale for Major Changes to Finalized PI ^b Compared to Applicant's Draft PI
INDICATIONS AND USAGE	The indication statement was modified to specify that the indication is for 12 weeks of treatment in adult and pediatric patients 11 years of age and older with eosinophilic esophagitis (EoE).
	(b) (4) were removed from the indication statement because they are more appropriately described (b) (4) section.
DOSAGE AND ADMINISTRATION	A Limitations of Use statement was added to convey that EOHILIA has not been shown to be safe and effective for the treatment of EoE for longer than 12 weeks. Trial SHP621-302 failed to show efficacy on the primary endpoint at 36 weeks and therefore there is no evidence of benefit beyond 12 weeks of treatment. See Section 1.
	The phrase (b) (4) was removed from the recommended treatment duration of 12 weeks given that Eohilia is not intended to be given for (b) (4).
DOSAGE AND ADMINISTRATION	The administration instructions were updated to remove (b) (4). The food effect study did not show a clinically meaningful effect of food. The instructions clarify that Eohilia should not be taken with food or liquid at the time of ingestion and to wait for ≥30 minutes to eat or drink after taking Eohilia. (b) (4)
	(b) (4) See Section 8.2.
WARNINGS AND PRECAUTIONS	<i>Hypercorticism and Adrenal Axis Suppression</i> The recommendation for use of Eohilia in patients with moderate hepatic impairment was (b) (4) to allow dosing in these patients along with monitoring for signs/symptoms of hypercorticism. The review team determined that the increase in the exposure (3.5-fold higher AUC) for subjects with moderate hepatic impairment compared to subjects with normal hepatic function does not preclude safe use of the drug given the limited treatment duration of 12 weeks. Additionally, the contribution to efficacy of local versus systemic concentrations of budesonide in the esophagus is unknown. Therefore, dosage reduction is not recommended.
	The increased exposure in subjects with moderate hepatic impairment is lower than the exposure in subjects with normal hepatic function following a dose of the LD, Entocort EC. Refer to Section 8.1 of the multidisciplinary December 17, 2021 integrated review (DARRTS Reference ID: 4907153).

Full Prescribing Information Sections ^a	Rationale for Major Changes to Finalized PI ^b Compared to Applicant's Draft PI
	<i>Immunosuppression and Increased Risk of Infection</i> Systemic corticosteroids are associated with activation of latent infections due to special pathogens. This safety information does not appear consistently in all labeling for these products. Therefore, these risks were added for Eohilia and should be included for all corticosteroids administered orally or by injection, where it is missing. Updated to include the esophagus in the description of the locations of localized infections with <i>Candida albicans</i> given that esophageal candidiasis was reported in clinical trials. <i>Kaposi's Sarcoma</i> Systemic corticosteroids are associated with increased risk of Kaposi's sarcoma. This safety information does not appear consistently in all labeling for these products. Therefore, the risk was for Eohilia and should be included for all corticosteroids administered orally or by injection, where it is missing. <i>Erosive Esophagitis</i> A new subsection was added to describe the cases of erosive esophagitis that occurred in subjects without erosions at baseline who received Eohilia in Study 1 (Trial SHP621-301). See Section 7.7.3. To mitigate this adverse reaction, instructions were included to advise patients/caregivers to report new onset or worsening symptoms of erosive esophagitis and to consider EGD evaluation. <i>Effect on Growth</i> A new subsection was added to describe the risk for reduction of growth velocity in pediatric patients and to emphasize the maximum duration of treatment of 12 weeks. Although effects on growth were not observed during Trial 101-06 or Trial 301, these trials were limited to 12 weeks in duration. Diminished growth velocity is an established class effect of corticosteroids. Additionally, suppression of long bone growth was observed in nonclinical studies of budesonide oral suspension. See Section 7.1.
ADVERSE REACTIONS, <i>Clinical Trials Experience</i>	The safety results from both Study 1 (Trial SHP621-301) and Study 2 (Trial MPI 101-06) are described. Study 2 (Trial SHP621-301) was added and (b) (4) (b) (4) The most common adverse reactions in ≥2% of subjects receiving Eohilia and at a greater rate than placebo in Studies 1 and 2 are respiratory tract infection, gastrointestinal mucosal candidiasis, headache, gastroenteritis, throat irritation, adrenal suppression, and erosive esophagitis. See Section 7.6. Additional details on cases of erosive esophagitis were added to supplement the information in the WARNINGS AND PRECAUTIONS section.

Full Prescribing Information Sections ^a	Rationale for Major Changes to Finalized PI ^b Compared to Applicant's Draft PI
DRUG INTERACTIONS	(b) (4)
USE IN SPECIFIC POPULATIONS	<i>Pediatric Use</i> This subsection was revised to describe the information that supported the pediatric indication (i.e., adequate and well-controlled studies in adult and pediatric subjects 11 years of age and older with PK data in pediatric subjects aged 11 to 17 years). Systemic effects such as hypercorticism and adrenal axis suppression and reduction in growth velocity are summarized to reflect the specific risks associated with the use of the drug in pediatric patients, as described in the WARNINGS AND PRECAUTIONS section. <i>Geriatric Use</i> Revised to remove the statement that (b) (4) <i>Hepatic Impairment</i> See (b) (4) above regarding the recommendation to monitor patients with moderate hepatic impairment (b) (4)
OVERDOSAGE	This section was updated to (b) (4)
CLINICAL PHARMACOLOGY	<i>Mechanism of Action</i> Removed Mention of (b) (4) <i>Pharmacodynamics</i> Updated to remove (b) (4) <i>Pharmacokinetics</i> Updated to include information from the food effect study (TAK-721-1003) that showed that the small increase in systemic exposure of budesonide due to food effect is not expected to be clinically meaningful. Updated to (b) (4)

Full Prescribing Information Sections ^a	Rationale for Major Changes to Finalized PI ^b Compared to Applicant's Draft PI
CLINICAL STUDIES	Section 14 was updated to add Study 2 (Trial MPI 101-06) to Study 1 (Trial SHP621-301). The results of the efficacy endpoints of histological remission and absolute change from baseline in DSQ combined score from both studies are reported separately using the FDA's preferred analyses. An additional evaluation of data from the subject-reported DSQ with inherent clinical meaningfulness (i.e., achieving no dysphagia or experiencing only dysphagia that "got better or cleared up on its own") provided more information and context to inform the meaningfulness of the statistically significant results of the symptomatic endpoint in lieu of anchor based analyses. See Section 6.3.1. (b) (4) A brief description of Trial SHP621-302 was added along with the results (i.e., "Treatment with EOHILIA did not demonstrate a statistically significant difference compared to subjects re-randomized to placebo for prespecified efficacy endpoints based on eosinophil count and/or clinical symptoms measured by the DSQ at Week 36") to support the limited duration of 12 weeks in the indication statement.

Full Prescribing Information Sections ^a	Rationale for Major Changes to Finalized PI ^b Compared to Applicant's Draft PI
Product Quality Sections	<i>Dosage Forms and Strengths</i> The review team recommended updates throughout the labels and labeling to clarify that the oral suspension is supplied as a unit-dose packet instead of a "stick pack." In response, the Applicant requested to update the existing materials through submission of a prior approval supplement within one month post launch to prevent delays in product availability. The team agreed that this was acceptable and will remind the Applicant of this agreement in the NDA Approval letter.
	<i>Description Information</i> (b) (4) was removed (b) (4) Section 11 (DESCRIPTION) allows for inclusion of important chemical and physical information related to the product, the term thixotropic was included in Section 11 because it is considered to be a factual physical property of the product.
	<i>How Supplied/Storage and Handling</i> The excursion temperature was added, as well as a warning not to freeze the oral suspension.

Source: Reviewer-generated table

^a Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table ¹ Some Sections may not be included because those sections may not have major issues (or changes).

^b For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.

Abbreviations: ACTH, adrenocorticotrophic hormone; EGD, esophagogastroduodenoscopy; PI, Prescribing Information

23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- Prescribing Information
- Patient Package Insert
- Instructions for Use

24. Postmarketing Requirements and Commitments

The following postmarketing commitments were requested of the Applicant.

- Conduct a randomized, double blind, placebo-controlled clinical trial to evaluate the safety, efficacy, and pharmacokinetics of Eohilia (budesonide oral suspension) in pediatric patients 1 to less than 11 years of age with active eosinophilic esophagitis.
- Perform a lactation study (milk only) in lactating women who have received Eohilia (budesonide oral suspension) to assess concentrations of budesonide in breast milk using a validated assay and the potential effects on the breastfed infant.

After receipt of the initial response from the Applicant to the requested PMCs, the review team provided additional rationale for the request to emphasize the importance of the postmarketing commitment to conduct a pediatric study with BOS.

On January 23, 2024, the review team communicated the following to the Applicant (DARRTS Reference ID: 5315669).

Pediatric patients less than 12 years of age with EoE are experiencing an unmet medical need for safe and effective therapies. The prevalence of this serious condition is increasing in the US. Based on data from insurance claims within the Truven MarketScan database, the prevalence of EoE increased from 79/100,000 in patients in 2015 to 117/100,000 patients in 2018 ([Kamat et al. 2021](#)). Using US Census population estimates for 2018, this extrapolates to 382,786 patients ([United States Census Bureau](#)). Although the estimated prevalence in children younger than 10 years of age is lower than the overall population estimates at 68/100,000, the complex and heterogeneous symptom expression in pediatric patients may be resulting in under recognition and delayed diagnosis ([Kamat et al. 2021](#)). Additionally, children often develop eating strategies to cope with their symptoms, and this may also delay symptom recognition and subsequent diagnosis. Again, using US Census population estimates for 2018, current prevalence estimates extrapolate to almost 30,000 children younger than 10 years of age with EoE in the US that are currently without access to safe and effective therapies ([United States Census Bureau](#)).

Both the symptoms of EoE (e.g., failure to thrive, vomiting, gagging, food impaction, abdominal pain) and adaptive behaviors necessary to avoid symptoms (e.g., dietary modification, food avoidance) cause significant morbidity and negative impacts on pediatric patients and their caregivers. Additionally, dietary modifications and compensatory behaviors can cause psychosocial issues and lead to substantially impaired quality of life for patients and their caregivers ([DeBrosse et al. 2011](#)) ([Falk 2014](#)) ([Straumann and Katzka 2018](#)). Furthermore, as a result of their disease, pediatric patients with active EoE and their families may experience frequent disruptions and loss of productivity in school and work. Safe and effective treatment can reduce the impact of EoE on the immediate morbidity and burdens of disease faced by younger pediatric patients and their families. Maintaining control of active disease during childhood may reduce the risk for long-term complications (e.g., stricture, food impaction). This may be especially important for pediatric patients who develop active disease early in life who face a prolonged disease duration compared to patients who develop active disease during adolescence or adulthood.

Although available formulations of corticosteroids developed for orally-inhaled administration for the treatment of asthma are currently used as off-label therapies for the treatment of EoE, these products have not been found to be safe or effective, and data are needed to identify the appropriate dose(s) and frequency of administration to support their use. Furthermore, patient compliance with these therapies can be limited by the need to adapt currently available formulations for topical use (e.g., homemade slurry preparations for swallowing, such as mixing contents of inhaled products for asthma with Splenda, honey, or other sweeteners). This also results in unstandardized dosing and administration of products that have not been established to be safe or effective for EoE ([Syverson et al. 2023](#)).

As part of the March 17, 2022 Type A Meeting Request, you included “Appendix 1. EoE Commentary for BOS.” In this document, academicians, researchers, and clinicians described the significant impact and challenges experienced by patients with EoE and their families.

There is a pressing need for FDA approved medications to treat eosinophilic esophagitis (EoE) in the United States... Symptoms of poor growth, feeding intolerance, abdominal pain, vomiting, chest pain, and heartburn in children can evolve into dysphagia and food impaction in adolescents and adults due to esophageal strictures or narrowing ([Furuta and Katzka 2015](#)) ([Muir and Falk 2021](#)). Costs related to EoE are substantial, as are nonmonetary impacts such as missed work and school for both patients and caregivers, social isolation, and overlapping mental illness ([Jensen et al. 2015](#)) ([Hiremath et al. 2018](#)) ([Harris et al. 2013](#)) ([Taft et al. 2021](#)) ([Reed et al. 2020](#)) ([Jensen et al. 2020](#)). Notably, all pharmacologic options in the United States are used off-label and therefore suboptimal and difficult to obtain.

We have heard from multiple stakeholders, including these physicians and the advocacy groups supporting patients with EoE, of the substantial burdens directly affecting children living with EoE and their families.

We remain committed to continued collaboration with Takeda to promote the availability of therapies that have been found to be safe and effective for all patients with EoE. While we acknowledge that budesonide oral suspension (BOS) [otherwise known as TAK-721] has an orphan drug designation for the “treatment of patients with eosinophilic esophagitis” (ODD 06-2274) and is therefore exempt from the Pediatric Research Equity Act (PREA) postmarketing requirements, we respectfully request that Takeda consider the unmet needs faced by younger pediatric patients with EoE and their families when determining the future development of BOS. In recognition of the existing unmet need for therapies to treat EoE in this population, FDA strongly encourages Takeda to agree to conduct the study in patients less than 11 years of age described in the previously communicated postmarketing commitment. When considered with the existing data from the BOS development program, the proposed trial may provide sufficient data to support an indication for the treatment of EoE in these younger pediatric patients. We look forward to your response.

Conduct a randomized, double-blind, placebo-controlled clinical trial to evaluate the safety, efficacy, and pharmacokinetics of Eohilia (budesonide oral suspension) in pediatric patients 1 to less than 11 years of age with active eosinophilic esophagitis.”

In response to the review team’s communication, included above, the Applicant agreed to conduct the requested postmarketing commitment to conduct a clinical trial in pediatric patients according to the following schedule:

Final Protocol Submission: 08/2026

Trial Completion: 06/2029

Final Report Submission: 12/2029

The Applicant did not agree to conduct the requested lactation study.

25. Financial Disclosure

Table 43. Covered Clinical Studies: Trial MPI 101-06 and Trial SHP621-301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 650		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 7		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 5 Proprietary interest in the product tested held by investigator: 1 Significant equity interest held by investigator: 1 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 4		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, U.S. Food and Drug Administration

26. References

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27. Review Team

Table 44. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Mary Chung
Nonclinical team leader	Sushanta Chakder
OCP reviewer(s)	Youssef Mousa
OCP team leader(s)	Insook Kim
Clinical reviewer	Sarrit Kovacs
Clinical team leader	Erica Lyons
Statistical analyst	Ping Li
Statistical reviewer	Joshua Sampson
Statistical team leader	Paul Imbriano
Patient-Focused Statistical Scientists reviewer and team leader	Monica Morell and Lili Garrard
Cross-disciplinary team leader	Erica Lyons
Division director (OB)	Laura Lee Johnson
Division director (clinical)	Jessica J. Lee

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

Table 45. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ Application Team Lead	Hamid Shafiei
OPQ/ Drug Product	Hamid Shafiei
OPQ/ Drug Substance	Friedrich Burnett, Lawrence Perez (secondary), Donna Christner (tertiary)
OPQ/ Manufacturing (Process and Facilities)	Khalid Khan, Cassie Abellard
OPDP	Meeta Patel, Adewale Adeleye
DMPP/ Patient Labeling Team	Kelly Jackson, Marcia Williams
DPMH/ Pediatrics	Ethan Hausman, Shetarra Walker (TL)
DPMH/ Maternal Health	Jane Liedtka, Tamara Johnson (TL)
OSE/DMEPA	Sherly Abraham, Damon Birkemeier (Acting TL)

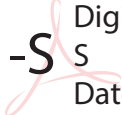
Abbreviations: OPQ, Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management

27.1. Reviewer Signatures

See next page.

Table 46. Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biometrics Reviewer	Monica Morell Office of Biostatistics Division of Biometrics III/ Patient Focused Statistical Scientists	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 1, 6	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp: Monica C. Morell -S  Digitally signed by Monica C. Morell -S Date: 2024.02.07 13:19:10 -05'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biometrics Reviewer	Joshua Sampson Office of Biostatistics Division of Biometrics III	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 1, 6	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp:  Digitally signed by Joshua N. Sampson - Date: 2024.02.07 13:04:04 -05'00'				
Biometrics Team Leader	Paul Imbriano Office of Biostatistics Division of Biometrics III	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 1, 6	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp:  Digitally signed by Paul M. Imbriano -S Date: 2024.02.07 13:12:17 -05'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biometrics Team Leader	Lili Garrard Office of Biostatistics Division of Biometrics III/ Patient Focused Statistical Scientists	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 1, 6	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp: Lili Garrard -S Digitally signed by Lili Garrard -S Date: 2024.02.07 13:21:54 -05'00'				
Biometrics Division Director	Laura Lee Johnson Office of Biostatistics Division of Biometrics III	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 1, 6	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp: Laura L. Johnson -S Digitally signed by Laura L. Johnson -S Date: 2024.02.07 13:29:24 -05'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Reviewer	Youssef Mousa Office of Clinical Pharmacology/Genome Targeted Therapy Group Division of Inflammation and Immune Pharmacology (DIIP)	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5.2, 8, 14	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp: Youssef Mousa -S (Affiliate) Digitally signed by Youssef Mousa -S (Affiliate) Date: 2024.02.07 13:42:17 -05'00'				
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Signature/date/time stamp: Insook Kim -S Digitally signed by Insook Kim -S Date: 2024.02.07 13:45:55 -05'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Management Regulatory Project Manager	Mary Chung Other Office of Regulatory Operations	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 12	Based on my assessment of the application: ☐ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	
Signature/date/time stamp: Mary H. Chung -S Digitally signed by Mary H. Chung -S Date: 2024.02.07 13:49:45 -05'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Reviewer	Sarrit Kovacs Office of Immunology and Inflammation Division of Gastroenterology	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 1, 2, 3, 4, 7, 8.3, 8.4, 10, 11, 16, 17, 23, 24, and 25	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp:  Sarrit M. Kovacs -S Digitally signed by Sarrit M. Kovacs -S Date: 2024.02.07 14:20:59 -05'00'				
Cross-Disciplinary Cross-Disciplinary Team Lead	Erica Lyons Office of Immunology and Inflammation Division of Gastroenterology	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 1 and All	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp:  Erica M. Lyons -S Digitally signed by Erica M. Lyons -S Date: 2024.02.07 16:18:26 -05'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Division Director	Jessica Lee Office of Immunology and Inflammation Division of Gastroenterology	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections Approved: All	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp: Jessica J. Lee -S Digitally signed by Jessica J. Lee -S Date: 2024.02.07 16:45:50 -05'00'				

Abbreviations: IA, Interdisciplinary Assessment
Include "IA" for authors who contributed to the Interdisciplinary Assessment and add "Abbreviations: IA, Interdisciplinary Assessment" as a table note.

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/

ERICA M LYONS
02/08/2024 03:02:22 PM

JESSICA J LEE
02/08/2024 03:03:51 PM

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	213976
Priority or standard	Priority
Submit date(s)	10/15/2020
Received date(s)	10/15/2020
PDUFA goal date	4/15/2021
Division/office	Division of Gastroenterology (DG)
Review completion date	12/17/2021
Established/proper name	Budesonide
(Proposed) proprietary name	Eohilia
Pharmacologic class	Corticosteroid
Code name	TAK-721/SHP621
Applicant	Takeda Pharmaceuticals USA, Inc.
Dosage form(s)/formulation(s)	Oral suspension as a single-dose stick pack 2 mg/ 10 mL
Dosing regimen	2 mg orally twice daily
Applicant proposed indication(s)/ population(s)	For the treatment of eosinophilic esophagitis (EoE), (b) (4) in adult and adolescent patients 11 years and older (b) (4)
Proposed SNOMED indication	Eosinophilic esophagitis (235599003)
Regulatory action	Complete response
Approved dosage (if applicable)	N/A
Approved indication(s)/ population(s) (if applicable)	N/A
Approved SNOMED term for indication (if applicable)	N/A

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Glossary

ACTH	adrenocorticotrophic hormone
AE	adverse event
AETERM	adverse event term
ANCOVA	analysis of covariance
AUC	area under the concentration-time curve
BID	twice daily
BOS	budesonide oral suspension
BTD	Breakthrough Therapy Designation
CI	confidence interval
C _{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CMH	Cochran-Mantel-Haenszel
CR	complete response
CSR	clinical study report
DR	Discipline Review
DSQ	Dysphagia Symptom Questionnaire
eCDF	empirical cumulative distribution function
eCTD	electronic common technical document
EGD	esophagogastroduodenoscopy
EoE	eosinophilic esophagitis
F2F	face-to-face
FAS	full analysis set
FDA	Food and Drug Administration
GM-CSF	granulocyte macrophage colony stimulating factor
HPA	hypothalamic-pituitary-adrenal
HPF	high-power field
IND	investigational new drug
IP	investigational product
IR	information request
ISS	integrated summary of safety
NDA	new drug application
NRI	nonresponder imputation
OLE	open-label extension
OPQ	Office of Pharmaceutical Quality
PBO	placebo
PDUFA	Prescription Drug User Fee Act
PGIS	Patient Global Impression of Severity
P-gp	P-glycoprotein
PK	pharmacokinetic
PPI	proton pump inhibitor
PRO	patient-reported outcome
PT	preferred term
QD	once daily

NDA 213976

Budesonide oral suspension (Eohilia)

SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
TBM	to-be-marketed
TEAE	treatment-emergent adverse event

I. Executive Summary

1. Summary of Regulatory Action

The new drug application (NDA) 213976 for budesonide oral suspension (BOS, also known as SHP621/TAK-721, proposed trade name of Eohilia) was submitted by Takeda Pharmaceutical USA under a rolling review on October 15, 2020. BOS is an oral formulation of budesonide, an anti-inflammatory corticosteroid with a high glucocorticoid effect and a weak mineralocorticoid effect. The Applicant is proposing to rely on the U.S. Food and Drug Administration's (FDA's) findings of safety as reflected in the approved product labeling for the listed drug Entocort EC (NDA 021324 for the treatment and maintenance of clinical remission of mild to moderate Crohn's disease; budesonide 3 mg delayed-release hard gelatin capsules), and published literature, as permitted in Section 505(b)(2) of the Federal Food Drug and Cosmetic Act.

The Applicant's proposed indication is the treatment of eosinophilic esophagitis (EoE), (b) (4) in adult and adolescent patients 11 years and older. To support the evaluation of safety and efficacy of BOS in subjects with EoE, the Applicant conducted initial treatment and extension phase 3 clinical trials (SHP621-301 [Trial 301] and SHP621-302 [Trial 302]). Although described and reported independently, these trials were conducted with a shared study population.

The NDA was reviewed by the multidisciplinary review team, and the review team does not recommend approval; the signatory authority concurs with the review team's recommendation to take a Complete Response (CR) action. Although the identified risks of treatment with BOS can be mitigated through labeling and further evaluated during routine pharmacovigilance, the Applicant failed to establish that short- or long-term treatment with BOS provides meaningful benefit to patients with EoE.

In the absence of established benefit, the overall benefit-risk assessment is not favorable as described in the Benefit-Risk Framework [below](#). For detailed information supporting the basis for this CR action, refer to the reviews included in this Integrated Assessment document, the noted supplementary discipline reviews, and the Product Quality review. The review team's determination was presented to the Medical Policy and Program Review Council on March 10, 2021, and the Council unanimously agreed that a CR was the appropriate regulatory action based on the data presented.

On March 19, 2021, the Division issued a Discipline Review (DR) Letter to the Applicant detailing the concerns with the ability of the submitted data to support the demonstration of efficacy for BOS for the treatment of patients with EoE. In response to the DR Letter, the Applicant submitted a multiple module information amendment on March 29, 2021. This amendment included post hoc analyses of a newly defined subgroup of trial subjects (i.e., subjects without prior history of dilation) from Trial 301. As a result of this submission, multiple Information Requests (IRs) were sent to the Applicant during the review period. The final response to these IRs was received from the Applicant on September 17, 2021.

The Application was discussed again with the Medical Policy and Program Review Council on November 3, 2021, and the Council unanimously agreed with the Division that a CR continued to be the appropriate regulatory action for the application. The Council further recommended that the Applicant conduct a controlled long-term study in order to demonstrate persistent efficacy of budesonide in patients with EoE. Although the post hoc subgroup analyses submitted on March 29, 2021 may be useful to facilitate the generation of a potential novel hypothesis to inform a future study of BOS, neither the review team nor senior leadership within the Center for Drug Evaluation and Research considered the post hoc analysis results to be sufficient to resolve the significant issues encountered during the review of the NDA.

The following comments will be communicated to the Applicant in the CR letter.

CLINICAL/ STATISTICAL:

As was conveyed in the Filing Communication – Filing Review Issues Identified Letter dated December 14, 2020, and subsequently communicated in the Discipline Review Letter dated March 19, 2021, our review identified deficiencies with the ability of the submitted data to demonstrate the short- and long-term efficacy of BOS for the treatment of EoE. We have completed our review of NDA 213976, and have determined that neither the data submitted in the NDA, nor the data submitted to the NDA during review of the application, are adequate to support the demonstration of efficacy of BOS for the treatment of EoE in adult and adolescent patients 11 years and older.

1. The results from the evaluation of the symptomatic coprimary endpoint in trial SHP621-301, while statistically significant, were not representative of clinically meaningful change. Throughout the conduct of the development program and the course of the review, we expressed our concerns with the selection of the ≥ 30 percent Dysphagia Symptom Questionnaire (DSQ) responder threshold and cautioned you that evidence was needed to support its clinical meaningfulness. The anchor-based analyses that you provided, conducted using the data from the 12-week initial treatment phase 3 trial SHP621-301, do not support that the selected threshold constituted a clinically meaningful within-patient change.

In addition, although a statistically significant response was observed on the histologic coprimary endpoint in trial SHP621-301, the contribution of that finding to support a determination of benefit is unclear due to the lack of sustained histologic response observed in subjects maintained on treatment with BOS in trial SHP621-302. Further, there are inadequate data to demonstrate that short-term improvement in histologic response predicts improvement in meaningful clinical outcomes.

2. The evaluation of the key secondary efficacy endpoint of absolute change from baseline in 14-day DSQ combined score for trial SHP621-301 did not demonstrate that subjects treated with BOS had meaningful benefit compared to those treated with placebo. Although statistically significant results were reported on this prespecified alpha-controlled symptomatic secondary endpoint, the treatment difference between BOS and placebo groups was small, and the assessment period was not supported by the 7-day Patient Global Impression of Severity (PGIS). A treatment difference was not observed

on evaluation of the change in 7-day DSQ absolute combined score (conducted to match the 7-day assessment period of the PGIS).

3. As EoE is a chronic relapsing condition, data to establish the benefit of long-term treatment for a candidate therapeutic is needed to support a determination of durability of effect. The need for long-term efficacy data to support your application has been emphasized throughout the development program, and we refer you to the following communications under IND 103173:

- November 12, 2014 Type B End-of-Phase 2 meeting (meeting minutes finalized on November 30, 2014)
- July 13, 2015 Type C meeting (meeting minutes finalized on July 15, 2015)
- November 2, 2016 ‘Initial Comprehensive Multidisciplinary Breakthrough Therapy Type B Meeting’ (meeting minutes finalized on November 4, 2016)
- June 25, 2019 Type B Pre-NDA face-to-face meeting (meeting minutes finalized on June 27, 2019)
- May 20, 2020 Type B Pre-NDA teleconference (meeting minutes finalized on June 2, 2020)

On review of your submitted phase 3 trial SHP621-302 efficacy data, the benefit of long-term treatment with BOS for patients with EoE was not established. The trial did not yield statistically significant results on the pre-specified long-term efficacy endpoint of relapse on both histology and symptoms in the individual subject.

4. The data submitted to the NDA during review of the application from post hoc subgroup analyses of subjects without prior history of dilation for the 12-week initial treatment period are inadequate to support the demonstration of efficacy for BOS for the treatment of patients with EoE. Dilation status was collected during screening for eligibility criteria, and dilation-naïve status was identified as a subgroup of interest for efficacy analyses only *after* data unblinding and completion of the SAP-specified analyses. The variable (i.e., dilation status) used to identify the subpopulation in trial SHP621-301 is not reliable, as a substantial portion of these subjects were identified by self-report, and it was not possible to confirm the dilation status for these subjects from medical records. On analysis of the 7-day DSQ combined score (to match the 7-day PGIS anchor) in subjects with medical record confirmation of dilation status, minimal separation between treatment groups over the 12-week treatment period was observed.

Information needed to resolve the deficiencies:

To resolve the above-noted deficiencies, we recommend you leverage the existing data to inform the design of a new adequate and well-controlled study including adolescent and adult subjects with EoE in a prespecified subpopulation (e.g., subjects without a prior history of dilation, subjects with more severe dysphagia symptoms at baseline) to support chronic administration of BOS. If subjects with a prior history of dilation are to be included for analysis, medical record documentation of the procedure should be available for these subjects.

We recommend a treatment period of at least 24 weeks' duration to assess efficacy for both clinical and histologic endpoints, followed by an extension period to provide a total treatment period of at least 52 weeks' duration to ensure adequate exposure to allow for characterization of the safety profile and the durability of response in the intended population.

This new study should assess prespecified symptomatic and histologic coprimary endpoints. To aid in the interpretation of the DSQ results, an appropriate range of within-patient score change that patients consider to be clinically meaningful should be proposed using anchor-based methods (e.g., patient global impression scale as an anchor), supplemented with empirical cumulative distribution function (eCDF) curves using data pooled across treatment arms. You should complete this study before resubmitting the application.

We look forward to engaging with you as you consider the study design and population selection for a future trial of BOS in patients with EoE and advise you to continue to benefit from the frequent interactions with FDA available to you under your granted breakthrough therapy designation. This application may need discussion at an advisory committee meeting during the next review cycle.

ADDITIONAL COMMENTS:

We have the following additional comments/recommendations that are not approvability issues:

1. You did not conduct a food effect study with either the phase 3 formulation or the to-be-marketed (TBM) formulation of your proposed product. Therefore, the effect of food on the pharmacokinetics (PK) and safety of your drug product to inform dosing instructions in relation to meal intake is unknown. We have determined that the potential effect of food on budesonide exposure from BOS cannot be predicted based on available data/rationale, and a dedicated food effect study is needed. Your product is an oral suspension of corticosteroid budesonide, where adverse events including hypercortisolism and adrenal axis suppression have been shown to be concentration dependent. Considering this, assessing any factor that could potentially increase budesonide exposure is critical. Therefore, you should conduct a dedicated food effect study to inform the prescribing information for BOS and include the results of this study in the resubmission.
2. In the current submission, you provided limited dissolution data with the proposed dissolution method collected at the time of batch release. If approval of your proposed product needs manufacturing any new batch to resolve the deficiencies, provide full-profile dissolution data (n= 12) from that newly manufactured batch collected at the time of batch-release in the next submission. If no new batch manufacturing is required for approval of your product in terms of resolving the deficiencies, only upon approval of the proposed drug product, collect full-profile dissolution data (n= 12) for the first six commercial batches at the time of batch-release and provide these data to the FDA in your annual report.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Eosinophilic esophagitis (EoE) is a chronic immune- or antigen-mediated esophageal disease clinically characterized by signs and symptoms related to esophageal dysfunction and histologically characterized by eosinophil-predominant inflammation (Liacouras et al. 2011). Left untreated, EoE leads to esophageal stricture, dysphagia, and risk of food impaction (Warners et al. 2018). Furthermore, treatment cessation can lead to a recurrence of EoE clinical symptoms and histologic activity (Dellon et al. 2020). - In patients with EoE, clinical features and histologic activity can vary independently. Patients can have a reduction or resolution in signs and symptoms despite ongoing histologic activity. Conversely, patients can have histologic remission (defined as a change in peak eosinophils per high-power field (HPF) from a count greater than or equal to 15 to less than or equal to 6) with persistent clinical symptoms (Dellon et al. 2013).	EoE is a serious condition and can profoundly impact patients' health and well-being. As EoE is a chronic condition, data to demonstrate long-term efficacy are needed to support the treatment of this chronic condition. Because the clinical features and histologic activity of EoE can vary independently, the treatment goals of EoE include resolution or reduction of the signs and symptoms of active disease to provide relief to the patient, and healing or control of the esophageal inflammation and its complications. For a drug to demonstrate benefit as a therapy for EoE, efficacy should be demonstrated on both histologic response and through clinically meaningful improvement on symptoms and/or signs. As there are no approved therapies for EoE, a placebo comparator should be used for these studies.
Current Treatment Options	The current standard of care for EoE includes dietary modification and off-label use of topical corticosteroids intended for local action on the esophageal mucosa. Systemically acting corticosteroids, such as prednisone, are also used but are typically reserved for more severe or recalcitrant disease. Because of the potential for significant toxicity, long-term use of systemic corticosteroids is generally not recommended. There are data to suggest that swallowed, topically acting corticosteroids may be effective in resolving acute clinical and pathological features of EoE (Liacouras et al. 2011); however the safety and efficacy of these products for the treatment of EoE have not been	As the safety and effectiveness of off-label therapies has not been established, there is a need for novel therapies to treat EoE. Standardized formulations that reliably deliver the appropriate amount of drug, as well as data to inform the appropriate dosing regimen, are needed. Additionally, long-term data are needed to support the use of these products in patients with EoE.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	established. Additionally, currently used topical formulations were not designed for esophageal administration, and information is needed to inform the appropriate dose and frequency of administration for these products. Furthermore, patient compliance can be limited by the need to adapt currently available formulations for topical use. There are no FDA-approved pharmacological treatments for EoE.	
Benefit	- As part of Trial 301, the Applicant demonstrated a statistically significant result for their coprimary efficacy endpoint of histologic response (peak eosinophil count of ≤ 6 per high-power field across all available esophageal levels) and reduction in dysphagia symptoms ($\geq 30\%$ reduction in the Dysphagia Symptom Questionnaire [DSQ] combined score [sum of points for responses to questions 2+3]) after 12 weeks of treatment. However, the clinical meaningfulness of the $\geq 30\%$ DSQ responder threshold (determined using phase 2 data) cannot be supported based on the Applicant's anchor-based analyses in phase 3 (a threshold ranging between 50% and 57% was determined by the Applicant as meaningful to subjects [62% to 75% for adolescents and 48% to 52% for adults] and based on the analysis results and figures the Applicant provided, FDA determined that the threshold should be at least 67% [overall]). - The Applicant was advised multiple times during the development program for budesonide oral suspension (BOS) that the $\geq 30\%$ responder threshold would need to be supported by additional data to demonstrate that the effect was clinically meaningful to subjects. - Based on the data submitted, FDA determined the prespecified symptomatic coprimary endpoint for Trial 301 was not sufficient to support the demonstration of short-term symptomatic efficacy for BOS. Additional analyses were conducted using the prespecified alpha-controlled secondary endpoint of absolute change on the DSQ. These analyses were conducted using both the 14-day DSQ score (prespecified) and the 7-day DSQ score (to match the recall	Although statistically significant results were reported for the coprimary endpoints for Trial 301, the observed change on both the prespecified coprimary symptomatic endpoint ($\geq 30\%$ reduction in the DSQ combined score) and key secondary endpoint (absolute change on the DSQ) did not constitute meaningful within-patient improvement. This was despite the deviation from the prespecified 2-category improvement target anchor change category on the PGIS to a more inclusive revised target anchor of 1-category of improvement. As the data from both the coprimary and key secondary symptomatic endpoints did not indicate that treatment with BOS leads to clinically meaningful change, efficacy during the initial treatment period (Trial 301) was not demonstrated. EoE is a chronic condition for which long-term treatment is needed. Long-term efficacy was not established by the extension study, Trial 302. Upon review of the application, neither short nor long-term efficacy has been demonstrated for BOS for the treatment of adolescents and adults with EoE. Although the post hoc analyses (submitted by the Applicant March 29 – September 17, 2021) are potentially supportive of a novel hypothesis to inform future study of BOS, they are not sufficient to resolve the substantial issues encountered during the review of the NDA. Significant data quality issues were identified during the review of the application. Although the issues related to the evaluation of the symptomatic coprimary endpoint were adequately resolved through communication with the Applicant, the review

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	period of the 7-day Patient Global Impression of Severity [PGIS] anchor). Twenty-five of 303 subjects who reported PGIS both at baseline and at Week 16 had a 2-category improvement on the PGIS, the prespecified target anchor change category that was determined to constitute a clinically meaningful within-patient change by the Applicant and the review team. As too few subjects met the prespecified 2-category improvement target anchor, the Applicant decided after completion of the trial to proceed with a 1-category improvement on the PGIS as the target anchor change category. For the 14-day analysis, a minimal difference of <10% in the proportion of subjects experiencing improvement between BOS and the placebo was found in the FDA-determined meaningful change range. For the 7-day analysis, no difference between BOS and placebo was identified in the range where subjects were considered to have a meaningful improvement. • Trial 302 did not demonstrate a statistically significant result for their primary efficacy endpoint of relapse during the 36-week treatment period. Therefore, the long-term efficacy of BOS was not demonstrated. • Post hoc analyses of the 12-week initial treatment period in subjects without a history of prior dilation were submitted to the application during the review period; however, there were significant limitations to the ability of these data to support a determination of benefit. – The defining variable for this subpopulation (i.e., dilation history) was unreliable, as a substantial proportion of these subjects were identified via self-report only. – On FDA analysis of the 7-day DSQ combined score (to match the 7-day PGIS anchor), minimal separation between treatment groups was observed. – No data were submitted to support the Applicant's assumption that dilation-naïve status is directly related to higher baseline symptom scores. – The subgroup was defined only after data unblinding and completion of the statistical analysis plan (SAP)-specified analyses.	team was unable to confirm the source data for the histologic coprimary endpoint. As resolution of this issue would not impact the conclusion that substantial evidence of efficacy had not been demonstrated for either short- or long-term treatment with BOS in patients with EoE, additional efforts to resolve the issue were not pursued during the review cycle.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- EoE is a chronic condition. The submitted post hoc analyses do not address long-term efficacy. Long-term efficacy is needed to support the treatment of this chronic condition. • For the evaluation of histologic response, the protocol prespecified at least two biopsy samples be collected at each esophageal level. From these samples, the maximum eosinophil count would be used to calculate the peak eosinophil count for each subject. Since the Applicant did not provide the cell counts for the individual biopsy samples, FDA could not verify that the values reported for each esophageal level were the maximum count assessed. • For the evaluation of dysphagia symptom response, the reference date used for DSQ combined score calculation was not consistent between the subject daily diary source data and the psychometric analysis data for 16% of the subjects; however, this discrepancy did not change the efficacy results.	
Risk and Risk Management	• BOS is an oral formulation of budesonide, a corticosteroid product with a well-established safety profile as reflected in the prescribing information for the listed drug (LD), Entocort EC. • Corticosteroid class effects include upper respiratory tract infection, headache, sinusitis, nausea, vomiting, dyspepsia, hypertension, increased weight, psychiatric disturbance, increased transaminases, adrenal suppression, and cushingoid effects. • A notable imbalance was observed in the proportion of subjects treated with BOS with abnormally low cortisol values following an adrenocorticotrophic hormone (ACTH) stimulation test compared to placebo in Trial 301 at Week 16. In Trial 301, the BOS and placebo treatment arms had a similar proportion of subjects noted to have adrenal suppression at the baseline at Week 4 (3.8% versus 5.0%). After 12 weeks of treatment (at week 16), a higher percentage of subjects who received BOS 2 mg twice daily (BID) had abnormal ACTH stimulated serum cortisol levels (9.1%) when compared to subjects in placebo group (3.4%).	The observed risk profile for BOS was largely reflective of that described in the FDA-approved product labeling for the LD. Adrenal suppression occurred at a greater rate in those treated with BOS than placebo. Although noted to occur less frequently than as described with the LD, this risk should be appropriately communicated to patients and providers. Additionally, patients and prescribers should be informed of the risk for the adverse events potentially related to the topical administration and formulation of BOS (i.e., esophageal candidiasis, oropharyngeal candidiasis, gastritis, gastritis erosive, throat irritation, and herpes simplex esophagitis). Although only observed in a single subject, the severity and seriousness of the event of herpes simplex esophagitis are significant with regard to potential risks of BOS use. As such, this risk should be appropriately communicated to patients and providers. The effect of food on the pharmacokinetics (PK) and safety of BOS has not been assessed to inform dosing instruction(s) in

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	In Trial 302, abnormal ACTH stimulated peak cortisol levels (≤ 18 $\mu\text{g/dL}$) were observed at Week 36 for 7.6% of subjects who were treated with BOS in Trial 302 (from 4.2% at Trial 301 baseline and 6.4% at Trial 302 screening), and 11.1% of subjects who received placebo in Trial 302 (from 4.5% at 301 baseline and 8.7% at Trial 302 screening). The interpretability of the results from Trial 302 is limited, as all subjects received BOS during either Trial 301 or Trial 302. On review of the data presented in the prescribing information for the LD, the hypothalamic-pituitary-adrenal (HPA) axis suppression potential of BOS 2 mg appears to be lower than that observed with the use of Entocort EC. This may be due to lower systemic exposure of budesonide in subjects treated with BOS compared to Entocort EC. • Although the observed adverse event profile for BOS was largely consistent with the known class effects of corticosteroid products, additional adverse events emerged during the safety review as likely or potentially related to the formulation and topical administration of BOS including esophageal candidiasis, oropharyngeal candidiasis, gastritis, gastritis erosive, throat irritation, and herpes simplex esophagitis. • No clinically significant trends in vital sign data were observed during the review. • The Applicant did not conduct a food effect study with either the phase 3 formulation or the to-be-marketed (TBM) formulation of their proposed product.	relation to meal intake. Although not an application approvability issue, a dedicated food effect study is needed to inform the prescribing information for BOS.

2.2. Conclusions Regarding Benefit-Risk

EoE is a serious condition with no approved therapies. EoE can lead to esophageal stricture, dysphagia, and risk of food impaction. Evaluation of both histology and clinical symptoms is integral to diagnostic assessment and disease monitoring for this condition, but these elements can vary independently in patients with EoE. As such, candidate therapeutics should demonstrate benefit on both histologic response and symptoms and/or signs to support a determination of efficacy. EoE is a chronic condition for which long-term treatment is needed. There is a need for novel therapies to treat EoE.

To support the evaluation of safety and efficacy of BOS in subjects with EoE, the Applicant conducted initial treatment and extension phase 3 clinical trials in a shared study population (Trial 301 and Trial 302, respectively). Although statistically significant results were reported on the coprimary endpoints after 12 weeks of treatment in Trial 301, the observed changes on both the prespecified coprimary symptomatic endpoint ($\geq 30\%$ reduction in the DSQ combined score) and key secondary endpoint (absolute change on the DSQ) did not constitute meaningful within-patient improvement. Trial 302 did not demonstrate a statistically significant result on the primary efficacy endpoint of relapse during the 36-week treatment period.

On March 19, 2021, a DR Letter was issued to the Applicant outlining concerns regarding the ability of the submitted data to support a demonstration of either short- or long-term efficacy of BOS for the treatment of EoE. The Applicant responded to the letter on March 29, 2021 by submitting post hoc subgroup analyses of subjects with a history of prior dilation versus dilation-naïve subjects for the 12-week initial treatment period only. As a result of this submission, multiple IRs were sent to the Applicant during the review period. The final response to these IRs was received from the Applicant on September 17, 2021. The findings from these analyses were inadequate and unreliable to support a determination of short-term benefit for these subjects. Additionally, the submitted analyses did not address long-term efficacy needed to support the treatment of this chronic condition. Long-term data on prespecified symptomatic and histologic coprimary endpoints from a new clinical investigation of BOS for the treatment of EoE are necessary to provide substantial evidence of efficacy to support the regulatory approval of BOS.

Although significant data quality issues were identified during the review of the application, these issues were either resolved during the review (symptomatic coprimary endpoint) or determined to not impact the review team's conclusion that substantial evidence of efficacy has not been demonstrated for either short- or long-term treatment with BOS in subjects with EoE (histologic coprimary endpoint).

Regarding the evaluation of risk, BOS is an oral formulation of budesonide, a corticosteroid product with a well-established safety profile as reflected in the prescribing information for the LD, Entocort EC. Corticosteroid class effects include upper respiratory tract infection, headache, sinusitis, nausea, vomiting, dyspepsia, hypertension, increased weight, psychiatric disturbance, increased transaminases, adrenal suppression, and cushingoid effects. Although the observed adverse event profile for BOS was largely consistent with the known class effects of corticosteroid products, additional adverse events emerged during the safety review as likely or potentially related to the formulation and topical administration of BOS including esophageal candidiasis, oropharyngeal candidiasis, gastritis, gastritis erosive, throat irritation, and herpes simplex esophagitis.

Additionally, the effect of food on the pharmacokinetics (PK) and safety of BOS has not been assessed to inform dosing instruction(s) in relation to meal intake. Although not an application approvability issue, a dedicated food effect study is needed to inform the appropriate timing of BOS administration in relation to food intake.

In the absence of established benefit, the overall benefit-risk assessment is not favorable to support the approval of BOS for the treatment of EoE, (b) (4) in adult and adolescent patients 11 years and older.

II. Interdisciplinary Assessment

3. Introduction

The Applicant submitted NDA 213976 for budesonide oral suspension (BOS, also known as SHP621/TAK-721, proposed trade name of Eohilia) 2 mg/10 mL on October 15, 2020 (via a rolling NDA submission), seeking U.S. Food and Drug Administration (FDA) approval for a new formulation and dosage of budesonide “for the treatment of eosinophilic esophagitis (EoE), (b) (4) in adult and adolescent patients 11 years and older.” BOS is formulated as a white to yellow, cherry-flavored, thixotropic, viscous oral suspension taken in 10 mL single-dose stick packs twice daily (morning and evening).

The Applicant is proposing to rely on FDA’s findings of safety as reflected in the approved product labeling for the listed drug Entocort EC (NDA 021324 for Crohn’s disease; budesonide 3 mg delayed-release hard gelatin capsules), as well as published literature, as permitted in Section 505(b)(2) of the Federal Food Drug and Cosmetic Act.

BOS is a topical anti-inflammatory corticosteroid with high affinity to glucocorticoid receptors. Glucocorticoids are believed to either directly or indirectly suppress the transcription of inflammatory genes, cytokines, recruitment of inflammatory cells, and the release of inflammatory mediators. The Applicant stated that budesonide has been shown to reduce immune cell activation and production of proinflammatory cytokines, thus preventing epithelial cell dysfunction by inhibiting the activation of T cells and monocytes. The anti-inflammatory actions of corticosteroids are thought to contribute to their efficacy in EoE. However, as the Applicant stated in the proposed prescribing information for BOS, “the precise mechanism of corticosteroid actions on inflammation in EoE is not known.”

To establish a bridge between BOS and Entocort EC, the Applicant conducted a relative bioavailability study (Study SHP621-101) in healthy volunteers.

To support the evaluation of safety and efficacy of BOS in subjects with EoE, the Applicant conducted initial treatment and extension phase 3 clinical trials. Although described and reported independently, these trials were conducted with a shared study population:

Trial SHP621-301 (Trial 301) was a phase 3, randomized, multicenter, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of BOS treatment administered twice daily for 12 weeks, conducted in adolescents and adults, ages 11 to 55 years (inclusive) with EoE and dysphagia. The trial evaluated coprimary efficacy endpoints at week 16 (baseline was week 4 after a 4-week placebo lead-in period) of (1) histologic response (defined as a peak eosinophil count of ≤ 6 per high-power field across all available esophageal levels) and (2) reduction in dysphagia symptoms (defined as a $\geq 30\%$ reduction in the Dysphagia Symptom Questionnaire [DSQ] combined score [sum of points for responses to questions 2+3]). Trial 301 also included a prespecified alpha-controlled secondary endpoint of absolute change on the DSQ.

Trial SHP621-302 (Trial 302) was a phase 3, multicenter, double-blind extension study to Trial 301 to evaluate the efficacy, safety, and tolerability of BOS treatment administered twice daily (morning and evening) for 36 weeks. Trial 302 was conducted in adolescents and adults, ages 11 to 55 years (inclusive) with EoE and dysphagia, who completed the Trial 301 induction study. Subjects who were assessed to have achieved both histologic and symptomatic response as defined by the coprimary endpoints for Trial 301 were included in the randomized withdrawal part of Trial 302, and all other subjects were assigned to receive BOS in Trial 302. The randomized withdrawal part of Trial 302 evaluated a primary endpoint of relapse (yes/no) during the 36-week randomized double-blind period for Applicant-identified Trial 301 BOS “full responders” (defined as having achieved ≤ 6 eosinophils/HPF across all available esophageal levels and at least a 30% reduction in DSQ at the final treatment evaluation visit for Trial 301). Relapse was defined as an eosinophilic count of ≥ 15 per high-power field in two of three levels of the esophagus and a minimum of 4 days of dysphagia (answering “yes” to question 2 in the DSQ) in the two-week period prior to the scheduled visit.

Additionally in the NDA, the Applicant provided data from a phase 2 dose-ranging trial in children and adolescents (MPI 101-01), a phase 2 trial of BOS in adolescents and adults (MPI 101-06), and an ongoing open-label continued access phase 3 trial in adolescents and adults (SHP621-303). All of these studies contributed data to inform the clinical safety evaluation for BOS as a candidate therapeutic for patients with EoE. Although the Applicant positioned the phase 2 study MPI 101-06 as key to the determination of efficacy, due to differing study design features (i.e., version of the DSQ, anchor scales, primary endpoints, and study population [including age and baseline peak eosinophil counts]), the review team determined that the data from this trial were more appropriately positioned to provide supportive safety data.

Finally, during the review, the Applicant provided data from post hoc analyses in a subgroup of dilation-naïve subjects from Trial 301 (i.e., the 12-week initial treatment period) in support of the evaluation of efficacy for BOS. This subgroup was identified after data unblinding and completion of the statistical analysis plan (SAP)-specified analyses.

3.1. Review Issue List

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

3.1.1.1. Lack of Clinical Meaningfulness of the $\geq 30\%$ DSQ Responder Threshold

The prespecified symptomatic coprimary endpoint for Trial 301 was statistically significant; however, the clinical meaningfulness of the $\geq 30\%$ DSQ responder threshold (selected by the Applicant based on phase 2 data) is not supported by the phase 3 data. In order to understand the amount of improvement in DSQ combined score that is considered meaningful to subjects, a 2-category improvement on the 5-category Patient Global Impression of Severity (PGIS) was prespecified by the Applicant and agreed upon by the review team. However, the Applicant made the decision after completion of the trial to rely on a 1-category improvement to support the anchor-based meaningful change analyses due to the limited number of subjects reporting a 2-category improvement in Trial 301. The deviation from the prespecified 2-category improvement target anchor was not communicated directly with the FDA, instead the change

was only described in the Applicant's psychometric analysis report submitted as part of the NDA. The review team conducted independent assessment on the change in the target anchor category and concluded that a 1-category improvement on the PGIS was acceptable to support further anchor-based meaningful change analyses (see Section [16.3](#) for details). Using the 1-category improvement on the PGIS as the revised target anchor change category, the Applicant's submitted anchor-based analyses from Trial 301 resulted in a responder threshold range of approximately 50% to 57%. Subsequent FDA anchor-based analyses determined that the responder threshold should be at least 67%. Treatment differences between budesonide and placebo groups at either of these threshold values (i.e., 50% or 67%) were not nominally statistically significant.

Although the $\geq 30\%$ DSQ responder threshold was carried forward for use in phase 3 based on phase 2 data, the Applicant was counselled several times regarding concerns with the $\geq 30\%$ DSQ responder threshold and that phase 3 data analyses and sensitivity analyses would be needed to confirm this responder threshold as clinically meaningful in phase 3 (i.e., communications under reference investigational new drug [IND] 103173: the November 12, 2014, type B end-of-phase 2 meeting; a September 3, 2015, email to the Sponsor; a September 15, 2015, advice/information request letter; a February 15, 2018, advice/information request letter; a September 17, 2018, advice/information request letter; a February 7, 2019, advice/information request letter; and the May 20, 2020, type B pre-NDA meeting).

3.1.1.2. Lack of Meaningful Short-Term Efficacy on Key Secondary Endpoint

The review team determined that the prespecified symptomatic coprimary endpoint for Trial 301 was not sufficient to support the demonstration of short-term efficacy for BOS. Additional analyses were conducted using the prespecified alpha-controlled secondary endpoint of absolute change on the DSQ combined score. Although statistically significant results were reported on the secondary endpoint of change from baseline in the 14-day DSQ absolute change combined score, the difference between budesonide and placebo groups was small, and the 14-day assessment period used for the DSQ score was not consistent with the 7-day assessment period used for the PGIS anchor. Additional analyses were conducted using the 7-day DSQ score (to match the recall period of the 7-day PGIS), and no difference between BOS and placebo was identified in the range that subjects considered to be a meaningful improvement.

3.1.1.3. Lack of Demonstration of Long-Term Efficacy

The prespecified primary efficacy endpoint in Trial 302 of relapse (yes/no) during the 36-week randomized double-blind period for Applicant-identified Trial 301 BOS "full responders" was not statistically significant. The apparent lack of demonstrated benefit was supported by FDA review of subject-level data submitted by the Applicant upon FDA request.

3.1.1.4. Submission of Post Hoc Subgroup Analyses Late in the Review Cycle

On March 29, 2021, in response to the DR Letter dated March 19, 2021, the Applicant submitted a multiple module information amendment including analyses for the symptomatic coprimary efficacy endpoint on the post hoc subpopulation of subjects from Trial 301 without prior history of dilation. This submission was then followed by multiple FDA information requests (IRs) and

Applicant responses, the last of which was received on September 17, 2021. Several limitations of these data precluded their use to support a determination of benefit as described below.

- The defining variable for this subpopulation (i.e., dilation history) was unreliable, as a substantial proportion of these subjects were identified via self-report only without medical record confirmation.
- On FDA analysis of the 7-day DSQ combined score (to match the 7-day PGIS anchor), minimal separation between treatment groups was observed.
- No data were submitted to support the Applicant's assumption that dilation-naïve status is directly related to higher baseline symptom scores.
- The subgroup was defined only after data unblinding and completion of the SAP-specified analyses.
- The submitted analyses do not address long-term efficacy for this chronic condition.

Although these data were inadequate to be considered supportive of a determination of efficacy, the review team evaluated the data to determine whether they could be useful for informing the design of future studies in this rare disease with unmet need.

3.1.1.5. Data Quality

The review team was unable to confirm the derived data from the source (i.e., subject-level) data for both coprimary endpoints based on the original submission.

For the histologic response, the protocol prespecified at least two biopsy samples be collected at each esophageal level. From these samples, the maximum eosinophil count would be used to calculate the peak eosinophil count for each subject. Since the Applicant did not provide the cell counts for the individual biopsy samples, FDA could not confirm that the values reported for each esophageal level were the maximum count using the submitted data.

For the dysphagia symptom response, the reference date used for DSQ combined score calculation was not consistent between the subject daily diary source data and the psychometric analysis data for 16% of the subjects.

FDA issued multiple IRs to evaluate the data quality issues. The Applicant responded with submissions of updated biopsy data and detailed source diary data by July 9, 2021. Although the review team was able to achieve acceptable resolution of the data quality issues regarding the evaluation of the symptomatic data, the Applicant confirmed that complete subject-level data for the histologic assessment were not available. The review team determined that the remaining data quality issues and inconsistencies in reporting (e.g., reference subject visit dates, reported values for peak eosinophil count on biopsy evaluation) would not impact the conclusion that substantial evidence of efficacy had not been demonstrated for either short- or long-term treatment with BOS in patients with EoE.

3.1.2. Key Review Issues Relevant to Evaluation of Risk

3.1.2.1. HPA Axis Suppression

A notable imbalance was observed in the proportion of subjects treated with BOS with abnormally low cortisol values following an adrenocorticotrophic hormone (ACTH) stimulation test compared to those who received placebo in Trial 301 at Week 16.

3.1.2.2. Identified Risks Related to BOS Formulation and Administration

BOS is a corticosteroid product formulated for topical administration to the esophagus. Although the observed adverse event profile for BOS was largely consistent with the known class effects of corticosteroid products, the following additional adverse events emerged during the safety review as likely or potentially related to the formulation and topical administration of BOS: esophageal candidiasis, oropharyngeal candidiasis, gastritis, gastritis erosive, throat irritation, and herpes simplex esophagitis.

3.1.2.3. Lack of Food Effect Study

The Applicant did not conduct a food effect study with either the phase 3 formulation or the to-be-marketed (TBM) formulation of their proposed product. Therefore, the effect of food on the pharmacokinetics (PK) and safety of the Applicant's drug product to inform dosing instruction(s) in relation to meal intake was not defined in the application.

3.2. Approach to the Review

The focus of the efficacy review were the data generated from the initial treatment and extension phase 3 clinical trials (Trials 301 and 302). The Applicant included one additional phase 2 study (MPI 101-06) to support the determination of safety and efficacy of BOS as a candidate therapy for EoE. Although the Applicant has stated that all three studies are considered pivotal to the determination of efficacy, as described earlier, due to differing study design features (i.e., version of the DSQ, anchor scales, primary endpoints, and study population including age and baseline peak eosinophil counts), the review team determined that trial MPI 101-06 was more appropriately positioned as supportive to the evaluation of safety.

For the evaluation of safety, data from trials MPI 101-06, 301, and 302 were evaluated independently. Additionally, pooled safety data were evaluated including data from all healthy volunteers or subjects with EoE who received at least one dose of the investigational product (BOS [any dose] or placebo [during the double-blind treatment periods]) in phase 1 trial SHP621-101 (healthy volunteers); phase 2 trials MPI 101-01 and MPI 101-06; and phase 3 trials SHP621-301, SHP621-302, and SHP621-303 (until the data cut-off date August 14, 2020). For additional description of the approach to the safety review, see Section [7.4](#) below.

Table 3. Pivotal Clinical Trials Submitted in Support of Efficacy and Safety Determination for BOS

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized	Number of Centers (all U.S. only)
SHP621-301 (NCT02605837)	Adolescent and adult subjects (11-55 years of age, inclusive) with EoE	Phase 3 R, DB, PG, PC, MC, 3-period efficacy, safety, and tolerability initial treatment study	Dosage: BOS 2 mg BID (qAM pc and hs); PBO 2 mg BID (qAM pc and hs); Oral Number treated: 318 Duration: 12-week DB treatment period	<u>Coprimary:</u> Histologic response and dysphagia symptom response ^[1] <u>Secondary:</u> Change in DSQ combined score from baseline	322	72
SHP621-302 (NCT02736409)	Adolescent and adult subjects (11-55 years of age, inclusive) with EoE who completed the SHP621-301 initial treatment study	Phase 3 R, DB, PG, PC, MC, 3-period efficacy, safety, and tolerability extension study to SHP621-301 A randomized withdrawal period was stratified by treatment assignment and treatment response in the SHP621-301 study. Only subjects who were "full responders" ² in the SHP621-301 study were eligible to enter the randomized withdrawal period to receive either BOS 2 mg twice daily or PBO at a 1:1 ratio.	Dosage: BOS 2 mg BID (qAM pc and hs); PBO 2 mg BID (qAM pc and hs); Oral Number treated: 219 Number of subjects in randomized withdrawal period: 48 (23 PBO, 25 BOS) Duration: 36-week treatment period	<u>Primary:</u> Relapse ^[2] during the 36-week double-blind randomized withdrawal period (for SHP621-301 "full responders" ^[3]) <u>Secondary:</u> Long-term response (both histologic and symptomatic) ^[4]	219	70

Source: Reviewer-created table

^[1] Dysphagia symptom response defined as ≥30% reduction in the DSQ combined score (sum of points for responses to questions 2+3) from baseline to week 16 (end of 12-week double-blind treatment period)^[2] Relapse, as a binary response (either with a relapse or not), was defined as meeting both the eosinophil histology relapse criterion (eosinophil count of ≥15/HPF and the dysphagia symptom relapse criterion (a minimum of 4 days of dysphagia [with answer 'Yes' for question 2 in DSQ] in the 2-week period prior to the scheduled visit, as determined by the DSQ)^[3] Defined as ≤6 eosinophils/HPF across all available esophageal levels and at least a 30% reduction in DSQ at the final treatment evaluation visit^[4] Defined as a binary response over the 36-week period in the Trial 301 BOS nonresponders (defined as all randomized subjects who did not respond or partially responded to assigned BOS treatment in Trial 301 and who received at least 1 dose of IP in Trial 302), where histologic response was defined as a peak eosinophil count of ≤6/HPF across all available esophageal levels at week 36 AND dysphagia symptom response was defined as ≥30% reduction in the DSQ combined score (questions 2+3) from baseline at week 36. Two baselines were evaluated – Trial 301 baseline and Trial 302 baseline.

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; DB, double-blind; DSQ, Dysphagia Symptom Questionnaire; EoE, eosinophilic esophagitis; hs, at bedtime; MC, multicenter; PBO, placebo; PC, placebo-controlled; PG, parallel group; qAM pc, every morning after meals; R, randomized

Table 4. Clinical Trials Submitted in Support of the Safety Determination for BOS and to Provide Additional Supportive Data^[1]

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized^[2]	Number of Centers (all U.S. only)
SHP621-101	Healthy adult subjects	Phase 1 OL, SC, single-dose, R, 2-sequence, 5-period, 5-treatment crossover, relative bioavailability study	15-day treatment period (at clinical research site): Single oral dose of each of 5 treatments, 1 every 3 days: •Treatment A: BOS MB-9 formulation 2 mg •Treatment B: Entocort EC 9 mg •Treatment C: BOS MB-7 formulation 2 mg •Treatment D: MB-9 formulation with (b) (4) variant (also known as SB-10) 2 mg •Treatment E: BOS MB-9 formulation with increased (b) (4) variant 2 mg	<u>Primary:</u> PK <u>Secondary:</u> PK, safety, and tolerability	22	1
MPI 101-01 (NCT00762073)	Subjects ages 2 to 18 years (inclusive) with symptomatic EoE	Phase 2 R, DB, PG, PC, MC, 2-period, dose-ranging study	Dosage: Low dose group: BOS 0.05 mg/mL hs and PBO qAM pc; Medium dose group: BOS 0.2 mg/mL hs and PBO qAM pc; High dose group: BOS 0.2 mg/mL hs and qAM pc; PBO group: PBO hs and qAM pc Number treated: 82 Duration: 12-week DB treatment period and 3-week taper	<u>Primary:</u> Response to therapy (defined by both an EoE clinical symptom response and a histologic response) <u>Secondary:</u> Histologic response and remission	82	20

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized^[2]	Number of Centers (all U.S. only)
MPI 101-06 (NCT01642212)	Adolescent and adult subjects (11-40 years of age, inclusive) with EoE	Phase 2 R, DB, PG, PC, MC, 3- period efficacy, safety, and tolerability study with OL extension	Dosage: BOS 2 mg BID (qAM pc and hs); PBO 2 mg BID (qAM pc and hs); Oral Number treated: 93 Duration: 12-week DB treatment period and 24-week OL extension	<u>Coprimary:</u> Histologic response and change in DSQ combined score from baseline to the final treatment period evaluation <u>Secondary:</u> Change in DSQ score over time	93	24
SHP621-303 (NCT03245840)	Adolescent and adult subjects (11-55 years of age, inclusive) with EoE who completed both SHP621-301 SHP621-302 studies	Phase 3 OL extension study to Trial SHP621-302 to provide continued access to BOS treatment	Dosage BOS 2 mg BID (qAM pc and hs); adjustments in dose regimen may be made Number treated: 131 (as of the data cut-off of August 14, 2020) Duration: Continued access until October 2023 or until BOS is commercially available.	Long-term safety and tolerability	131 (as of the data cut-off of August 14, 2020)	44

Source: Reviewer created table

^[1] Includes all submitted clinical trials, even if not reviewed in-depth^[2] If no randomization, then replaced with "Actual Enrolled"

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; DB, double-blind; DSQ, Dysphagia Symptom Questionnaire; EoE, eosinophilic esophagitis; hs, at bedtime; MC, multicenter; OL, open-label; PBO, placebo; PC, placebo-controlled; PG, parallel group; PK, pharmacokinetic; qAM pc, every morning after meals; R, randomized; SC, single-center

4. Patient Experience Data

The Applicant included the DSQ, a patient-reported outcome (PRO) instrument, as a coprimary endpoint in their 12-week induction study (Trial 301) and as part of the primary endpoint in their 36-week maintenance study (Trial 302) to assess subjects' symptom of dysphagia.

Table 5. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical outcome assessment data submitted in the application		
☒	Patient-reported outcome	1 , 2 , 3 , 6 , 12 , 16 , 16.3
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☒	Patient-focused drug development meeting summary	16
☒	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

Table 6. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class	Budesonide is a corticosteroid.
Mechanism of action	Budesonide is an anti-inflammatory corticosteroid and has a high glucocorticoid effect and a weak mineralocorticoid effect. The affinity of budesonide to glucocorticoid receptors, which reflects the intrinsic potency of the drug, is about 200-fold that of cortisol and 15-fold that of prednisolone. The precise mechanism of corticosteroid actions on inflammation in EoE is not known. Inflammation is an important component in the pathogenesis of EoE. Corticosteroids have a wide range of inhibitory activities against multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukocytes, and cytokines) involved in allergic and nonallergic-mediated inflammation. These anti-inflammatory actions of corticosteroids may contribute to a treatment effect in EoE.
Active moieties	Budesonide
QT prolongation	Not evaluated
General Information	
Bioanalysis	Validated HPLC/MS/MS methods (#42-1709 and #CN51830PLVAL) were used to determine the concentrations of budesonide in human plasma.
Healthy volunteers versus subjects	There is no significant difference in the PK parameters or exposure of budesonide following BOS administration between healthy volunteers and subjects with EoE.
Drug exposure at steady state following the therapeutic dosing regimen (or single dosage, if more relevant for the drug)	Budesonide Exposure at Steady State Following Administration of BOS
	Parameter^[1]
	Geometric Mean (% CV)
	AUC _{0-tau} (h·pg/mL) 5071 (58.1)
	C _{max} (pg/mL) 914.8 (59.2) or 2.1nM
	Median T _{max} (h) (min-max) 2 (0.5, 4)
Range of effective dosage(s) or exposure	The relationship between budesonide exposure from BOS and the efficacy endpoint for EoE has not been evaluated. In adolescent and adult subjects, dosages 0.5 mg QD, 2 mg QD, and 2 mg BID were studied in a phase 2 trial. Although there was dose-dependent increase in histologic response (peak <6 eos/hpf), a dose-response relationship for clinical response was not observed (Study MPI 101-01). Of note, the definition of clinical response in the phase 2 trial was different from the endpoint used in the phase 3 trial. Dosage higher than 2 mg BID was not studied. In phase 3 trial, only one dose level, 2 mg BID was studied.
Maximally tolerated dosage or exposure	An MTD was not determined. The highest evaluated dose of BOS formulation in humans was 2 mg BID (in dose ranging MPI 101-01 study and all other safety and efficacy phase 3 studies).

Characteristic	Drug Information
Dosage proportionality	Budesonide PK is dose-proportional following repeated administration in the dose range of 0.5 to 2 mg based on the population PK analysis.
Accumulation	Single dose and multiple dose PK were not assessed in the same study to evaluate accumulation potential of budesonide.
Time to achieve steady state	Not evaluated
Bridge between to-be-marketed and clinical trial formulations	The final to-be-marketed solution formulation (SB-10) was bioequivalent to the clinical trial formulation (MB-9 solution formulation used in the pivotal study) in term of budesonide systemic exposures (AUC _{0-tau}) and the C _{max} (Study SHP621-101).
Absorption	
Bioavailability	Absolute bioavailability of budesonide from BOS was not measured for the proposed formulation. The geometric mean AUC and C _{max} of budesonide for the proposed product, BOS 2 mg (phase 3 formulation and TBM formulation) were 32% to 33% and 71% to 73% of those of the listed product Entocort EC 9 mg, respectively.
T _{max}	Median: 2 hrs.
Food effect (fed/fasted)	Not evaluated, see Section 7.7.3 Lack of Food Effect Study.
Geometric least square mean and 90% CI	
Distribution	
Volume of distribution	1886 L
Plasma protein binding	85% to 90% (based on the label for the listed drug, Entocort EC)
Drug as substrate of transporters	Based on in vitro data, budesonide is a substrate for P-gp, but not a substrate of BCRP, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2.
Elimination	
Mass balance results	According to Entocort EC label: After oral as well as intravenous administration of micronized [3H]-budesonide, approximately 60% of the recovered radioactivity was found in urine. The major metabolites, including 6β-hydroxy budesonide and 16α-hydroxy prednisolone, are mainly renally excreted as intact or in conjugated forms. No unchanged budesonide was detected in urine.
Clearance	394.4 L/h (CL/F)
Half-life	3.3 hrs
Metabolic pathway(s)	According to Entocort EC label: Budesonide is primarily metabolized via CYP3A4 to its 2 major metabolites, 6β-hydroxy budesonide and 16α-hydroxy prednisolone. The corticosteroid activity of these metabolites was negligible (less than 1/100) in relation to that of the parent compound.
Primary excretion pathways (% dosage)	According to Entocort EC label: 60% of the recovered radioactivity was found in urine. The major metabolites, including 6β-hydroxy budesonide and 16α-hydroxy prednisolone, are mainly renally excreted as intact or in conjugated forms. No unchanged budesonide was detected in urine.

Characteristic	Drug Information
	Intrinsic Factors and Specific Populations
Body weight	Population PK analysis indicated that higher body weight was associated with higher individual estimated V_c and thus lower C_{max} compared to low body weight; subjects with low body weight were predicted to have 46% higher C_{max} compared to subjects with high body weight (28 kg versus 99.2 kg, 1252 pg/mL versus 855 pg/mL) which was not expected to be clinically significant.
Age	Population PK analysis did not find any significant effects of age (either continuous or categorical) on the PK of budesonide.
Renal impairment	The PK of budesonide in subjects with renal impairment has not been studied.
Hepatic impairment	The proposed product was not studied in subjects with hepatic impairment. According to Entocort EC label, the subjects with moderate hepatic impairment had a 3.5-fold higher AUC compared to the healthy subjects with normal hepatic function while the subjects with mild hepatic impairment had an approximately 1.4-fold higher AUC. The C_{max} values demonstrated similar increases. The increased systemic exposure in subjects with mild hepatic impairment was not considered to be clinically relevant. Subjects with severe liver impairment (Child-Pugh class C) were not studied.
Drug Interaction Liability (drug as perpetrator)	
Inhibition/induction of metabolism	Inhibition Based on the C_{max} of budesonide ($\sim 2.1nM=0.915$ ng/mL) and in vitro studies, the proposed product is not expected to inhibit major CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) in vivo. Induction In vitro, budesonide did not induce CYP1A2, or CYP2B6, at concentrations up to 34.5nM and CYP3A at concentration of 1.86μM.
Inhibition/induction of transporter systems	Based on the IC_{50} values for each transporter and maximum concentration at the proposed therapeutic clinical dose 2 mg BID, budesonide is unlikely to inhibit P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2 transporters.

Source: Reviewer's table based on data from Sections 8.1, 8.2, and 14 of the Entocort EC prescribing information. Available from drugs@fda: <https://www.accessdata.fda.gov/scripts/cder/daf/>. Accessed March 20, 2021

^[1] Parameters were obtained from pivotal phase 3 study (SHP621-301) in adult EoE subjects

Abbreviations: AUC, area under the curve; $AUC_{0-\tau}$, area under the curve during a dosing interval; BCRP, breast cancer resistance protein; BID, twice daily; BOS, budesonide oral suspension; C_{max} , maximum plasma concentration; CV, coefficient of variation; CYP, cytochrome P450; EoE, eosinophilic esophagitis; eos, eosinophils; HPLC, high performance liquid chromatography; IC_{50} , half maximal inhibitory concentration; MS, mass spectrometry; MTD, maximum tolerated dose; P-gp, P-glycoprotein; PK, pharmacokinetic; QD, once daily; T_{max} , time to maximum plasma concentration; V_c , central volume of distribution.

5.1. Nonclinical Assessment of Potential Effectiveness

Budesonide is a synthetic corticosteroid and has a high glucocorticoid effect and a weak mineralocorticoid effect. The affinity of budesonide to glucocorticoid receptors is about 200-fold higher than that of cortisol and 15-fold higher than prednisolone. The nonclinical evidence of the effectiveness of BOS in EoE comes from the listed drug and published pharmacodynamic studies using in vitro and in vivo animal models of inflammation. Although the effectiveness of BOS has not been directly tested in models of EoE, the anti-inflammatory effects of BOS were tested in various nonclinical models of inflammation.

In an in vitro model of inflammation of cultured T-84 epithelial monolayers, budesonide dose-dependently inhibited T-84 abnormalities and prevented epithelial dysfunction in this model by inhibiting activation of T-cells and monocytes (McKay et al. 1996). In cultured adherent blood monocytes and alveolar macrophages, stimulated with lipopolysaccharide, budesonide caused a partial suppression of IL-1 β and IL-6. In contrast, the stimulation of granulocyte macrophage colony stimulating factor (GM-CSF) was almost completely stimulated in the culture (Linden and Brattsand 1994).

In an L2-IL5OXA EoE mouse model, the role of GM-CSF in esophageal inflammation was assessed by analyses of the expression of GM-CSF mRNA and protein. Significantly increased levels of esophageal GM-CSF expression, predominantly in the esophageal eosinophils, was detected in the L2-IL5OXA mouse EoE model during active inflammation. GM-CSF neutralization in L2-IL5OXA EoE mice resulted in a significant diminution of epithelial eosinophilia in addition to basal cell hyperplasia and vascular remodeling (McNamee et al. 2017).

6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

The Applicant's proposed dose, 2 mg twice daily (BID), was the dose evaluated in the pivotal Trial 301 and was based on the result of a phase 2, placebo-controlled, dose-ranging study (MPI 101-01) in pediatric subjects 2 to 18 years of age with EoE. Of note, the dose ranging study was not conducted in adult subjects ≥ 18 years of age.

In Study MPI 101-01, a total of 81 subjects were randomized 1:1:1:1 into one of four treatment groups: placebo, 0.35 or 0.5 mg once daily (QD; low dose), 1.4 or 2.0 mg QD (medium dose), and 1.4 or 2.0 mg BID (high dose) depending on age of subjects as shown in [Table 7](#) below.

Table 7. Dosing, Trial MPI 101-01

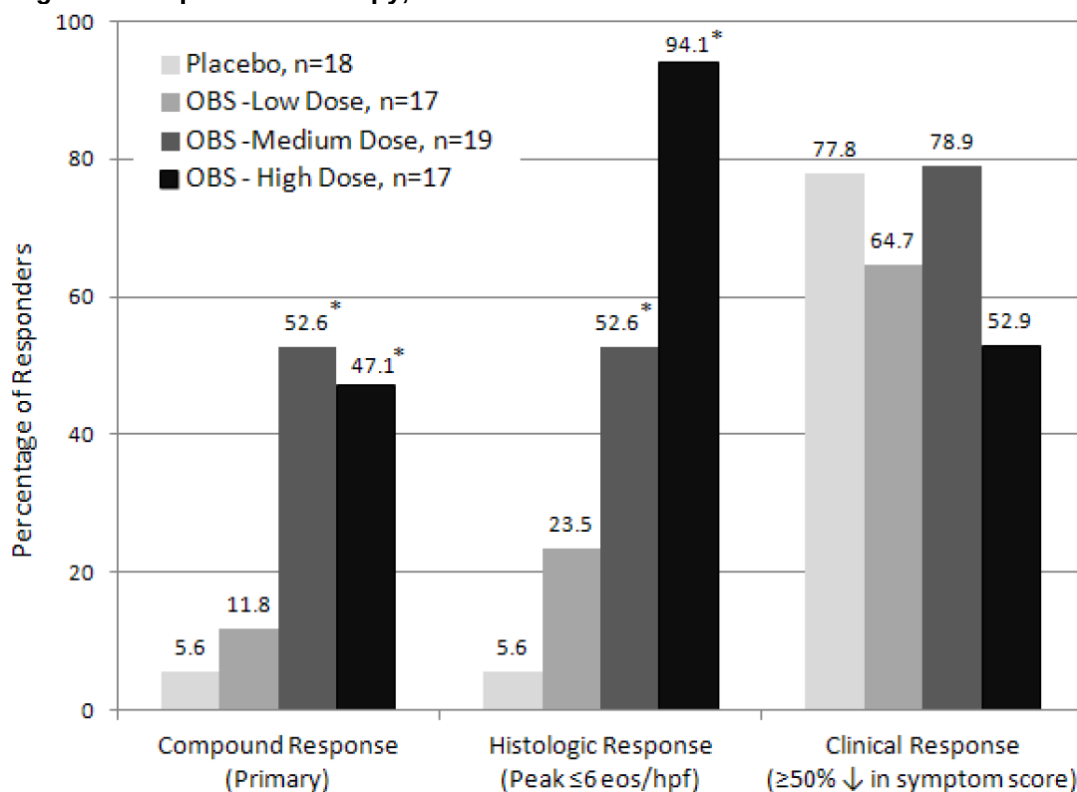
Dose Group	Concentration (mg/mL)	Morning Dose (mg)	Evening Dose (mg)	Total Dose/Day (mg/day)
Placebo				
Age 2 to 9 years	0.0	Placebo	Placebo	0.0
Age 10 to 18 years	0.0	Placebo	Placebo	0.0
Low				
Age 2 to 9 years	0.05	Placebo	0.35	0.35
Age 10 to 18 years	0.05	Placebo	0.5	0.5
Medium				
Age 2 to 9 years	0.2	Placebo	1.4	1.4
Age 10 to 18 years	0.2	Placebo	2.0	2.0
High				
Age 2 to 9 years	0.2	1.4	1.4	2.8
Age 10 to 18 years	0.2	2.0	2.0	4.0

Source: Applicant submitted CSR MPI 101-01 p. 5

In Trial MPI 101-01, the response to therapy was defined as a $\geq 50\%$ reduction from baseline in the EoE Clinical Symptom Score and a maximum peak eosinophil count of ≤ 6 per high-power field (HPF) from the esophageal biopsies at the final treatment evaluation. Of note, the maximum peak eosinophil count of ≤ 6 per HPF was also assessed as a coprimary endpoint in Trial 301 while a different assessment (DSQ combined score) was used for clinical response.

Based on the Applicant's analysis, statistically significant response to therapy was achieved in 52.6% of subjects in the medium dose BOS group and 47.1% of subjects in the high dose BOS group. There was no statistically significant difference in response rate between the low dose BOS (11.8%) and placebo (5.6%) treatment groups ([Figure 1](#)). The dose-response relationship for the efficacy endpoint was driven by the histologic response (i.e., peak eosinophil count to ≤ 6 per HPF) while no treatment effects were observed at any doses for clinical response based on the EoE Clinical Symptom Score compared to placebo treatment. Notably, a high placebo effect (77.8%) was observed for the clinical response.

Figure 1. Response to Therapy, Trial MPI 101-01

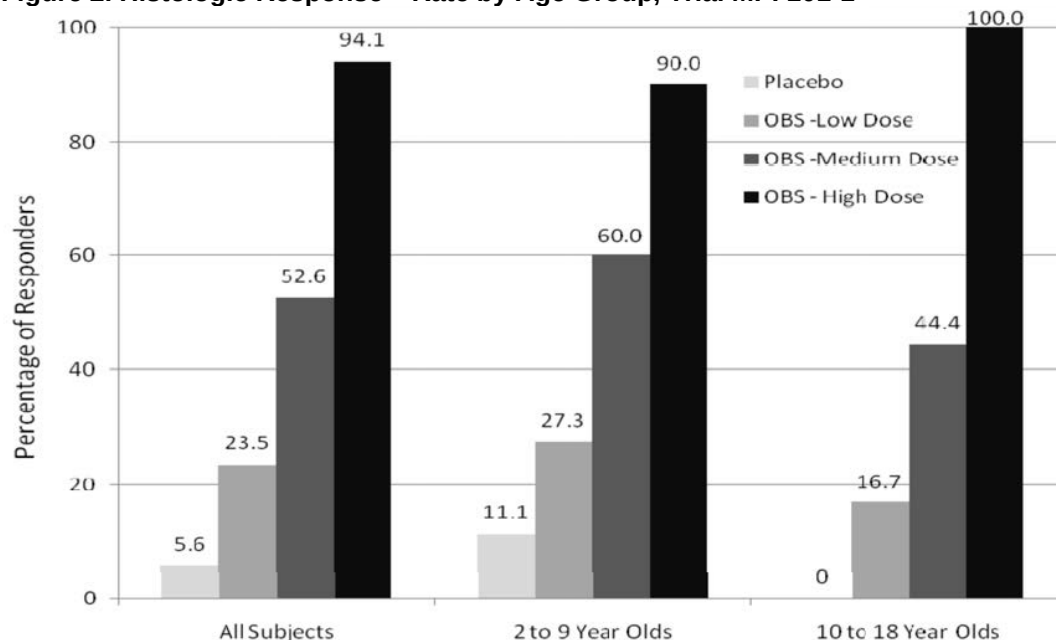


Source: Applicant submitted MPI 101-01 CSR, Table 14.2.1.1, Table 14.2.4.1, and Table 14.2.2.1

p<0.02 for the comparison of OBS and placebo for each endpoint

Abbreviations: eos, end of study; hpf, high power field; OBS, oral budesonide suspension

Dose-dependent increase in histologic response rates were generally similar for subjects 2 to 9 years of age and subjects 10 to 18 years of age ([Figure 2](#)).

Figure 2. Histologic Response^[1] Rate by Age Group, Trial MPI 101-1

Source: Module 5.3.5.1, Applicant submitted MPI 101-01 CSR, Section 11.4.1.2.1, Figure 3

^[1] Peak eosinophil count to ≤ 6 /HPF

Abbreviations: HPF, high power field; OBS, oral budesonide suspension

Dose-dependent responses were also observed in two secondary endpoints, rate of histologic remission (i.e., peak eosinophil count ≤ 1 per HPF) and improvement in gross endoscopic findings (i.e., total endoscopy score). The rate of histologic remission was significantly greater in the medium and high BOS dose groups than in the placebo group (0%, 11.8%, 42.1%, and 76.5% remission, in the placebo, low, medium, and high BOS dose groups, respectively).

Based on the above dose-response data, the Applicant selected the high dose, 2 mg BID dose, for Trial 301 in subjects 11 to 55 years of age with EoE. The Applicant did not perform exposure response analysis in this study.

It should be noted that although the histological response was clearly shown at two high doses, the studied doses did not show any improvement in clinical responses compared to placebo treatment. It is unknown if a higher dose would have shown a better response than the placebo treatment for the clinical response given the high placebo rate of 78% and given that doses higher than 2 mg BID were not studied. Because the dose-response relationship was not studied in adult subjects with the clinical endpoint used in the phase 3 trial, whether a dose-response may have been different for adult subjects from the observed dose-response relationship in pediatric subjects in the phase 2 trial is unknown.

6.2. Clinical Trials Intended to Demonstrate Efficacy

6.2.1. Results of Analyses, Trials 301 and 302

Trial 301 evaluated the short-term efficacy and safety of BOS, and Trial 302 was conducted to evaluate the long-term efficacy and safety of BOS in subjects identified by the Applicant as Trial 301 “full responders” (defined as having both ≤ 6 eosinophils per HPF across all available

esophageal levels and $\geq 30\%$ reduction in DSQ combined scores at the final treatment evaluation for Trial 301). These trials are discussed separately below.

6.2.2. Trial 301

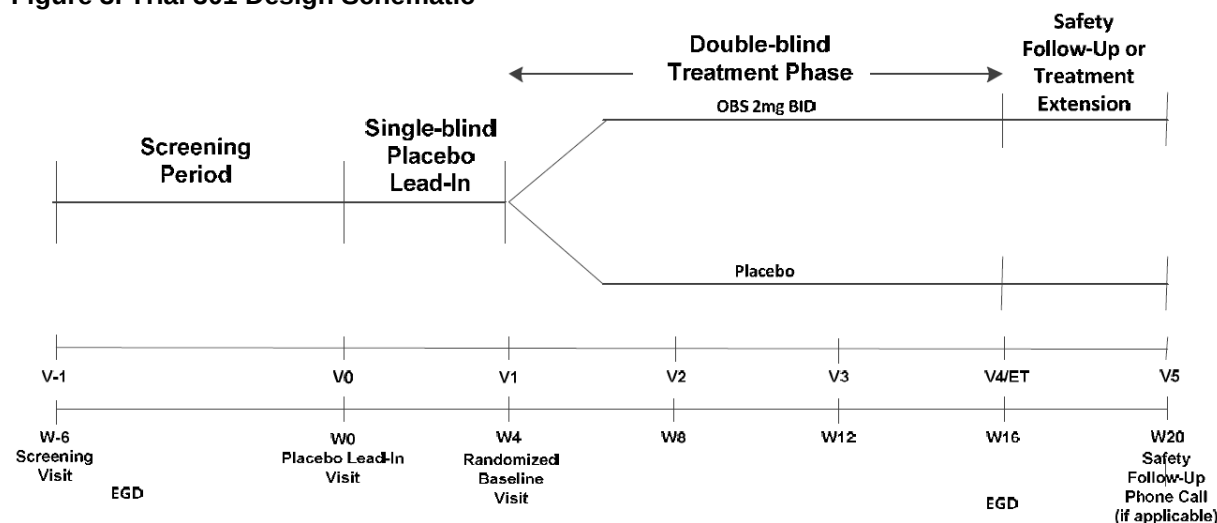
6.2.2.1. Design, Trial 301

Trial 301 was a phase 3, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of BOS treatment administered twice daily (every morning after meals and at bedtime) for 12 weeks in adolescents and adults, 11 to 55 years of age (inclusive) with EoE and symptoms of dysphagia.

As shown in [Figure 3](#), subjects were randomized 2:1 to receive either BOS 2 mg or placebo. This study consisted of 3 periods: a 3- to 6-week screening period, 4-week single-blind placebo lead-in period, and a 12-week double-blind treatment period. At least 306 subjects were planned to be randomized 2:1 to budesonide or placebo.

Trial 301 was designed to show superiority of BOS to placebo on two coprimary endpoints, histologic response and dysphagia symptom response. Histologic response was defined as a peak eosinophil count of ≤ 6 per HPF across all available esophageal levels at Week 16 visit (after 4 weeks of screening and 12-week double-blinded treatment). Dysphagia symptom response was defined as $\geq 30\%$ reduction in the DSQ combined score (sum of questions 2+3) from baseline. The DSQ combined score was calculated using the DSQ daily diary data within a 14-day analysis window prior to the actual clinical visit at Week 16 or baseline.

Figure 3. Trial 301 Design Schematic



Source: Applicant submitted Summary of Clinical Efficacy Figure 2, p. 30

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; EG, esophagogastroduodenoscopy; ET, end of treatment

6.2.2.2. Eligibility Criteria, Trial 301

Selected eligibility criteria for Trial 301 are listed below.

Inclusion Criteria

- Subject is male or female aged 11 to 55 years (inclusive) at time of consent.

- Subject has histologic evidence of EoE with a peak eosinophil count of ≥ 15 per HPF, from 2 of 3 (proximal, mid-, and/or distal) levels of the esophagus at the screening endoscopy.
- Subject has a history of clinical symptoms of esophageal dysfunction (e.g., eating problems, abdominal pain, heartburn, dysphagia, vomiting, food impaction, weight loss) intermittently or continuously at screening (Visit -1).
- Subject must have experienced dysphagia (response of “yes” to question 2 on DSQ) on a minimum of 4 days and completed the DSQ on $\geq 70\%$ of days in any 2 consecutive weeks of the screening period and in the last 2 weeks prior to the baseline visit (Visit 1).
- Subject must not have proton pump inhibitor (PPI)-responsive EoE based on esophageal biopsies performed after the subject has been on at least 8 weeks of high-dose PPI therapy (high-dose therapy refers to the total daily dose, which may have been administered as a once- or twice-daily dosing regimen). This may occur at the time of the qualifying esophagogastroduodenoscopy (EGD, in which case the same PPI regimen must be continued), or this may have been done previously (in which case PPI therapy may have been stopped if there was no response to therapy based on esophageal biopsy results).
- Subject will be on a stable (no changes) diet ≥ 3 months prior to the screening visit (Visit -1).
- Subject is willing and able to continue any dietary therapy, environmental therapy, and/or medical regimens (including gastric acid suppression; see exclusions below) in effect at the screening visit (Visit -1). There should be no change to these regimens during study participation.

Exclusion Criteria

- Subject has used immunomodulatory therapy within 8 weeks prior to the qualifying EGD or between the qualifying EGD and baseline visit (Visit 1) or anticipates using immunomodulatory therapy during the treatment period (except for any ongoing regimen of allergy shots). Use of long-acting immunomodulatory therapy (e.g., Rituxan) within 3 months of the qualifying EGD should be reviewed with the medical monitor.
- Subject has been using swallowed topical corticosteroid for EoE or systemic corticosteroid for any condition within the 4 weeks prior to the qualifying EGD, between the qualifying EGD and baseline visit (Visit 1) or anticipates use during the treatment period; any temporary use or initiation of new steroid treatment during the study should be documented and discussed with the medical monitor prospectively but cannot occur within 4 weeks of the final EGD.
- Subject has been on inhaled or intranasal steroids and has not been on stable treatment for ≥ 3 months prior to screening visit (Visit -1). Subjects on intranasal or inhaled steroids need to stay on a stable treatment during study participation.
- Subject has initiated, discontinued, or changed dosage regimen of PPIs, H2 antagonists, antacids, antihistamines, or leukotriene inhibitors for any condition (such as gastroesophageal reflux disease, asthma or allergic rhinitis) within the 4 weeks prior to the qualifying EGD, between the qualifying esophagogastroduodenoscopy and baseline visit (Visit 1), or anticipates changes in the use of such medications during the treatment period.
- Subject has been using cytochrome P450 3A4 (CYP450 3A4) inhibitors (e.g., ketoconazole, grapefruit juice) within the 2 weeks prior to the baseline visit (Visit 1) or within five half-

lives (whichever is greater) or anticipates using such medications during the treatment period.

- Subject has an appearance on qualifying EGD of an esophageal stricture (high-grade), as defined by the presence of a lesion that does not allow passage of a diagnostic adult upper endoscope (e.g., with an insertion tube diameter of >9 mm).
- Subject is on a pure liquid diet or the 6-food elimination diet.
- Subject has had an esophageal dilation within the 3 months prior to screening (Visit -1).
- Subject has presence of esophageal varices at the screening endoscopy. Subject has any current disease of the gastrointestinal tract, aside from EoE, including eosinophilic gastritis, enteritis, colitis, or proctitis; inflammatory bowel disease; or celiac disease.
- Subject has other diseases causing or associated with EoE, including hypereosinophilic syndrome, collagen vascular disease, vasculitis, achalasia, or parasitic infection.
- Subject has current evidence of oropharyngeal or esophageal candidiasis.
- Subject has acute or chronic viral infection or immunodeficiency condition, including tuberculosis, fungal, bacterial, viral/parasite infection, ocular herpes simplex, herpes esophagitis, or chicken pox/measles.
- Subject has upper gastrointestinal bleeding within 4 weeks prior to the screening visit (Visit -1) or between the screening visit and baseline visit (Visit 1).
- Subject has evidence of active infection with *Helicobacter pylori*.
- Subject has evidence of unstable asthma within 4 weeks prior to the screening visit (Visit 1) and between the screening visit and baseline visit (Visit 1).

6.2.2.3. Statistical Analysis Plan, Trial 301

The Applicant submitted the SAP on March 14, 2019, after the last subject completed Trial 301 on February 15, 2019 (according to the Clinical Study Report SHP621-301, received July 31, 2019). Therefore, FDA did not review the SAP prior to completion of Trial 301.

The analysis population for the coprimary and key secondary efficacy endpoints was defined as the full analysis set (FAS) which consisted of all randomized subjects who received at least one dose of study medications. All tests were performed at the two-sided 0.0499 alpha level to preserve an overall alpha level at 0.05. A 0.0001 alpha was spent on an independent unblinded interim analysis that concluded with no sample size re-estimation.

The coprimary endpoints were analyzed using a Cochran-Mantel-Haenszel test with histologic response or dysphagia symptom response as dependent variable, stratified by baseline age group and diet restriction. A nonresponder imputation (NRI) approach was used for missing data due to early trial discontinuation or lack of available peak eosinophil count or DSQ combined score at Week 16. Further, at each visit, a DSQ combined score was considered missing if less than 8 reported diaries were available within the 14-day visit window after applying a window shift

rule.¹ The number of diaries reported with nonmissing data was referred to as “reported diaries.” The DSQ diary data for a given day was considered missing if the diary was not reported or if the diary was reported but the answer to question 1 was “No.” During development under IND 103173, the review team recommended no application of a window shift rule for the DSQ diary data and a missing DSQ score at a visit should be defined as less than 4 days of observed diary in either of the weeks during the 14-day analysis window.

The key secondary efficacy endpoint, change in DSQ combined score from baseline to Week 16, was assessed using a one-way analysis of covariance (ANCOVA) model with treatment group and age group as factors and the baseline DSQ score as a continuous covariate based on nonmissing (observed case) data only. To be consistent with the primary analysis of efficacy, the review team evaluated this key secondary endpoint with an ANCOVA model including treatment group, age group, and diet restriction as factors. The window shift rule was not applied, and missing data were imputed using a pattern mixture model (a multiple imputation approach).

A hierarchical testing procedure was applied to control the alpha for the multiple endpoints at a 0.0499 level. If both coprimary endpoints were significant, then the key secondary endpoint was tested.

The team identified the following limitations that could impact the derivation of DSQ combined score and thus, the interpretability of the results:

- The window shift rule to cope with missing DSQ daily diary data was inappropriate and could allow for searching at least eight diary records in a 14-day window. When applied, this could result in a 28-day range prior to the Week 16 visit.
- The missing daily dairy rule to treat a day the subject answered “No” to DSQ question 1 as missing was not well justified. The trial did not collect information on the reason a subject did not take solid food for a given day (i.e., answered “No” to DSQ question 1). Approximately 10% subjects in each treatment group answered “No” to DSQ question 1 for at least one day during a 14-day period at baseline or Week 16.
- The SAP defined the DSQ combined score as “missing” where there were fewer than eight daily diary records in a 14-day window. Not specifying a minimum number of records per week allowed unbalanced reporting across the 2-week assessment period (e.g., entries with 7 reporting days in one week and only 1 reporting day in another week were considered acceptable). Note that, as stated above, the review team communicated this limitation to the Applicant during the IND phase of development and recommended calculating the DSQ combined score when data are available for at least 4 out of 7 days in each of the two weeks. The Applicant did not follow the FDA’s recommendation.

See Sections [6.3](#) and [16.2](#) for further discussion of these concerns.

¹ Window shift rule: For subjects with less than 8 reported diaries in the 14-day visit window prior to Week 16 visit day, the Applicant made adjustments by shifting to earlier diary entries to locate the most recent 14-day period with the minimum number of reported diaries. Such 14-day periods cannot be shifted for more than 7 days not including the study visit day) when calculating DSQ combined score at Baseline Visit 1 (Week 4), Visit 2 (Week 8) and Visit 3 (Week 12), and cannot be shifted for more than 14 days prior to the Visit 4 (Week 16) (not including the visit day of Visit 4) for the DSQ combined score at the final treatment period evaluation.

6.2.2.4. Results of Analyses, Trial 301

Baseline Demographics and Clinical Characteristics

Of the 985 subjects screened, 322 were randomized into the trial, and 318 received at least one dose of treatment (FAS/safety set). Overall, the majority of subjects in this trial were male (60%), white (95%), and adults (87%). The median age was 34 years with a range of 11 to 56 years of age. Two percent of all subjects were black/African American, and these five subjects were randomized to the BOS group. Demographic factors and baseline disease characteristics were generally balanced between these two groups, as summarized in [Table 8](#).

Table 8. Baseline Demographic and Clinical Characteristics, FAS/Safety Population, Trial 301

Demographic and Clinical Characteristics	BOS 2 mg BID (N=213)	Placebo (N=105)	Total (N=318)
Sex, n (%)			
Female	84 (39.4)	43 (41.0)	127 (39.9)
Male	129 (60.6)	62 (59.0)	191 (60.1)
Age (years)			
Mean (SD)	33.8 (11.9)	33.9 (12.1)	33.9 (12.0)
Median	34.0	34.6	34.2
Min, max	11.1, 56.0	11.4, 54.8	11.1, 56.0
Age groups, n (%)			
<18 years	27 (12.7)	14 (13.3)	41 (12.9)
≥18 years	186 (87.3)	91 (86.7)	277 (87.1)
Race, n (%)			
American Indian or Alaska Native	1 (0.5)	0	1 (0.3)
Black or African American	5 (2.3)	0	5 (1.6)
Other	7 (3.3)	3 (2.9)	10 (3.1)
White	200 (93.9)	101 (96.2)	301 (94.7)
Native Hawaiian or Other Pacific Islander	0	1 (1.0)	1 (0.3)
Time since diagnosis ^[1] (months)			
N	212	101	313
Mean (SD)	49.3 (56.9)	38.9 (40.9)	45.9 (52.4)
Median	28.0	24.8	26.1
Min, max	0, 450	0, 153	0, 450
History of dilation ^[1] , n (%)	88 (41)	45 (43)	133 (42)
Baseline DSQ combined score			
N	211	105	316
Mean (SD)	30.3 (13.9)	30.4 (13.1)	30.4 (13.7)
Median	30.3	29.4	30.3
Min, max	2.3, 66.0	0.0, 61.4	0.0, 66.0
Baseline peak eosinophil count			
N	213	104	317
Mean (SD)	74.5 (39.2)	76.6 (45.0)	75.2 (41.1)
Median	68.0	67.0	68.0
Min, max	6, 220	18, 253	6, 253

Source: Review team's analyses and the Applicant's information request response submitted on November 19, 2020.

^[1] Due to the limitations on the Applicant's datasets and records, results for time to diagnosis of EoE and history of dilation could not be confirmed

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; DSQ, Dysphagia Symptom Questionnaire; EoE, eosinophilic esophagitis; FAS, full analysis set; N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation

Disposition

Subject disposition is summarized in [Table 9](#). Approximately 33% of the subjects screened were enrolled in the trial. The majority of subjects (93%) in each randomized treatment group remained in the trial at the Week 16 data cutoff. The most frequent reasons for discontinuation were withdrawal by subject (5%) and adverse events (AEs) (1.3%). No information was provided for the reasons for withdrawal by subject.

Table 9. Subject Disposition, Trial 301

Disposition Outcome	BOS 2 mg BID	Placebo
Randomized set, n	215	107
FAS, n	213	105
Safety set, n	213	105
Disposition event in FAS/Safety set	N=213	N=105
Primary reason for not complete study, n (%)	11 (5.2)	11 (10.5)
Adverse event	1 (0.5)	3 (2.9)
Withdrawal by subject	8 (3.8)	8 (7.6)
Noncompliance with study drug	1 (0.5)	0
Physician decision	1 (0.5)	
Completed study, n (%)	202 (94.8)	94 (89.5)
Subject consent to participate in the extension study (SHP621-302), n (%)	161 (75.6)	70 (66.7)

Source: Review team's adaptation of Trial 301 CSR Table 4 on Page 80, results were verified.

Abbreviations: BOS, budesonide oral suspension; FAS, full analysis set; N, number of subjects in treatment arm; n, number of subjects in specified population or group

Treatment Compliance Rate

The SAP defined treatment compliance as a compliance rate within a range of 70% to 130% inclusive. The trial observed the treatment compliance rate during the double-blinded treatment period that ranged from 11% to 210% with a mean rate of 87% (median: 88%). The Applicant reported that 11% subjects had major deviations related to overall noncompliance with study medication. Subgroup analyses based on treatment compliance did not indicate any differences in treatment response by compliance.

Primary and Key Secondary Efficacy Results, Trial 301

The results presented below are based on the Applicant's derived datasets that were submitted to the NDA. Data quality issues prevented confirmation of the histologic coprimary endpoint results from the source or subject level datasets, although this did not impact the overall determination of efficacy. See Section [6.3.5](#) for details. As EoE is a clinicopathologic disorder in which clinical symptoms and histologic activity can vary independently, demonstration of efficacy on both histologic and symptomatic coprimary endpoints is needed to support a determination of benefit.

Coprimary Endpoints

Histologic Response: The BOS treatment group had a statistically significantly higher proportion of histologic responders (53.1%) in comparison with those treated with placebo (1%), p-value<0.001. It should be noted, however, that although the evaluation of histologic response through the assessment of peak eosinophil count has been recognized as an important element of both the diagnosis and monitoring of patients with EoE, all available clinical consensus practice

guidelines (Dellon et al. 2013; Dellon et al. 2018; Furuta et al. 2007; Hirano and Aceves 2014; Hirano et al. 2020; Liacouras et al. 2011), in addition to describing the independent variation between clinical symptoms and histology, acknowledge that there is inadequate data to demonstrate that improvement in histologic response is associated with improvement in clinical outcomes. Recent clinical guidelines for the management of EoE conclude that, “Moreover, symptom and pathology outcomes are often discordant with one another, although disease remission currently remains anchored in histologic criteria. Evidence that the assessment of biologic activity with endoscopic and histologic parameters after treatment will reduce long-term disease complications is limited” (Hirano and Aceves 2014). Efforts to identify assessments that may be predictive of clinical outcomes are ongoing (Dellon and Hirano 2018). As EoE is a chronic disorder, evidence of long-term treatment benefit is needed to support a determination of efficacy. Consequently, the contribution of the reported histologic response from Trial 301 to the overall determination of benefit is of unclear value due to the lack of sustained histologic response observed in subjects maintained on treatment with BOS in Trial 302 as shown in [Figure 6](#) below.

Dysphagia Symptom Response: The BOS treatment group had a statistically significantly higher proportion of symptomatic responders based on at least a 30% improvement responder threshold in comparison with those treated with placebo (52.6% versus 39.1%) with a p-value of 0.024. Although nominally statistical results were reported for this prespecified symptomatic coprimary endpoint for Trial 301, the clinical meaningfulness of the $\geq 30\%$ DSQ responder threshold is not supported by the phase 3 data. See Section [6.3.1](#). Using a 1-category change on the PGIS as the target anchor change category (altered from the prespecified 2-category change due to the limited number of subjects who experienced 2-category change), the Applicant’s submitted anchor-based analyses from Trial 301 resulted in a responder threshold range of approximately 50% to 57%. Subsequent FDA anchor-based analyses determined that the responder threshold should be at least 67%. Treatment difference between budesonide and placebo groups at this threshold value was not nominally statistically significant.

Table 10. Coprimary Efficacy Results at Week 16, FAS, Trial 301

Coprimary Endpoint	BOS 2 mg BID N=213 n (%)	Placebo N=105 n (%)	Treatment Difference ^[1] (95% CI)	p-Value
Histologic response	113 (53.1)	1 (1.0)	52 (43.3, 59.1)	<0.001
Dysphagia symptom response				
$\geq 30\%$ improvement	112 (52.6)	41 (39.1)	13 (1.6, 24.3)	0.024
$\geq 67\%$ improvement	70 (32.9)	24 (22.9)	10 (-1.1, 19.2)	0.075 ^[2]

Source: Review team’s Analysis

^[1] Treatment difference was the adjusted difference based on the CMH test stratified by age group and diet restriction. The 95% confidence interval (CI) used Newcombe method

^[2] P-value is not statistically significant.

Abbreviations: BID, twice daily; BOS, budesonide; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; FAS, full analysis set

Key Secondary Endpoint

A statistically significant treatment difference in change from baseline on DSQ combined score between BOS and placebo treatment groups (based on derived DSQ score) was observed with a mean difference of -4 (95% confidence interval [CI]: -7, -0.3) and a p-value of 0.035 based on the FDA recommended sensitivity analysis ([Table 11](#)).

Table 11. Mean (SD) Change From Baseline in DSQ Combined Score, FAS, Trial 301

Key Secondary Endpoint	BOS 2 mg BID N=213	Placebo N=105	Treatment Difference (95% CI)	p-Value
Prespecified primary analysis based on observed case only ^[1]	-13 (1.2)	-9 (1.5)	-4 (-7.1, -0.8)	0.015
FDA preferred analysis using imputed data by pattern mixture model ^[2]	-9 (2)	-5 (2)	-4 (-7.3, -0.3)	0.035

Source: Review team Adaptation of Trial 301 CSR tables and the Applicant's Information Request response submitted on February 9, 2021

^[1] Results were based on ANCOVA model with factors of treatment group and age group, as prespecified in the statistical analysis plan

^[2] FDA preferred analysis using ANCOVA model with factors treatment group, age group and diet restriction. A DSQ combined score was considered missing if there were at least 4 days of missing daily diary records in either of the week in the 14-day window. The window shift rule was not applied.

Abbreviations: ANCOVA, analysis of covariance; BOS, budesonide; CI, confidence interval; DSQ, Dysphagia Symptom Questionnaire; FAS, full analysis set; SD, standard deviation

Although statistically significant results were reported on the secondary endpoint of change from baseline in 14-day DSQ absolute change combined score, the difference between BOS and placebo groups was small and the 14-day assessment period used for the DSQ score was not consistent with the 7-day assessment period used for the PGIS anchor. This limited the interpretability of clinically meaningful change for the 14-day DSQ absolute change analysis. Additional analyses were conducted using the 7-day DSQ score (to match the recall period of the 7-day PGIS), and no difference between BOS and placebo was identified in the range that subjects considered to be a meaningful improvement. See Section [6.3.2](#).

Subgroup and Sensitivity Analyses

Sensitivity analyses were performed for the coprimary endpoints and key secondary endpoint to evaluate the robustness of the primary efficacy results. These analyses did not support the demonstration of a meaningful treatment effect.

Additionally, subgroup analyses by diet restriction, age, sex, race, and geographic region were performed to assess the consistency of the results observed from the primary efficacy analyses. Subgroup analyses for baseline PGIS and treatment compliance rate group for the primary efficacy analyses and key secondary endpoint were also requested from the Applicant and reviewed. These analyses did not support the demonstration of a meaningful treatment effect.

On March 29, 2021, in response to the DR Letter, the Applicant submitted results from previously unspecified post hoc subgroup analyses of the symptomatic coprimary endpoint and key secondary endpoint in dilation-naïve subjects in the intent-to-treat population (defined as all randomized subjects) for the 12-week initial treatment period only. While dilation status was collected during screening for eligibility criteria, dilation-naïve status was identified as a subgroup of interest for efficacy analyses only after data unblinding and completion of SAP-specified analyses.

In addition to limitations and uncertainties inherent to post hoc analyses, the interpretability of these analyses was further limited by the unreliability of the variable used to define the subgroup. Dilation status of subjects in Trial 301 was determined based on either medical record confirmation, where available, or self-report. Self-reported dilation status without confirmation from medical records is considered unreliable, as subjects may have confused upper endoscopy with dilation or not able to recall whether dilation was performed during the procedure.

Approximately 25% of the intent-to-treat population had no medical record confirmation of their dilation status, and 36% of the dilation-naïve subgroup had no medical record confirmation of their dilation status ([Table 12](#)).

Table 12. Dilation History Source Data, ITT, Trial 301

Source Data	Number of Subjects		
	With Prior Dilation	Dilation-Naïve	Total
Dilation history source documentation, n			
Medical record confirmation, n (%)			
Subject self-report only, n (%)			

(b) (4)

Source: Applicant's Information Request response dated May 3, 2021
Abbreviations: ITT, intent-to-treat

When the analyses were limited to subjects with medical record confirmation of dilation status, analysis of the 7-day DSQ combined score (to match the 7-day PGIS anchor) showed minimal separation between treatment groups over the 12-week treatment period ([Table 13](#)).

Table 13. 7-Day DSQ Combined Score^[1] Dilation-Naïve Subgroup Based on Medical Record Confirmation Only

DSQ Combined Score	BOS 2 mg BID (N=81)	Placebo (N=37)
Baseline		
Available, n		
Missing, n		
Mean (SEM)		
Week 16		
Available, n		
Missing, n		
Mean (SEM)		
Change from baseline at Week 16		
Available, n		
Missing, n		
Mean (SEM)		
Difference in LS Mean		

(b) (4)

Source: Applicant's Information Request response dated May 3, 2021

From analysis of covariance (ANCOVA) model with treatment group, age group, and diet restriction as factors and baseline DSQ score as a continuous covariate.

^[1] 7-day DSQ combined score matches the recall period of the PGIS anchor scale

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; DSQ, Dysphagia Symptom Questionnaire; LS, least squares; SEM, standard error of means

Furthermore, there are no data available to confirm that dilation-naïve status is directly related to higher baseline symptom scores, as claimed by the Applicant, to support that the results could be generalizable to the newly considered intended use population (i.e., dilation-naïve patients with EoE).

6.2.3. Trial 302

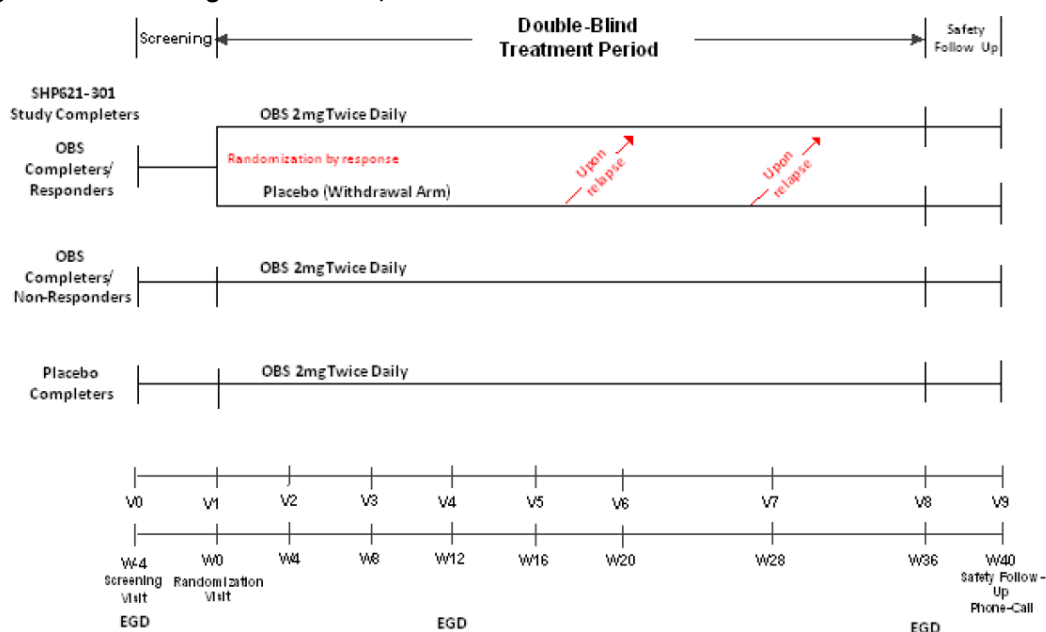
6.2.3.1. Design, Trial 302

Subjects who completed Trial 301 were eligible to enter into Trial 302; a phase 3, double-blind extension study to evaluate the efficacy, safety, and tolerability of BOS treatment administered twice daily for 36 weeks. Trial 302 consisted of three periods: a screening period of up to 4 weeks during which the subjects continued treatment as assigned in Trial 301, a 36-week double-blind treatment period, and a 4-week safety follow-up.

Subjects who were assigned to BOS treatment in Trial 301 classified as “full responders” by the Applicant (defined as having both ≤ 6 eosinophils per HPF across all available esophageal levels and $\geq 30\%$ reduction in DSQ combined scores at the final treatment evaluation) were eligible to enter a randomized withdrawal period to receive either BOS 2 mg twice daily or placebo. For these subjects, randomization was 1:1 and was stratified by age (adults and adolescents). Subjects who were rerandomized to placebo were changed to BOS 2 mg twice daily upon relapse. The efficacy analysis population for Trial 302 was limited to BOS “full responders” from Trial 301.

Subjects who were randomized to BOS in Trial 301 and were classified as partial or nonresponders at the end of the trial or were assigned to placebo, were eligible to enter into Trial 302 and receive BOS 2 mg. Subjects, site staff, and study team members remained blinded to treatment assignment. These subjects were included in the safety evaluation as discussed in Section 7 below.

Figure 4. Trial Design Schematic, Trial 302



EGD=esophagogastroduodenoscopy; BOS (BOS)=oral budesonide suspension

Note: The IP was originally referred to as oral budesonide suspension (OBS) and is now referred to as budesonide oral suspension (BOS).

Note 2: The nonresponder group also includes partial responders.

Source: Applicant submitted Summary of Clinical Efficacy Figure 3, p. 31

6.2.3.2. Eligibility Criteria, Trial 302

To be eligible for enrollment into Trial 302, subjects must have completed Trial 301. The eligibility criteria for Trial 301 were summarized in Section 6.2.2.2. Eligibility criteria were reassessed during the 4-week screening period prior to randomization in Trial 302.

6.2.3.3. Statistical Analysis Plan, Trial 302

As with Trial 301, the Applicant and the review division did not agree on the Trial 302 SAP prior to the trial completion. A draft SAP for Trial 302 was received on July 10, 2019. FDA

issued an Advice/Information Request to the Applicant containing recommendations for revisions to the SAP on November 21, 2019. The final SAP for Trial 302 was received on December 9, 2019. The final SAP did not address FDA recommendations for the application of the window shift rule for the primary analysis or the potential interpretation issue associated with treating DSQ diary record as missing when a subject answered “No” to DSQ question 1.

Trial 302 was designed to show superior long-term treatment effect of BOS compared to placebo. The SAP planned for 40 “full responders” from Trial 301 to be randomized 1:1 to budesonide or placebo. The primary endpoint of relapse (defined as an eosinophil count of ≥ 15 eosinophils per HPF from at least 2 of 3 levels of the esophagus and at least 4 days of dysphagia in the 14-day period prior to the scheduled visit) was evaluated at the Week 36 visit of the double-blinded randomized withdrawal period. All tests were performed at the one-sided 0.025 alpha level. The Trial 301 BOS “full responder” FAS population was used for the primary and key secondary analyses of efficacy and included all randomized subjects who received at least one dose of investigational product in Trial 302 and who were determined by the Applicant to be “full responders” to the BOS treatment during Trial 301.

The primary efficacy analysis of the primary endpoint and the key secondary endpoints used a Fisher’s exact test based on NRI data. A hierarchical testing with fixed sequence procedure was used to control the type I error for the multiple endpoints at one-sided alpha level of 0.025. If the primary endpoint was significant, the secondary endpoints would be tested.

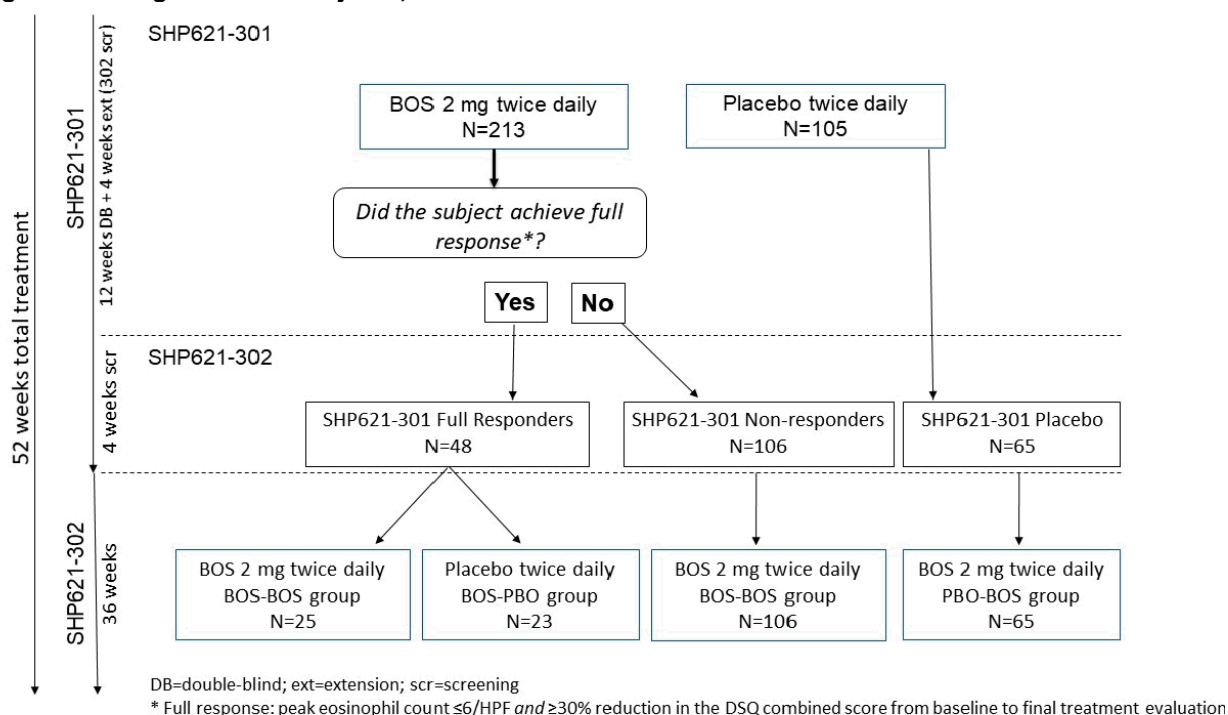
Subgroup analyses were not conducted due to the limited sample size for the Trial 301 BOS “full responder” FAS. The Applicant conducted efficacy analyses in Trial 301 nonresponders; however, there was no comparator for Trial 301 nonresponders in Trial 302. This review does not include efficacy results from Trial 301 nonresponders.

6.2.3.4. Results of Analyses, Trial 302

Baseline Demographics and Clinical Characteristics

The efficacy analysis population for Trial 302 consisted of 48 of the 64 subjects who were in the completed Trial 301 in the BOS group and were considered BOS “full responders” by the protocol’s definition. Of these 48 subjects, 25 were rerandomized to the BOS group and 23 were rerandomized to the placebo group ([Figure 5](#)). As with Trial 301, most subjects in this trial were white (96%) adults (85%), and the median age was 37 years ranging from 11 to 56 years of age. Subjects had a mean (SD) baseline DSQ combined score of 10 (11) and a mean (SD) total peak eosinophil count of 2 (2). Although there were more males in the placebo arm, and more females in the BOS arm, this was likely attributable to the limited sample size. No other significant differences were noted on comparison of the baseline demographic and clinical characteristics between groups.

Figure 5. Assignment of Subjects, Trial 301 to Trial 302



Note: The nonresponder group also includes partial responders.

Source: Applicant submitted clinical summary of efficacy Figure 4. p. 31
Abbreviations: BOS, budesonide oral suspension; PBO, placebo

Disposition

Of the FAS of Applicant-identified Trial 301 BOS “full responder” subjects, most of the rerandomized subjects (75%) completed the trial at Week 36. There were 7 subjects who did not complete the trial, 3 (12%) in those who received BOS in Trial 302 and 4 (17.4%) in those who received placebo in Trial 302. No information was provided for the reasons for withdrawal by subject.

Table 14. Subject Disposition, Trial 301 BOS “Full Responder” FAS, Trial 302

	BOS 2 mg BID N=25 n (%)	Placebo N=23 n (%)	Total N=48 n (%)
Disposition Outcome			
Completed study	22 (88.0)	19 (82.6)	36 (75.0)
Discontinued study	3 (12.0)	4 (17.4)	7 (14.6)
Adverse event	1 (4.0)	0	1 (2.1)
Withdrawal by subject	2 (8.0)	4 (17.4)	6 (12.5)

Source: Review team’s adaptation of Trial 302 CSR Table 4. p. 94
Abbreviations: BOS, budesonide oral suspension; FAS, full analysis set; PBO, placebo

Primary and Key Secondary Efficacy Results

Trial 302 did not demonstrate statistically significant results on the prespecified efficacy endpoint of rate of relapse on both histology and clinical symptoms in the individual subject. The proportion of relapse by Week 36 was lower in the budesonide group (24%) than that in the placebo group (43%) with a treatment difference of -19% (95% CI: -45.2%, 8.2%) and a p-value

of 0.13 as shown in [Table 15](#). Although not eligible for hierarchical assessment, results from the secondary endpoints are also shown below in [Table 15](#).

Table 15. Primary and Secondary Efficacy Results, Trial 301 BOS “Full Responders” FAS, Trial 302

Endpoints	BOS 2 mg BID N=25 n (%)	Placebo N=23 n (%)	Treatment Difference BOS-Placebo (95% CI ^[1])	p-Value ^[2]
Primary endpoint over 36-week period				
Relapse (both histology and DSQ)	6 (24)	10 (43)	-19 (-0.45, 0.08)	0.13
Secondary endpoints at week 36				
Histology response	13 (52)	7 (30)	22 (-0.07, 0.49)	0.11
Symptomatic (DSQ) response to SHP621-301 baseline	21 (84)	18 (78)	6 (-0.18, 0.)	0.44
Symptomatic (DSQ) response to SHP621-302 baseline	10 (40)	9 (39)	1 (-0.27, 0.29)	0.59

Source: Review team’s adaptation of Study 302 CSR Tables 8, 10, 15

^[1] The 95% confidence interval (CI) used the exact CI.

^[2] P-value was based on the Fisher’s exact test

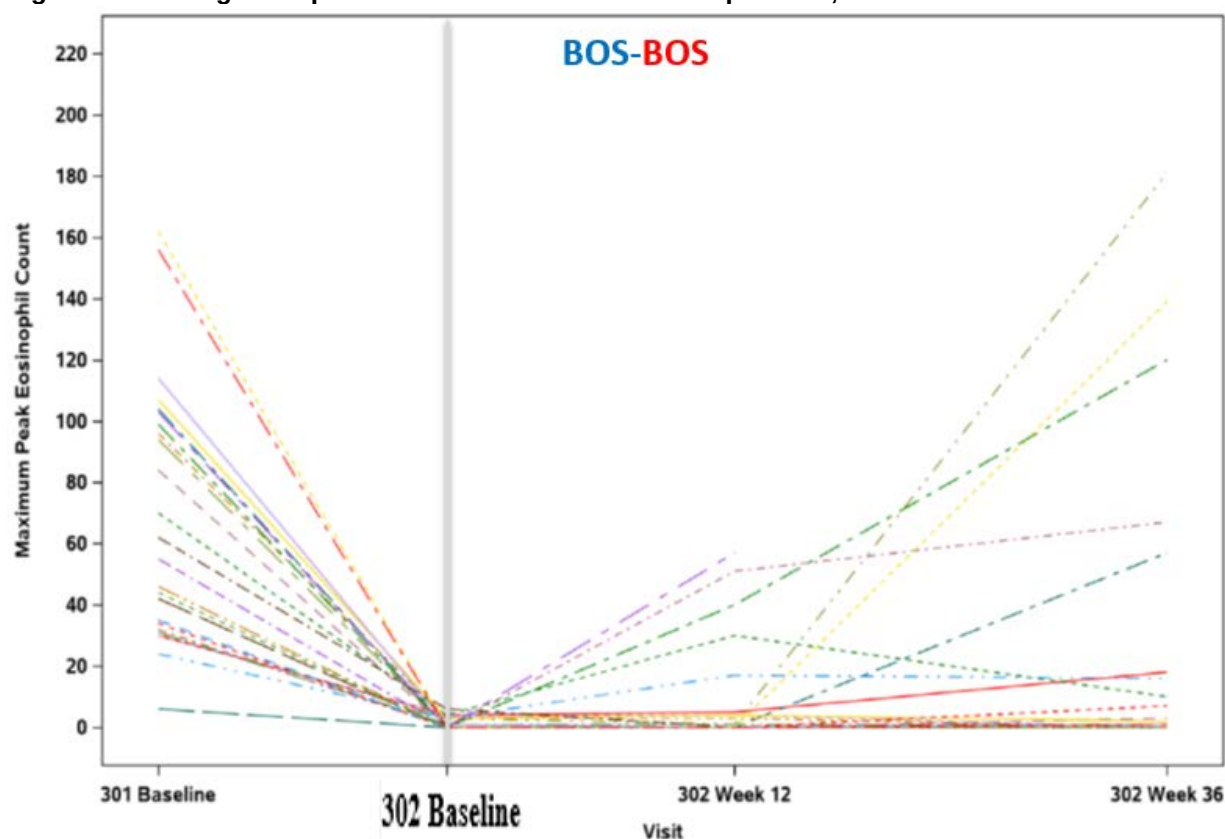
Abbreviations: BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; DSQ, Dysphagia Symptom Questionnaire; FAS, full analysis set; PBO, placebo

Additional Analyses

The review team explored the pattern of long-term efficacy for budesonide in dysphagia symptom response, DSQ combined score, and peak eosinophil count by group by analyzing the derived subject-level data over the duration of Trials 301 and 302. Upon review, no clear trend toward treatment benefit for either treatment arm was observed.

[Figure 6](#) below demonstrates the peak eosinophil count over Trials 301 and 302 in the 25 subjects identified by the Applicant as BOS “full responders” who were re-randomized to continue to receive BOS in Trial 302. The lack of sustained histologic response in these subjects further supports the FDA determination that long-term efficacy was not demonstrated to support long-term treatment with BOS for this chronic condition. Observed increases in esophageal eosinophils despite continued therapy has been also reported in the literature (Collins et al. 2019; Eluri et al. 2017).

Figure 6. Histologic Response in Trial 301 BOS “Full Responders,” Trials 301 and 302



Source: Applicant's February 9, 2021 Response to FDA Information Request

6.3. Key Review Issues Relevant to Evaluation of Benefit

6.3.1. Lack of Clinical Meaningfulness of the $\geq 30\%$ 14-Day DSQ Responder Threshold

Issue

- The prespecified $\geq 30\%$ reduction in 14-day DSQ score responder threshold was based on phase 2 data and cannot be applied directly to phase 3 data due to several differences in instrument selection.
- The prespecified $\geq 30\%$ reduction in 14-day DSQ score responder threshold did not represent a clinically meaningful within-patient improvement based on the data from the phase 3 Trial 301.

Background

Sub-Issue 1

The $\geq 30\%$ 14-day DSQ responder threshold was prespecified by the Applicant based on phase 2 data, which used a different 1) version of the DSQ PRO instrument, 2) anchor scale, and 3) recall

period for the anchor scale than was used in the phase 3 trials. During the IND phase, FDA cautioned the Applicant that further evidence would be needed to support the $\geq 30\%$ 14-day DSQ responder threshold as clinically meaningful using phase 3 data and sensitivity analyses (IND 103173: November 12, 2014, type B end-of-phase 2 meeting; July 13, 2015, type C guidance meeting; September 15, 2015, advice/information request letter; September 17, 2018, advice/information request letter; February 7, 2019, advice/information request letter; May 20, 2020, type B pre-NDA meeting).

FDA's concerns with the $\geq 30\%$ 14-day DSQ responder threshold established using phase 2 data were further confirmed by the Applicant's own analyses. The Applicant's psychometric analysis report stated that *"Notably, direct comparisons between the anchor-based thresholds estimated using SHP621-301/SHP621-302 data and Hudgens et al. (2017) [based on phase 2 data] cannot be made because SHP621-301/SHP621-302 only included the PGIS (which asks patients their current dysphagia severity for the past 7 days) and Hudgens et al. only included the Patient Global Impression of Change (i.e., the Patient Global Impression of Change; which asks patients to rate the change in their dysphagia symptoms from baseline)."*

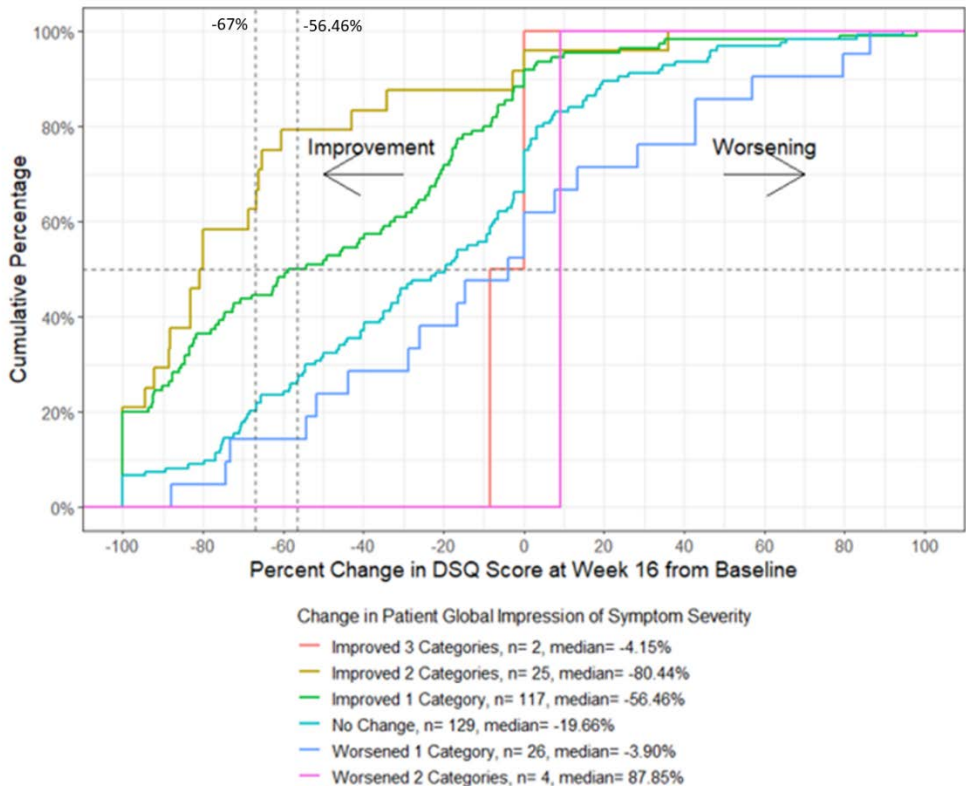
Sub-Issue 2

Using phase 3 data (Trial 301) with the PGIS anchor scale, the Applicant's anchor-based analyses suggested a meaningful within-patient change threshold range of 49.9% to 56.6%. The Applicant stated in the psychometric analysis report that this threshold *"is a more conservative estimate than Takeda's use of 30% based on "A little better" Patient Global Impression of Change category published in Hudgens et al."* Based on the FDA's anchor-based analyses, the 14-day DSQ responder threshold varied by baseline PGIS and should be at least 67%. It should be noted that there are generalizability and overfitting concerns with using the same phase 3 data both to demonstrate treatment efficacy and evaluate meaningful change; however, overfitting would likely yield a smaller improvement responder threshold rather than a larger one.

Assessment

The Applicant initially defined a 2-category improvement on the 5-category PGIS as the target anchor change category that constitutes a clinically meaningful within-patient change. However, due to small number of subjects reporting a 2-category improvement in Trial 301, the Applicant relied on a 1-category improvement on the 5-category PGIS as the target anchor change category that constitutes a clinically meaningful within-patient improvement (refer to Section [16.3](#) for more details on the selection of the target anchor change category). The Applicant examined the distribution of the percent change from baseline in 14-day DSQ combined score by category change in PGIS, based on pooled data from all study arms. A meaningful within-patient improvement threshold range of 49.9% (mean) to 56.6% (median) was proposed by the Applicant based on the percent change in 14-day DSQ combined scores for subjects who reported a 1-category improvement on PGIS. However, as can be seen in the empirical cumulative distribution function (eCDF) plot below ([Figure 7](#)), the false positive rates were above 20% in the Applicant's proposed threshold range. The FDA's anchor-based analyses using the PGIS as an anchor suggested that the meaningful within-patient improvement threshold range should be at least 67% in order to minimize the false positive rates (see [Figure 7](#)).

Figure 7. eCDF, Percent Change in 14-Day DSQ Combined Score at Week 16 From Baseline by PGIS Category of Change From Baseline, Trial 301



Source: Patient-Focused Statistical Support reviewer generated figure
Abbreviations: DSQ, Dysphagia Symptom Questionnaire; eCDF, empirical cumulative distribution function; PGIS, Patient Global Impression of Severity

When subjects’ baseline global impression of dysphagia symptom severity was taken into account when assessing the percent change in 14-day DSQ combined score from baseline, the median percent change in 14-day DSQ scores for different baseline symptom severity varied. As shown in [Table 16](#) below, the majority of subjects had mild and moderate global dysphagia symptom severity at baseline. A 90.4% change in 14-day DSQ combined score from baseline would be needed to ensure that at least 50% of subjects who reported mild global dysphagia symptom severity at baseline experience a meaningful change of 1-category improvement on the PGIS.

Table 16. Percent Change in 14-Day DSQ Combined Score at Week 16 From Baseline for Subjects Who Achieved a 1-Category Improvement on PGIS by Baseline, Trial 301

PGIS at Baseline	N	Percentile				
		10 th	25 th	50 th	75 th	90 th
Mild	54	-100.00	-100.00	-90.42	-70.67	-38.72
Moderate	52	-84.04	-59.59	-22.76	-2.86	8.45
Severe	9	-39.68	-22.19	-15.57	-7.44	-6.53
Very severe	2	-10.06	-10.06	-3.74	2.58	2.58

Source: Patient-Focused Statistical Support reviewer generated table
Abbreviations: DSQ, Dysphagia Symptom Questionnaire; PGIS, Patient Global Impression of Severity

Additional Analyses

The review team conducted additional exploratory analyses to evaluate whether the prespecified $\geq 30\%$ 14-day DSQ responder threshold was meaningful for subpopulations defined by age (adolescent versus adult), number of dysphagia days, and baseline disease severity by 14-day DSQ score; however, none of these analyses supported the Applicant's prespecified $\geq 30\%$ 14-day DSQ responder threshold as representative of meaningful improvement from the subject perspective. Refer to Section [16.3](#)) for more details.

Conclusion

The prespecified $\geq 30\%$ 14-day DSQ responder threshold did not 1) translate between phase 2 and phase 3 studies, and 2) represent a clinically meaningful within-patient improvement based on the phase 3 data (Trial 301). Any efficacy analysis results based on the prespecified $\geq 30\%$ 14-day DSQ responder threshold represent a statistical outcome rather than a clinically meaningful outcome.

6.3.2. Lack of Meaningful Short-Term Efficacy on Key Secondary Endpoint

Issue

Meaningful short-term efficacy was not demonstrated upon review of the data from the key secondary endpoint of absolute change in the DSQ combined score.

Background

The review team determined the prespecified symptomatic coprimary endpoint for Trial 301 was not sufficient to support the demonstration of short-term efficacy for BOS. Additional analyses were conducted using the prespecified alpha-controlled secondary endpoint of absolute change on the DSQ. Although statistically significant results were reported on the secondary endpoint of change from baseline in 14-day DSQ absolute change combined score, the difference between the BOS and placebo groups was small, and the 14-Day assessment period used for the DSQ Score is not consistent with the 7-Day assessment period used for the PGIS anchor. Additional analyses were conducted using the 7-Day DSQ Score (to match the recall period of the 7-Day PGIS), and no difference between BOS and placebo was identified in the range that subjects considered to be a meaningful improvement.

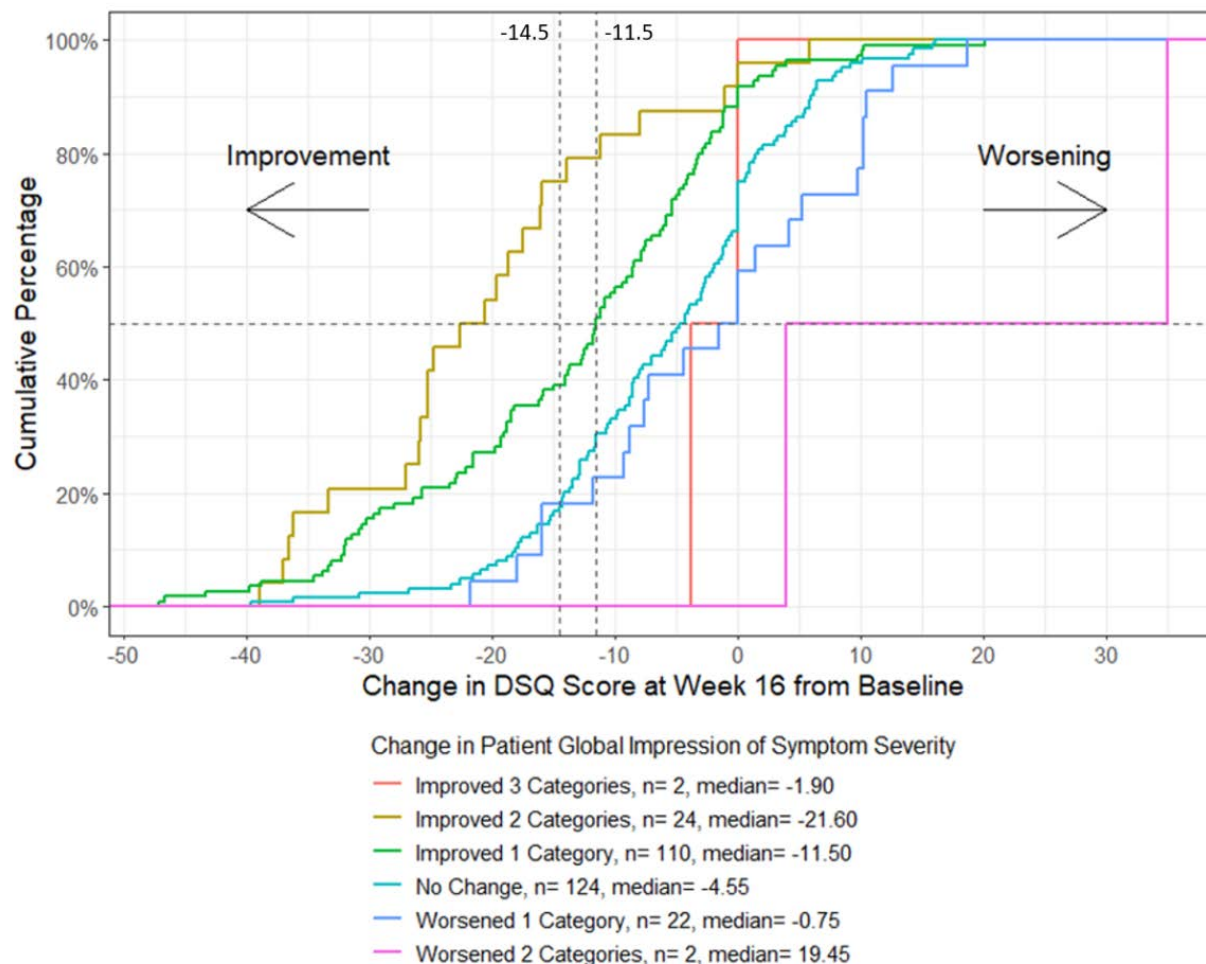
Assessment

Using anchor-based methods (i.e., PGIS with a 7-day recall period as an anchor), supplemented with eCDF curves using data pooled across trial arms (see [Figure 8](#) below), the Applicant proposed a range between 11.5-point (median) and 13.6-point (mean) improvement in the 14-day absolute DSQ combined score from baseline based on the change in 14-day absolute DSQ combined scores for subjects who reported a 1-category improvement on PGIS. The anchor-based analyses conducted by the review team did not support the Applicant's proposed range due to higher false positive rates (e.g., $>20\%$ subjects who reported no change are classified as experiencing meaningful change) in the Applicant's proposed range.

The FDA's anchor-based analyses using the PGIS as an anchor suggested that the meaningful within-patient improvement threshold range in the 14-day absolute DSQ combined score should

be at least 14.5-point in order to minimize the false positive rates. Details of the FDA anchor-based analyses are described in Section 16.3.

Figure 8. eCDF, Change in 14-Day Absolute DSQ Combined Score at Week 16 From Baseline by PGIS Category of Change From Baseline, Trial 301



Source: Patient-Focused Statistical Support reviewer generated figure

Abbreviations: DSQ, Dysphagia Symptom Questionnaire; eCDF, empirical cumulative distribution function; PGIS, Patient Global Impression of Severity

When subjects' baseline global impression of dysphagia symptom severity was taken into account to assess the change in 14-day absolute DSQ combined score from baseline, the median change in 14-day absolute DSQ scores for different baseline symptom severity varied. As shown in Table 17 below, the majority of subjects had mild and moderate global dysphagia symptom severity at baseline. A 17.2-point improvement in 14-day absolute DSQ combined score from baseline would be needed to ensure that at least 50% of subjects who reported mild global dysphagia symptom severity at baseline experienced a meaningful change of 1-category improvement on the PGIS. Therefore, the review team determined that a meaningful within-patient improvement range should be between 14.5-point and 17.2-point improvement in the 14-day absolute DSQ combined score from baseline.

Table 17. Change in 14-Day Absolute DSQ Combined Score at Week 16 From Baseline for Subjects Who Achieved a 1-Category Improvement on PGIS by Baseline PGIS, Trial 301

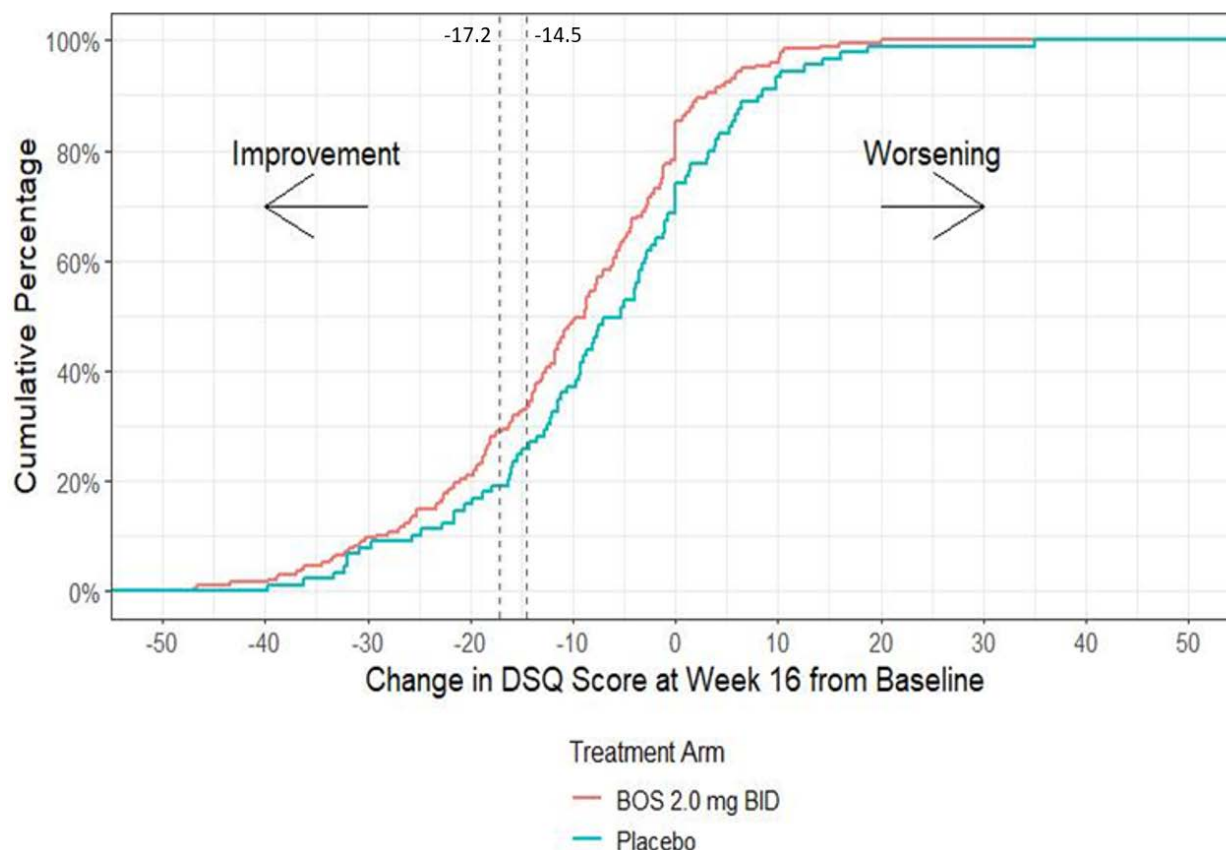
PGIS at Baseline	N	Percentile				
		10th	25th	50th	75th	90th
Mild	50	-34.15	-28.00	-17.20	-10.80	-3.55
Moderate	50	-29.95	-18.80	-8.10	-1.20	3.00
Severe	8	-15.00	-8.80	-5.85	-3.60	-2.60
Very severe	2	-4.70	-4.70	-1.50	1.70	1.70

Source: Patient-Focused Statistical Support reviewer generated table

Abbreviations: DSQ, Dysphagia Symptom Questionnaire; PGIS, Patient Global Impression of Severity

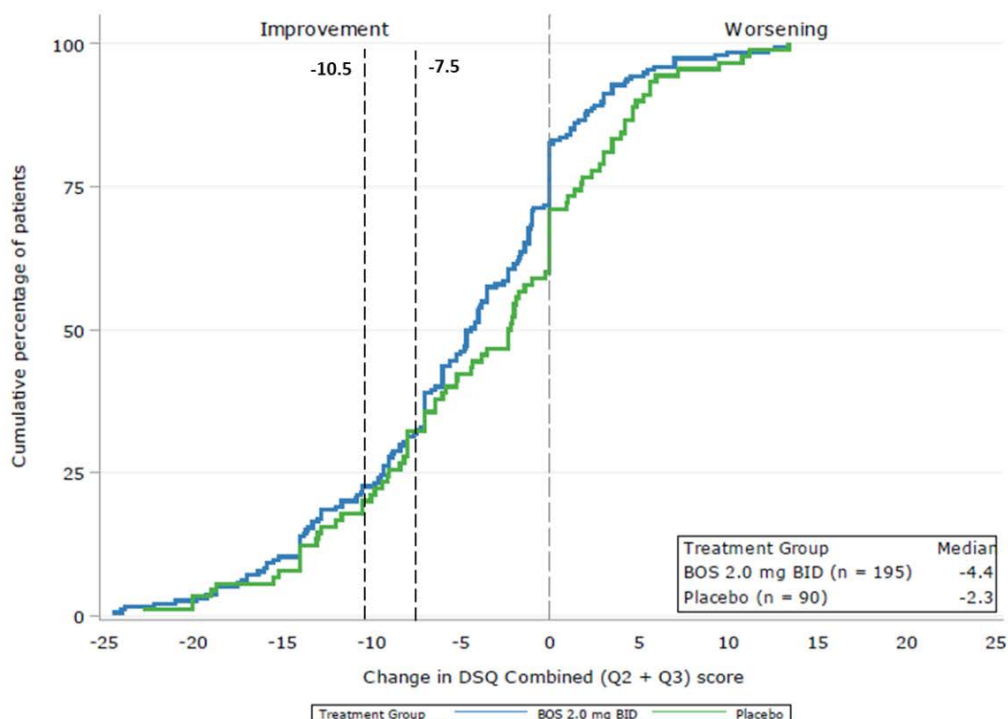
To further evaluate the clinical relevance of the observed treatment effect, the Applicant submitted a supportive graph (i.e., eCDF) of within-patient changes in 14-day absolute DSQ combined score from baseline with separate curves for each treatment arm. The review team was able to replicate this supportive graph (see [Figure 9](#) below). There appears to be separation between the two curves based on visual inspection in the FDA-proposed meaningful change range of 14.5-point and 17.2-point improvement. However, the difference in the proportion of subjects reported as experiencing a meaningful improvement between BOS (28.9% to 33.5%) and placebo (19.1% to 28.9%) was <10% in this range. Note that to allow for comparative analyses with the data generated from the change in PGIS anchor categories (i.e., anchor-based methods), the eCDF curves were created using raw change scores consistent with the current recommendation in the FDA guidance for industry *Eosinophilic Esophagitis: Developing Drugs for Treatment* (September 2020).

Figure 9. eCDF, Change in 14-Day Absolute DSQ Combined Score at Week 16 From Baseline by Treatment Arm, Trial 301



Source: Patient-Focused Statistical Support reviewer generated figure
Abbreviations: BID, twice daily; BOS, budesonide oral suspension; DSQ, Dysphagia Symptom Questionnaire; eCDF, empirical cumulative distribution function

Additionally, it should be noted that the interpretability of the anchor-based analyses is limited by the difference in assessment periods between the 14-day absolute DSQ score and the PGIS 7-day recall period. Thus, the anchor-based analyses results are not directly comparable to the 14-day absolute DSQ data. The review team requested additional meaningful within-patient change analyses using a 7-day absolute DSQ score such that the assessment period would align with the PGIS 7-day recall period. Based on a 1-category improvement on the PGIS, the review team determined that the meaningful within-patient improvement threshold should be at least -7.5 (false positive rate <20%) for the 7-day absolute DSQ combined score. Based on a 2-category improvement on the PGIS, the median change in 7-day absolute DSQ combined score is -10.5. The additional analyses using the 7-day absolute DSQ score, as comparable to the PGIS, show that there is little to no separation between BOS and placebo in the range (-10.5 to -7.5) that subjects considered to be a meaningful improvement (see [Figure 10](#) below).

Figure 10. eCDF, Change in 7-Day Absolute DSQ Combined Score at Week 16 From Baseline by Treatment Arm, Trial 301

Source: Modified from Figure 30.1.233.9 from Applicant's response to February 15, 2021 Information Request
 Abbreviations: BID, twice daily; BOS, budesonide oral suspension; DSQ, Dysphagia Symptom Questionnaire; eCDF, empirical cumulative distribution function

Conclusion

Although statistically significant results were reported on the secondary endpoint of change from baseline in 14-day DSQ absolute change combined score, the difference between BOS and placebo groups was small, and the 14-day assessment period used for the 14-day DSQ score is not consistent with the 7-day assessment period used for the PGIS anchor. Additional analyses were conducted using the 7-day DSQ score (to match the recall period of the 7-day PGIS), and no difference between BOS and placebo was identified in the range that subjects considered to be a meaningful improvement. The evaluation of the key secondary efficacy endpoint for Trial 301 did not demonstrate that subjects treated with BOS had meaningful benefit compared to those treated with placebo.

6.3.3. Lack of Demonstration of Long-Term Efficacy

Issue

Long-term efficacy of BOS was not demonstrated in Trial 302.

Background

The prespecified primary efficacy endpoint in Trial 302 of relapse (yes/no) during the 36-week randomized double-blind period for Applicant-identified Trial 301 BOS “full responders” was not statistically significant.

Assessment

In addition to confirming that the results from Trial 302 did not demonstrate a treatment effect for BOS over placebo on both the primary and secondary endpoints (see Section [6.2.3.4](#)), the review team explored the pattern of long-term efficacy for BOS in dysphagia symptom response, DSQ combined score, and peak eosinophil count by group by analyzing the derived subject-level data over the duration of Trials 301 and 302. Upon review, no clear trend toward treatment benefit for either BOS or placebo treatment arms was observed.

Conclusion

The submitted efficacy data from Trial 302 do not support a benefit for long-term treatment with BOS for subjects with EoE.

6.3.4. Submission of Post Hoc Subgroup Analyses Late in the Review Cycle

Issue

Five months into the review cycle, the Applicant submitted post hoc subgroup analyses of the 12-week initial treatment period in subjects without prior history of dilation.

Background

In response to the March 19, 2021, DR Letter informing the Applicant of deficiencies leading to concerns regarding the ability of the submitted data to support a demonstration of either short- or long-term efficacy of BOS for the treatment of EoE, the Applicant submitted a multiple module information amendment including post hoc analyses for the symptomatic coprimary efficacy endpoint on the subpopulation of subjects from Trial 301 without prior history of dilation for the 12-week treatment period only. As a result of this submission, multiple IRs were sent to the Applicant during the review period. The final response to these IRs was received from the Applicant on September 17, 2021.

Assessment

Significant limitations to the ability of these data to support the efficacy of BOS precluded their use to enable a determination of benefit. There limitations included:

- The defining variable for this subpopulation (i.e., dilation history) was unreliable, as a substantial proportion of these subjects were identified via self-report only without medical record confirmation.
- FDA analysis of the 7-day DSQ combined score (to match the 7-day PGIS anchor) demonstrated minimal separation between treatment groups.
- No data were submitted to support the Applicant's assumption that dilation-naïve status is directly related to higher baseline symptom scores.
- The subgroup was defined only after data unblinding and completion of the SAP-specified analyses.
- The submitted analyses do not address long-term efficacy for this chronic condition.

Although, these data were inadequate to be considered supportive of a determination of efficacy, the review team evaluated the data to determine whether they could be useful for informing the design of future studies in this rare disease with unmet need.

Conclusion

Although the submitted post hoc efficacy data from the post hoc analyses in dilation-naïve subjects may be useful for the purposes of hypothesis generation, they are not adequate to support the efficacy of BOS for the treatment of EoE.

6.3.5. Data Quality

Issue

The review team was unable to confirm the derived data from the source (subject-level) data for both coprimary endpoints in Trial 301 based on the original submission.

Background

For the histologic assessment, the protocol prespecified that at least two biopsy samples were to be collected at each esophageal level. From these samples, the maximum eosinophil count would be used to calculate the peak eosinophil count for each subject. Since the Applicant did not provide the cell counts for the individual biopsy sample, the review team could not confirm that the values reported for each esophageal level were the maximum count present from the biopsies obtained.

For the dysphagia symptom response, the reference date used for 14-day DSQ combined score calculation was not consistent between the subject daily diary source data and the psychometric analysis data for 16% of the subjects who completed Week 16 of Trial 301.

Assessment

Multiple IRs were sent to the Applicant in an attempt to resolve the data quality issues identified during the review of the application. For the histology data, according to the Applicant, the central pathologist recorded only one peak eosinophil count for each esophageal level. The central pathology team charter did require multiple biopsies collected from each esophageal level, but data from each sample were not recorded. The statistical data analysts from Analytics and Informatics Staff verified the histologic coprimary endpoint based on the revised histologic datasets from the available central histology source worksheets for Trials 301 submitted on July 9, 2021. However, the Applicant could not confirm how many biopsy samples were collected at each esophageal level.

The Applicant submitted updated DSQ score diary data on May 16, 2021, per the Agency's request. Forty-three percent of Trial 301 completers (295 subjects with observed data on Week 16) had discrepant Week 16 14-day DSQ combined scores between calculations using the source reference date in the revised daily diary datasets and using the reference date in the original submission.

The inconsistencies in 43% of Trial 301 completers led to changes in dysphagia responder status (i.e., the prespecified symptomatic coprimary endpoint based on 14-day DSQ combined score)

for 5% of completers. However, the results of revised analyses remained consistent with the original results on the symptomatic coprimary endpoint and key secondary endpoint.

Conclusion

The Applicant confirmed that complete subject-level data for the histologic assessment was not available for Trial 301 and 302. Inconsistencies related to the DSQ data were resolved or determined to not influence Trial 301 analysis results. As the results from Trial 302 were not supportive of a demonstration of benefit, additional efforts to resolve inconsistencies related to DSQ data from Trial 302 were not pursued.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The nonclinical safety profile of budesonide has been extensively evaluated in comprehensive pharmacology, pharmacokinetic, and toxicology studies to support the approval of currently marketed budesonide containing products. It has also been widely documented in the published literature. In addition, supplemental studies were conducted with the new formulation of BOS to support the EoE indication in the proposed patient population. The nonclinical studies submitted to the NDA for BOS consisted of juvenile animal toxicity studies in rats and dogs to support dosing in pediatric patients and a series of genotoxicity studies to qualify an impurity (b) (4).

(b) (4) The toxicity of BOS was evaluated in juvenile rats and dogs for 91-days following oral administration. All observed effects were expected pharmacological effects following administration of a potent glucocorticoid, with no novel toxicities identified. The degradation impurity (b) (4) was mutagenic in the Ames assay; however, it did not induce mutagenicity in the 28-day rat *Pig-A* assay. There were no significant safety concerns identified in the toxicology studies conducted following oral administration of BOS in rats and dogs.

In the 91-day juvenile toxicity study in rats (PND22), daily administration of BOS at doses of 0.05, 0.2, 0.6, and 1.5 mg/kg/day was generally well tolerated. Seven unscheduled deaths were observed in this study. The deaths were attributed to urogenital inflammation (secondary to immunosuppression) and dosing error. Significant reductions in body weight and food consumption occurred in a dose-dependent manner. Classic effects of glucocorticoids were noted, including lymphocyte and leukocytic changes; clinical chemistry changes consistent with glucocorticoid administration; adrenal atrophy; lymphoid depletion in the thymus, lymph nodes, Peyer's patch, and spleen; decreased cellularity in bone marrow; hyperostosis and physal atrophy; atrophy of the stomach; and decreased bone length of the tibia and femur. The effects observed following BOS administration were consistent with the pharmacological effects of glucocorticoids. The no observed adverse effect levels for daily administration of BOS for 91 days in juvenile rats was 0.05 mg/kg/day.

In the 91-day juvenile toxicity study in dogs (6 weeks), BOS was administered at 0.05, 0.2, and 0.6 mg/kg/day. Gross and histopathology assessments showed expected glucocorticoid-related changes. There were 10 unscheduled deaths following BOS administration, which were

attributed to pharmacologically mediated immunosuppression and/or inguinal hernias. Cushing disease-like changes and steroid hepatopathy were noted at doses of ≥ 0.2 mg/kg/day. The test article-related effects observed were decreased body weight gain, decreased food consumption, leukocytic/lymphocyte changes, adrenal cortical atrophy, lymphoid depletion in lymphoid organs, decreased cellularity in bone marrow, hyperostosis and physal atrophy, and suppression of long bone growth. With the exception of the expected pharmacologic actions of this class of compound, no apparent unexpected or adverse toxicity was observed with BOS at the doses tested.

In the Segment I fertility and early embryonic developmental toxicity study in rats, there was a significant reduction in maternal body weight gain, prenatal viability, and the viability of the pups at birth and during lactation at a dose of 20 μ g/kg/day. These findings were more pronounced at the high dose of 80 μ g/kg/day. Budesonide had no effect on fertility at doses up to 80 μ g/kg/day.

In the embryofetal developmental toxicity study in pregnant rats, there was a decrease in food consumption and body weight gain in the budesonide treated animals. At a dose of 100 μ g/kg/day, there was increased fetal loss and fetal abnormalities. Fetal abnormalities including umbilical eventration and reduced ossification of skull bones along with sternal or vertebral defects were observed at a dose of 500 μ g/kg/day. In the embryofetal developmental toxicity study in rabbits following subcutaneous administration of budesonide, there was a decrease in food consumption and in body weight gains at doses of 25 and 125 μ g/kg/day. There was an increase in visceral abnormalities at doses of 2 and 25 μ g/kg/day. Skeletal anomalies (skull and vertebral defects) were increased at a dose of 25 μ g/kg/day. There was an increase in maternal abortion, effects on fetal development, and a reduction in litter weights at doses up to approximately 25 μ g/kg/day.

In the Segment III pre- and postnatal development study in rats, a slight prolongation of gestational period was noted. There was no test article related effects on parturition, nursing, and lactation. In the mid- and high-dose dams, there was a decrease in body weight gain. At a dose of ≥ 20 μ g/kg/day, maternal toxicity was observed, offspring survival was reduced, and surviving offspring had decreased mean body weights at birth and during lactation.

In the standard in vitro and in vivo genotoxicity tests, budesonide was not mutagenic. The degradation impurity (b) (4) was mutagenic in the Ames assay up to 1500 μ g/plate and was negative in the *Pig-A* gene mutation assay at doses up to and including 0.50 mg/kg/day in males and 0.20 mg/kg/day in females.

In the 2-year oral carcinogenicity study in rats, there was a statistically significant increase in incidences of gliomas in males dosed with 50 μ g/kg and primary hepatocellular tumors in the males dosed with ≥ 25 μ g/kg. There were no tumor findings in the female rats. In an additional 2-year carcinogenicity study in rats, the only tumor findings were increased incidences of hepatocellular tumors at an oral dose of 50 μ g/kg. Budesonide was not carcinogenic in mice at doses up to 200 μ g/kg/day.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

The adverse event profile of corticosteroid drugs is well-characterized due to their widespread use as therapeutics for multiple inflammatory conditions. This is reflected in the prescribing information for the application's listed drug, Entocort EC, which, in addition to a contraindication related to hypersensitivity to budesonide or any of the ingredients in Entocort EC, includes warnings and precautions related to hypercortisolism and adrenal axis suppression, symptoms of steroid withdrawal in patients transferred from other systemic corticosteroids, increased risk of infections (including serious and fatal chicken pox and measles), and other established corticosteroid-associated adverse effects.

In consideration of these known class effects and FDA's evaluation of the Applicant's submitted safety data, several potential signals were identified for additional consideration during the review. The following group queries were conducted in addition to the evaluation of safety data using the individual preferred terms:

- Adrenal suppression (adrenal insufficiency, adrenal suppression, ACTH stimulation test abnormal, blood cortisol abnormal, blood cortisol decreased)
- Candidiasis (esophageal and oropharyngeal)
- Respiratory infection (upper respiratory tract infection, respiratory tract infection, sinusitis, nasopharyngitis, rhinitis)
- Mucosal irritation (erosive duodenitis, gastritis erosive, erosive esophagitis, gastrointestinal ulcer, esophageal ulcer, gastritis)

See Section [7.6.1.7](#) for additional description of the grouped queries that were examined.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

Not applicable. BOS is not yet commercially available in any country.

7.4. FDA Approach to the Safety Review

The safety review of this 505(b)(2) application focused primarily on the data from the 12-week double-blind treatment period of the phase 3 initial treatment trial (Trial 301) and the 36-week double-blind treatment extension period of the phase 3 trial (Trial 302). See [Table 3](#).

Additionally, the Applicant submitted data from a phase 1 trial in adult healthy volunteers (SHP621-101), a phase 2 dose-ranging trial in children and adolescents with EoE (MPI 101-01), a phase 2 trial in adolescents and adults with EoE (MPI 101-06), and an ongoing phase 3 trial in adolescents and adults with EoE (SHP621-303). A summary of the clinical trials that contributed data to inform the clinical safety evaluation for BOS as a candidate therapeutic for patients with EoE is located in [Tables 3](#) and [4](#).

Clinical trial data were independently analyzed using Python, R, JMP, and JMP Clinical software. All safety assessments and conclusions are those of the review team unless otherwise

specified. The review team did not identify any major data quality or integrity issues that precluded performing a thorough safety review.

Analyses of Trial 301 represent events that occurred through Week 16 (end of the 12-week double-blind treatment period of the initial treatment study). Analyses of Trial 302 represent events that occurred through the end of the 36-week double-blind extension treatment period following completion of Trial 301. Subjects identified by the Applicant as Trial 301 BOS “full responders” were randomized in Trial 302 to either BOS or placebo; all other subjects from Trial 301 including all placebo completers (responders and nonresponders) received double-blind BOS in Trial 302.² Although the double-blind was maintained in Trial 302, as all subjects included in Trial 302 had exposure to BOS during the study (either in Trial 301 or Trial 302), the ability of the Trial 302 safety analyses to generate definitive conclusions is limited. Additional safety data were provided after the completion of both Trials 301 and 302 from the open-label extension study (Trial SHP621-303, Trial 303). All subjects received BOS 2 mg BID in Trial 303.

Pooling of Safety Data Across Clinical Trials

In addition to evaluation of the safety data from both pivotal phase 3 trials (Trials 301 and 302),³ the safety review also includes evaluation of pooled data across the phase 1, 2, and 3 clinical trials listed in [Table 3](#) and [Table 4](#) which contributed to the integrated summary of safety (ISS) analyses. To ensure a thorough evaluation of all available controlled safety information, the data from the phase 2 MPI 101-06 trial⁴ were also reviewed independently. However, no new safety signals were identified from the review of Trial MPI 101-06 results, and the data on AEs, laboratory findings, and vital signs were consistent with those observed during the evaluation of the phase 3 trials and the ISS databases.

The ISS safety database (i.e., overall safety set) included three groups of subjects for comparison: BOS 2 mg BID group, Any BOS Dose group, and Induction Placebo group. See Section [17.2](#) for details regarding which subjects were included in each comparator group.

7.4.1. Safety Analysis Plan and Definitions

The prespecified safety analysis plan and definitions were reviewed and agreed upon during protocol development and during the pre-NDA meeting on May 20, 2020. Descriptive statistics were used to summarize the safety outcomes. The Applicant translated verbatim AE terms to Medical Dictionary for Regulatory Activities preferred terms (PTs) for the events reported in Trials 301, 302, and 303 using version 18.0 and in phase 2 Trial MPI 101-06 using version 15.0.

² Note: Only the 48 subjects who were identified by the Applicant as Trial 301 BOS “full responders” were included in the placebo-controlled randomized withdrawal part of Trial 302 (25 subjects were randomized to receive BOS 2 mg BID and 23 subjects were randomized to receive placebo); the remaining 171 subjects (BOS partial or nonresponders [as defined by the Applicant] and all placebo recipients in Trial 301 [regardless of assessed response]) were assigned to receive double-blind BOS 2 mg BID in Trial 302.

³ The individual trial safety databases include 318 subjects from phase 3 Trial 301 (213 received BOS 2 mg BID and 105 received placebo), 219 subjects from phase 3 Trial 302 (131 subjects were rerandomized or assigned from BOS 2 mg BID in Trial 301 to BOS 2 mg BID in Trial 302; 65 subjects were assigned from placebo in Trial 301 to BOS 2 mg BID in Trial 302; and 23 subjects were rerandomized from BOS 2 mg BID in Trial 301 to placebo in Trial 302).

⁴ 93 subjects from phase 2 trial MPI 101-06 (42 received placebo and 51 received BOS 2 mg BID).

The translations were reviewed and generally found acceptable, except for where FDA PT recoding was noted in this review. See Section [17.1](#) for the Agency's PT recoding for the phase 3 Trials 301 and 302.

The Applicant's proposed AE definitions including severity, relatedness, outcome, treatment-emergence (i.e., whether an AE is considered to be a treatment-emergent AE), and classification as serious were reviewed and found to be acceptable.

7.5. Adequacy of Clinical Safety Database

The safety database was adequate for a comprehensive safety assessment of BOS 2 mg BID for the proposed indication, subject population, dosage regimen, and duration.

The two phase 2 studies (MPI 101-01 and MPI 101-06) and two phase 3 studies (Trials 301 and 302) included 426 unique subjects who were exposed to BOS. An additional 131 subjects received at least one dose of BOS in the ongoing phase 3 open-label extension study (SHP621-303) as of the cut-off date of August 14, 2020. The overall safety databases include 292 subjects who were exposed to the to-be-marketed dose of BOS 2 mg BID for a total exposure of 85.82 in person-years. A total of 448 subjects were included in the Any BOS Dose group for a total exposure of 113.13 in person-years. A total of 168 subjects were included in the Induction Placebo group for a total exposure of 26.72 in person-years.⁵

[Table 18](#) and [Table 19](#) summarize the exposure periods for Trial 301 and Trial 302, respectively.

Table 18. Duration of Exposure, Safety Population, Trial 301^[1]

Variable	BOS 2 mg BID N=213	Placebo N=105
Duration of treatment (weeks)		
Mean (SD)	14.5 (2.9)	13.75 (3.9)
Median (min, max)	15.4 (2.1, 21.0)	15.3 (0.1, 20.6)
Subjects treated, by duration, n (%)		
≤1 week	0	2 (1.9)
>1 to ≤4 weeks	4 (1.9)	4 (3.8)
>4 to ≤8 weeks	6 (2.8)	4 (3.8)
>8 to ≤12 weeks	24 (11.3)	18 (17.1)
>12 to ≤16 weeks	123 (57.7)	57 (54.3)
>16 weeks	56 (26.3)	20 (19.0)

Source: Reviewer created table adapted from CSR for Trial 301 p. 134 Table 25

^[1] Duration for Trial 301 includes from the first dose of IP after randomization to the last dose of IP in the 4-week treatment extension phase prior to Trial 302

Abbreviations: BOS, budesonide oral suspension; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; SD, standard deviation

⁵ Our calculation of the total exposure years was slightly different from the Applicant's. The Applicant's calculation was as follows: 87.23 in person-years for the BOS 2 mg BID group, 115.97 in person-years for the Any BOS Dose group, and 24.97 in person-years for the Induction Placebo group.

Table 19. Duration of Exposure to Investigational Product, Safety Population, Trial 302

Variable	BOS (Trial 301)- BOS (Trial 302) N=131	PBO (Trial 301)- BOS (Trial 302) N=65	BOS (Trial 301)- PBO (Trial 302) N=23	Total N=219
Duration of treatment (weeks)				
Mean (SD)	31.4 (9.9)	31.7 (9.9)	28.8 (9.8)	31.2 (9.9)
Median (minimum, maximum)	36.0 (2.7, 41.1)	35.9 (0.9, 39.1)	35.1 (7.6, 37.0)	35.9 (0.9, 41.1)

Source: Reviewer created table adapted from CSR for Trial 302 p. 188-189 Table 29

Abbreviations: BOS, budesonide oral suspension; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; PBO, placebo; SD, standard deviation

[Table 20](#) summarizes the exposure periods for all subjects treated with BOS in Trial 301 and Trial 302. Of note, only 34 subjects had exposure to BOS 2 mg BID beyond 52 weeks.

Table 20. Duration of Exposure, All Subjects Treated With BOS, Trials 301 and 302

Variable	BOS 2 mg BID N=278 n (%)
Subjects treated, by duration	
>0 to ≤4 weeks	5 (1.8)
>4 to ≤12 weeks	35 (12.6)
>12 to ≤20 weeks	55 (19.8)
>20 to ≤28 weeks	13 (4.7)
>28 to ≤36 weeks	39 (14.0)
>36 to ≤44 weeks	28 (10.1)
>44 to ≤52 weeks	69 (24.8)
>52 weeks	34 (12.2)

Source: Reviewer created table from adex.xpt

Abbreviations: BOS, budesonide oral suspension; N, number of subjects in treatment arm; n, number of subjects with given treatment duration

7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database

7.6.1. Safety Findings and Concerns, Trials 301 and 302

The following subsections include safety findings and concerns identified during the review of data from Trial 301 (phase 3 initial treatment) and Trial 302 (phase 3 extension). As noted above, the safety data for the supportive phase 2 Trial MPI 101-06 were also reviewed independently as well as in contribution to the ISS. No new safety signals or laboratory abnormalities were noted on the independent review of the data from Trial MPI 101-06.

As stated earlier in this integrated assessment, subjects identified by the Applicant as Trial 301 BOS “full responders” were randomized in Trial 302 to either BOS or placebo; all other subjects from Trial 301 (partial and nonresponders treated with BOS) and all placebo completers (regardless of assessed response) received double-blind BOS in Trial 302. Although the double-blind was maintained in Trial 302, all subjects included in Trial 302 had exposure to BOS during the study (either in Trial 301 or Trial 302); therefore, the ability of the Trial 302 safety analyses to generate definitive conclusions is limited.

The safety data as presented below includes the treatment grouping assignment from both Trials 301 and 302 to provide an estimated duration of exposure to the assigned IP. The duration of

BOS exposure was equivalent between the two groups of subjects who received BOS in both Trials 301 and 302 – the 25 randomized withdrawal subjects and the 106 subjects who were not in the randomized withdrawal part of the study. On independent review of the TEAEs in Trial 302 from the 25 randomized withdrawal subjects who received BOS in Trial 302, the findings were comparable to the larger population of 131 subjects who received BOS in Trial 302 (including both the randomized withdrawal and non-randomized withdrawal subjects).

7.6.1.1. Overall Treatment-Emergent Adverse Event Summary, Trials 301 and 302

[Table 21](#) provides a summary of treatment-emergent adverse events (TEAEs) reported for Trial 301. Upon review of the TEAEs in Trial 301, there were no notable differences in the percentage of BOS versus placebo subjects who experienced any TEAEs, SAEs, or TEAEs leading to study drug modification or interruption. A greater proportion of subjects treated with BOS than those that received placebo reported moderate or severe TEAEs, and a greater proportion of subjects who received placebo than those treated with BOS had TEAEs leading to study drug discontinuation.

Table 21. Overview of Treatment-Emergent Adverse Events, 12-Week Initial Treatment Period, Controlled Trial Safety Population, Trial 301

Event Category	BOS 2 mg BID N=213 n (%)	Placebo N=105 n (%)	Risk Difference (95% CI) ^[1]
Any TEAE	130 (61.0)	64 (61.0)	0.0 (-11.4, 11.4)
Moderate or severe TEAEs	61 (28.6)	26 (24.8)	3.8 (-6.4, 14.0)
Any SAE	2 (0.9)	1 (1.0)	-0.1 (-2.4, 2.2)
SAE with fatal outcome	0	0	0.0 (0.0, 0.0)
TEAE leading to discontinuation of IP	3 (1.4)	5 (4.8)	-3.4 (-7.8, 1.0)
TEAE leading to dose modification of IP	4 (1.9)	1 (1.0)	0.9 (-1.7, 3.5)
TEAE leading to interruption of IP	4 (1.9)	1 (1.0)	0.9 (-1.7, 3.5)
TEAE leading to reduction of IP	0	0	0.0 (0.0, 0.0)
TEAE leading to delay of IP	0	0	0.0 (0.0, 0.0)

Source: adae.xpt; Software: Python

Grading Scale: The severity (intensity) of AEs was assessed as mild, moderate, and severe.

^[1] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.

Abbreviations: BOS, budesonide oral suspension; CI, confidence interval; IP, investigational product; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event; TEAE, treatment-emergent adverse event

[Table 22](#) provides a summary of TEAEs reported for Trial 302. Upon review of the TEAEs in Trial 302, no predictable trends in any TEAEs, moderate or severe TEAEs, SAEs, or TEAEs leading to study drug discontinuation, modification, or interruption were observed across the three double-blind treatment groups. A higher percentage of subjects who received BOS in Trial 302 reported moderate or severe TEAEs and had TEAEs leading to study drug discontinuation than those who received placebo in Trial 302. Conversely, a higher percentage of subjects who received placebo in Trial 302 had TEAEs leading to study drug interruption than subjects who received BOS in Trial 302.

Table 22. Overview of Treatment-Emergent and Serious Adverse Events, 36-Week Double-Blind Treatment Period, Safety Population, Trial 302

Event Category	BOS (Trial 301)- BOS (Trial 302) N=131 n (%)	PBO (Trial 301)- BOS (Trial 302) N=65 n (%)	Total Receiving BOS in Trial 302 ^[1] N=196 n (%)	BOS (Trial 301)- PBO (Trial 302) N=23 n (%)
Any TEAE	93 (71.0)	49 (75.4)	142 (72.4)	14 (65.2)
Moderate or severe TEAEs	53 (40.5)	23 (35.4)	76 (38.8)	8 (34.8)
Any SAE	6 (4.6)	5 (7.7)	11 (5.6)	1 (4.3)
SAE with fatal outcome	0	0	0	0
TEAE leading to discontinuation of IP	6 (4.6)	4 (6.2)	10 (5.1)	0
TEAE leading to dose modification of IP	4 (3.1)	2 (3.1)	6 (3.1)	1 (4.3)
TEAE leading to interruption of IP	4 (3.1)	2 (3.1)	6 (3.1)	1 (4.3)
TEAE leading to reduction of IP	0	0	0	0
TEAE leading to delay of IP	0	0	0	0

Source: adae.xpt; Software: Python

Grading Scale: The severity (intensity) of AEs was assessed as mild, moderate, and severe.

^[1] This includes both "BOS (Trial 301)-BOS (Trial 302)" and "PBO (Trial 301)-BOS (Trial 302)" subjects

Abbreviations: BOS, budesonide oral suspension; CI, confidence interval; IP, investigational product; N, number of subjects in treatment arm; n, number of subjects with at least one event; PBO, placebo; SAE, serious adverse event; TEAE, treatment-emergent adverse event

7.6.1.2. Deaths, Trials 301 and 302

No deaths were reported in Trial 301 or 302.

7.6.1.3. Serious Adverse Events, Trials 301 and 302

[Table 23](#) provides a summary of SAEs reported for Trial 301. A review of the SAEs in Trial 301 yielded no notable findings when comparing BOS to placebo subjects.

Table 23. Serious Adverse Events, Safety Population, Trial 301

Preferred Term	BOS 2 mg BID N=213 n (%)	Placebo N=105 n (%)	Risk Difference (95% CI) ^[1]
Subjects reporting ≥1 SAE	2 (0.9)	1 (1.0)	-0.1 (-2.4, 2.2)
Gastroenteritis	1 (0.5)	0	0.5 (-0.4, 1.4)
Localized intraabdominal fluid collection	1 (0.5)	0	0.5 (-0.4, 1.4)
Sepsis	1 (0.5)	0	0.5 (-0.4, 1.4)
Ovarian cyst	0	1 (1.0)	-1.0 (-2.9, 0.9)

Source: adae.xpt; Software: Python

^[1] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.See Section [17.1](#) for FDA PT recoding for Trial 301

Abbreviations: BOS, budesonide oral suspension; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SAE, serious adverse event

[Table 24](#) provides a summary of SAEs reported for Trial 301. Upon review of the SAEs in Trial 302, no predictable trends were observed when comparing events across the three double-blind treatment groups. Although hypersensitivity reactions were observed in subjects who began BOS

in Trial 302 after receiving placebo in Trial 301, these events were attributed to known reactions to foods or other items known to provoke an allergic response (i.e., gadolinium contrast). Of the SAEs, a severe event of herpes simplex viral esophagitis occurred in a 16-year-old subject in Trial 302, which was considered related to BOS.

Table 24. Serious Adverse Events, Safety Population, Trial 302

Preferred Term	BOS (Trial 301)- BOS (Trial 302)N=131	PBO (Trial 301)- BOS (Trial 302)N=65	Total Receiving BOS in Trial 302 ^[1] N=196	BOS (Trial 301)- PBO (Trial 302) N=23
	n (%)	n (%)	n (%)	n (%)
Subjects reporting ≥1 SAE	6 (4.6)	5 (7.7)	11 (5.6)	1 (4.3)
Hypersensitivity ^[2]	0	3 (4.6)	3 (1.5)	0
Abortion spontaneous	1 (0.8)	0	1 (0.5)	0
Appendicitis	1 (0.8)	0	1 (0.5)	0
Drug hypersensitivity ^[3]	1 (0.8)	0	1 (0.5)	0
Fracture	1 (0.8)	0	1 (0.5)	0
Hypoxia	1 (0.8)	0	1 (0.5)	0
Noncardiac chest pain	1 (0.8)	0	1 (0.5)	0
Head injury	0	1 (1.5)	1 (0.5)	0
Herpes simplex	0	1 (1.5)	1 (0.5)	0
Neck injury	0	1 (1.5)	1 (0.5)	0
Back pain	0	0	0	1 (4.3)

Source: adae.xpt; Software: Python

See Section 17.1 for FDA PT recoding for Trial 302

^[1] This includes both "BOS (Trial 301)-BOS (Trial 302)" and "PBO (Trial 301)-BOS (Trial 302)" subjects

^[2] One subject had anaphylactic shock due to cross-contamination of food, one subject had an anaphylactic reaction to cashews, and one subject had anaphylaxis to wheat

^[3] One subject had anaphylaxis due to the administration of gadolinium contrast

Abbreviations: BOS, budesonide oral suspension; N, number of subjects in treatment arm; n, number of subjects with adverse event; PBO, placebo; SAE, serious adverse event

Of the 17 serious adverse events (SAEs) that occurred across both Trial 301 and Trial 302, all were resolved, none led to permanent discontinuation of the investigational product (IP) or from the study, and 16/17 (94.1%) were considered unrelated to the IP.

7.6.1.4. Dropouts and/or Discontinuations Due to Adverse Events, Trials 301 and 302

In Trial 301, three BOS subjects (1.4%) and five placebo subjects (4.8%) discontinued IP due to TEAEs (Table 25). Of the 12 TEAEs leading to discontinuation, nine were observed in the placebo group (five of which were considered to be related to the IP: esophageal candidiasis, mood swings, mouth ulceration, dizziness, headache, and adrenal insufficiency). The three TEAEs leading to discontinuation in the BOS group (i.e., adrenal insufficiency, esophageal candidiasis, and esophageal stenosis) were all considered to be related to the IP. One BOS subject (reporting esophageal stenosis) and three placebo subjects (reporting mood swings, dizziness, and headache [1 subject], and mouth ulceration) also discontinued the study.

Table 25. Treatment-Emergent Adverse Events Leading to Discontinuation of IP, Safety Population, Trial 301

Preferred Term	BOS 2 mg BID N=213 n (%)	Placebo N=105 n (%)	Risk Difference (95% CI) ^[1]
Subjects reporting ≥1 TEAE leading to discontinuation of IP	3 (1.4)	5 (4.8)	-3.4 (-7.8, 1.0)
Adrenal insufficiency	1 (0.5)	0	0.5 (-0.4, 1.4)
Esophageal candidiasis	1 (0.5)	0	0.5 (-0.4, 1.4)
Esophageal stenosis	1 (0.5)	0	0.5 (-0.4, 1.4)
Diarrhea	0	1 (1.0)	-1.0 (-2.9, 0.9)
Dizziness	0	1 (1.0)	-1.0 (-2.9, 0.9)
Gastroesophageal reflux disease	0	1 (1.0)	-1.0 (-2.9, 0.9)
Headache	0	1 (1.0)	-1.0 (-2.9, 0.9)
Mood swings	0	1 (1.0)	-1.0 (-2.9, 0.9)
Mouth ulceration	0	1 (1.0)	-1.0 (-2.9, 0.9)
Nausea	0	1 (1.0)	-1.0 (-2.9, 0.9)
Psoriatic arthropathy	0	1 (1.0)	-1.0 (-2.9, 0.9)
Vomiting	0	1 (1.0)	-1.0 (-2.9, 0.9)

Source: adae.xpt; Software: Python

^[1] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.

See Section 17.1 for the Agency's PT recoding for Trial 301.

Abbreviations: BOS, budesonide oral suspension; CI, confidence interval; IP, investigational product; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; TEAE, treatment-emergent adverse event

Of the subjects included in Trial 302, 10/219 (4.6%) subjects who received BOS discontinued IP due to TEAEs, while zero placebo subjects discontinued IP due to TEAEs ([Table 26](#)). Upon review of the TEAEs leading to discontinuation of IP in Trial 302, the most common reason for discontinuation noted in subjects receiving BOS was “blood cortisol decreased.” No Applicant-identified Trial 301 BOS “full responder” in either group (randomized to either BOS or placebo in Trial 302) had a TEAE leading to discontinuation of IP.

Table 26. Treatment-Emergent Adverse Events Leading to Discontinuation of IP, Safety Population, Trial 302

Preferred Term	BOS (Trial 301)- BOS (Trial 302)N=131 n (%)	PBO (Trial 301)- BOS (Trial 302)N=65 n (%)	Total Receiving BOS in Trial 302 ^[1] N=196 n (%)	BOS (Trial 301)- PBO (Trial 302) N=23 n (%)
Subjects reporting ≥1 TEAE leading to discontinuation of IP	6 (4.6)	4 (6.2)	10 (5.1)	0
Blood cortisol decreased	0	3 (4.6)	3 (1.5)	0
Nausea	2 (1.5)	0	2 (1.0)	0
Vomiting	2 (1.5)	0	2 (1.0)	0
Adrenal suppression	1 (0.8)	0	1 (0.5)	0
Dysphagia	1 (0.8)	0	1 (0.5)	0
Esophageal food impaction	1 (0.8)	0	1 (0.5)	0
Esophageal stenosis	1 (0.8)	0	1 (0.5)	0
Esophagitis	1 (0.8)	0	1 (0.5)	0
Pregnancy	1 (0.8)	0	1 (0.5)	0
Arthralgia	0	1 (1.5)	1 (0.5)	0
Cushingoid	0	1 (1.5)	1 (0.5)	0
Edema peripheral	0	1 (1.5)	1 (0.5)	0
Weight increased	0	1 (1.5)	1 (0.5)	0

Source: adae.xpt; Software: Python

See Section 17.1 for the Agency's PT recoding for Trial 302

^[1] This includes both "BOS (Trial 301)-BOS (Trial 302)" and "PBO (Trial 301)-BOS (Trial 302)" subjects

Abbreviations: BOS, budesonide oral suspension; CI, confidence interval; IP, investigational product; N, number of subjects in treatment arm; n, number of subjects with adverse event; PBO, placebo; PT, preferred term; TEAE, treatment-emergent adverse event

7.6.1.5. Treatment-Emergent Adverse Events, Trials 301 and 302

[Table 27](#) displays the TEAEs in Trial 301 that occurred in at least 2% of subjects treated with BOS and occurred at a higher rate than placebo (a risk difference of greater than 1.0). The most common TEAEs observed in subjects treated with BOS were oropharyngeal candidiasis and headache, both of which were reported in 10/213 subjects (4.7%). Although occurring in less than 2% of BOS subjects, the following TEAEs had a risk difference between BOS and placebo of greater than 1.0: arthralgia, adrenal suppression,⁶ hirsutism, hypertension, and transaminases increased. It was noted that the same percentage of subjects across the treatment groups experienced at least one TEAE (61.0% BOS and 61.0% placebo).

⁶ Note that "adrenal suppression" does not include the PTs of "adrenal insufficiency," "ACTH stimulation test abnormal," or blood cortisol related preferred terms. See Section 7.6.1.7 for the "ACTH, cortisol abnormal/decreased" FDA grouped query results.

Table 27. Treatment-Emergent Adverse Events (in ≥2% of Subjects Treated With BOS and/or a Risk Difference of >1.0), Safety Population, Trial 301

Preferred Term	BOS 2 mg BID N=213 n (%)	Placebo N=105 n (%)	Risk Difference (95% CI) ^[1]
Subjects with ≥1 TEAE ^[2]	130 (61.0)	64 (61.0)	0.0 (-11.4, 11.4)
Oropharyngeal candidiasis	10 (4.7)	0	4.7 (1.9, 7.5)
Headache	10 (4.7)	2 (1.9)	2.8 (-1.1, 6.7)
Gastroenteritis	7 (3.3)	1 (1.0)	2.3 (-0.7, 5.3)
Esophagitis	5 (2.3)	0	2.3 (0.3, 4.3)
Esophageal candidiasis	8 (3.8)	2 (1.9)	1.9 (-1.8, 5.6)
Sinusitis	10 (4.7)	3 (2.9)	1.8 (-2.5, 6.1)
Nasopharyngitis	11 (5.2)	4 (3.8)	1.4 (-3.3, 6.1)
Procedural pain	5 (2.3)	1 (1.0)	1.3 (-1.5, 4.1)

Source: adae.xpt; Software: Python

^[1] Risk difference column shows difference (with 95% confidence interval) between BOS and placebo^[2] Total number of subjects who reported at least one TEAE

See Section 17.1 for the Agency's PT recoding for Trial 301

Abbreviations: BOS, budesonide oral suspension; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; TEAE, treatment-emergent adverse event

[Table 28](#) displays the TEAEs that occurred in at least 2% of subjects who received BOS in Trial 302.

As shown in [Table 28](#) below, more subjects who continued to receive BOS in Trial 302 experienced at least 1 TEAE than did subjects who switched to placebo in Trial 302 (72.4% versus 65.2%).

Table 28. Treatment-Emergent Adverse Events in ≥2% of Subjects Treated With BOS in Trial 302, Safety Population, Trial 302

Preferred Term	BOS (Trial 301)- BOS (Trial 302)N=131 n (%)	PBO (Trial 301)- BOS (Trial 302)N=65 n (%)	Total Receiving BOS in Trial 302 ^[1] N=196 n (%)	BOS (Trial 301)- PBO (Trial 302) N=23 n (%)
Subjects with ≥1 TEAE ^[2]	93 (71.0)	49 (75.4)	142 (72.4)	15 (65.2)
Upper respiratory tract infection	13 (9.9)	3 (4.6)	16 (8.2)	1 (4.3)
Vomiting	13 (9.9)	1 (1.5)	14 (7.1)	0
Nausea	9 (6.9)	4 (6.2)	13 (6.6)	2 (8.7)
Nasopharyngitis	7 (5.3)	3 (4.6)	10 (5.1)	4 (17.4)
Diarrhea	5 (3.8)	4 (6.2)	9 (4.6)	1 (4.3)
Esophageal candidiasis	4 (3.1)	5 (7.7)	9 (4.6)	0
Sinusitis	5 (3.8)	3 (4.6)	8 (4.1)	2 (8.7)
Blood cortisol decreased	4 (3.1)	4 (6.2)	8 (4.1)	1 (4.3)
Gastritis	6 (4.6)	1 (1.5)	7 (3.6)	0
Cough	5 (3.8)	2 (3.1)	7 (3.6)	1 (4.3)
Throat irritation	5 (3.8)	2 (3.1)	7 (3.6)	0
Hypersensitivity	3 (2.3)	4 (6.2)	7 (3.6)	0
Influenza	5 (3.8)	1 (1.5)	6 (3.1)	2 (8.7)
Abdominal pain	3 (2.3)	3 (4.6)	6 (3.1)	1 (4.3)
Headache	3 (2.3)	3 (4.6)	6 (3.1)	1 (4.3)
Fatigue	4 (3.1)	1 (1.5)	5 (2.6)	2 (8.7)
Acne	3 (2.3)	2 (3.1)	5 (2.6)	1 (4.3)
Gastroenteritis	3 (2.3)	2 (3.1)	5 (2.6)	2 (8.7)
Fracture	3 (2.3)	2 (3.1)	5 (2.6)	0

Preferred Term	BOS (Trial 301)- BOS (Trial 302)N=131	PBO (Trial 301)- BOS (Trial 302)N=65	Total Receiving BOS in Trial 302 ^[1] N=196	BOS (Trial 301)- PBO (Trial 302) N=23
	n (%)	n (%)	n (%)	n (%)
Oropharyngeal candidiasis	3 (2.3)	2 (3.1)	5 (2.6)	0
Transaminases increased	3 (2.3)	2 (3.1)	5 (2.6)	0
Mood swings	2 (1.5)	3 (4.6)	5 (2.6)	2 (8.7)
Urinary tract infection	1 (0.8)	4 (6.2)	5 (2.6)	0
Constipation	3 (2.3)	1 (1.5)	4 (2.0)	1 (4.3)
Dysphagia	3 (2.3)	1 (1.5)	4 (2.0)	2 (8.7)
Sleep disorder	3 (2.3)	1 (1.5)	4 (2.0)	1 (4.3)
Dyspepsia	3 (2.3)	1 (1.5)	4 (2.0)	0
Ear infection	3 (2.3)	1 (1.5)	4 (2.0)	0
Hypertension	3 (2.3)	1 (1.5)	4 (2.0)	0
Esophageal stenosis	3 (2.3)	1 (1.5)	4 (2.0)	0
Urine leukocyte esterase positive	3 (2.3)	1 (1.5)	4 (2.0)	0
Depression	2 (1.5)	2 (3.1)	4 (2.0)	1 (4.3)
Blood urine present	2 (1.5)	2 (3.1)	4 (2.0)	0
Contusion	2 (1.5)	2 (3.1)	4 (2.0)	0
Gastritis erosive	2 (1.5)	2 (3.1)	4 (2.0)	0
Hypercholesterolaemia	1 (0.8)	3 (4.6)	4 (2.0)	0
Protein urine present	1 (0.8)	3 (4.6)	4 (2.0)	0
Tooth infection	1 (0.8)	3 (4.6)	4 (2.0)	0
Weight increased	1 (0.8)	3 (4.6)	4 (2.0)	0

Source: adae.xpt; Software: Python

Total number of subjects who reported at least one TEAE

^[1] This includes both "BOS (Trial 301)-BOS (Trial 302)" and "PBO (Trial 301)-BOS (Trial 302)" subjects

See Section 17.1 for the Agency's PT recoding for Trial 301See Section 17.1 for the Agency's PT recoding for Trial 301

Abbreviations: BOS, budesonide oral suspension; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; PBO, placebo; TEAE, treatment-emergent adverse event

On review, the TEAEs observed to occur most commonly in subjects treated with BOS during Trial 302 included: upper respiratory tract infection, vomiting, nausea, nasopharyngitis, diarrhea, esophageal candidiasis, sinusitis, and blood cortisol decreased. TEAEs related to PTs of esophageal candidiasis, oropharyngeal candidiasis, gastritis, gastritis erosive, and throat irritation were considered likely related to the formulation and topical administration (oral suspension) of BOS. Analyses of TEAEs in the subgroup of adolescent subjects from the induction safety set were comparable with the results of the full subject population for Trials 301, 302, and the ISS.

7.6.1.6. Laboratory Findings, Trials 301 and 302

A notable imbalance was observed in the proportion of BOS subjects with abnormally low cortisol values following an ACTH stimulation test compared to placebo subjects in Trial 301 at Week 16 as shown in [Table 29](#).

Table 29. ACTH Stimulation Test Values, Safety Population, Trial 301

Variable	BOS 2 mg BID n (%)	Placebo n (%)	Risk Difference (95% CI)^[1]
Week 4 screening maximum cortisol post-dose ACTH			
n	211	100	NA
Subjects with abnormal peak cortisol levels ≤18 µg/dL	8 (3.8)	5 (5.0)	-1.2 (-6.2, 3.8)
Very low unstimulated AM cortisol <1 µg /dL (baseline)	0	1 (1.0)	-1 (-3, 1)
Week 16 maximum cortisol post-dose ACTH			
n	198	87	NA
Subjects with abnormal peak cortisol levels ≤18 µg /dL	18 (9.1)	3 (3.4)	5.7 (0.1, 11.2)
Very low unstimulated AM cortisol <1 µg /dL (baseline)	4 (2.0)	0	2 (0.1, 4)

Source: adlb.xpt; Software: R

^[1] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator

Abbreviations: ACTH, adrenocorticotrophic hormone; BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval

In Trial 302, an imbalance across treatment groups at Week 36 in the proportion of subjects with abnormally low cortisol values following an ACTH stimulation test was not observed as shown in [Table 30](#); however, the interpretability of this finding is limited as all subjects in Trial 302 received BOS during the conduct of Trials 301/302.

Table 30. ACTH Stimulation Test Values, Safety Population, Trial 302

Variable	BOS (Trial 301)- BOS (Trial 302)N=131 n (%)	PBO (Trial 301)- BOS (Trial 302)N=65 n (%)	Total Receiving BOS in Trial 302^[1] N=196 n (%)	BOS (Trial 301)- PBO (Trial 302) N=23 n (%)
301 baseline maximum cortisol post-dose ACTH				
n	130	62	192	22
Subjects with abnormal peak cortisol levels ≤18 µg /dL	4 (3.1)	4 (6.5)	8 (4.2)	1 (4.5)
Very low unstimulated AM cortisol <1 µg /dL (baseline)	0	1 (1.6)	1 (0.5)	0
302 screening maximum cortisol post-dose ACTH				
n	127	61	188	23
Subjects with abnormal peak cortisol levels ≤18 µg /dL	10 (7.9)	2 (3.3)	12 (6.4)	2 (8.7)
Very low unstimulated AM cortisol <1 µg /dL (baseline)	2 (1.6)	0	2 (1.0)	0
Week 36 maximum cortisol post-dose ACTH				
n	96	49	145	18
Subjects with abnormal peak cortisol levels ≤18 µg /dL	7 (7.3)	4 (8.2)	11 (7.6)	2 (11.1)
Very low unstimulated AM cortisol <1 µg /dL (baseline)	3 (3.1)	2 (4.1)	5 (3.4)	1 (5.6)

Source: adlb.xpt; Software: R

^[1] This includes both "BOS (Trial 301)-BOS (Trial 302)" and "PBO (Trial 301)-BOS (Trial 302)" subjects

Abbreviations: ACTH, adrenocorticotrophic hormone; BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; PBO, placebo

With the exception of ACTH stimulation test values, no clinically meaningful trends or changes were identified upon review of hematology and chemistry laboratory data or vital signs when comparing BOS- to placebo-treated subjects in Trials 301 and 302.

7.6.1.7. FDA Grouped Queries

In consideration of the known class effects of budesonide, the review team identified several potential signals for additional consideration. To further characterize these issues, the following group queries were conducted in addition to the evaluation of safety data using the individual preferred terms.

- Adrenal suppression (adrenal insufficiency, adrenal suppression, ACTH stimulation test abnormal, blood cortisol abnormal, blood cortisol decreased)
- Candidiasis (esophageal and oropharyngeal)
- Respiratory infection (upper respiratory tract infection, respiratory tract infection, sinusitis, nasopharyngitis, rhinitis)
- Mucosal irritation (erosive duodenitis, gastritis erosive, erosive esophagitis, gastrointestinal ulcer, esophageal ulcer, gastritis)

Upon review of the data from these queries, as shown in [Table 31](#), a significant risk of candidiasis with BOS versus placebo was observed in Trial 301. The data from these queries also show that the risk difference was greater for BOS than placebo subjects for respiratory infection and adrenal effects.

Table 31. FDA Grouped Queries by Preferred Term, Safety Population, Trial 301

Grouped Query Preferred Term	BOS 2 mg BID N=213 n (%)	Placebo N=105 n (%)	Risk Difference (95% CI) ^[1]
Candidiasis	16 (7.5)	2 (1.9)	5.6 (1.2, 10.0)
Oropharyngeal candidiasis	10 (4.7)	0	4.7 (1.9, 7.5)
Esophageal candidiasis	8 (3.8)	2 (1.9)	1.9 (-1.8, 5.6)
Nasopharyngitis, sinusitis, respiratory tract infection, upper respiratory tract infection, rhinitis	28 (13.1)	11 (10.5)	2.6 (-4.8, 10.0)
Sinusitis	10 (4.7)	3 (2.9)	1.8 (-2.5, 6.1)
Nasopharyngitis	11 (5.2)	4 (3.8)	1.4 (-3.3, 6.1)
Respiratory tract infection	2 (0.9)	0	0.9 (-0.4, 2.2)
Upper respiratory tract infection	5 (2.3)	3 (2.9)	-0.6 (-4.4, 3.2)
Rhinitis	0	1 (1.0)	-1.0 (-2.9, 0.9)
ACTH, cortisol abnormal/decreased	14 (6.6)	6 (5.7)	0.9 (-4.6, 6.4)
Adrenal suppression	3 (1.4)	0	1.4 (-0.2, 3.0)
ACTH stimulation test abnormal ^[2]	8 (3.8)	3 (2.9)	0.9 (-3.2, 5.0)
Adrenal insufficiency	2 (0.9)	0	0.9 (-0.4, 2.2)
Blood cortisol decreased	1 (0.5)	2 (1.9)	-1.4 (-4.2, 1.4)
Blood cortisol abnormal	0	2 (1.9)	-1.9 (-4.5, 0.7)
Erosions, ulcers, and gastritis	3 (1.4)	3 (2.9)	-1.5 (-5.1, 2.1)
Erosive duodenitis	1 (0.5)	0	0.5 (-0.4, 1.4)
Gastritis	2 (0.9)	1 (1.0)	-0.1 (-2.4, 2.2)
Gastrointestinal ulcer	0	2 (1.9)	-1.9 (-4.5, 0.7)

Source: adae.xpt; Software: Python

^[1] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.

^[2] Note that not all subjects with an abnormal ACTH stimulation test (see [Table 29](#)) were identified as an AE using a corresponding AE Preferred Term

See Section [17.1](#) for FDA PT recoding for Trial 301

Abbreviations: ACTH, adrenocorticotropic hormone; BOS, budesonide oral suspension; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event

As with Trial 301, higher rates of candidiasis, respiratory infection, and adrenal effects were also observed in subjects treated with BOS in Trial 302. Additionally, a higher proportion of subjects

treated with BOS in Trial 302 experienced gastrointestinal symptoms, as shown in [Table 32](#). These observed effects are expected given the established safety profile and associated adverse effects of corticosteroid products.

Table 32. FDA Grouped Queries by Preferred Term, Safety Population, Trial 302

Grouped Query Preferred Term	BOS (Trial 301)-BOS (Trial 302) N=131 n (%)	PBO (Trial 301)-BOS (Trial 302) N=65 n (%)	Total Receiving BOS in Trial 302^[1] N=196 n (%)	BOS (Trial 301)-PBO (Trial 302) N=23 n (%)
Candidiasis	7 (5.3)	6 (9.2)	13 (6.6)	0
Esophageal candidiasis	4 (3.1)	5 (7.7)	9 (4.6)	0
Oropharyngeal candidiasis	3 (2.3)	2 (3.1)	5 (2.6)	0
ACTH, cortisol abnormal/decreased	7 (5.3)	5 (7.7)	12 (6.1)	1 (4.3)
Blood cortisol decreased	4 (3.1)	4 (6.2)	8 (4.1)	1 (4.3)
Adrenal suppression	2 (1.5)	0	2 (1.0)	0
ACTH stimulation test abnormal	1 (0.8)	1 (1.5)	2 (1.0)	0
Erosions, ulcers, and gastritis	9 (6.9)	3 (4.6)	12 (6.1)	1 (4.3)
Gastritis	6 (4.6)	1 (1.5)	7 (3.6)	0
Gastritis erosive	2 (1.5)	2 (3.1)	4 (2.0)	0
Erosive esophagitis	2 (1.5)	1 (1.5)	3 (1.5)	0
Erosive duodenitis	1 (0.8)	0	1 (0.5)	0
Gastrointestinal ulcer	0	0	0	1 (4.3)
Nasopharyngitis, sinusitis, respiratory tract infection, upper respiratory tract infection, rhinitis	23 (17.6)	9 (13.8)	32 (16.3)	6 (26.1)
Upper respiratory tract infection	13 (9.9)	3 (4.6)	16 (8.2)	1 (4.3)
Nasopharyngitis	7 (5.3)	3 (4.6)	10 (5.1)	4 (17.4)
Sinusitis	5 (3.8)	3 (4.6)	8 (4.1)	2 (8.7)
Respiratory tract infection	0	1 (1.5)	1 (0.5)	0

Source: adae.xpt; Software: Python

See Section [17.1](#) for FDA PT recoding for Trial 302

^[1] This includes both "BOS (Trial 301)-BOS (Trial 302)" and "PBO (Trial 301)-BOS (Trial 302)" subjects

Abbreviations: ACTH, adrenocorticotrophic hormone; BOS, budesonide oral suspension; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; PBO, placebo

7.6.1.8. Evaluation for Drug-Induced Liver Injury

Upon review of the safety data for potential drug-induced liver injury, there were no Hy's law cases and no imbalances across treatment arms noted in phase 3 Trials 301 and 302 that would warrant further investigation. There were eight cases noted of either isolated elevated transaminases or bilirubin (two subjects treated with BOS and two subjects who received placebo in Trial 301, three subjects treated with BOS and one subject who received placebo in Trial 302); however, none of these elevations appeared to be prolonged and they all were noted to resolve without intervention or discontinuation of the investigational product. Additionally, an alternative potential etiology for elevated enzymes was provided by the Applicant for all subjects except one who was found to be overweight/obese with a BMI of 29.4.

7.6.2. Safety Findings and Concerns, Integrated Summary of Safety

7.6.2.1. Overall Adverse Event Summary, ISS

The ISS safety database (i.e., overall safety set) includes three groups of subjects for comparison: BOS 2 mg BID group, Any BOS Dose group, and Induction Placebo group. See Section 17.2 for details regarding which subjects were included in each comparator group.

Table 33 provides a summary of the TEAEs and SAEs that were reported in the ISS dataset. A greater proportion of subjects who received BOS 2 mg BID had moderate or severe TEAEs, SAEs, and TEAEs leading to discontinuation, dose modification, or interruption of the IP compared to placebo. The occurrence of these aforementioned TEAEs for the Any BOS Dose group of subjects was comparable with the rates seen in the BOS 2 mg BID group.

Table 33. Overview of Treatment-Emergent Adverse Events, Safety Population, ISS

	BOS 2 mg BID N=292	Any BOS Dose N=448	Induction PBO N=168
Event Category	n (%)	n (%)	n (%)
Any TEAE	224 (76.7)	337 (75.2)	98 (58.3)
Moderate or severe TEAEs	146 (50.0)	192 (42.9)	42 (25.0)
Any SAE	22 (7.5)	25 (5.6)	1 (0.6)
SAE with fatal outcome	1 (0.3)	1 (0.2)	0
TEAE leading to discontinuation of IP	19 (6.5)	19 (4.2)	5 (3.0)
TEAE leading to dose modification of IP	16 (5.5)	16 (3.6)	1 (0.6)
TEAE leading to interruption of IP	16 (5.5)	16 (3.6)	1 (0.6)

Source: adae.xpt; Software: Python

Grading Scale: The severity (intensity) of AEs was assessed as mild, moderate, and severe.

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; ISS, integrated summary of safety; N, number of subjects in treatment arm; n, number of subjects with at least one event; PBO, placebo; SAE, serious adverse event; TEAE, treatment-emergent adverse event

7.6.2.2. Deaths, ISS

There was one SAE of death reported in the open-label extension trial SHP621-303. A male, 18-year-old, white subject died by suicide (b) (6). The Applicant stated that “minimal details were available about the circumstances of the death other than those noted in the autopsy report. The autopsy report described a history of allergies, marijuana use, vaping, and alcohol use (with positive toxicology screen for all noted substances and a finding of hepatic steatosis).” The subject took his first dose of BOS (2 mg twice daily) almost two years before committing suicide. This case was reported to FDA as a suspected unexpected serious adverse reaction.

7.6.2.3. Serious Adverse Events, ISS

As shown in Table 34, SAEs were reported more frequently in the BOS 2 mg BID group compared to the Induction Placebo group. Of these events, herpes simplex (found to be herpes simplex esophagitis on further review as described above) was concerning for potential relation to BOS exposure. Additionally, hypersensitivity was only noted to occur in the BOS groups. The significance of this finding is uncertain as corticosteroid exposure would be anticipated to blunt rather than potentiate an allergic response. The remaining SAEs did not occur at a frequency that permitted the identification of trends between groups.

Table 34. Serious Adverse Events, Safety Population, ISS

Preferred Term	BOS 2 mg BID	Any BOS Dose	Induction PBO
	N=292 n (%)	N=448 n (%)	N=168 n (%)
Any SAE	22 (7.5)	25 (5.6)	1 (0.6)
Hypersensitivity ^[1]	4 (1.4)	4 (0.9)	0
Abortion spontaneous	2 (0.7)	2 (0.4)	0
Appendicitis	2 (0.7)	2 (0.4)	0
Completed suicide	1 (0.3)	1 (0.2)	0
Depression	1 (0.3)	1 (0.2)	0
Diet refusal	0	1 (0.2)	0
Drug hypersensitivity ^[2]	1 (0.3)	1 (0.2)	0
Food poisoning	0	1 (0.2)	0
Humerus Fracture	1 (0.3)	1 (0.2)	0
Gastroenteritis	1 (0.3)	1 (0.2)	0
Hand fracture	0	1 (0.2)	0
Head injury	1 (0.3)	1 (0.2)	0
Herpes simplex	1 (0.3)	1 (0.2)	0
Hypoxia	1 (0.3)	1 (0.2)	0
Localized intraabdominal fluid collection	1 (0.3)	1 (0.2)	0
Neck injury	1 (0.3)	1 (0.2)	0
Noncardiac chest pain	1 (0.3)	1 (0.2)	0
Obesity	1 (0.3)	1 (0.2)	0
Overdose	1 (0.3)	1 (0.2)	0
Petit mal epilepsy	1 (0.3)	1 (0.2)	0
Rhabdomyolysis	1 (0.3)	1 (0.2)	0
Road traffic accident	0	1 (0.2)	0
Sepsis	1 (0.3)	1 (0.2)	0
Spinal compression fracture	1 (0.3)	1 (0.2)	0
Ovarian cyst	0	0	1 (0.6)

Source: adae.xpt; Software: Python

^[1] One subject had anaphylactic shock due to cross-contamination of food, one subject had an anaphylactic reaction to cashews, one subject had anaphylaxis to wheat, and one subject had an anaphylactic reaction to nuts

^[2] One subject had anaphylaxis following administration of gadolinium contrast

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; ISS, integrated summary of safety; N, number of subjects in treatment arm; n, number of subjects with at least one event; PBO, placebo; SAE, serious adverse event

7.6.2.4. Treatment-Emergent Adverse Events, ISS

Across the ISS comparator groups of BOS 2 mg BID group and Induction Placebo group, the observed TEAEs were similar to those reported in Trials 301 and 302 (see Tables 33 and 34). An additional group of Any BOS Dose was identified in the ISS. Review of the safety findings from this group was consistent with the findings from the BOS 2 mg BID group.

In summary, no new safety signals or trends were revealed during the review of the ISS TEAE data, and the data were consistent with that reported from Trials 301 and 302.

7.6.2.5. Laboratory Findings, ISS

No clinically meaningful trends or changes were identified upon review of hematology and chemistry laboratory data or vital signs across the ISS comparator groups. Of note, as ACTH stimulation testing was not included as a standard assessment for all trials included in the ISS, it was not included as a reviewed variable during the ISS evaluation of laboratory findings.

7.7. Key Review Issues Relevant to Evaluation of Risk

7.7.1. HPA Axis Suppression

Issue

An imbalance was observed in the proportion of subjects treated with BOS with abnormally low cortisol values following an ACTH stimulation test compared to placebo in Trial 301 at Week 16.

Background

As hypothalamic-pituitary-adrenal (HPA) axis suppression is a known class effect of corticosteroid use, dedicated ACTH stimulation testing was conducted in Trials 301 and 302. The HPA axis suppression potential of BOS was also evaluated by measuring morning cortisol levels in phase 2 studies. As ACTH stimulation testing is a more reliable assessment of HPA axis suppression compared to the evaluation of morning cortisol levels, the review primarily focused on the results of ACTH stimulation test in Trials 301 and 302.

Assessment

ACTH stimulation testing was conducted at baseline and after respective treatment periods in individual phase 3 studies. Blood samples were collected just prior to and approximately 30- and 60-minutes following injection (intramuscular or intravenous) of synthetic ACTH (250 µg) to measure the stimulated level of cortisol. Adrenal suppression or abnormal ACTH stimulated serum cortisol levels were defined as peak ACTH stimulated serum cortisol of ≤ 18 µg/dL after synthetic ACTH injection.

In Trial 301, the BOS and placebo treatment arms had a similar proportion of subjects noted to have adrenal suppression at the baseline at Week 4 (3.8% versus 5.0%). After 12 weeks of treatment (at Week 16), a higher percentage of subjects who received BOS 2 mg BID had abnormal ACTH stimulated serum cortisol levels (9.1%) when compared to subjects in the placebo group (3.4%). See [Table 29](#).

In Trial 302, abnormal ACTH stimulated peak cortisol levels (≤ 18 µg/dL) were observed at Week 36 for 7.6% of subjects who received BOS (from 4.2% at Trial 301 baseline and 6.4% at Trial 302 screening), and 11.1% of subjects who received placebo (from 4.5% at Trial 301 baseline and 8.7% at Trial 302 screening). See [Table 30](#).

HPA Suppression Comparison Adolescent and Adult Subjects

As shown in [Table 35](#), upon comparative analysis of ACTH stimulation testing between adolescent and adult subjects, abnormal ACTH stimulated peak cortisol levels (≤ 18 µg/dL) were more common among pediatric subjects compared to adult subjects both at baseline (i.e., Week 4) and Week 16 (after 12 weeks of treatment). Both pediatric and adult subjects treated with BOS had a higher proportion of abnormal ACTH stimulated peak cortisol levels at the end of the treatment period (Week 16) than those receiving placebo. Additionally, the increase in percentage of subjects (comparing baseline to Week 16) who developed abnormal ACTH stimulation testing based on a peak value of ≤ 18 µg/dL was larger for pediatric than adult

subjects treated with BOS (8% versus 4.8%) or placebo (6.6% versus -3.2%). This suggests that pediatric patients are more likely to have abnormal ACTH stimulation testing than adults at baseline and may be more likely to develop abnormal ACTH stimulation testing after exposure to BOS; however, the interpretability of this finding is limited by the small number of adolescent subjects assessed.

Table 35. ACTH Stimulation Test Values by Age, Safety Population, Trial 301

Variable	BOS 2 mg BID n (%)		Placebo n (%)	
	<18 Years	≥18 Years	<18 Years	≥18 Years
Week 4 screening maximum cortisol postdose ACTH				
n	27	184	13	87
Subjects with abnormal peak cortisol levels ≤18 µg/dL	2 (7.4)	6 (3.3)	1 (7.7)	4 (4.6)
Very low unstimulated AM cortisol <1 µg/dL (baseline)	0	0	0	1 (1.1)
Week 16 maximum cortisol postdose ACTH				
n	26	172	14	73
Subjects with abnormal peak cortisol levels ≤18 µg/dL	4 (15.4)	14 (8.1)	2 (14.3)	1 (1.4)
Very low unstimulated AM cortisol <1 µg/dL (baseline)	1 (3.8)	3 (1.7)	0	0

Source: adlb.xpt; Software: R

Abbreviations: ACTH, adrenocorticotrophic hormone; AM, morning; BID, twice daily; BOS, budesonide oral suspension

[Table 36](#) displays the ACTH stimulation test results from Trial 302. No additional divergent findings were observed between pediatric and adult subjects upon evaluation of the ACTH stimulation testing results from Trial 302; however, the ability to identify associations between BOS exposure and ACTH stimulation testing results across treatment groups in Trial 302 is limited, as all subjects received BOS in either Trial 301 or Trial 302.

Table 36. ACTH Stimulation Test Values by Age, Safety Population, Trial 302

Variable	BOS (Trial 301)-BOS (Trial 302) N=131 n (%)		PBO (Trial 301)-BOS (Trial 302) N=65 n (%)		Total Receiving BOS in Trial 302 ^[1] N=196 n (%)		BOS (Trial 301)-PBO (Trial 302) N=23 n (%)	
	<18 Years	≥18 Years	<18 Years	≥18 Years	<18 Years	≥18 Years	<18 Years	≥18 Years
301 baseline maximum cortisol postdose ACTH								
n	16	114	10	52	26	166	3	19
Subjects with abnormal peak cortisol levels ≤18 µg/dL	1 (6.3)	3 (2.6)	1(10.0)	3 (5.8)	2 (7.7)	6 (3.6)	0	1 (5.3)
Very low unstimulated AM cortisol <1 µg/dL (baseline)	0	0	0	1 (1.9)	0	1 (0.6)	0	0
302 screening maximum cortisol postdose ACTH								
n	15	112	11	50	26	162	3	20
Subjects with abnormal peak cortisol levels ≤18 µg/dL	2 (13.3)	8 (7.1)	2 (18.2)	0	4 (15.4)	8 (4.9)	1 (33.3)	1 (5.0)
Very low unstimulated AM cortisol <1 µg/dL (baseline)	0	2 (1.8)	0	0	0	2 (1.2)	0	0
Week 36 maximum cortisol postdose ACTH								
n	13	83	10	39	23	122	2	16
Subjects with abnormal peak cortisol levels ≤18 µg/dL	1(7.7)	6(7.2)	1(10.0)	3(7.7)	2(8.7)	9(7.4)	1(50.0)	1(6.3)
Very low unstimulated AM cortisol <1 µg/dL (baseline)	0	3(3.6)	0	2(5.1)	0	5(4.1)	0	1(6.3)

Source: adlb.xpt; Software: R

^[1] This includes both "BOS (Trial 301)-BOS (Trial 302)" and "PBO (Trial 301)-BOS (Trial 302)" subjects

Abbreviations: ACTH, adrenocorticotrophic hormone; AM, morning; BOS, budesonide oral suspension

HPA Suppression Comparison with the Listed Drug, Entocort EC:

After 8 weeks of treatment with 9 mg Entocort EC (Elan Pharma International Limited 2016) once daily in pediatric subjects 8 to 17 years of age with mild to moderate active Crohn's disease, the proportion of subjects with abnormal ACTH stimulated peak cortisol level (≤ 18 µg/dL) was 75%, compared to 9.1% of subjects with EoE between 11 to 55 years of age after 12 weeks of treatment with BOS 2 mg BID in Trial 301. This may be due to lower systemic exposure of budesonide in the BOS formulation compared to Entocort EC. For details of this evaluation, please see the clinical pharmacology supplementary review finalized April 15, 2021 (DARRTS Reference ID: 4780092).

Conclusion

The percentage of subjects with abnormal ACTH stimulated serum cortisol was higher in the BOS group than in the placebo group after 12 weeks of treatment in Trial 301. A longer duration of treatment in Trial 302 did not appear to significantly increase the percentage of subjects with abnormal ACTH stimulated peak cortisol levels compared to Trial 301. In addition to having a greater risk of an abnormal ACTH stimulation response at baseline, adolescent subjects appeared to have a greater risk of developing an abnormal ACTH stimulation response compared to adults after exposure to BOS, although the interpretability of this finding is limited by the small number of adolescent subjects assessed. Adrenal suppression is a known corticosteroid class effect for this product and should be appropriately communicated to patients and providers.

7.7.2. Identified Risks Related to BOS Formulation and Administration

Issue

BOS is a corticosteroid product formulated for topical effect on the esophagus. Although the observed adverse event profile for BOS was largely consistent with the known class effects of corticosteroid products, additional adverse events emerged during the safety review as likely or potentially related to the formulation and topical administration of BOS.

Assessment

Upon review of the application's adverse event data; esophageal candidiasis, oropharyngeal candidiasis, gastritis, gastritis erosive, and throat irritation were seen at higher rates in subjects treated with BOS compared to those treated with placebo. Of these, the risk for the development of mucosal candidiasis emerged as a prominent safety signal. Additional consideration was given to the evaluation of a severe SAE of herpes simplex viral esophagitis, which was considered BOS-related.

Conclusion

Patients and prescribers should be informed of the risk for the adverse events potentially related to the topical administration and formulation of BOS. Although herpes esophagitis was only observed in a single subject, the severity and seriousness of the event are significant with regard to potential risks of BOS use. As such, this risk should be appropriately communicated to patients and providers.

7.7.3. Lack of Food Effect Study

Issue

The Applicant did not conduct a food effect study with either the phase 3 formulation or the TBM formulation of their proposed product. Therefore, the effect of food on the PK and safety of the Applicant's drug product to inform dosing instruction(s) in relation to meal intake is not defined in the application.

Background

The Applicant was informed during the May 20, 2020, pre-NDA meeting and in the filing comments that comparative systemic exposure of budesonide from the proposed product under the fed and fasted state should be assessed with the proposed product (with TBM formulation) to inform the appropriate dosing instruction in the label.

Assessment

In response to comments during pre-NDA meeting and the filing comments, the Applicant stated the reason for the absence of food effect study, claiming (b) (4)

(see Section 8.3).

The review team, while acknowledging Applicant's justification, determined the potential effect of food on budesonide exposure from BOS cannot be predicted based on available data/rationale, and a dedicated food effect study is needed. The proposed product is an oral suspension of corticosteroid budesonide, which is often used chronically, where adverse events including hypercortisolism and adrenal axis suppression, have been shown to be concentration dependent. Considering this, assessing any factor that could potentially increase budesonide exposure is critical.

In the phase 3 Trial 301, subjects were instructed to administer the morning dose after a meal and evening dose at bedtime, though the exact time interval between the meal and dose administration was not clear. Additionally, subjects were instructed not to ingest food or liquids for 30 minutes after the dose administration.

In the proposed label, the Applicant recommends not taking BOS with food or liquid and not eating or drinking for 30 minutes after taking BOS. The proposed label does not specify the timing of dosing in relation to meal (e.g., 30 min before meal) and potential impacts of meal timing or content (e.g., high-fat meal) on budesonide systemic exposure were not evaluated during the phase 3 trials.

Conclusion

Although not an approvability issue, it is imperative to assess the effect of food for the proposed oral suspension to provide appropriate information to patients and prescribers in regard to the timing of BOS administration relative to food intake.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Hepatic Impairment

A dedicated hepatic impairment study was not performed in this submission with the proposed product, BOS. Instead, the Applicant proposed to rely on the information from the listed drug, Entocort EC, label for Section 5 Warning and Precautions, and Section 12.3 Pharmacokinetics (Elan Pharma International Limited 2016).

For the listed drug, no dosage adjustment is recommended for mild hepatic impairment (Child-Pugh class A), a dose reduction to 3 mg from 9 mg is recommended for moderate hepatic impairment (Child-Pugh class B) based on a 3.5-fold higher area under the concentration-time curve (AUC) in subjects with moderate hepatic impairment than in subjects with normal liver function. The listed drug is not recommended in patients with severe hepatic impairment (Child-Pugh class C).

Similar to the listed drug label, the Applicant proposed avoiding use of their product in patients with severe hepatic impairment (Child-Pugh class C) and recommended no dosage adjustment in patients with mild hepatic impairment (Child-Pugh class A). (b) (4)

The Applicant's proposal is acceptable as the impact of hepatic impairment on the systemic exposure to budesonide is expected to be similar for both the proposed product and the LD and no PK or clinical data are available for patients with severe hepatic impairment. (b) (4)

Renal Impairment

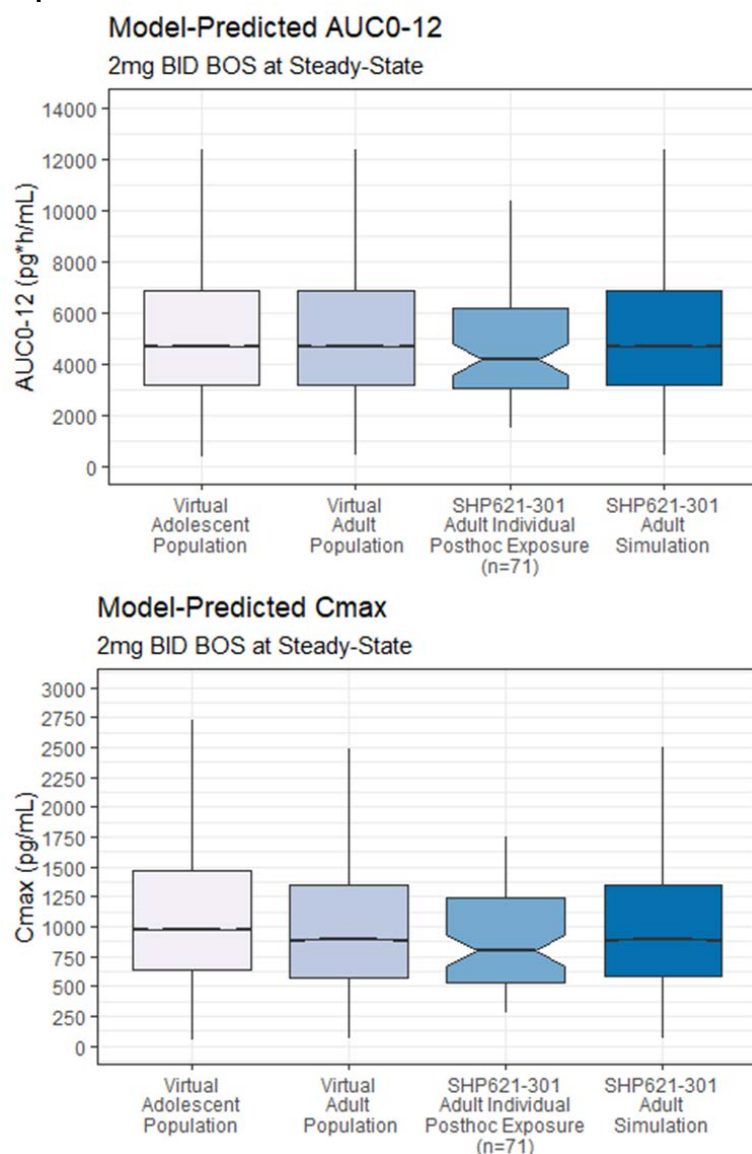
The Applicant did not conduct a dedicated renal impairment study with the proposed product, BOS. The proposed label did not include specific information for patients with renal impairment in Section 8 or in Section 12.3. The label of the listed drug, Entocort EC, also does not recommend dosage adjustment for these patients.

The effects of renal impairment on PK are unknown for the proposed product and the listed drug. Unchanged budesonide is not detectable in urine and is mainly excreted in urine as metabolites per the listed drug label. Given that systemic exposure to budesonide is estimated to be lower under the proposed dosage regimen (2 mg BID) compared to the listed drug at the recommended dose (Entocort EC 9 mg QD) based on the relative bioavailability study (SHP621-101), the potential risk for patients with renal impairment is not greater for the proposed product than the listed drug. Therefore, the absence of dosage adjustment for patients with renal impairment,

consistent with the listed drug label, is acceptable. See the April 15, 2021, clinical pharmacology supplementary review (DARRTS Reference ID: 4780092) for additional details.

Body Weight

According to population PK analysis, body weight had no impact on budesonide clearance, but had a significant effect on the central volume of distribution, where higher body weight was associated with higher individual estimated central volume of distribution. This resulted in similar steady-state AUC_{0-12} and 11.5% higher median C_{max} values predicted in adolescents compared to adults (median body weight 52.9 kg versus 83.9 kg) after 2 mg BID of the SB-10 (to-be-marketed) formulation ([Figure 11](#)). C_{max} was also predicted to be 46.4% higher in low weight adolescents (28 kg, C_{max} 1,252 pg/mL) compared to high weight adolescents (99.2 kg, C_{max} 855 pg/mL). Neither safety nor efficacy outcomes are expected to differ based on the predicted differences in C_{max} according to age group (adolescents versus adults) or weight in adolescents (low weight adolescents versus high weight adolescents). Per the Entocort EC label, budesonide systemic exposure (mean AUC) was 17% higher in pediatric subjects 9 to 14 years of age with Crohn's disease than in adult subjects.

Figure 11. Predicted Steady-State Exposure Following 2 mg BID in Adolescent and Adult Population

The SB-10 (to-be-marketed) formulation was used for simulation of exposure in virtual adults and virtual adolescents in order to compare exposure with the same formulation. The SB-10 formulation and the formulation used in Trial 301 had no significant differences in exposure.

Source: Reviewer's Analysis

Abbreviations: AUC, area under the curve; BID, twice daily; BOS, budesonide oral suspension; C_{max}, maximum plasma concentration

8.2. Drug Interactions

Effects of Other Drugs on Budesonide

Budesonide is a substrate for CYP3A4. Therefore, concomitant administration of budesonide with CYP3A4 inhibitors, including grapefruit juice, is not recommended based on the labeling of the listed drug, Entocort EC. Concomitant oral administration of a strong CYP3A4 inhibitor (ketoconazole) caused an 8-fold increase of the systemic exposure to oral budesonide. In addition, intake of grapefruit juice, which also inhibits CYP3A4 activity, increased the systemic

exposure of oral budesonide by 2-fold. Conversely, induction of CYP3A4 potentially could result in the lowering of budesonide plasma concentrations (Elan Pharma International Limited 2016).

Based on the Applicant's in vitro studies, budesonide is not a substrate of transporters, breast cancer resistance protein, OATP1B1, OATP1B3, OAT1, OAT3 and OCT2, but it is a substrate for P-glycoprotein (P-gp; see Section 14).

The Applicant did not conduct an in vivo drug-drug interaction study to evaluate the potential effects of concomitant P-gp inhibitor on the PK of budesonide. However, in a drug-drug interaction study with ketoconazole, an inhibitor of both P-gp and CYP3A4, ketoconazole increased the exposure of budesonide by 8-fold (Elan Pharma International Limited 2016). Based on these results, concomitant use of P-gp inhibitor should be avoided given the magnitude of the PK change by ketoconazole, while the relative contribution between P-gp inhibition and CYP3A4 inhibition cannot be quantitated.

Effects of Budesonide on Other Drugs

Based on the results of in vitro studies, budesonide is unlikely to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A or induce CYP1A2, CYP2B6 and CYP3A4, major CYP enzymes in humans. The geometric mean C_{max} of budesonide at the intended clinical dose (i.e., 2 mg BID) in subjects with EoE (~2.1nM, 914 pg/mL, obtained from phase 3 Trial 301) is substantially lower than the in vitro half maximal inhibitory concentration values for major CYP enzymes (>10μM).

Similarly, budesonide is unlikely to affect the pharmacokinetics of concomitant drugs via the inhibition of P-gp, breast cancer resistance protein, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2 based on in vitro studies (see Section 14.1).

8.3. Food Effect

The Applicant's proposed dosing instruction in the label is to not take the proposed product with food or liquid and to not eat or drink for 30 minutes after taking the proposed product. The proposal for not eating or drinking for 30 minutes is consistent with the dosing instruction for the phase 3 trial, and the rationale is to maximize the contact between the proposed product, a viscous suspension, and the esophagus.

The proposed label does not specify the timing of food in relation to drug administration (e.g., before or after). Food effect on the PK has not been studied. However, budesonide systemic exposure appeared to be similar (<15% difference) between Trial 301 (in subjects with EoE with the phase 3 formulation under the fed condition) and Study SHP621-101 (healthy subjects under fasting condition with both the phase 3 and TBM formulations, see Table 37. (b) (4)



Table 37. Summary of Systemic Budesonide Pharmacokinetic Exposure Following BOS Oral Administration

Study	SHP621-301	SHP621-101 ^[1]	SHP621-101 ^[1]
Formulation	Phase 3 (MB-9)	Phase 3 (MB-9)	TBM (SB-10) Formulation
BOS dose	2 mg BID	2 mg single dose	2 mg single dose
Population	Subjects with EoE	Healthy subjects	Healthy subjects
Fasting/fed conditions	Fed (morning dose after breakfast, likely fed)	Fasted	Fasted
Geometric mean (CV%): AUC _{0-T} or AUC _{0-inf} (ng·hr/mL)	5.07 (58.1%)	4.52 (54.2%)	4.99 (53.0%)
Geometric mean (CV%): C _{max} (ng/mL)	0.915 (59.2%)	1.063 (49.9%)	1.093 (55.7%)
Median (range): T _{max} (hr)	2 (0.5, 4)	1.5 (0.5, 2)	1.5 (0.75, 2)

Source: Table 10, Summary of Biopharmaceutics study, Module 5.3.5.1, Trial 301 CSR, Section 14; Table 14.2.3.3; Module 5.3.1.2, SHP621-101 CSR, Section 14, Table 14.2.3.1.2

^[1] A bridging study had established bioequivalence between the TBM formulation and phase 3 formulation (Study SHP621-101).

Abbreviations: AUC_{0-inf}, area under the concentration-time curve from the time of dosing to infinity based on extrapolation; AUC_{0-T}, area under the concentration-time curve from the time of dosing to the last measurable concentration; BID, twice daily; BOS, budesonide oral suspension; C_{max}, maximum observed concentration; CV, coefficient of variation; TBM, to-be-marketed; T_{max}, time of maximum concentration.

The Applicant's proposed dosing instruction in relation to food intake is acceptable. However, the food effect study should be conducted to inform the patients and prescribers on the appropriate timing of BOS administration relative to food intake.

8.4. Plans for Pediatric Drug Development

Although this development program received Orphan Designation in December 2006 and is therefore exempt from Pediatric Research Equity Act requirements, the application included an assessment and a request for indication for pediatric patients ages 11 years and older. As additional data are needed to support the efficacy of BOS in adults and adolescents, assessment of the adequacy of pediatric development plans for patients younger than 11 years of age will be deferred to the receipt of a subsequent submission to address the deficiencies noted during the review of this application.

8.5. Pregnancy and Lactation

The proposed draft labeling has been revised by the Division of Pediatric and Maternal Health to comply with the Pregnancy and Lactation Labeling Rule. Clinical pharmacology and the Division of Pediatric and Maternal Health will provide updated labeling for the lactation section in the next review cycle. Please see the March 17, 2021, Maternal Health Labeling Review by Jane Liedtka for the proposed draft lactation labeling and for additional details.

9. Product Quality

The Office of Pharmaceutical Quality (OPQ) review team has assessed NDA 213976 with respect to the chemistry, manufacturing, and controls (CMC) section of the NDA and has determined that it meets all of those applicable standards to support the identity, strength, quality, and purity that it purports and all drug substance. The product-related manufacturing, packaging, and testing facilities have acceptable CGMP status. An overall manufacturing

inspection recommending approval was issued on March 29, 2021. However, the labeling negotiation has not been completed in this review cycle. Therefore, from an OPQ perspective, this NDA is not deemed ready for approval in its present form. As such, OPQ recommends a complete response action from a product quality perspective until further review and agreement of the labeling has been completed when the NDA is resubmitted. Note that the following non-approvability comment from OPQ biopharmaceutics team should be included in the “ADDITIONAL COMMENTS” section of the Complete Response Letter:

In the current submission, you provided limited dissolution data with the proposed dissolution method collected at the time of batch release. If approval of your proposed product needs manufacturing of any new batch to fulfill the CR requirements, provide full-profile dissolution data (n=12) from that newly manufactured batch collected at the time of batch-release in the next submission. If no new batch manufacturing is required for approval of your product in terms of fulfilling the CR requirements, only upon approval of the proposed drug product, collect full-profile dissolution data (n=12) for the first six commercial batches at the time of batch-release and provide these data to FDA in your annual report.

For additional details on the product quality review, the reader is referred to the Integrated Quality Assessment (IQA) from OPQ dated April 6, 2021 in DARRTS.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure

Three clinical site inspections were conducted to support the review of this application. The conclusion is that the studies were conducted adequately, and the data generated are suitable to evaluate the proposed indication. Review of the financial disclosures did not raise any concerns about the validity or reliability of the data. Please see Section [20](#) for a summary of other inspection findings and Section [23](#) for financial disclosures.

11. Advisory Committee Summary

An Advisory Committee was not held during the review of this NDA; however, the application was presented at the March 10, 2021 and November 3, 2021 Medical Policy and Program Review Council meetings and a discussion of key review issues at each timepoint (i.e., lack of clinical meaningfulness of the $\geq 30\%$ DSQ responder threshold, lack of meaningful short-term efficacy on the key secondary endpoint of 14-day DSQ absolute change, and lack of demonstration of long-term efficacy as well as inadequacy of the submitted post hoc analyses to support a determination of efficacy) resulted in agreement that the submitted data do not support the short- or long-term efficacy of BOS for the treatment of EoE. The Council concurred with the review team that a complete response was the appropriate action for the application.

III. Appendices

12. Summary of Regulatory History

On December 20, 2006, Meritage Pharma, Inc. (hereafter, ‘Meritage’) obtained Orphan Drug Designation for the treatment of pediatric eosinophilic esophagitis (EoE). FDA received investigational new drug (IND) 103173 on August 5, 2008, for the evaluation of budesonide oral suspension (BOS; referred to as oral budesonide suspension [OBS] by Meritage) for the treatment of patients with EoE. The Sponsor for the new IND was Meritage, and the IND was subsequently activated on September 4, 2008. Meritage did not hold a pre-IND (PIND) meeting with the Agency. There were multiple follow-up type C meeting interactions between FDA and Meritage, which were used to discuss the Sponsor’s phase 2 studies (i.e., studies MPI 101-01 and MPI 101-06) along with their patient-reported outcome (PRO) instrument (i.e., the Dysphagia Symptom Questionnaire [DSQ]). During this time period, and specifically on June 29, 2011, Meritage broadened their Orphan Drug Designation to the treatment of EoE. The multiple meetings between FDA and Meritage culminated in a face-to-face (F2F) type B end-of-phase 2 meeting on November 12, 2014 (meeting minutes finalized on November 30, 2014), in which FDA provisionally agreed to the Sponsor’s proposed coprimary endpoint approach for their phase 3 program (i.e., separately evaluating histology through biopsy and symptomatology through the use of the DSQ).

On March 18, 2015, the IND was transferred to Shire Viropharma Inc. (hereafter ‘Shire’). Shire referred to the product as ‘SHP621,’ and they continued to engage the Agency with a follow-up type C meeting on July 13, 2015 (meeting minutes finalized on July 15, 2015), that was used to gain alignment on their phase 3 trials (i.e., induction trial SHP621-301 and maintenance trial SHP621-302) in EoE subjects 11 to 55 years of age. On May 31, 2016, BOS/SHP621 was granted Breakthrough Therapy Designation (BTD) for the treatment of patients with EoE, which was based on the histology and symptomatology data obtained from the noted phase 2 studies (i.e., MPI 101-01 and MPI 101-06). Under the BTD granted status, Shire engaged FDA on multiple occasions starting with the 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 pediatric] development, clinical pharmacology, biostatistics, clinical outcome assessment, patient-focused statistics, statistics, nonclinical, and product quality). A point of disagreement at the ‘Initial Comprehensive Multidisciplinary Breakthrough Therapy Type B Meeting’ was in regard to whether the results from the induction trial alone (i.e., Trial SHP621-301) would be sufficient to file an NDA. Shire and FDA agreed to discuss this issue at a future meeting. This future F2F meeting ultimately occurred on June 25, 2019 (meeting minutes finalized on June 27, 2019), in which FDA firmly stated that the induction data (from Trial SHP621-301) alone would not be sufficient to file an NDA and that longer-term maintenance data (specifically from Trial SHP621-302) would be needed to support chronic administration. The Agency’s position was based on FDA guidance for industry *Eosinophilic Esophagitis: Developing Drugs for Treatment* (September 2020), which was issued as a draft guidance earlier that calendar year on February 6, 2019. This FDA guidance was later finalized on September 16, 2020.

FDA, on multiple occasions, reiterated their concerns to the Sponsor regarding their proposed 30% DSQ responder threshold for the symptomatic coprimary endpoint for the phase 3 program under IND 103173. Specifically, the Agency emphasized that the Sponsor needed to confirm that their chosen percent responder threshold represented a clinically meaningful within-patient change using the phase 3 data. This was done via advice letters and formal emails sent to the Sponsor on September 15, 2015, February 15, 2018, September 17, 2018, and February 7, 2019. This was also communicated at the previously noted type C F2F meeting on July 13, 2015 and in minutes from the type B Pre-NDA meeting on May 20, 2020. (b) (4)

(b) (4)

On May 20, 2020, the Sponsor held a type B pre-NDA teleconference with FDA to discuss all elements of their program along with the overall clinical and regulatory filing plan in preparation for their 505(b)(2) NDA submission, which was planned during the latter half of calendar year 2020. The minutes for this meeting were finalized on June 2, 2020. The notable outcome from this meeting was that the Sponsor's maintenance trial, SHP621-302, did not show clinical benefit for EoE subjects treated with BOS with respect to histology and symptomatology. FDA communicated to the Sponsor that this would ultimately be an NDA review issue. FDA used the opportunity to again communicate to the Sponsor that they would need to establish a clinically meaningful within-patient change for the responder threshold that was prespecified for the symptomatic (using the DSQ) coprimary endpoint (specifically for the induction trial, SHP621-301). A separate Chemistry, Manufacturing, and Controls (CMC)-only type B pre-NDA teleconference was also held earlier with the Office of Pharmaceutical Quality on April 20, 2020 (meeting minutes finalized on May 21, 2020). A follow-up CMC-only type A teleconference was held on July 28, 2020 (meeting minutes finalized on July 30, 2020), in order to align on a contingency plan for the future NDA with respect to current Good Manufacturing Practice compliance issues associated with the future Applicant's planned commercial drug substance manufacturing site.

On August 20, 2020, the IND was transferred to Takeda Development Center Americas, Inc. (hereafter, 'Takeda'). Takeda subsequently recoded the drug name to 'TAK-721,' and they continued engaging the Agency under the product's BTG-granted status. FDA granted Takeda's rolling review request for their NDA on August 28, 2020. The Applicant for the NDA was specifically Takeda Pharmaceuticals USA, Inc., which is a wholly owned subsidiary of Takeda Development Center Americas, Inc. On August 31, 2020, Takeda submitted the first agreed upon piece of the NDA, which covered electronic common technical document (eCTD) module 4 and associated nonclinical module 2 elements along with all pertinent regulatory information included in module 1. On September 29, 2020, Takeda submitted the second agreed upon piece of the NDA, which covered eCTD module 5 and associated clinical/translational module 2 elements along with all supporting information (e.g., meeting minutes/advice under reference IND 103173, etc.) and product labeling included in module 1. The Applicant's proposed indication was 'for the treatment of eosinophilic esophagitis (EoE), (b) (4) (b) (4) in adult and adolescent patients 11 years and older.'

On October 15, 2020, Takeda submitted the third and final agreed upon piece of the NDA, which covered eCTD module 3 and associated CMC module 2 elements along with all CMC supporting information included in module 1. The NDA, submitted pursuant to section 505(b)(2) of the

Federal Food, Drug, and Cosmetic Act, was officially filed on December 14, 2020, under a priority review. The Applicant's proposed proprietary name of "Eohilia" was also deemed conditionally acceptable shortly before filing on November 25, 2020, which was consistent with the conditional acceptability of the same name that was previously proposed under the reference IND (deemed conditionally acceptable under the IND on December 10, 2019, after the initially proposed (b) (4) was deemed unacceptable under the IND on August 6, 2019).

For a description of additional regulatory interactions with the Applicant during the review of the NDA, see Section [1](#).

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under the IND

No nonclinical toxicology studies were submitted in the IND (103173). Only references to nonclinical safety assessment from approved budesonide products were submitted to the IND.

13.2. Individual Reviews of Studies Submitted to the NDA

Please see the nonclinical supplementary review that was signed into DARRTS on March 18, 2021 (Reference ID: 4764652).

14. Clinical Pharmacology: Additional Information and Assessment

14.1. In Vitro Studies

Please see the clinical pharmacology supplementary review that was signed into DARRTS on April 15, 2021 (Reference ID: 4780092).

14.2. In Vivo Studies

Please see the clinical pharmacology supplementary review that was signed into DARRTS on April 15, 2021 (Reference ID: 4780092).

Summary of Assessment

Phase 1 study SHP621-101: Relative bioavailability and bioequivalence study in healthy volunteers.

The Applicant conducted this in vivo bridging to compare systemic budesonide exposure between a single dose of the proposed product, BOS 2 mg, with a single dose of the listed drug, Entocort EC 9 mg. The geometric mean AUC_{0-t}, AUC_{0-inf}, and C_{max} of budesonide for BOS were

33.6%, 33.5%, and 71.1% of those for Entocort EC 9 mg, respectively, and do not meet the bioequivalence criteria. Under the proposed dosing regimen (i.e., 2 mg BID) the daily AUC and C_{max} of budesonide from BOS at steady state is estimated to be 70% and 71%, respectively, of that from Entocort EC 9 mg QD, the highest approved dose for Crohn's disease. The estimated lower systemic exposure at steady state justifies the reliance on the previous findings of nonclinical safety and clinical pharmacology information for the listed drug. The Applicant conducted their own efficacy and safety trial for the proposed new indication in the EOE patient population as discussed in Sections 6 and 7.

Relative bioavailability (Study SHP621-101) was also compared in this study between the clinical formulation (MB-9, A) used in the phase 3 study and the to-be-marketed formulation (MB-9 with (b) (4) D) (Table 38).

Table 38. Comparison of Relative Bioavailability and Bioequivalence Analysis Between the To-Be-Marketed Formulation and the Clinical Formulation Used in the Phase 3 Trial

Parameter (units)	Treatment Comparison	Ratio of Geometric LS Means		Ratio 90% CI	
		Applicant Calculated	Reviewer Calculated	Applicant Calculated	Reviewer Calculated
C_{max} (pg/mL)	D/A	1.050	1.028	94.2 to 116.9	92.22 to 114.50
AUC _{0-t} (hr·pg/mL)	D/A	1.044	1.050	93.9 to 116.1	94.24 to 116.95
AUC _∞ (hr·pg/mL)	D/A	1.028	1.038	92.2 to 114.5	92.52 to 116.52

Source: Reviewer's analysis and Module 5.3.1.2, SHP621-101 Amendment 1- Report Body, Table 13, Page 60.

A: A single oral dose of BOS MB-9 formulation 2 mg: 0.2 mg/mL in volumes of 10 mL (2 mg budesonide) (phase 3 formulation).

D: A single oral dose of BOS MB-9 formulation with (b) (4) variant 2 mg: 0.2 mg/mL in volumes of 10 mL (2 mg budesonide) (To-be-marketed formulation).

Abbreviations: AUC, area under the curve; BOS, budesonide oral suspension; CI, confidence interval; C_{max} , maximum plasma concentration; D/A, to-be-marketed formulation; LS, least squares

The above analysis demonstrated that the systemic exposure of budesonide after a single dose of the phase 3 formulation was equivalent to that of the TBM formulation (D/A).

14.3. Pharmacometrics

Please see the clinical pharmacology supplementary review that was signed into DARRTS on April 15, 2021 (Reference ID: 4780092).

Summary of Assessment

A population PK model was developed to characterize the PK of budesonide in adults and adolescents (11 to <18 years old) using data from the Study SHP621-101, MPI 101-01, and SHP621-301. The Applicant's population PK model adequately characterized PK in adults and adolescents.

Population PK analysis found that the MB-7 formulation was associated with slightly decreased relative bioavailability and slightly shorter absorption lag time. Population PK analysis also found that higher body weight resulted in higher individual estimated apparent central volume of distribution and thus slightly lower C_{max} compared to low body weight. This difference in predicted C_{max} is not expected to be clinically significant for adults and adolescents. Additionally, the population PK model found no significant effects of age (either continuous or categorical) on the PK of budesonide.

There were no clinically significant differences in model-predicted steady-state exposure parameters (AUC_{0-12} , C_{max} , and C_{min}) between a virtual adult population and a virtual adolescent population after twice daily (BID) administration of the 2 mg BOS SB-10 (to-be-marketed) formulation.

15. Trial Design: Additional Information and Assessment

Not applicable.

16. Efficacy: Additional Information and Assessment

16.1. The Dysphagia Symptom Questionnaire

The DSQ version 5 is a well-defined and reliable PRO instrument for measuring dysphagia in adult and adolescent patients with EoE, based on evidence of content validity from participant interviews and evidence of measurement properties using data from Trial 301. Refer to the supplementary review finalized in DARRTS by the Division of Clinical Outcome Assessment (DCOA) on March 29, 2021 (Reference ID: 4768072), for more information.

The DSQ version 5 consists of four questions assessing avoidance of solid food, symptoms of dysphagia, and painful swallowing, as shown in [Table 39](#).

Table 39. DSQ Items, Response Options, and Item Scoring

DSQ Questions (Version 5)	Response Options	Scoring
1. Since you woke up this morning, did you eat solid food?	Yes	Patient continues Not scored
	No	Patient stops Questions 2 through 4 are set to missing
2. Since you woke up this morning, has food gone down slowly or been stuck in your throat or chest?	Yes	2 points
	No	0 points
3. For the most difficult time you had while swallowing food today, 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	0 points
	Yes, I had to drink liquid to get relief	1 point
	Yes, I had to cough and/or gag to get relief	2 points
	Yes, I had to vomit to get relief	3 points
	Yes, I had to seek medical attention to get relief	4 points

DSQ Questions (Version 5)	Response Options	Scoring
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 today?	None, I had no pain	0 points
	Mild	1 point
	Moderate	2 points
	Severe	3 points
	Very severe	4 points

Source: DSQ version 5 evidence dossier dated September 14, 2020, Table 2
Abbreviations: DSQ, Dysphagia Symptom Questionnaire

The DSQ scoring method used to support the coprimary endpoint (the “combined score”) is defined as the sum of scores of questions 2 and 3 prorated for a 14-day period:

$$\text{DSQ combined score} = ((\text{Sum of daily DSQ question 2 and question 3 responses}) \times 14 \text{ days}) / (\text{Number of daily diaries with nonmissing data in the selected 14-day period})$$

The possible range of daily scores for question 2 + question 3 is 0 to 6. Therefore, over a 14-day period, the range of possible DSQ combined scores is 0 to 84.

16.2. Supplementary Statistical Methods

This section summarizes additional statistical analyses methods for Trial 301 coprimary efficacy endpoints and key secondary endpoint after 12 weeks of double-blind treatment. Coprimary endpoints included histologic response and dysphagia symptom response, histology response was defined as a peak eosinophil count of ≤ 6 per high-power field across all available esophageal levels, and dysphagia symptom response was defined as $\geq 30\%$ reduction in the DSQ combined score from baseline. Key secondary endpoint was defined as change in DSQ combined score (questions 2+3) from baseline to the completion of 12-week treatment.

These methods also were applied to the related key secondary endpoints in Trial 302.

16.2.1. Methods to Handle Missing Data

16.2.1.1. Missing Data Approach for Derivation of DSQ Score

The Applicant applied the following methods to handle missing data when deriving the DSQ daily diary score in addition to the summary of the statistical analysis plan (SAP) in Section [6.2](#).

- Subjects who were missing 4 days or more of DSQ daily diary data in either week or 7 days in the last 2 weeks at a postbaseline visit, the dysphagia symptom response were treated as nonresponders without applying the window shift rule.
- An alternative window shift rule was applied for postbaseline data (14-day periods cannot be shifted for more than 7 days at every visit).
- Worst case imputation for DSQ combined score when the answer to Question 1 was “No” using the worst (maximum) value from nonmissing days during that 14-day period.
- Best case imputation for DSQ combined score when the answer to Question 1 was “No” using the best (minimum) value from nonmissing days during that 14-day period.

16.2.1.2. Missing Data Approach for Coprimary Endpoints and Key Secondary Endpoint

Coprimary Endpoints (Binary)

If at least 5% of subjects or more had missing responses for either of the coprimary efficacy endpoints in either treatment group, the missing responses for coprimary efficacy endpoints were imputed using the following methods:

- Distribution-based imputation: The subjects with missing responses of coprimary efficacy endpoints were assigned randomly according to the distribution of responders with available data for each of the coprimary endpoints (i.e., those with nonmissing data) across the 2 treatment groups by age and diet restriction strata.
- Cochran-Mantel-Haenszel (CMH) test with multiple imputations by using SAS procedures PROC MI and PROC MIANALYZE: Missing responder status values were imputed by the logistic regression model with variables treatment group, age group, and diet restriction. Repeated the process K (K=50) times, using the procedure described above to form K completed datasets.

Key Secondary Endpoint (Continuous)

The SAP stated that if at least 10% subjects or more were missing DSQ combined score after 12-week treatment in either treatment arm, the pattern-mixture model was used to summarize the effect of missing patterns on treatment effect (i.e., missing due to no solid food taken or reasons to drop out early). The clinical study report (CSR) reported that the pattern-mixture model used a control-based pattern imputation method, missing data due to drop out in the BOS arm were imputed assuming missing not at random while intermittent missing data in the BOS arm and all missing data in the placebo group were imputed assuming missing at random.

16.2.2. Sensitivity Analyses

16.2.2.1. Coprimary Endpoints

For each coprimary endpoint, the sensitivity analyses included a logistic regression with treatment, age and diet restriction group factors in the full analysis set (FAS) using the nonresponder imputation (NRI) data; a repeated primary CMH test in the per-protocol set (excluding all subjects with major protocol deviations) based on NRI data; and repeated primary CMH tests in the FAS using various missing data approaches (a responder imputation, a distribution based multiple imputation and a multiple imputation). For the DSQ based coprimary endpoint, additional sensitivity analyses repeated the primary CMH test in the FAS using four different missing data imputation approaches mentioned in Section [16.2.1.1](#).

16.2.2.2. Key Secondary Efficacy Endpoint

The SAP prespecified the following sensitivity analyses for key secondary endpoint.

- Analysis of covariance (ANCOVA) model of the primary analysis on absolute change of DSQ combined scores was repeated in FAS using four missing data handling methods described in the beginning of this Section. If a subject's DSQ combined score after 12-week treatment was incalculable after missing data handling method 1 or method 2, the value for this subject was considered as missing and excluded from the ANCOVA analyses.

- ANCOVA model used data imputed by the pattern mixture model with at least 10% missing DSQ combined score.

The review Division requested additional sensitivity analyses to evaluate the EoE guidance recommended change from baseline in DSQ combined score after 12-week treatment (key secondary endpoint).

16.2.3. Efficacy Results

16.2.3.1. Short-Term Efficacy, Trial 301

This section reports additional details pertaining to the efficacy results after 12 weeks of double-blinded treatment with BOS and placebo. Subject demographics, baseline characteristics and disposition, and primary and key secondary efficacy results are in Section [6.2](#).

Treatment Compliance

The SAP defined treatment compliance as a compliance rate of 70% to 130% inclusive. The trial observed the treatment compliance during the double-blinded treatment period ranged from 11% to 210% with a mean rate of 87% (median: 88%). The CSR reported that 11% of subjects had major deviations related to overall noncompliance with study medication.

The review team considered a common treatment compliance within the range of 80% to 120% used for other indications. [Table 40](#) summarized the compliance rate by groups and found 28% of FAS subjects had a compliance rate less than 80%. Subgroup analyses based on treatment compliance did not indicate any differences in treatment response by compliance (see [Figure 12](#) and [Figure 13](#)).

Table 40. Summary of Subject Medication Compliance, FAS, Trial 301

Medication Compliance Rate Groups, n	Placebo N=104	BOS 2.0 mg BID N=213	Total N=317
<80%	26	64	90
80% to 120%	76	147	223
>120%	2	2	4

Source: Reviewer's analysis

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; FAS, full analysis set; N, number of subjects in treatment group; n, number of subjects with indicated compliance

Primary and Key Secondary Efficacy Results

The results presented are based on the Applicant's derived datasets that were submitted to the NDA. The primary and key secondary DSQ based endpoints results used the window shift rule based on the derived DSQ score unless otherwise noted. The histologic response results used derived value at an esophageal level in lieu of source data from a biopsy level.

Data quality issues prevented confirmation of these results from the source or subject-level datasets (see Section [16.2.4](#) for details).

Additionally, there were several limitations identified that could impact the derivation of DSQ combined score and thus, the interpretability of the results. These included

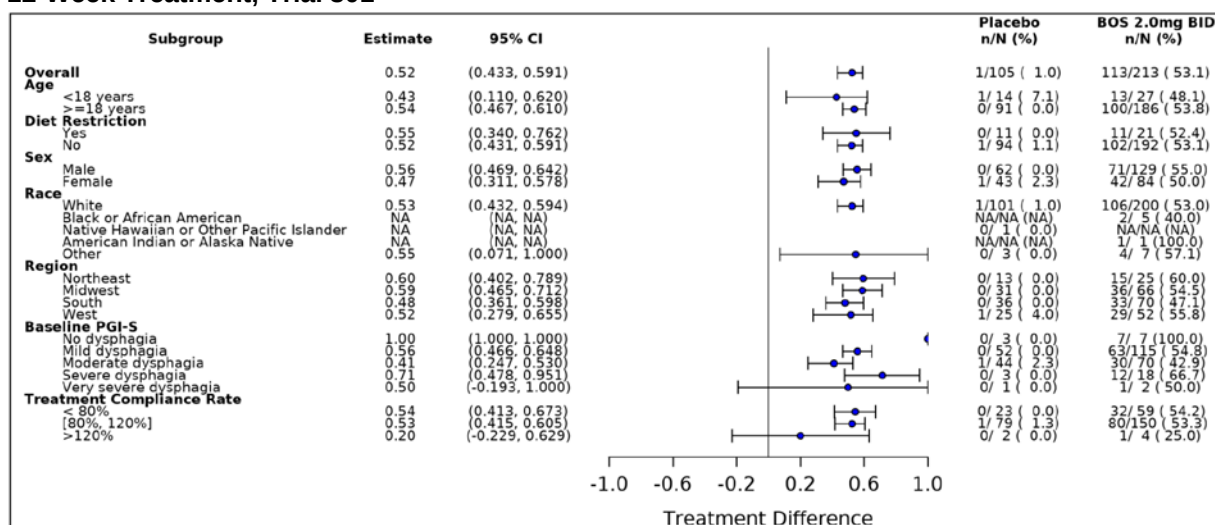
- The window shift rule to cope with missing DSQ daily diary data was inappropriate and could allow for searching at least eight diary records in a 14-day window. When applied, this could result in a 28-day range prior to the Week 16 visit.

- The missing daily dairy rule to treat a day the subject answered “No” to DSQ question 1 as missing was not well justified. The trial did not collect information on the reason a subject did not take solid food for a given day (i.e., answered “No” to DSQ question 1). Approximately 10% of subjects in each treatment group answered “No” to DSQ question 1 for at least one day during a 14-day period at baseline or Week 16.
- The SAP defined the DSQ combined score as “missing” where there were fewer than eight daily diary records in a 14-day window. Not specifying a minimum number of records per week allowed unbalanced reporting across the 2-week assessment period (e.g., entries with 7 reporting days in one week and only 1 reporting day in another week were considered acceptable).

Subgroup and Sensitivity Analyses

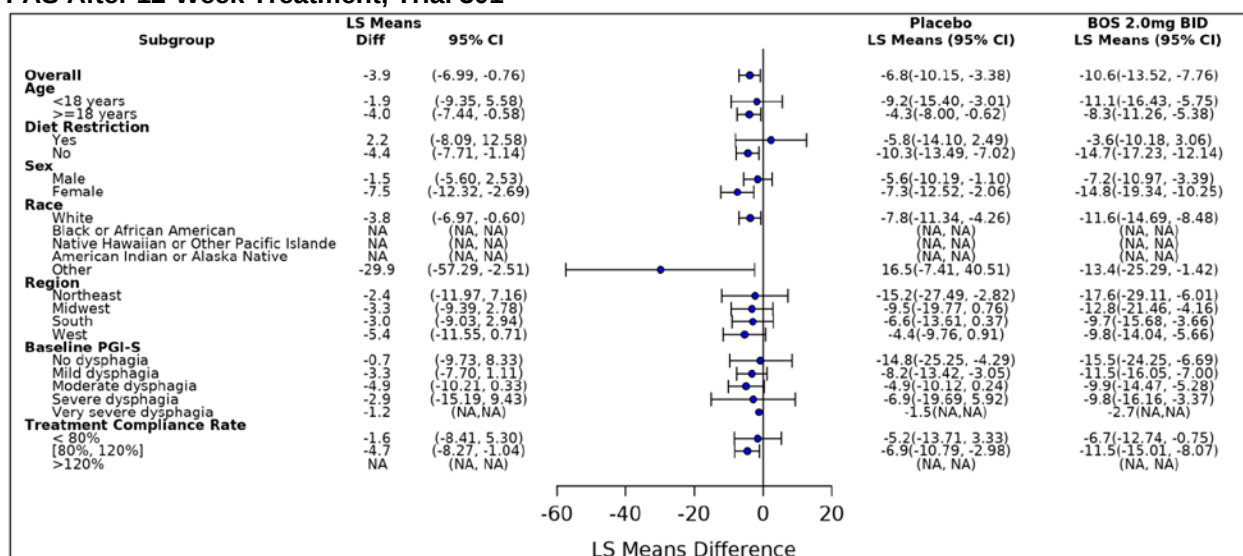
Subgroup analyses by diet restriction, age, sex, and race were performed for both coprimary endpoints to assess the consistency of the results observed from the primary efficacy analyses. The review team also requested subgroup analyses for geographic region, baseline Patient Global Impression of Severity (PGIS), and treatment compliance rate group for the primary efficacy analyses and key secondary endpoint. Majority of these analyses were consistent with the primary results and supported statistically significant differences (Figures 12, 13, and 14).

Figure 12. Forest Plot of Treatment Difference in Subgroups for Histology Response in FAS After 12-Week Treatment, Trial 301



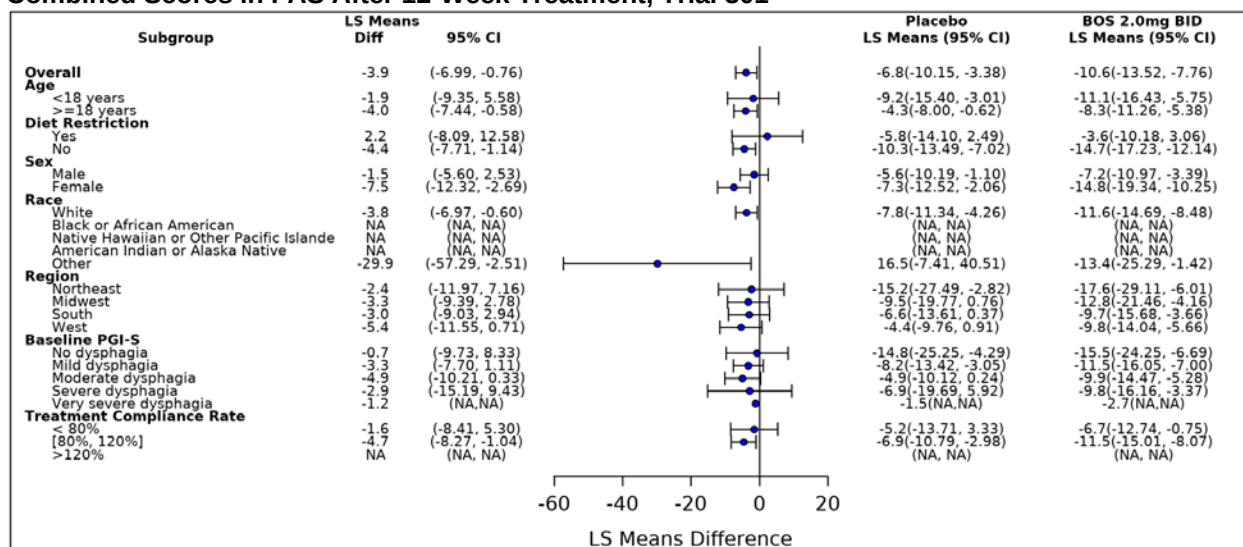
Source: The Applicant's Information Request response submitted on Feb. 9, 2021.

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; FAS, full analysis set; NA, not applicable

Figure 13. Forest Plot of Treatment Difference in Subgroups for Dysphagia Symptom Response in FAS After 12-Week Treatment, Trial 301

Source: The Applicant's Information Request response submitted on Feb. 9, 2021

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; FAS, full analysis set; LS, least squares; NA, not applicable

Figure 14. Forest Plot of Treatment Difference in Subgroups for Absolute Change in DSQ Combined Scores in FAS After 12-Week Treatment, Trial 301

Source: The Applicant's Information Request response submitted on Feb. 9, 2021

Note that the DSQ scores derivation used the window shift rule

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; DSQ, Dysphagia Symptom Questionnaire; FAS, full analysis set; LS, least squares; NA, not applicable

Sensitivity analyses were performed for the coprimary endpoints and key secondary endpoint to evaluate the robustness of the primary efficacy results. These analyses results were consistent with the primary findings of statistically significant treatment differences between treatment arms except for one of the dysphagia symptom responder results using the best-case imputation data. See Trial 301 CSR for details on the Applicant's sensitivity analyses results on coprimary endpoints.

This subsection reports additional FDA requested sensitivity analyses and exploratory analyses on coprimary and key secondary endpoint. The team also requested descriptive analyses and graphic presentation of the data to assist clinical meaningfulness of the statistically significant findings.

Coprimary Endpoints

Histologic Response

To examine for any potential differences in response due to esophageal level, proximal, central, and distal, an exploratory analysis was conducted using the response at each esophageal level. As shown in [Table 41](#), the response for subjects treated with BOS was statistically significantly greater than the response for placebo subjects regardless of esophagus level. Note this analysis used derived data not subject-level data.

Table 41. Supportive Analyses on Histology Endpoint Based on Each Esophageal Level Data in the FAS After 12-Week Treatment, Trial 301

Histological Response	Placebo N=105 n (%)	BOS 2.0 mg BID N=213 n (%)	Treatment Difference (95% CI)	p-Value
Coprimary endpoint: maximum across three esophageal levels	1 (1%)	113 (53%)	52% (43%, 59%)	<0.001
Central esophagus	10 (10%)	137 (64%)	55% (46%, 63%)	
Distal esophagus	3 (3%)	123 (58%)	55% (47%, 62%)	
Proximal esophagus	24 (23%)	168 (79%)	56% (46%, 66%)	

Source: Statistical reviewer's analysis

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; FAS, full analysis set

DSQ – 30% Responder

The sensitivity analyses of the dysphagia symptom response (30% cutoff) were generally consistent with the statistically significant primary result. The only exception was the sensitivity analysis using a responder imputation with a p-value of 0.35; this may be due to a higher amount of missing data in the placebo group (15.2%) relative to 7.5% in the BOS group. Section 11.1.1.1 of the CSR reported the sensitivity analyses in detail.

Key Secondary Endpoint

DSQ – Absolute Change From Baseline

For the DSQ instrument, there was a concern on the impact of considering a day as missing when a subject answered no to question 1. Therefore, an Information Request (IR) was sent to the Applicant to evaluate this concern. As reported by the Applicant ([Table 42](#)) there were about 10% of subjects who had at least one day answered as “No” to question one. Since the Applicant did not ask the subjects why they answered no to question one, a sensitivity analysis was conducted where these days were considered as having dysphagia (worst case imputations reported in [Table 43](#)). Results are shown in [Table 42](#). The review team requested corresponding sensitivity analyses using the worst-case imputation approach that did not affect the efficacy outcome. Results are shown in [Table 43](#).

Table 42. Distribution of Subjects Answered “No” to DSQ Question 1 for at Least One Day During the 14-Day Period by Visit in FAS, Trial 301

Visit	Placebo n/N (%)	BOS 2.0 mg BID n/N (%)	Treatment Difference in Percentages (95% CI)
Baseline	13/105 (12.4)	20/212 (9.4)	-2.9 (-10.37, 4.48)
Week 8	8/101 (7.9)	21/207 (10.1)	2.2 (-4.46, 8.91)
Week 12	7/94 (7.4)	17/195 (8.7)	1.3 (-5.35, 7.89)
Week 16	8/90 (8.9)	19/198 (9.6)	0.7 (-6.46, 7.88)

Source: The Applicant's Information Request response submitted on Jan. 14, 2021. The 95% CI is calculated based on normal approximation.

If fewer than 8 available diaries within the 14-day period, the most recent 8 reported diaries in a consecutive 14-day period were used. Such 14-day periods could be shifted for no more than 14 days prior to the visit 4 (week 16), and no more than 7 for other scheduled visits.

The 95% CI is calculated based on normal approximation.

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; DSQ, Dysphagia Symptom Questionnaire; N, number of evaluable subjects at each visit; n, number of subjects indicating “no”

Several sensitivity analyses were conducted to evaluate the impact of missing data on the analyses. Most of the sensitivity analyses (18 out of 21) resulted in a statistically significant treatment difference. Results are shown in [Table 43](#).

Table 43. Sensitivity Analyses of Change From Baseline on DSQ Combined Score in FAS After 12-Week Treatment, Trial 301

Impact of Missing Data on Absolute Change in DSQ Combined Score	Missing Data Approaches			
	Pattern Mixture Model		Observed Case Only	
	Treatment Difference (95%CI)	p-Value	Treatment Difference (95%CI)	p-Value
With the window shift rule:				
ANCOVA model with factors treatment and age (SAP prespecified)				
Primary analysis (Rule ii ^[2])	-3.3 (-6.7, 0.1)	0.054 ^[4]	-4.4 (-7.9, -1.0)	0.012
Impute "No" to Question 1 (No solid food) with worst value within 14 days			-4.4 (-8.0, -0.9)	0.014
Without the window shift rule:				
ANCOVA model with factors treatment and age (IR response)				
Rule i ^[1]	-3.5 (-7.0, -0.01)	0.049	-4.2 (-7.6, -0.8)	0.015
Rule ii ^[2]	-3.3 (-6.7, 0.1)	0.054 ^[5]	-4.4 (-7.9, -1.0)	0.012
Worst case + Rule i ^[3]	-3.7 (-7.3, -0.2)	0.039	-4.4 (-8.0, -1.0)	0.014
Worst case + Rule ii ^[4]	-3.7 (-7.2, -0.1)	0.044	-4.7 (-8.2, -1.2)	0.009
ANCOVA model with factors treatment, age, and diet restriction (IR response)				
Rule i	-3.6 (-6.9, -0.2)	0.040	-4.4 (-7.7, -1.0)	0.011
Rule ii	-3.3 (-6.7, 0.1)	0.05 ^[5]	-4.5 (-7.9, -1.1)	0.009
Worst case + Rule i	-3.79 (-7.3, -0.3)	0.035	-4.6 (-8.1, -1.2)	0.009
Worst case + Rule ii	-3.79 (-7.3, -0.3)	0.033	-4.9 (-8.3, -1.4)	0.006

Source: Statistical Reviewer's Adaptation of Trial 301 CSR tables and the Applicant's Information Request response tables submitted on Feb. 9, 2021

^[1] Rule i: Subjects who were missing ≥4 days of DSQ daily diary in either week or ≥7 days in the last 2 weeks at a postbaseline visit, were treated as missing.

^[2] Rule ii: Subjects who are missing ≥6 days of DSQ daily diary during the 14-day period prior to a postbaseline visit, were treated as missing.

^[3] Worst Case Imputation + Rule i: Rule i and worst-case imputation that defined as when the subject answered "No" to Question 1, the daily DSQ combined score value was imputed as 6.

^[4] Worst Case Imputation + Rule ii: Rule ii and worst-case imputation that defined as when the subject answered "No" to Question 1, the daily DSQ combined score value was imputed as 6.

^[5] These results were not statistically significant.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; DSQ, Dysphagia Symptom Questionnaire; FAS, full analysis set; IR, Information Request; SAP, statistical analysis plan

To understand the relationship between clinical meaningfulness and statistical significance on the key secondary endpoint, the team requested an exploratory descriptive analysis on mean number of dysphagia days during a 14-day period (window shift rule applied). Results are shown in [Table 44](#). After a 12-week treatment, the BOS group had an additional 0.7 days of reduction (95% CI: -2, 0.4) on average dysphagia days in a 14-day period than that in the placebo group. In contrast, the treatment difference on absolute change in DSQ combined score (shown in [Table 11](#)) was -4 using the FDA preferred analysis method.

Table 44. Summary of Number of Days Subjects Experienced Dysphagia by Visit, Trial 301

Number of Dysphagia Days in a 14-Day Period	Placebo (N=105)	BOS 2.0 mg BID (N=213)	Treatment Difference (95% CI)
Baseline, n	105	211	
Mean (SD)	8.8 (3.23)	8.8 (3.31)	-0.1 (-0.83, 0.72)
Median (minimum, maximum)	9.0 (0, 14)	9.0 (1, 14)	
Week 8, n	101	203	
Mean (SD)	7.2 (4.01)	6.6 (4.25)	-0.6 (-1.58, 0.42)
Median (minimum, maximum)	7.0 (0, 14)	7.0 (0, 14)	
Week 12, n	94	193	
Mean (SD)	6.9 (4.17)	5.7 (4.32)	-1.2 (-2.27, -0.15)
Median (minimum, maximum)	7.0 (0, 14)	5.0 (0, 14)	
Week 16, n	89	198	
Mean (SD)	6.0 (4.53)	5.3 (4.29)	-0.7 (-1.80, 0.39)
Median (minimum, maximum)	6.0 (0, 14)	4.0 (0, 14)	

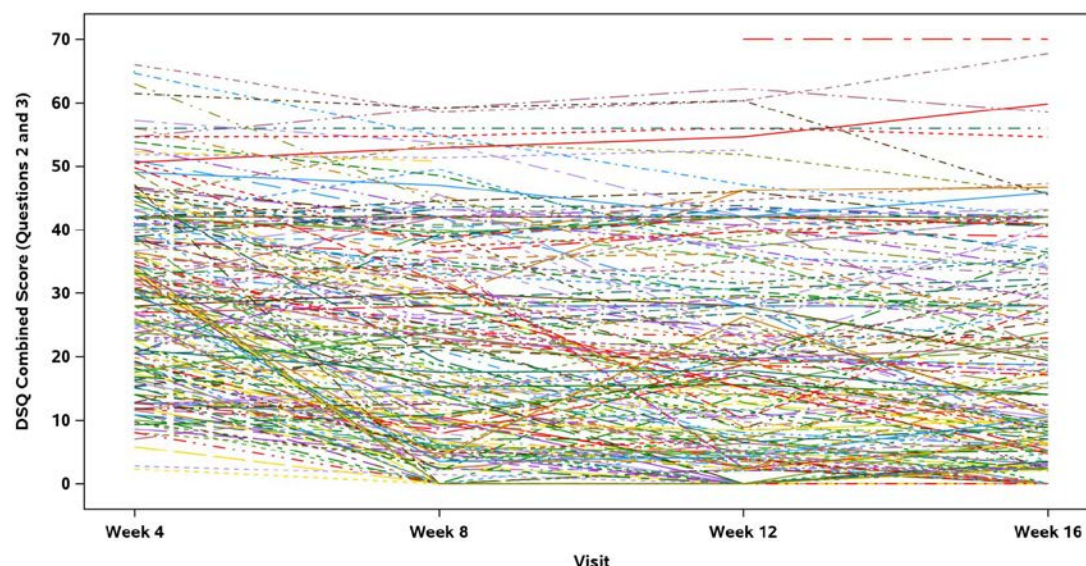
Source: Reviewer's adaptation of the Applicant's Information Request response dated January 24, 2021

Note that the window shift rule was applied to determine a 14-day period.

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; N, number of subjects in treatment group; n, number of subjects at indicated visit; SD, standard deviation

Spaghetti plots were also requested from the Applicant that showed no clear subject-level trend for the DSQ combined score over time in either treatment arm (Figures 15 and 16).

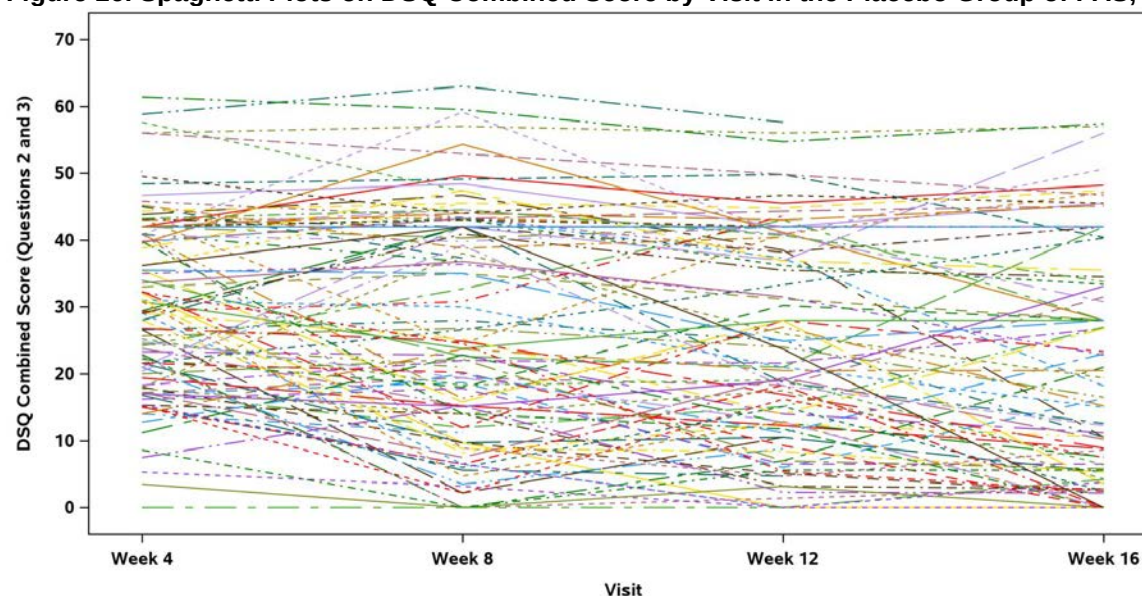
Figure 15. Spaghetti Plots on DSQ Combined Score by Visit in the Budesonide Group of FAS, Trial 301



Source: Applicant's Information Request response dated February 22, 2021

Abbreviations: DSQ, Dysphagia Symptom Questionnaire; FAS, full analysis set

Figure 16. Spaghetti Plots on DSQ Combined Score by Visit in the Placebo Group of FAS, Trial 301



Source: Applicant's Information Request response dated February 22, 2021
Abbreviations: DSQ, Dysphagia Symptom Questionnaire; FAS, full analysis set

Post hoc Subgroup Analyses in Dilation-Naïve Subjects

This a summary statistical assessment of the Applicant's post hoc subgroup analysis results of two endpoints in dilation-naïve subjects in the intent-to-treat population (defined as all randomized subjects). [Table 45](#) summarizes the post hoc analyses included in multiple submissions and IR responses after the March 19, 2021 DR letter. These subgroup analyses were not pre-specified in the SAP or reported in the Trial 301 CSR. Determination of dilation-naïve status based on medical self-report only was considered unreliable. The Applicant confirmed that 36% of dilation-naïve subgroup subjects had a self-reported dilation status that could not be verified by medical records.

Care should be taken in interpreting subgroup results as a larger estimated treatment effect for a subgroup may be a random extreme value instead of an accurate identification of a subgroup with a truly larger treatment effect compared to the overall population. The post hoc nature and potentially the large number of subgroup analyses that were conducted could also increase the probability of a chance finding, and the estimated treatment effect in this subgroup may be biased. As such, all subgroup analysis results should be considered hypothesis generating.

Table 45. The Applicant's Post Hoc Subgroup Analyses on Key Secondary Endpoint in Dilation-Naïve ITT Population. Trial 301

(b) (4)

16.2.3.2. Long-Term Efficacy, Trial 302

Trial 302 rerandomized 48 BOS subjects from Trial 301 who were considered full responders (defined as having both ≤ 6 eosinophils per high-power field across all available esophageal levels and at least a 30% reduction in DSQ combined scores at the final treatment evaluation). The primary endpoint, the relapse (defined as an eosinophil count of ≥ 15 eosinophils per high-power field from at least 2 of 3 levels of the esophagus and at least 4 days of dysphagia in the 14-day period prior to the scheduled visit), and key secondary endpoints (histology response and dysphagia symptom response defined similarly to Trial 301) were evaluated at Week 36 visit of the double-blinded randomized withdrawal period. Refer to Section [6.2](#) for study design and SAP.

It is important to note that the Trial 301 full responder definition used the 30% cutoff to select a dysphagia responder. As the results from Trial 302 were not significant, the impact of this concern was not evaluated.

Baseline Demographics and Clinical Characteristics

The efficacy analysis population for Trial 302 consisted of 48 of the 64 subjects who were in the completed Trial 301 in the BOS group and were considered full responders. Of these 48 subjects, 25 were rerandomized to the BOS group and 23 were rerandomized to the placebo group. As with Trial 301, most subjects in this trial were White (96%), adults (85%) and the median age was 37 years ranging from 11 to 56 years of age. Subjects had a mean (standard deviation [SD]) baseline DSQ combined score of 10 (11) and a mean (SD) total peak eosinophil count of 2 (2). Although there were more males in the placebo arm (approximately 70%) and more females in the BOS arm (44%), this was likely attributable to the limited sample size. No other significant differences were noted on comparison of the baseline demographic and clinical characteristics between groups.

Table 46. Baseline Demographic and Clinical Characteristics, Trial 301 DSQ Full Responders FAS, Trial 302

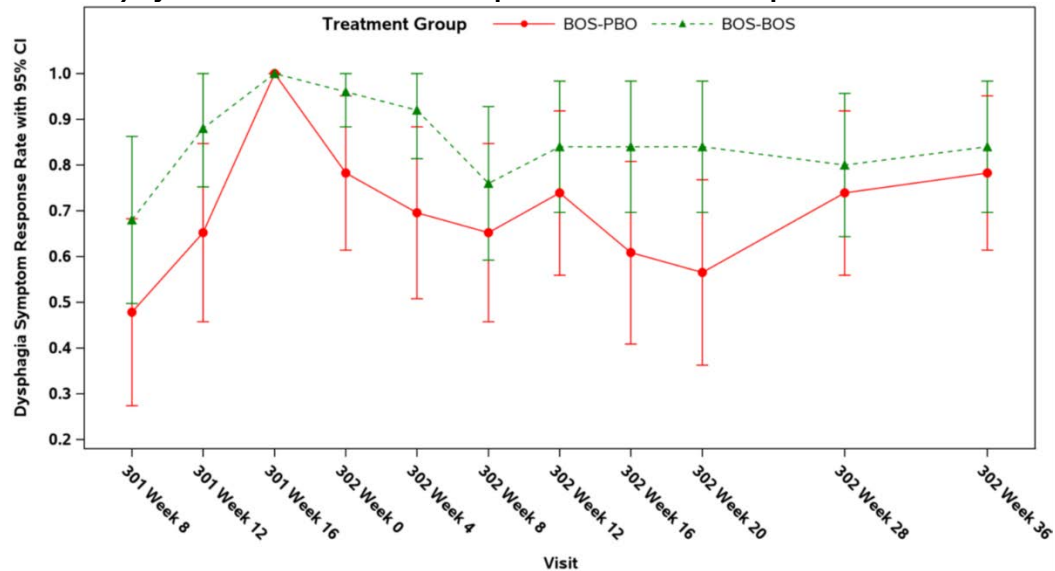
Characteristic	BOS-BOS N=25	BOS-PBO N=23	Total N=48
Sex, n (%)			
Female	11 (44.0)	7 (30.4)	18 (37.5)
Male	14 (56.0)	16 (69.6)	30 (62.5)
Age, years			
Mean (SD)	36.2 (14.1)	35.6 (11.7)	35.9 (12.9)
Median	35	37	37
Minimum, maximum	11, 56	13, 55	11, 56
Age groups			
<18 years	4 (16.0)	3 (13.0)	7 (14.6)
≥18 years	21 (84.0)	20 (87.0)	41 (85.4)
Race, n (%)			
Black or African American	1 (4.0)	0	1 (2.1)
Other	0	1 (4.3)	1 (2.1)
White	24 (96.0)	22 (95.7)	46 (95.8)
Baseline DSQ combined score			
Mean (SD)	9.7 (10.7)	8.3 (10.0)	9.0 (10.3)
Median	4.7	5.3	5.1
Minimum, maximum	0, 37.0	0, 31.5	0, 37.0
Baseline peak eosinophil count			
Mean (SD)	0.3 (1.2)	0.2 (0.5)	0.3 (0.9)
Median	0	0	0
Minimum, maximum	0, 6	0, 2	0, 6

Source: Statistical reviewer's analyses

Abbreviations: BOS, budesonide oral suspension; DSQ, Dysphagia Symptom Questionnaire; FAS, full analysis set; N, number of subjects in treatment group; n, number of subjects with given characteristic; PBO, placebo; SD, standard deviation

Additional Analyses

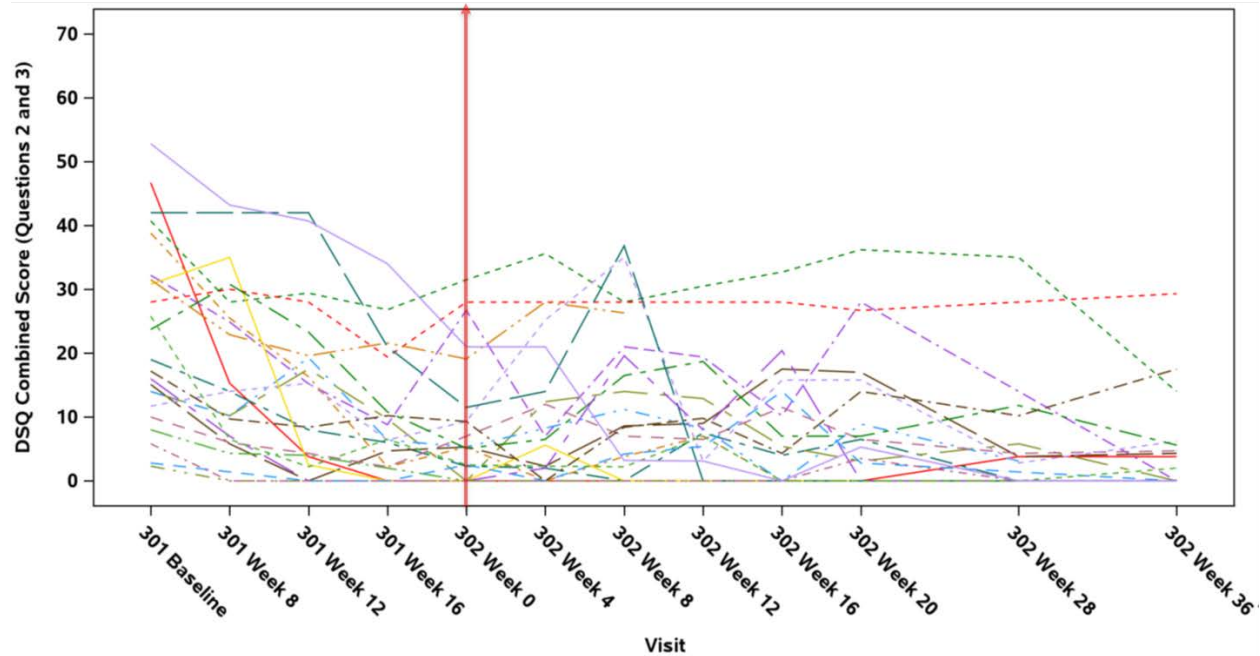
The review team explored the pattern of long-term efficacy for budesonide in dysphagia symptom response ([Figure 17](#)), DSQ combined score (Figures [18](#) and [19](#)), and peak eosinophil count (Figures [20](#) and [21](#)) by group by looking at the derived subject-level data over the duration of Trials 301 and 302. On review, no clear trend toward treatment benefit for either treatment arm was observed.

Figure 17. Proportions of Subjects with Dysphagia Symptom Response (30% Reduction From 301 Baseline) by Visit and Treatment Group in 301 BOS Full Responder FAS

Source: The Applicant's Information Request response dated December 31, 2020

Note: There were 23 BOS-PBO subjects and 25 BOS-BOS subjects. The analyses used nonresponder imputation data

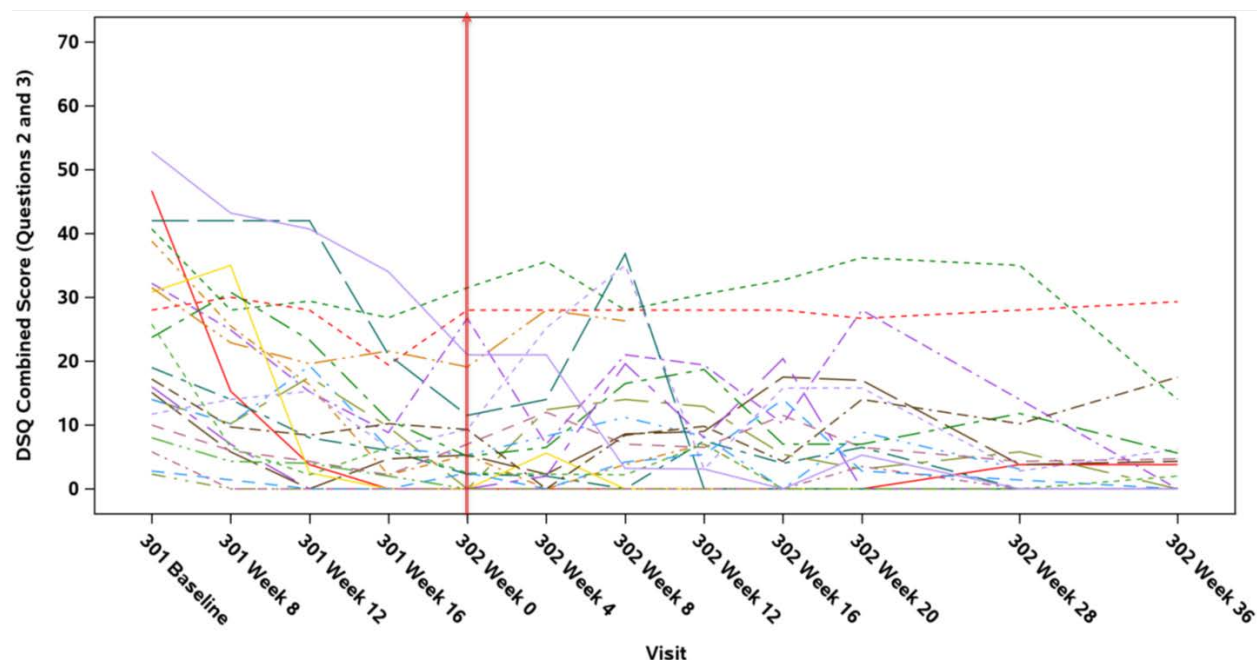
Abbreviations: BOS, budesonide oral suspension; CI, confidence interval; FAS, full analysis set; PBO, placebo

Figure 18. Spaghetti Plots on DSQ Combined Scores in the BOS-PBO Group in Trial 301 Full Responder FAS, Trial 302

Source: Statistical Reviewer's adaptation of the Applicant's Information Request response dated February 9, 2021

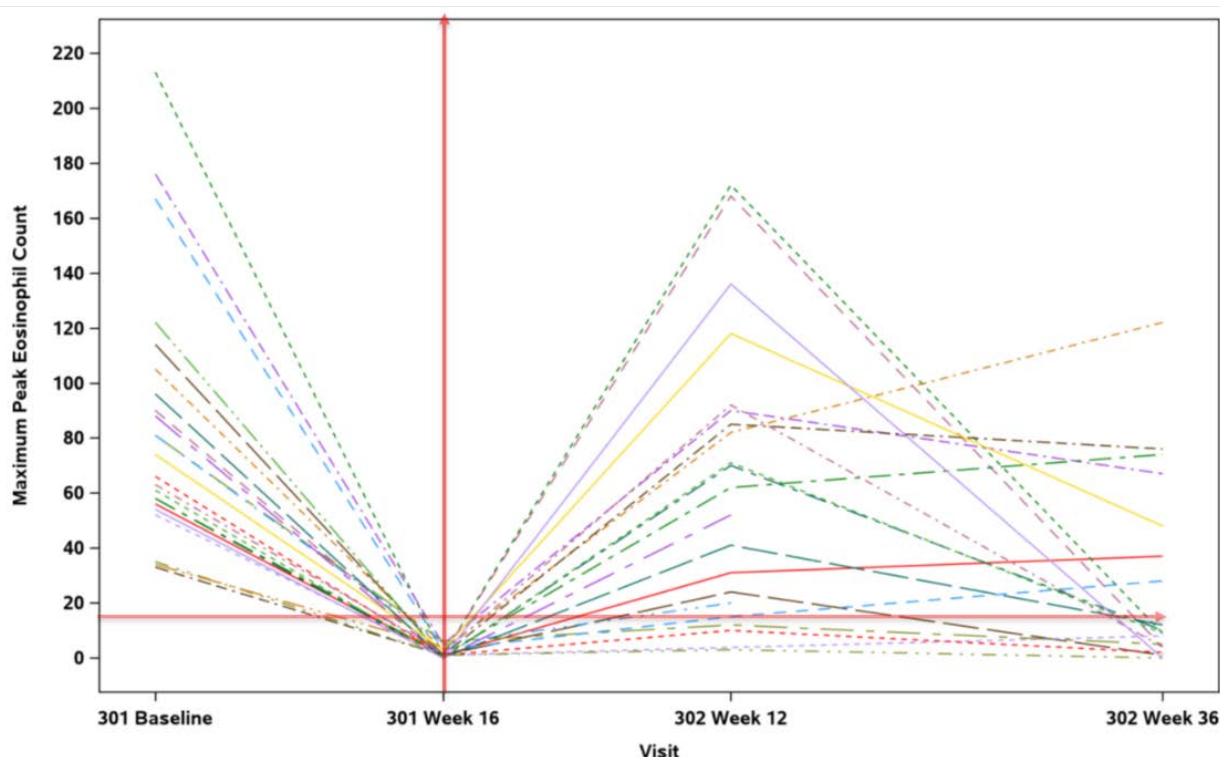
Abbreviations: BOS, budesonide oral suspension; DSQ, Dysphagia Symptom Questionnaire; FAS, full analysis set; PBO, placebo

Figure 19. Spaghetti Plots on DSQ Combined Scores in the BOS-BOS Group in Trial 301 Full Responder FAS, Trial 302



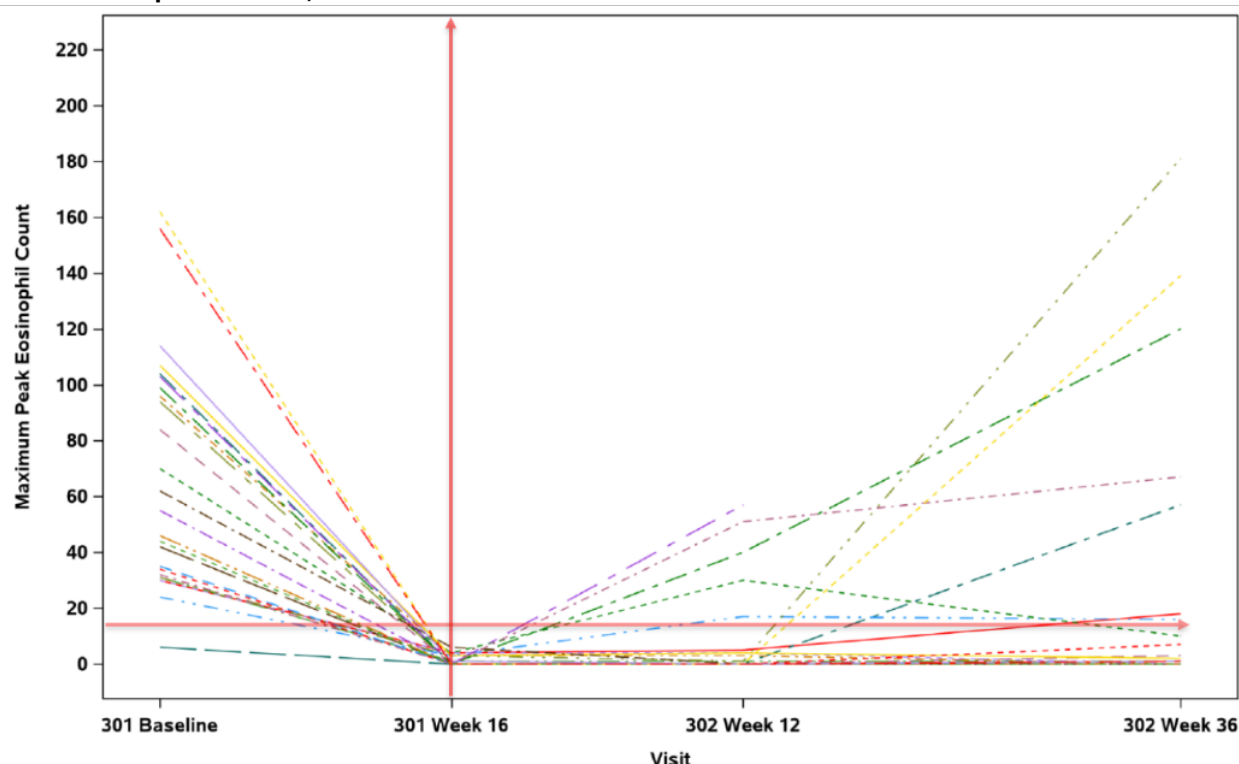
Source: Statistical Reviewer's adaptation of the Applicant's Information Request response dated February 9, 2021.
Abbreviations: BOS, budesonide oral suspension; DSQ, Dysphagia Symptom Questionnaire; FAS, full analysis set

Figure 20. Spaghetti Plots on Histology Peak Eosinophil Counts in the BOS-PBO Group in Trial 301 Full Responder FAS, Trial 302



Source: Statistical Reviewer's adaptation of the Applicant's Information Request response dated February 9, 2021.
Note that many BOS-PBO subjects had a relapse at Week 12. 30% (7/23) BOS-PBO subjects had histologic response at Week 36.
Abbreviations: BOS, budesonide oral suspension; FAS, full analysis set; PBO, placebo

Figure 21. Spaghetti Plots on Histology Peak Eosinophil Counts in the BOS-BOS Group in Trial 301 Full Responder FAS, Trial 302



Source: Statistical Reviewer's adaptation of the Applicant's Information Request response dated February 9, 2021.
Note that some BOS-BOS subjects experienced relapse at Week 12 then at Week 36. 52% (13/25) BOS-BOS subjects had histologic response at Week 36 with a 15% cutoff.
Abbreviations: BOS, budesonide oral suspension; FAS, full analysis set

16.2.4. Data Quality

For the histologic assessment, the protocol prespecified at least two biopsy samples be collected at each esophageal level, proximal, central, and distal. From these samples, the maximum eosinophil count would be used to calculate the peak eosinophil count for each subject. Since the Applicant did not provide the cell counts for the individual biopsy samples, it could not be confirmed that the values reported for each esophageal level were the maximum count.

For the dysphagia symptom response, the reference date used for DSQ combined score calculation was not consistent between the subject daily diary source data and the psychometric analysis data for 16% of the FAS subjects who completed Trial 301. The inconsistency ranged from one day to 18 days. [Table 47](#) reported a snapshot of seven subjects with different reference dates by variable "SVSTDTC" of the daily dairy source data and by variable "RefDate" of the psychometric analysis data. The former, the subject daily diary data, should be the source data. However, this diary source data included multiple reference dates for the same visit for some of these 16% subjects. The SAP and CSR did not mention potential multiple reference dates for a subject's same visit or prespecified rules to handle this situation. The psychometric data that were submitted in response to an IR early in the review cycle did not contain an associated define file. Given these limitations, the reviewer could not validate the derived DSQ score used for the efficacy analyses from the original source dataset(s). Details on the resolution of data quality issues are discussed in [Section 6.3.5](#).

Table 47. An Example of Data Inconsistency Issues Between DSQ Score Source Datasets, Trial 301

USUBJID	SLDFOIL	SIWSTKIL	RLFTDYIL	AnalysisDate	RefDate	trtsdt	randdt	trtdurd	visit	svstdtc	svendtc	svstdy
(b) (6)	1	1	2				(b) (6)	112 WEEK 16			(b) (6)	77
	1	1	0					114 WEEK 16				79
	1	1	0					99 WEEK 16				86
	1	1	1					127 WEEK 16				79
	1	0	-999					100 WEEK 16				82
	1	1	1					144 WEEK 16				90
	1	1	1					99 WEEK 16				72

Source: Statistical reviewer's analysis using SDTM dataset "QS" and the psychometric data "DailyDSQ."

Note that this is a snapshot of the merged datasets and the abbreviations were not explained here since data define file was not provided for "DailyDSQ."

Abbreviation: DSQ, Dysphagia Symptom Questionnaire

16.3. Patient-Focused Statistical Support Supplementary Statistical Review

16.3.1. Interpretation of Change from Baseline in Absolute DSQ Combined Score

As discussed in Section 6.3.1, the review team determined that the prespecified symptomatic coprimary endpoint for Trial 301 was not sufficient to support the demonstration of short-term efficacy for BOS. Additional analyses were conducted using the prespecified alpha-controlled secondary endpoint of change from baseline in 14-day absolute DSQ combined score. This section details how anchor-based clinically meaningful within-patient change (improvement) from baseline in 14-day absolute DSQ combined score at the end of treatment (Week 16) was determined using phase 3 (Trial 301) data.

16.3.1.1. Patient Global Impression of Severity

Subjects completed the PGIS at each treatment visit from baseline through the final treatment period. Subjects were asked to rate the overall severity of their dysphagia (difficulty swallowing) over the past 7 days using a 5-point response scale: no dysphagia, mild dysphagia, moderate dysphagia, severe dysphagia, and very severe dysphagia. It should be noted that the PGIS is the only anchor scale administered in Trials 301 and 302. As such, the determination of the clinically meaningful within-patient change relied on the PGIS; subjects were classified according to the category of change from baseline at Week 16 in their dysphagia symptom based on the PGIS.

16.3.1.2. Anchor-Based Analyses

Anchor-based methods supplemented with empirical cumulative distribution function (eCDF) curves were utilized to establish the thresholds, or a range of thresholds, that constitute a clinically meaningful within-patient change from baseline in 14-day absolute DSQ combined score.

16.3.1.2.1. Baseline 14-Day Absolute DSQ Combined Score

In order to understand the amount of improvement in 14-day absolute DSQ combined score that is considered meaningful to subjects, it is helpful to first examine the distribution of baseline 14-day absolute DSQ combined scores by treatment arm (Table 48). The 14-day absolute DSQ

combined scores can range from 0 to 84 (see Section 16). In Trial 301, scores ranged from 2.3 to 66 in the treatment group and 0 to 61.4 in the placebo group. The means and medians for both groups were around 30, and less than 10% of subjects reported baseline 14-day DSQ combined score greater than 47.

Table 48. Distribution of Baseline 14-Day Absolute DSQ Combined Scores by Treatment Arm

Treatment	N	Mean	SD	Min	Max	Percentile				
						10 th	25 th	50 th	75 th	90 th
BOS 2 mg BID	211	30.3	13.9	2.3	66.0	12.0	18.5	30.3	42.0	46.7
Placebo	105	30.4	13.1	0.0	61.4	15.2	20.0	29.4	42.0	45.1

Source: Patient-Focused Statistical Support Reviewer's Table

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; DSQ, Dysphagia Symptom Questionnaire; Max, maximum; Min, minimum; N, number of subjects in study group; SD, standard deviation

16.3.1.2.2. Target Anchor Change Category on the PGIS

Currently there is no clear standard clinical definition for disease severity for EoE. Therefore, the PGIS is used in Trial 301 as a way to classify EoE disease severity based on dysphagia symptoms. A 2-category improvement on the PGIS was prespecified by the Applicant and the review team. However, the Applicant made the decision to rely on a 1-category improvement to support the anchor-based meaningful change analyses due to the limited number of subjects reporting a 2-category improvement in Trial 301. The deviation from the prespecified 2-category improvement target anchor was not communicated directly with the FDA, instead the change only was described in the Applicant's psychometric analysis report submitted as part of the NDA. A 1-category improvement in the PGIS anchor scale could occur in the following ways:

- Change from “very severe dysphagia” to “severe dysphagia”
- Change from “severe dysphagia” to “moderate dysphagia”
- Change from “moderate dysphagia” to “mild dysphagia”
- Change from “mild dysphagia” to “no dysphagia”

What subjects consider to be clinically meaningful improvement may be impacted by their baseline dysphagia symptom severity. Subjects' baseline symptom severity should be considered when determining clinically meaningful within-patient improvement thresholds. FDA was concerned that a 1-category improvement from “very severe dysphagia” to “severe dysphagia” may not be adequate to represent a meaningful improvement for subjects who started with “very severe” global dysphagia symptom severity at baseline. No qualitative data were collected in Trial 301 to support the evaluation of meaningful improvement. However, the distribution of baseline PGIS scores shows that only three subjects reported “very severe dysphagia” at baseline (Table 49). Among the three subjects, two subjects changed from “very severe dysphagia” to “severe dysphagia.” Therefore, we expected minimum impacts from these subjects in the determination of meaningful change thresholds. In addition, the four patterns of 1-category change (improvement) on the PGIS, listed above, were examined (Table 49). The majority of subjects experienced a 1-category improvement. Therefore, FDA concluded that a 1-category improvement on the PGIS was acceptable to support further anchor-based meaningful change analyses.

To evaluate the distribution of change in global dysphagia symptom severity between baseline and Week 16, a cross tabulation of the PGIS at baseline and at Week 16 was performed (Table 49). Change in global dysphagia symptom severity tends to vary among subjects with

different baseline symptom severity. The majority of subjects reported mild to moderate symptoms at baseline. For subjects who started with mild dysphagia symptoms, most reported no change (56%) followed by a 1-category improvement (34%) in their global dysphagia symptom at Week 16. For subjects who started with moderate dysphagia symptoms at baseline, most reported a 1-category improvement (47%) followed by no change (29%) at Week 16. For subjects who started with severe dysphagia symptoms at baseline, most reported a 1-category improvement (43%) followed by a 2-category improvement (33%) at Week 16. For the three subjects who started with very severe dysphagia symptom at baseline, two subjects reported a 1-category improvement at Week 16.

Table 49. Category Change (n (%)) in PGIS From Baseline to Week 16 by Baseline PGIS

PGIS at Baseline	Improved 3 Categories	Improved 2 Categories	Improved 1 Category	No Change	Worsened 1 Category	Worsened 2 Categories
None	0	0	0	6 (60%)	4 (40%)	0
Mild	0	0	54 (34%)	89 (56%)	15 (9%)	1 (1%)
Moderate	0	18 (17%)	52 (47%)	32 (29%)	5 (5%)	3 (3%)
Severe	1 (5%)	7 (33%)	9 (43%)	2 (10%)	2 (10%)	0
Very severe	1 (33%)	0	2 (67%)	0	0	0

Source: Patient-Focused Statistical Support Reviewer's Table

Abbreviation: PGIS, Patient Global Impression of Severity

16.3.1.2.3. Results

Refer to [Figure 8](#) for the eCDF plot of change in 14-day absolute DSQ combined score at Week 16 from baseline by PGIS category of change from baseline. In summary, the eCDF plot shows separation between the “1-category improvement” and “no change” curves. The Applicant’s proposed meaningful improvement range of 11.5-point to 13.6-point in the absolute DSQ combined score from baseline resulted in high false positive rates (e.g., >20% of subjects who reported no change were classified as experiencing meaningful change). The FDA’s anchor-based analyses using the PGIS as an anchor suggested that the meaningful within-patient improvement threshold range should be at least 14.5-point in order to minimize the false positive rates.

When subjects’ baseline global dysphagia symptom severity was taken into account to assess the change in 14-day absolute DSQ combined score from baseline, the majority of subjects had mild and moderate global dysphagia symptom severity at baseline (refer to [Table 17](#)). A 17.2-point improvement in 14-day absolute DSQ combined score from baseline would be needed to ensure that at least 50% of subjects who reported mild global dysphagia symptom severity at baseline experience a meaningful change of 1-category improvement on the PGIS. Therefore, FDA determined that a meaningful within-patient improvement range should be between 14.5-point and 17.2-point improvement in the 14-day absolute DSQ combined score from baseline.

Change in 14-day absolute DSQ combined score at Week 16 from baseline for subjects who achieved a 1-category improvement on PGIS by baseline PGIS was further examined by age group (Tables [50](#) and [51](#)). At each baseline PGIS category, adolescent subjects require a larger improvement in 14-day absolute DSQ combined score than adult subjects do. However, inferences based on the adolescent subject results should be taken with caution due to the small sample size.

Table 50. Change in 14-Day Absolute DSQ Combined Score at Week 16 From Baseline for Adolescent Subjects Who Achieved a 1-Category Improvement on PGIS by Baseline PGIS

PGIS at Baseline	N	Percentile				
		10 th	25 th	50 th	75 th	90 th
Mild	7	24.90	-18.80	-14.00	-8.55	-4.58
Moderate	8	-34.40	-30.30	-18.80	-12.60	-6.58
Severe	3	-14.0	-12.50	-10.00	-7.10	-5.36

Source: Patient-Focused Statistical Support Reviewer's Table

Abbreviation: DSQ, Dysphagia Symptom Questionnaire; PGIS, Patient Global Impression of Severity

Table 51. Change in 14-Day Absolute DSQ Combined Score at Week 16 From Baseline for Adult Subjects Who Achieved a 1-Category Improvement on PGIS by Baseline PGIS

PGIS at Baseline	N	Percentile				
		10 th	25 th	50 th	75 th	90 th
Mild	43	-34.40	-29.40	-18.50	-11.00	-3.76
Moderate	42	-26.30	-12.50	-6.20	-1.13	3.08
Severe	5	-7.56	-7.50	-4.00	-3.20	-2.84
Very severe	2	-4.06	-3.10	-1.50	0.10	1.06

Source: Patient-Focused Statistical Support Reviewer's Table

Abbreviations: DSQ, Dysphagia Symptom Questionnaire; PGIS, Patient Global Impression of Severity

To further evaluate the clinical relevance of the observed treatment effect, the eCDF plot of within-patient changes in 14-day absolute DSQ combined score from baseline by treatment arm (refer to [Figure 9](#)) shows separation between treatment arms based on visual inspection in the FDA-proposed meaningful change range of 14.5-point and 17.2-point improvement. In order to quantify the difference in the proportion of subjects reported as experiencing a meaningful improvement between treatment and placebo, the differences in response rates, and corresponding 95% confidence intervals (CIs) by treatment arm at Week 16 were examined by the FDA at various thresholds ([Table 52](#)). FDA examined a wide range of thresholds, which includes both the Applicant's proposed threshold range and FDA's proposed threshold range. As shown in [Table 52](#), the difference in response rates between the treatment arms (BOS 2 mg BID – placebo) are between 8.2% and 10.6% in the FDA's meaningful threshold range of 14.5-point and 17.2-point improvement.

Table 52. Proportion of Subjects Who Achieved Improvement at Week 16 From Baseline in 14-Day Absolute DSQ Combined Score at Various Thresholds

Threshold	BOS 2 mg BID N=213 n (%)	Placebo N=105 n (%)	Difference From Treatment (95% CI) ^[1]
≥-18.8 pt	47 (22.1%)	15 (14.3%)	7.8% (-1.8%, 15.8%)
≥-18.5 pt	51 (23.9%)	16 (15.2%)	8.7% (-1.2%, 16.9%)
≥-17.2 pt	57 (26.8%)	17 (16.2%)	10.6% (0.3%, 18.8%)
≥-15 pt	64 (30.1%)	23 (21.9%)	8.2% (-2.9%, 17.1%)
≥-14.5 pt	66 (31.0%)	23 (21.9%)	9.1% (-1.8%, 18.3%)
≥-14 pt	70 (32.9%)	24 (22.9%)	10.0% (-1.0%, 19.3%)
≥-13.6 pt	74 (34.7%)	24 (22.9%)	11.8% (0.8%, 21.2%)
≥-11.5 pt	89 (41.8%)	31 (29.5%)	12.3% (0.4%, 22.1%)
≥-10 pt	97 (45.5%)	33 (31.4%)	14.1% (2.3%, 24.3%)

Source: Patient-Focused Statistical Support Reviewer's Table

^[1] Cochran-Mantel-Haenszel (CMH) test stratified by age and diet restriction. Subjects who did not have efficacy data at the final treatment period evaluation Week 16 were classified as nonresponders.

Abbreviations: BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; DSQ, Dysphagia Symptom Questionnaire

16.3.1.3. Additional Sensitivity Analyses

As mentioned in Section 6.3.2, FDA requested additional meaningful within-patient change analyses using a 7-day absolute DSQ combined score such that the assessment period would align with the PGIS 7-day recall period. The 7-day absolute DSQ combined score was calculated in two ways: a prorated score and an unprorated score.

- The 7-day prorated absolute DSQ combined score is calculated as follows, with a possible score range of 0 to 62:

$$7\text{-day prorated absolute DSQ combined score} = (\text{Sum of daily DSQ Question 2 and Question 3 responses}) \times 7 \text{ days} / \text{Number of daily diaries with nonmissing data in the selected 7-day period}$$

- The 7-day unprorated absolute DSQ combined score is calculated as follows, with a possible score range of 0 to 6:

$$7\text{-day unprorated absolute DSQ combined score} = (\text{Sum of daily DSQ Question 2 and Question 3 responses}) / \text{Number of daily diaries with nonmissing data in the selected 7-day period}$$

As results using both the prorated and unprorated 7-day absolute DSQ combined scores were comparable, only the prorated 7-day absolute DSQ combined score results are presented in this review. The prorated 7-day absolute DSQ combined score is referred to as the “7-day DSQ combined score” throughout this section of the review.

Table 53 shows the distribution of the 7-day DSQ combined scores at baseline, Week 16, and change in DSQ combined scores from baseline to Week 16 by treatment arm. At baseline, the mean and median 7-day DSQ combined scores were around 15-point for both arms. The mean and median change in 7-day DSQ combined scores were larger for the treatment arm (-4.40 and -5.15, respectively) than for the placebo arm (-2.25 and -3.71, respectively).

Table 53. Distribution of Prorated 7-Day DSQ Combined Score at Baseline and Week 16, by Treatment Arm

Distribution of Prorated 7-day DSQ Combined Score (questions 2+3) at Baseline and Week 16, by Treatment Group (Full Analysis Set)

	n	Mean	SD	Min	Max	10 th Percentile	25 th Percentile	50 th Percentile	75 th Percentile	90 th Percentile
Baseline										
BOS 2.0 mg BID	212	14.93	7.480	0.0	33.3	4.67	8.40	15.17	21.00	23.33
Placebo	105	15.21	6.958	0.0	33.3	7.00	9.80	14.00	21.00	22.40
Week 16										
BOS 2.0 mg BID	195	9.67	8.685	0.0	34.0	0.00	2.00	7.00	17.50	21.00
Placebo	90	11.50	9.081	0.0	29.0	0.00	2.33	11.08	21.00	23.17
Change from Baseline at Week 16										
BOS 2.0 mg BID	195	-5.15	7.200	-24.5	13.4	-15.17	-9.33	-4.40	0.00	3.00
Placebo	90	-3.71	7.661	-22.8	13.4	-14.00	-9.00	-2.25	1.75	5.04

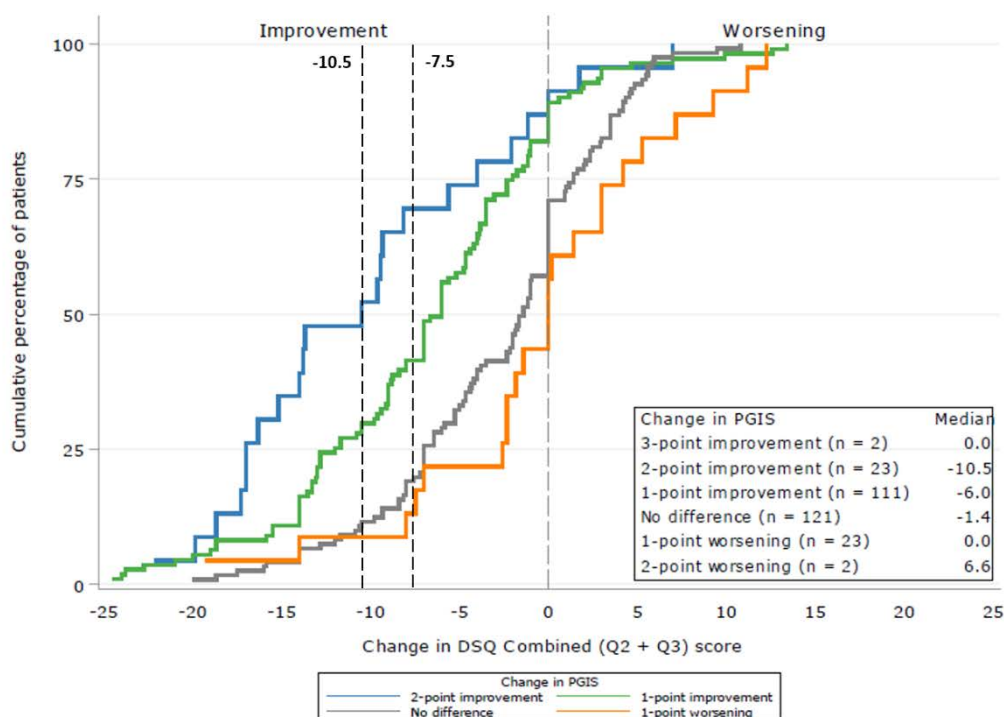
Source: Table 30.1.233.3 of the Applicant's response to FDA's February 15, 2021 Information Request
Abbreviations: BID, twice daily; BOS, budesonide oral suspension; DSQ, Dysphagia Symptom Questionnaire

The eCDF plot below (Figure 22) shows separation between the “1-category improvement” and “no change” curves. Based on a 1-category improvement on the PGIS, the median improvement in the 7-day DSQ combined score from baseline is -6.0. However, the false positive rate at this

threshold is >20%. A meaningful improvement threshold of at least -7.5 would be needed to minimize the false positive rates.

Figure 22. eCDF, Change From Baseline to Week 16 in 7-Day DSQ Combined Score by Change in PGIS

Figure 30.1.233.3. Empirical Cumulative Distribution Function Plot of Change from Baseline to Week 16 in DSQ Combined (Q2 + Q3) Prorated 7-day Average Score by Change in PGIS, Overall: Study SHP621-301

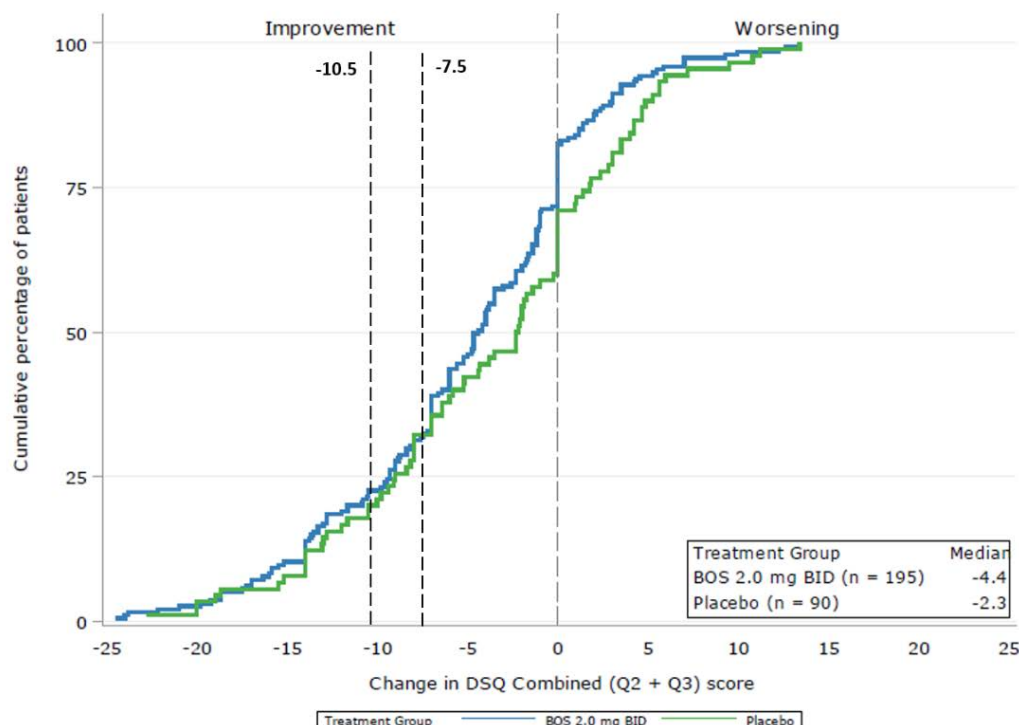


Source: Modified from Figure 30.1.233.3 of the Applicant's response to FDA's February 15, 2021 Information Request
Abbreviations: DSQ, Dysphagia Symptom Questionnaire; eCDF, empirical cumulative distribution function; PGIS, Patient Global Impression of Severity

The eCDF curves by treatment arm using the 7-day DSQ combined scores ([Figure 23](#)) shows little to no separation between treatment arms in the range that subjects consider a meaningful improvement. Separation between treatment arms was only observed in the region where improvement is less than 7.5-point.

Figure 23. eCDF, Change From Baseline in 7-Day DSQ Combined Score by Treatment Arm

Figure 30.1.233.9. Empirical Cumulative Distribution Plot of Change from Baseline to Week 16 in DSQ Combined (Q2 + Q3) Prorated 7-day Average Score by Treatment Group, Overall: Study SHP621-301



Source: Modified from Figure 30.1.233.9 of the Applicant's response to FDA's February 15, 2021 Information Request
Abbreviations: BID, twice daily; BOS, budesonide oral suspension; DSQ, Dysphagia Symptom Questionnaire; eCDF, empirical cumulative distribution function

16.3.2. Post Hoc Exploratory Subgroup Analyses in Dilation-Naïve Subjects

On March 19, 2021, FDA issued a DR letter to the Applicant outlining the deficiencies leading to concerns regarding the ability of the submitted data to support demonstration of either short- or long-term efficacy of BOS for the treatment of EOE. After receiving FDA's DR letter, the Applicant submitted post hoc subgroup analyses of subjects with a history of prior dilation versus dilation-naïve subjects for the 12-week initial treatment period only (see Section 6.3.4). For Trial 301, dilation history was collected as part of the medical history used to determine subject eligibility, as subjects with a history of dilation within 3 months were excluded from the trial and included in the original *adeoe* ADaM dataset submitted to the NDA. FDA sent an IR on April 6, 2021, asking the Applicant to clarify the source documentation used to determine subject dilation status in Trial 301. FDA sent an additional IR on April 16, 2021, asking the Applicant to provide a subject-level dataset that contains a variable to flag subjects as dilation-naïve. According to the Applicant's written response to FDA's IR dated April 6, 2021, a subject's dilation status was determined by either medical record confirmation or subject self-report only, which is considered unreliable (see Section 6.2.2.4). FDA sent another IR on September 9, 2021, requesting a subject-level dataset that identifies the source documentation (i.e., medical record confirmation or subject self-report only) used to determine each subject's dilation status.

FDA conducted post hoc exploratory efficacy analyses (refer to [Table 45](#)) and anchor-based meaningful change analyses to verify the Applicant's analyses results, using both the 14-day DSQ combined score and 7-day DSQ combined score for the following subgroups (a total of four analyses):

- Dilation-naïve subgroup where dilation status was defined by either medical record confirmation or subject self-report only
- Dilation-naïve subgroup where dilation status was defined by medical record confirmation

It should be noted that typically anchor-based meaningful change analysis would not be conducted when efficacy analyses are not nominally significant. For example, the 7-day DSQ combined score efficacy analysis for the dilation-naïve subgroup where dilation status was defined by medical record confirmation was not nominally significant (see [Table 13](#)). FDA conducted this exploratory analysis to provide a complete evaluation of the Applicant's post hoc analyses.

For each of the four anchor-based analyses mentioned above, Patient-Focused Statistical Support identified a meaningful change threshold range based on: 1) the median change in DSQ score for subjects who achieved a 1-category improvement in PGIS, and 2) the median change in DSQ score for subjects who reported mild dysphagia symptoms at baseline. Figures [24](#), [25](#), [26](#), and [27](#) show the eCDF curves of within-patient changes in DSQ score from baseline by treatment group for the four analyses. Although there appears to be some "separation" between treatment groups in Figures [24](#) and [25](#), FDA cannot interpret the analyses results given that the analyses populations included subjects whose dilation status was defined by self-report only, which is considered unreliable. When focusing on the dilation-naïve subgroup, including subjects whose dilation status was confirmed by medical record, there is no real separation between the treatment groups (see Figures [26](#) and [27](#)).

Figure 24. eCDF, Change From Baseline in 14-Day DSQ Combined Score by Treatment Arm for Dilation-Naïve Subgroup Based on Medical Record Confirmation and Self-Report Only

(b) (4)



Figure 25. eCDF, Change From Baseline in 7-Day DSQ Combined Score by Treatment Arm for Dilation-Naïve Subgroup Based on Medical Record Confirmation and Self-Report Only

(b) (4)



Figure 26. eCDF, Change From Baseline in 14-Day DSQ Combined Score by Treatment Arm for Dilation-Naïve Subgroup Based on Medical Record Confirmation Only

(b) (4)



Figure 27. eCDF, Change From Baseline in 7-Day DSQ Combined Score by Treatment Arm for Dilation-Naïve Subgroup Based on Medical Record Confirmation Only

(b) (4)

17. Clinical Safety: Additional Information and Assessment

17.1. FDA's Preferred Term Recoding for Phase 3 Trials SHP621-301 and SHP621-302

Some of the preferred terms (PTs) were recoded for phase 3 trials SHP621-301 and SHP621-302 as follows to aid in capturing any potential safety signals:

Oropharyngeal candidiasis (recoded) includes candida infection (only when the adverse event term [AETERM] stated “thrush”), oral candidiasis, oropharyngeal candidiasis, tongue fungal infection; Headache (recoded) includes headache, migraine; Gastroenteritis (recoded) includes gastric infection, gastroenteritis, gastroenteritis viral, gastrointestinal viral infection; Sinusitis (recoded) includes acute sinusitis, sinusitis; Transaminases increased (recoded) includes alanine aminotransferase increased, aspartate aminotransferase increased; adrenocorticotrophic hormone (ACTH) stimulation test abnormal (recoded) includes ACTH stimulation test abnormal, blood cortisol decreased (only when the AETERM stated that it was in relation to a stimulation test); Throat irritation (recoded) includes oropharyngeal pain (only when the AETERM stated “sore throat”), throat irritation; Dyslipidemia (recoded) includes dyslipidaemia, hyperlipidaemia; Hyperkalemia (recoded) includes blood potassium increased, hyperkalaemia; Intestinal polyp (recoded) includes duodenal polyp, large intestine polyp; Myalgia (recoded) includes myalgia,

pain (only when the AETERM stated “body aches”); Respiratory tract infection (recoded) includes respiratory tract infection, respiratory tract infection viral; Dermal cyst (recoded) includes dermoid cyst; Osteosclerosis (recoded) includes myosclerosis; Paraesthesia (recoded) includes genital paraesthesia, hypoaesthesia, paraesthesia; Pneumonia (recoded) includes pneumonia bacterial; Pruritus (recoded) includes pruritus, pruritus generalised; Hiatus hernia (recoded) includes diaphragmatic hernia, hiatus hernia; Diverticulum (recoded) includes diverticulum, diverticulum intestinal; Gastritis (recoded) includes chronic gastritis, gastritis; Lymphadenopathy (recoded) includes lymphadenopathy, lymphadenopathy mediastinal; Esophageal stenosis (recoded) includes acquired oesophageal web, oesophageal stenosis; Pain in extremity (recoded) includes metatarsalgia (only when the AETERM stated “metatarsalgia right foot”), pain in extremity; Disturbance in attention (recoded) includes disturbance in attention, feeling abnormal (only when the AETERM stated “mental foggiess”); Fracture (recoded) includes foot fracture, humerus fracture, rib fracture, upper limb fracture, wrist fracture; Hypersensitivity (recoded) includes allergy to plants, anaphylactic reaction, anaphylactic shock, food allergy, hypersensitivity; Urine ketone body present (recoded) includes ketonuria, urine ketone body present; Sleep disorder (recoded) includes insomnia, sleep disorder; Upper respiratory tract infection (recoded) includes upper respiratory tract infection, viral upper respiratory tract infection; Drug hypersensitivity (recoded) includes anaphylactic reaction (only when the AETERM stated “anaphylaxis due to gadolinium contrast”), drug eruption, drug hypersensitivity; Esophageal discomfort (recoded) includes sensation of foreign body (only when the AETERM stated “feeling of a lump in esophagus”); Vaginitis bacterial (recoded) includes vaginitis bacterial, vaginitis gardnerella; Weight decreased (recoded) includes abnormal loss of weight, weight decreased; Protein urine present (recoded) includes protein urine present, proteinuria; Abdominal pain (recoded) includes abdominal pain, abdominal pain lower, abdominal pain upper; Gastrointestinal ulcer (recoded) includes duodenal ulcer, gastric ulcer; Hyperbilirubinemia (recoded) includes blood bilirubin increased, hyperbilirubinaemia; Rash (recoded) includes rash, rash macular, rash pruritic; Herpes simplex (recoded) includes herpes simplex, oral herpes; Pyelonephritis (recoded) includes kidney infection, pyelonephritis; Hyperglycemia (recoded) includes blood glucose increased; Hypercholesterolemia (recoded) includes blood cholesterol increased, hypercholesterolaemia; Hyperhidrosis (recoded) includes hyperhidrosis, menopausal symptoms.

17.2. Comparator Groups for the ISS Safety Database

The integrated summary of safety (ISS) safety database (i.e., overall safety set) includes the following three groups of subjects for comparison:

- **BOS 2 mg BID group:** This group includes the following subjects:
 - **BOS 2 mg BID → placebo (PBO):** Subjects who received BOS 2 mg twice daily (BID) in Trial SHP621-301 and were rerandomized to placebo in Trial SHP621-302 (did not reinitiate BOS in Trials SHP621-302 or -303)
 - **BOS 2 mg BID:** Subjects randomized to BOS 2 mg BID in Trial SHP621-301, subjects randomized to BOS 2 mg BID in Trial SHP621-301 who continue on BOS in Trial SHP621-302 (and then in SHP621-303, if enrolled in that study); subjects randomized to BOS 2 mg BID during the double-blind treatment period of phase 2 trial MPI 101-06 and

who did not continue in the open-label extension (OLE) period of MPI 101-06; subjects randomized to BOS 2 mg BID in phase 2 trial MPI 101-01.

- PBO → BOS 2 mg BID: Subjects randomized to placebo in Trial SHP621-301 and who initiated BOS 2 mg BID in Trial SHP621-302, and continued on BOS in Trial SHP621-303 (or did not enroll in Trial SHP621-303)
- BOS 2 mg BID → PBO → BOS 2 mg BID: Subjects randomized to BOS 2 mg BID in Trial SHP621-301, who rerandomized to placebo in Trial SHP621-302, and then reinitiated treatment with BOS 2 mg BID in Trial SHP621-303; subjects randomized to BOS 2 mg BID in Trial SHP621-301, who rerandomized to placebo in Trial SHP621-302 and reinitiated treatment with BOS 2 mg BID in Trial SHP621-302 due to relapse on placebo (including subjects who may have also received BOS in Trial SHP621-303)
- Any BOS dose group: This group includes the following subjects:
 - All subjects included in the BOS 2 mg BID group
 - BOS 2 mg BID → BOS 2 mg QD: Subjects randomized to BOS 2 mg BID during the double-blind treatment period of phase 2 trial MPI 101-06 and who rolled over to the OLE period of Trial MPI 101-06 and received BOS 2 mg once daily (QD).
 - PBO → BOS 2 mg QD: Subjects randomized to placebo during the double-blind treatment period of Trial MPI 101-06 and initiated BOS 2 mg QD in the OLE period of Trial MPI 101-06.
 - BOS 1.4 mg BID: Subjects randomized to BOS 1.4 mg BID in phase 2 trial MPI 101-01
 - BOS 2 mg QD: Subjects randomized to BOS 2 mg QD in Trial MPI 101-01
 - BOS 1.4 mg QD: Subjects randomized to BOS 1.4 mg QD in Trial MPI 101-01
 - BOS 0.5 mg QD: Subjects randomized to BOS 0.5 mg QD in Trial MPI 101-01
 - BOS 0.35 mg QD: Subjects randomized to BOS 0.35 mg QD in Trial MPI 101-01
 - BOS 2 mg Single Dose group: Subjects who received a single dose of any formulation of BOS 2 mg in phase 1 trial SHP621-101
- Induction placebo group: This group includes subjects in the clinical program who received placebo during the double-blind induction period; this includes subjects randomized to placebo in phase 3 trial SHP621-301, subjects randomized to placebo during the double-blind treatment period of phase 2 trial MPI 101-06, and subjects randomized to placebo during the 12-week treatment period of phase 2 trial MPI 101-01.

18. Mechanism of Action / Drug Resistance: Additional Information and Assessment

Not applicable.

19. Other Drug Development Considerations: Additional Information and Assessment

Not applicable.

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

The Division of New Drug Study Integrity within the Office of Study Integrity and Surveillance was consulted to conduct on-site inspections for a clinical site and an analytical site associated with the conduct of the SHP621-101 in vivo bioequivalence study entitled, “A Phase 1, Open-label, Randomized, Two sequence, Five-period, Five-treatment Crossover Study Comparing the Pharmacokinetics of Four Budesonide Oral Suspension (BOS) Formulations and ENTOCORT[®] EC in Healthy Adults.” The Division of New Drug Study Integrity ultimately determined that inspections for both sites were not warranted due to (1) inspections recently being conducted under separate marketing applications and (2) both sites being in good current standing with respect to data integrity. The final Office of Study Integrity and Surveillance classification for the requested inspections was No Action Indicated.

21. Labeling Summary of Considerations and Key Additional Information

The Applicant’s proposed labeling was reviewed; however, agreement was not reached during the review cycle, and additional labeling negotiations will be needed upon receipt of the Applicant’s response to the CR action.

22. Postmarketing Requirements and Commitments

Postmarketing requirements and commitments will be determined upon receipt of a subsequent submission to address the deficiencies noted during the review of this application.

23. Financial Disclosure

Table 54. Covered Clinical Studies: MPI 101-06, SHP621-301, SHP621-302, SHP621-303

Was a list of clinical investigators provided: Yes		
Total number of investigators identified: 423		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)):		
Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0		
Significant payments of other sorts: 1		
Proprietary interest in the product tested held by investigator: 0		
Significant equity interest held by investigator: 0		
Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: Yes		
Number of investigators with certification of due diligence (Form FDA 3454, box 3): Enter text here.		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

24. References

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25. Review Team

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Office of Clinical Pharmacology Team Leader(s)	Dilara Jappar/ Insook Kim / Lian Ma (Pharmacometrics)
Clinical Reviewer	Sarrit Kovacs
Clinical Team Leader	Erica Lyons
Statistical Reviewer	Ling Lan
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Patient-Focused Statistical Support Reviewers Team Leader	Xin Yuan / Monica Morell Lili Garrard
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Abbreviations: OB, Office of Biostatistics

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Abbreviations: API, Active Pharmaceutical Ingredient; ATL, Application Team Leader; BE, bioequivalence; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DMPP, Division of Medical Policy Programs; DPMH, Division of Pediatric and Maternal Health; DPV, Division of Pharmacovigilance; DRM, Division of Risk Management; GLP, good laboratory practice; OMPA, Office of Pharmaceutical Manufacturing Assessment; ONDP, Office of New Drug Products; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OPRO, Office of Program and Regulatory Operations; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations; OSIS, Office of Study Integrity and Surveillance; PMS, Project Management Staff; RBPM, Regulatory Business Process Manager; RPM, Regulatory Project Manager; SRPM, Safety Regulatory Project Manager

Table 57. Signatures of Reviewers

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NDA 213976
Budesonide oral suspension (Eohilia)

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NDA 213976
Budesonide oral suspension (Eohilia)

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NDA 213976
Budesonide oral suspension (Eohilia)

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Office of Clinical Pharmacology Review

NDA Number	213976
Link to EDR	View submission in docuBridge
Submission Date	10/15/2020
Submission Type	Original NDA, 505(b)(2); Priority
Brand Name	Eohilia
Generic Name	Budesonide
Dosage Form/Strength	Oral suspension: 2 mg/10 mL single-dose stick packs
Route of Administration	Oral administration
Proposed Indication	For the treatment of eosinophilic esophagitis (EoE), (b) (4) in patients 11 years and older.
Proposed Dosage Regimen	2 mg twice daily
Applicant	Takeda Pharmaceuticals U.S.A. Inc.
Associated IND	IND 103173
OND Division	Division of Gastroenterology
OCP Division	Division of Inflammation and Immune Pharmacology (DIIP) Division of Pharmacometrics (DPM)
OCP Review Team	Suneet Shukla, Ph.D. (DIIP); Dilara Jappar, Ph.D. (Secondary reviewer, DIIP) Robyn Konicki, Pharm. D. (DPM) Lian Ma Ph.D. (TL, DPM) Insook Kim, Ph.D. (TL, DIIP)

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Glossary

ACTH	adrenocorticotrophic hormone
ALAG1	absorption lag time
AUC	area under the plasma concentration-time curve
BCRP	breast cancer resistance protein
BID	twice daily
BOS	budesonide oral suspension
CI	confidence interval
CL	clearance of the drug from plasma
CL/F	oral clearance
C _{max}	maximum (peak) plasma drug concentration
C _{min}	minimum plasma drug concentration
CV	coefficient of variation
CWRES	conditional weighted residual
CYP	cytochrome P450
DIIP	Division of Immune and Inflammation Pharmacology
EoE	eosinophilic esophagitis
F	relative bioavailability
GOF	goodness-of-fit
HPA	hypothalamic-pituitary adrenal
HPF	high-power field
hs	hora somni; bedtime
IC ₅₀	half-maximal inhibitory concentration
IIV	interindividual variability
IP	investigational product
IPRED	individual predicted concentration
KA	absorption rate constant
LLOQ	lower limit of quantitation
NDA	new drug application
OAT	organic anion transporter
OBS	oral budesonide solution
OCP	Office of Clinical Pharmacology
OCT	organic cation transporter
OFV	objective function value
OLE	open-label extension
pc	post cibum; after food
pcVPC	prediction-corrected visual predictive check
P-gp	P-glycoprotein
PK	pharmacokinetic
PRED	population predicted concentration
Q	intercompartmental clearance
qAM	every morning
QC	quality control
QD	once daily
RSE	relative standard error
TBM	to-be-marketed

tvKA	typical value of KA
V_c/F	apparent central volume of distribution
VCWT	effect of body weight on V_c
V_p	peripheral volume of distribution

1. Background

This is a supplementary review of the clinical pharmacology for the multidisciplinary integrated review for NDA 213976 for Eohilia® (budesonide oral suspension; BOS). NDA 213976 was submitted on October 15, 2020 via 505(b)(2) regulatory pathway with Entocort EC capsules (NDA 21324, approved on October 2, 2001) as the listed drug.

Budesonide is an anti-inflammatory corticosteroid with a high glucocorticoid effect and a weak mineralocorticoid effect. The Applicant's proposed indication is the treatment of eosinophilic esophagitis (EoE), (b) (4) in adult and adolescent patients 11 years and older.

2. Clinical Pharmacology: Additional Information and Assessment

2.1. In Vitro Studies

The following studies were conducted according to the Agency's guidances for industry on drug interaction studies (January 2020a; January 2020b) as below:

- The potential of budesonide being a substrate and an inhibitor for human uptake and efflux transporters ([Table 1](#) and [Table 2](#));
- The potential of budesonide being an inducer and an inhibitor of cytochrome P450 enzymes ([Table 3](#) and [Table 4](#))

Note that potential of budesonide being a substrate for CYP enzymes was relied on the labeling for the listed drug, Entocort EC capsules, and budesonide is extensively metabolized by CYP3A4 according to Entocort EC prescribing information.

Evaluation of Drug Transporters Involved in the Disposition of Budesonide

Table 1. In Vitro Assessments of Budesonide as a Substrate of Human Uptake and Efflux Transporters

Transporter	Conc Used (μM)	Results Efflux Ratio/ Influx Rate	Positive Controls ^[1]	Conclusion	Study Report	System
P-gp	0.2	23.8	1μM valspodar	Substrate of P-gp	Study 1	C2BBE1, MDR1-MDCK, MDCK
	2	21.4				
	20	8.39				
BCRP	0.2	1.84	0.5μM Ko143	Not a substrate of BCRP at the tested concentrations.	Study 1	C2BBE1, BCRP-MDCK, MDCK
	2	2.00				
	20	1.37				
OATP1B1	0.002	ND	0.15μM atorvastatin	Not a substrate of OATP1B1 at the tested concentrations	Study 1	OATP1B1-HEK, OATP1B3-HEK and vector-transfected HEK control cells
	0.2	<2				
	2	<2				
OATP1B3	0.002	ND	0.15μM atorvastatin	Not a substrate of OATP1B3 at the tested concentrations	Study 1	OATP1B1-HEK, OATP1B3-HEK and vector-transfected HEK control cells
	0.2	<2				
	2	<2				
OAT1	0.002	ND	10μM PAH	Not a substrate of OAT1 at the tested concentrations	Study 1	OAT1-HEK and vector-transfected HEK control cells
	0.2	<2				
	2	<2				
OAT3	0.002	ND	5μM furosemide	Not a substrate of OAT3 at the tested concentrations	Study 1	OAT3-HEK and vector-transfected HEK control cells
	0.2	<2				
	2	<2				
OCT2	0.002	ND	5μM MPP	Not a substrate of OCT2 at the tested concentrations	Study 1	OCT2-HEK and vector-transfected HEK control cells
	0.2	<2				
	2	<2				

Source: Clinical Pharmacology Reviewer's table

^[1] Positive controls: known substrates or inhibitors of the respective transporters;

Abbreviations: BCRP, breast cancer resistance protein; ER, efflux ratio; HEK, Human embryonic kidney, MDCK, madin-darby canine kidney; MDR 1, multi drug resistant protein 1; MPP: 1-methyl-4-phenylpyridinium iodide, ND, not determined; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter, PAH para-aminohippurate; P-gp, P-glycoprotein

Table 2. In Vitro Assessments of Budesonide as an Inhibitor of Human Uptake and Efflux Transporters

Transporter Drug	Results IC ₅₀ (μM)	Conclusion	Study Report	Positive Controls	Substrate	System
P-gp Budesonide (2μM)	>2	Not an inhibitor	Study 1	Valspodar 1μM	Digoxin 10μM	C2BBE1 MDR1-MDCK
BCRP Budesonide (2μM)	>2	Not an inhibitor	Study 1	Ko143 0.5μM	Cladribine 10μM	C2BBE1 BCRP-MDCK
OATP1B1 Budesonide (1.1μM)	>1.1	Not an inhibitor	Study 1	Rifamycin SV 10μM	Atorvastatin 0.15μM	OATP1B1-HEK, OATP1B3- HEK and vector-transfected HEK control cells
OATP1B3 Budesonide (1.1μM)	>1.1	Not an inhibitor	Study 1	Rifamycin SV 10μM	Atorvastatin 0.15μM	OATP1B1-HEK, OATP1B3- HEK and vector-transfected HEK control cells
OAT1 Budesonide (0.03μM)	>0.03	Not an inhibitor	Study 1	Probenecid 100μM	PAH 10μM	OAT1-HEK and vector- transfected HEK control cells
OAT3 Budesonide (0.03μM))	>0.03	Not an inhibitor	Study 1	Probenecid 100μM	Furosemide 2μM	OAT3-HEK and vector- transfected HEK control cells
OCT2 Budesonide (0.03μM)	>0.03	Not an inhibitor	Study 1	Repaglinide 600μM	MPP ⁺ 2μM	OCT2-HEK and vector- transfected HEK control cells

Source: Clinical Pharmacology Reviewer's table

Abbreviations: OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter

Reviewer Comments on Uptake and Efflux Transporter Substrate/Inhibition Studies:

The system for assessing the substrate and inhibitor potential efflux and uptake transporters, positive controls, probe substrate (for inhibitory assessment), and the concentrations of the controls used were acceptable per Agency's guidance In Vitro Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions (January 2020b). The concentrations of budesonide (0.002 to 20μM) used to evaluate the potential for being a transporter substrate were adequate based on the observed mean C_{max} of 2.1nM of budesonide after 2 mg twice daily dosing in the pivotal phase 3 study (SHP621-301). In addition, the concentration of budesonide (2μM) used for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) inhibition assays was acceptable as it was about 1/10th of the concentration (18.2μM) at the luminal side of the gastrointestinal wall based on 0.1×dose (2 mg)/250 mL per the FDA guidance. Further, it should also be noted that 1.1μM and 0.03μM of budesonide were used for inhibition of hepatic transporters (organic anion transporter [OAT] B1B1 and OATP1B3) and renal

transporters (OAT1, OAT3 and organic cation transporter [OCT] 2), respectively. These concentrations are more than 100 times of unbound C_{max} [I]₁ of budesonide (unbound C_{max} is 0.3nM, assuming 85-90% protein binding in the concentration range 0.43 to 99.02 ng/mL from ENTOCORT EC label) and is adequate based on the FDA guidance.

Evaluation of Inhibition and Induction of CYP Isoenzymes by Budesonide

Table 3. In Vitro Assessments of Budesonide as an Inducer of CYP Enzymes

Isozyme Test Article	Enzyme Activity Fold Induction ^[1] (3 Donors)	mRNA Content Fold Induction ^[2] (3 Donors)	Positive Control	Probe Substrate	System	Conclusion	Study Report
CYP1A2							
Budesonide (0.00345μM)	0.93/0.97/1.0	1.2/1.0/0.80	Omeprazole 50μM	Phenacetin (100μM)	Primary human hepatocytes; and mRNA measurements	Not an inducer	Study 2
Budesonide (0.010μM)	0.92/0.97/0.92	1.5/0.85/0.78					
Budesonide (0.0345μM)	0.83/1.2/0.93	1.4/1.1/1.0					
CYP2B6							
Budesonide (0.00345μM)	0.094/0.436/0.734	2.8/1.1/0.61	Phenobarbital 1,000μM	Bupropion (250μM)	Primary human hepatocytes; and mRNA measurements	Not an inducer	Study 2
Budesonide (0.010μM)	0.095/0.45/0.751	3.2/1.4/1.1					
Budesonide (0.0345μM)	0.101/0.463/0.672	3.5/1.2/0.59					
CYP3A							
Budesonide (0.0186μM)	0.291/2.53/0.462	1.4/0.95/0.63	Rifampicin 50μM	Midazolam (20μM)	Primary human hepatocytes; and mRNA measurements	Not an inducer	Study 2
Budesonide (0.186μM)	0.299/2.67/0.45	1/0.57/0.88					
Budesonide (1.86μM)	0.59/2.86/0.809	3.7/1/6.3					

Source: Clinical Pharmacology Reviewer's table

^[1] Fold-induction was calculated from the ratio of normalized enzyme activity (formation rate of probe substrate metabolite) of test or positive inducer-treated cells to that of vehicle control-treated cells

^[2] Fold-induction was calculated from the normalized mRNA level (2-ΔΔCt) of test- or positive inducer-treated cells relative to that of vehicle control-treated cells from triplicate measurements.

Abbreviations: CYP, cytochrome P450; mRNA, messenger ribonucleic acid

Table 4. In Vitro Assessments of Budesonide as an Inhibitor of CYP Enzymes

Isozyme Test Article	IC ₅₀ μM (No Preincubation)	IC ₅₀ μM (Time- Dependent) ^[1] Reversible/ Irreversible	CYP Assay	Positive Controls/ For TDI	System	Conclusion	Study Report
CYP1A2 Budesonide (0-10μM)	>10	10/10	Phenacetin Acetaminophen	α-Naphthoflavone/ Furafylline	Pooled Human liver microsome	Not an inhibitor	Study 3 Study 4
CYP2B6 Budesonide (0-10μM)	>10	10/10	Bupropion, OH bupropion	Thio-TEPA	Pooled Human liver microsome	Not an inhibitor	Study 3 Study 4
CYP2C8 Budesonide (0-10μM)	>10	10/10	Amodiaquine, Desethylamodiaquine	Montelukast/Gemfibrozil glucuronide	Pooled Human liver microsome	Not an inhibitor	Study 3 Study 4
CYP2C9 Budesonide (0-10μM)	>10	10/10	Diclofenac, 4'-OH diclofenac	Sulfaphenazole/ Tienilic acid	Pooled Human liver microsome	Not an inhibitor	Study 3 Study 4
CYP2C19 Budesonide (0-10μM)	>10	10/10	S-mephenytoin, 4'-OH mephenytoin	(+)-N-3-benzylirinanol/ Ticlopidine	Pooled Human liver microsome	Not an inhibitor	Study 3 Study 4
CYP2D6 Budesonide (0-10μM)	>10	10/10	Bufuralol, 1'-OH bufuralol	Quinidine/Paroxetine	Pooled Human liver microsome	Not an inhibitor	Study 3 Study 4
CYP3A Budesonide (0-10μM)	4.7	10/10	Midazolam, 1'-OH midazolam	Ketoconazole/ Troleandomycin	Pooled Human liver microsome	Not an inhibitor	Study 3 Study 4
Budesonide (0-10μM)	>10	10/10	Testosterone, 6β-OH testosterone				

Source: Clinical Pharmacology Reviewer's table

Positive controls: known inhibitors of respective CYP isoforms

^[1] Tested with a 15 min preincubation period.

^[2] Human liver microsomes (pooled)

Abbreviations: CYP, cytochrome P450

Reviewer Comments on Budesonide as Inducer and Inhibitor of CYP Enzymes:

The test system of primary human hepatocytes for CYP induction studies and pooled human liver microsome for the CYP inhibition studies, and positive controls used were considered adequate as they were based on the FDA recommendations (FDA 2016; January 2020b).

The assessment of induction of CYP1A2, CYP2B6, and CYP3A using concentrations of 0.00345 μ M to 0.0345 μ M for CYP1A2 and CYP2B6 and 0.0186 μ M – 1.86 μ M for CYP3A4 were acceptable since they span the range of therapeutic exposure of budesonide at the proposed clinical dose of 2 mg BID in EoE patients (mean C_{max} : ~0.002 μ M, 914 pg/mL). The concentrations of budesonide (0 to 10 μ M) used for CYP inhibition assays are also acceptable based on C_{max} at the therapeutic dose (2.1nM) and potential concentration in the gut (0.1 $\times$ dose (2 mg)/250 mL=1.82 μ M).

Assessment of In Vivo Drug-Drug Interaction Liability

No in vivo drug-drug interaction studies were conducted.

Effects of Other Drugs on Budesonide

In vitro studies conducted by the Applicant demonstrated that budesonide was not a substrate of BCRP, OATP1B1, OATP1B3, OAT1, OAT3 and OCT2, **but it was a substrate for P-gp.**

P-gp Inhibitors

The Applicant did not conduct an in vivo drug-drug interaction study to evaluate the potential of budesonide being a substrate for P-gp transporter. Nonetheless, according to the current approved label for the listed drug, Entocort, ketoconazole, an inhibitor of CYP3A4 and P-gp transporter, increased the exposure of budesonide by eight-fold in a clinical drug-drug interaction study with oral budesonide. Based on this drug-drug interaction information with a common inhibitor of P-gp and CYP3A4 (ketoconazole), we recommend that for the proposed label, in addition to CYP3A4 inhibitor, P-gp inhibitor should also be avoided with budesonide since the relative contribution of P-gp and CYP3A4 inhibition by ketoconazole and its individual impact on the PK of budesonide is unknown. Of note, per the Entocort label, grapefruit juice which inhibits CYP3A4 activity predominantly in the intestinal mucosa increased the systemic exposure to budesonide by 2-fold.

OCT2 Inhibitors

While in vitro study indicates that budesonide is not a substrate of OCT2, in vivo DDI study with cimetidine, an inhibitor of MATE1, MATE2K and OCT2, showed that administration of cimetidine resulted in a 52% and 31% increase in the budesonide peak plasma concentration and the AUC of budesonide, respectively per the Entocort EC labeling. This suggests the effects of cimetidine on budesonide may be attributed to other mechanisms, e.g., the inhibition of MATE1 and MATE2K or the effects of cimetidine on gastric pH.

Effects of Budesonide on Other Drugs

Substrates of Transporters

Budesonide is unlikely to affect the pharmacokinetics of concomitant drugs via the inhibition of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2 as in vitro IC_{50} values for these transporters were well above the C_{max} of budesonide (approximately 2.1nM from pivotal phase 3 study (SHP621-301)) at the proposed clinical doses, 2 mg twice daily. R-values for P-gp and BCRP were less than 10 for oral administration at intended clinical doses of 2 mg twice daily; R-values for OATP1B1 and OATP1B3 were less than 1.1; R-values for OAT1, OAT3 and OCT2 were less than 0.1 (refer to Module 5.3.2.2 (Takeda Pharmaceuticals)).

Substrates of CYP Enzymes

Assessment of induction of CYP1A2, CYP2B6, and CYP3A, using the fold-change in mRNA and in enzyme activity in human cultured hepatocytes, indicated budesonide is not an inducer of CYP enzymes at concentrations up to 0.0345 μ M for CYP1A2 and CYP2B6 and 1.86 μ M for CYP3A.

Further, budesonide is unlikely to result in drug interactions via inhibition of major CYP enzymes as the budesonide C_{max} of approximately 2.1nM was well below the in vitro IC_{50} of major CYP enzymes (>10 μ M), except when midazolam is used as a substrate (IC_{50} of 4.7 μ M). Budesonide (up to 10 μ M) is also did not show a time-dependent inhibition of all CYP enzymes tested in the study.

2.2. In Vivo Studies

Relative Bioavailability and Bioequivalence Study (SHP621-101)

Study Design

Study SHP621-101 was a phase 1, open-label, randomized, two-sequence, five-period, five-treatment crossover study comparing the pharmacokinetics of four budesonide oral suspension formulations and Entocort® EC in healthy adults.

Treatments

- A: A single oral dose of BOS MB-9 formulation: 0.2 mg/mL in volumes of 10 mL (2 mg budesonide) (phase 3 formulation).
- B: A single oral dose of Entocort® EC 9 mg (3×3 mg capsules).
- C: A single oral dose of BOS MB-7 formulation: 0.2 mg/mL in volumes of 10 mL (2 mg budesonide) (phase 2 formulation).
- D: A single oral dose of BOS MB-9 formulation with (b) (4) variant: 0.2 mg/mL in volumes of 10 mL (2 mg budesonide) (to-be-marketed [TBM] formulation).
- E: A single oral dose of BOS MB-9 formulation with increased (b) (4) variant: 0.2 mg/mL in volumes of 10 mL (2 mg budesonide).

Results

Table 5. Geometric Mean (%CV) PK Parameters for Budesonide From Different Formulations (Reviewer's Assessment and Applicant-Calculated PK Parameters), Study SHP621-101

Treatment	C _{max} (pg/mL)		AUC _{0-t} (hr·pg/mL)		AUC _∞ (hr·pg/mL)		Median T _{max} (hrs) (min-max)	
	Applicant-Calculated	Reviewer-Calculated	Applicant-Calculated	Reviewer-Calculated	Applicant-Calculated	Reviewer-Calculated	Applicant-Calculated	Reviewer-Calculated
A (Phase 3 formulation)	1063.35 (49.857)	1063.35 (49.86)	4257.20 (54.609)	4524.17 (54.211)	4515.96 (54.37)	4256.95 (54.61)	1.5 (0.5-2.00)	1.5 (0.5-2.00)
B (Entocort EC 9 mg)	1495.84 (61.256)	1495.84 (61.26)	12682.32 (63.239)	13744.51 (66.215)	14180.65 (65.97)	12684.19 (63.22)	4.0 (2.00-6.00)	4.0 (2.00-6.00)
C (Phase 2 formulation)	957.11 (52.163)	957.11 (52.16)	3732.63 (59.066)	3970.91 (57.968)	3996.07 (58.15)	3731.26 (59.17)	1.0 (0.5-2.00)	1.0 (0.5-2.00)
D (TBM formulation)	1092.68 (55.694)	1092.68 (55.69)	4469.13 (61.864)	4991.01 (53.042)	4694.72 (61.13)	4469.13 (61.86)	1.5 (0.75-2.00)	1.5 (0.75-2.00)

Source: Reviewer's analysis and Module 5.3.1.2, SHP621-101 Amendment 1- Report Body, Table 12, Page 59.

All values are presented as geometric mean (%CV) unless specified otherwise.

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Abbreviations: AUC_{0-t}, area under the plasma concentration-time curve from time 0 to the last measurable concentration; AUC_∞, area under the plasma concentration-time curve from time zero to infinity; C_{max}, maximum (peak) plasma drug concentration; PK, pharmacokinetic; TBM, to-be-marketed

Table 6. Comparison of Bioequivalence Analysis Between the Applicant Calculated and the Reviewer's Calculated Data, Study SHP621-101

Parameter Treatment Comparison	Ratio of Geometric LS Means		Ratio 90% CI	
	Applicant-Calculated	Reviewer-Calculated	Applicant-Calculated	Reviewer-Calculated
C _{max} (pg/mL)				
A/B	0.711	0.711	0.638–0.792	63.80–79.20
C/A	0.877	0.900	0.787–0.977	80.78–100.29
D/A	1.050	1.028	0.942–1.169	92.22–114.50
D/B	0.730	73.05	0.656–0.814	65.56–81.39
AUC _{0-t} (hr·pg/mL)				
A/B	0.336	0.318	0.301–0.374	28.32–35.67
C/A	0.878	0.877	0.791–0.974	78.68–97.64
D/A	1.044	1.050	0.939–1.161	94.24–116.95
D/B	0.352	0.352	0.316–0.393	31.63–39.25
AUC _∞ (hr·pg/mL)				
A/B	0.335	0.336	0.302–0.373	30.13–37.39
C/A	0.900	0.887	0.808–1.003	79.03–99.53
D/A	1.028	1.038	0.922–1.145	92.52–116.52
D/B	0.350	33.00	0.315–0.390	29.41–37.03

Source: Reviewer's analysis and Module 5.3.1.2, SHP621-101 Amendment 1- Report Body, Table 13, Page 60.

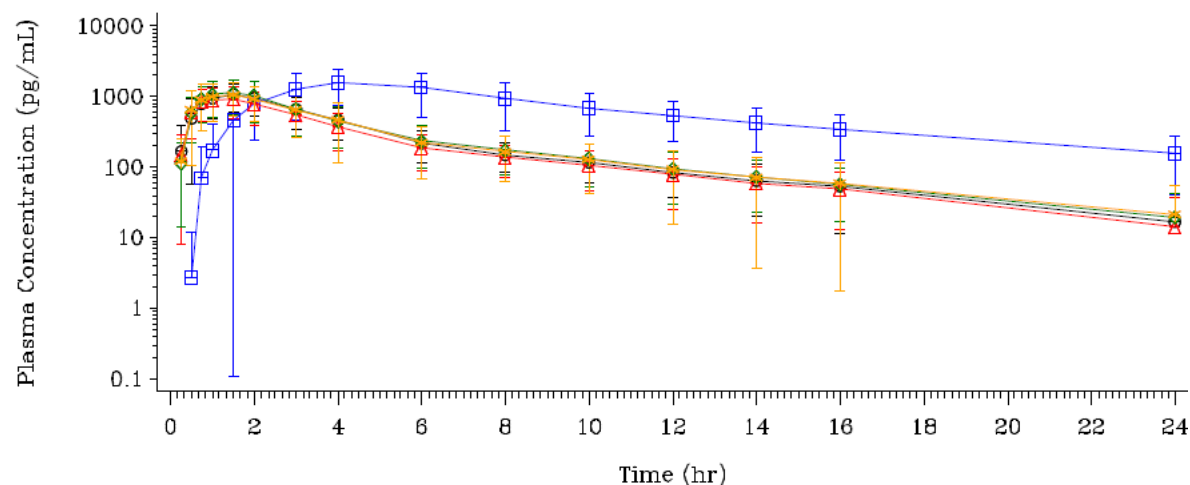
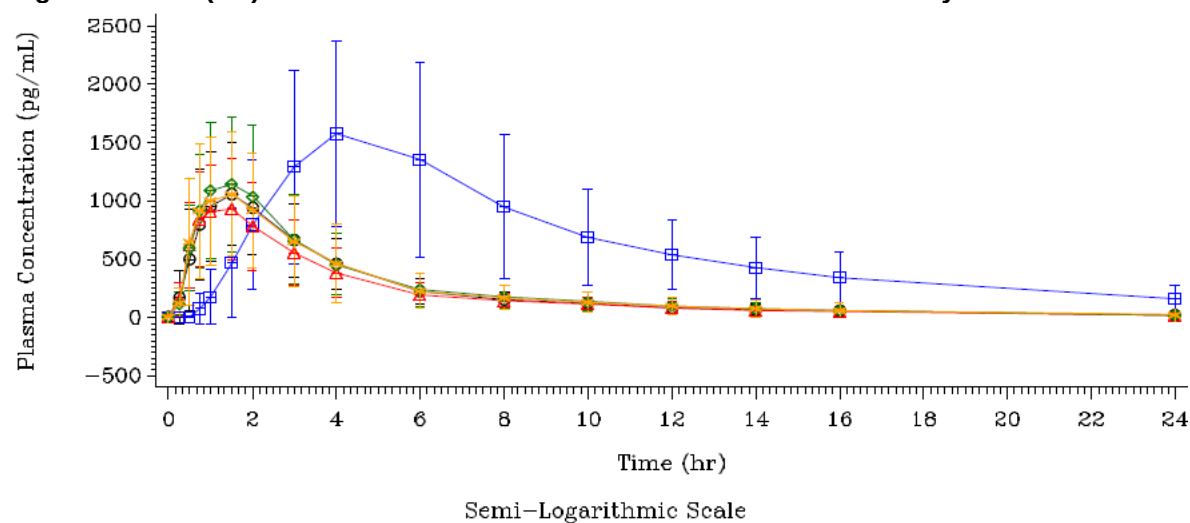
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Treatments: A: Phase 3 formulation, 2 mg; B: Entocort EC, 9 mg; C: Phase 2 formulation, 2 mg; D: To-be-marketed formulation, 2 mg

Abbreviations: CI, confidence interval; LS, least square

Individual budesonide plasma concentration versus time profiles are graphically represented on linear and semilogarithmic scales in [Figure 1](#). The plasma budesonide concentration-time profiles were similar for all treatments using the BOS formulations (Treatments A, C, D, and E). The plasma budesonide concentrations following oral administration of Entocort EC 9 mg (Treatment B) showed a delayed absorption with the peak plasma concentration achieved at approximately 4 hours after dosing, and the overall plasma budesonide exposure from Entocort EC 9 mg was higher than those from any of the BOS formulations given at 2 mg.

Figure 1. Mean (SD) Plasma Concentration-Time Profiles of Budesonide by Treatment



○—○—○ A □—□—□ B △—△—△ C ◇—◇—◇ D *—*—* E

Source: Study SHP621-301CSR, Section 14, Figure 14.2.1.1.

A: A single oral dose of BOS MB-9 formulation 2 mg: 0.2 mg/mL in volumes of 10 mL (2 mg budesonide).

B: A single oral dose of ENTOCORT® EC 9 mg (3×3 mg capsules).

C: A single oral dose of BOS MB-7 formulation 2 mg: 0.2 mg/mL in volumes of 10 mL (2 mg budesonide).

D: A single oral dose of BOS MB-9 formulation with (b) (4) variant 2 mg: 0.2 mg/mL in volumes of 10 mL (2 mg budesonide).

E: A single oral dose of BOS MB-9 formulation with increased viscosity (b) (4) 2 mg: 0.2 mg/mL in volumes of 10 mL (2 mg budesonide).

Abbreviations: BOS, budesonide oral suspension; SD, standard deviation.

Conclusion

Plasma concentrations of budesonide were analyzed by adequately validated bioanalytical assay methods. The in-study bioanalytical assay was found acceptable. See Section 2.5 for details. The systemic exposure of budesonide after a single dose of 2 mg of phase 3 formulation was bioequivalent to TBM formulation (D/A). The formulation MB-7 used in phase 2 dose-finding study (MPI 101-01) had approximately 10% to 12% lower AUC and C_{max} compared to phase 3 formulation (C/A).

The geometric mean AUC and $C_{\max}$ of budesonide for the proposed product, BOS 2 mg (phase 3 formulation and TBM formulation) were 33 % and 71 % of those of the listed drug, Entocort EC 9 mg, respectively (A/B and D/B).

Considering the difference in dosing regimen, after the proposed 2 mg twice daily dosing of the proposed product in adult EOE patients, the estimated $C_{\max}$ and AUC_{τ} for the proposed product is 915 pg/mL and 5071 h·pg/mL (Study: SHP621-301).

Based on a cross-study comparison, the $C_{\max}$ at steady-state in adult patients with EoE were similar to those in healthy subjects after single dose administration of 2 mg (915 pg/mL vs. 1092.68 pg/mL, respectively).

The lower systemic exposure of proposed product compared to the listed drug Entocort EC justifies the reliance on the previous findings of nonclinical safety and clinical pharmacology information for the listed drug.

Phase 2 Study: Dose-Ranging Study in Children and Adolescents (2 to 18 Years of Age, MPI-101-01)

Study Design

Study MPI-101-01 was a phase 2, randomized, double-blind, placebo-controlled, parallel-arm, dose-ranging in children and adolescents (2 to 18 years of age) for evaluating the efficacy and safety of two concentrations and two dosing regimens of oral budesonide suspension (OBS [MB-7]) in pediatric patients with EOE over a 12-week course of treatment. The objective was to identify an appropriate dose and dosing regimen for further development.

Treatments

Subjects were randomized to one of four treatment groups in a 1:1:1:1 ratio (approximately 20 subjects per treatment group). Randomization was stratified by age group (2 to 9 years of age and 10 to 18 years of age). The treatment period was 12 weeks and the subjects were administered MB-7 budesonide formulation orally twice daily during the treatment period, once in the morning after breakfast and once in the evening at bedtime as below ([Table 7](#)).

Table 7. Study Treatment by Dose Group and Age, Study MPI 101-01

Dose Group	Age Group (Years)	Budesonide Concentration (mg/mL)	Morning Dose (mg)	Evening Dose (mg)	Total Dose/Day (mg/day)
Placebo	2 to 9 10 to 18	0.0	Placebo	Placebo	0.0
Low	2 to 9 10 to 18	0.05	Placebo	0.35 ^a 0.5 ^a	0.35 0.5
Medium	2 to 9 10 to 18	0.2	Placebo	1.4 ^b 2.0 ^b	1.4 2.0
High	2 to 9 10 to 18	0.2	1.4 2.0	1.4 ^b 2.0 ^b	2.8 4.0

Source: Synopsis, Study report Study MPI-101-01, Page 5. [\CDSESUB1\evsprod\nda213976\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\eosinophilic-esophagitis\5351-stud-rep-contr\mpi-101-01\mpi-101-01-csr-legacy.pdf](#)

^a Budesonide concentration of 0.05 mg/mL

^b Budesonide concentration of 0.2 mg/mL

After 12-week treatment period was completed, each subject began a 3-week Taper Period. During Taper Week 1, all subjects received a single dose of study medication every morning (qAM) after food (pc); the budesonide concentration and volume were the same as taken for each evening dose during the treatment period. During Taper Weeks 2 and 3, all subjects continued to receive a dose qAM pc, but the dose volume was one half the volume taken during taper week 1 as shown in [Table 8](#).

Table 8. Dosing During Taper Period

	Dosing During Taper Period				
	Taper Week 1			Taper Weeks 2 & 3	
	Age group	OBS Volume (mL)	Budesonide (mg/day)	OBS Volume (mL)	Budesonide (mg/day)
Placebo	2 to 9 yr	7	0	3.5	0
	10 to 18 yr	10	0	5	0
Low	2 to 9 yr	7	0.35	3.5	0.175
	10 to 18 yr	10	0.5	5	0.25
Med	2 to 9 yr	7	1.4	3.5	0.7
	10 to 18 yr	10	2	5	1
High	2 to 9 yr	7	1.4	3.5	0.7
	10 to 18 yr	10	2	5	1

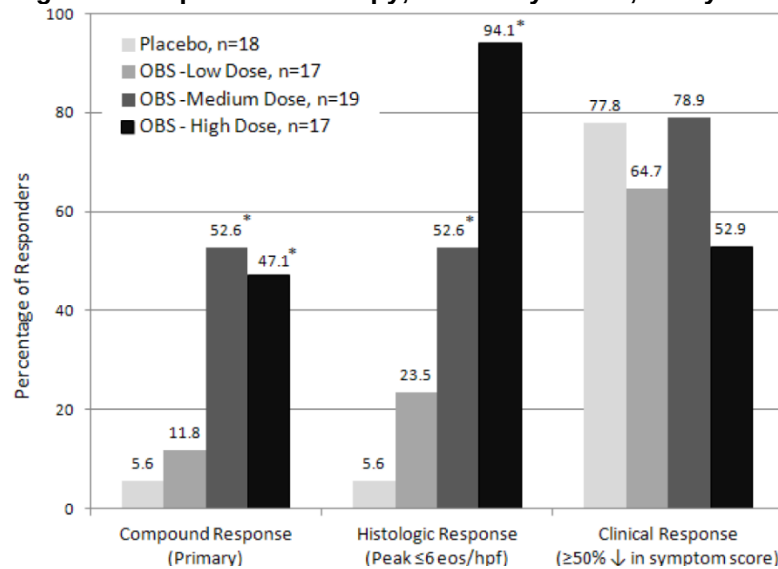
Source: Study MPI-101-01 CSR, Synopsis, Page 6. [\CDSESUB1\evsprod\nda213976\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\eosinophilic-esophagitis\5351-stud-rep-contr\mpi-101-01\mpi-101-01-csr-legacy.pdf](#)

Abbreviation: OBS, oral budesonide solution

Pharmacokinetic (PK) blood sampling was performed at Week 2, 4, 8, or at the final treatment evaluation; sites were to select one visit for each subject to collect all PK samples. Sampling times were at predose, and 0.5, 1, 2, 3, 4, 6, and 8 hours postdose. Morning unstimulated serum cortisol levels were also measured in all subjects at screening and after 2, 4, and 12 weeks of double-blind treatment.

Results

Figure 2. Response to Therapy, Full Analysis Set, Study MPI-101-01

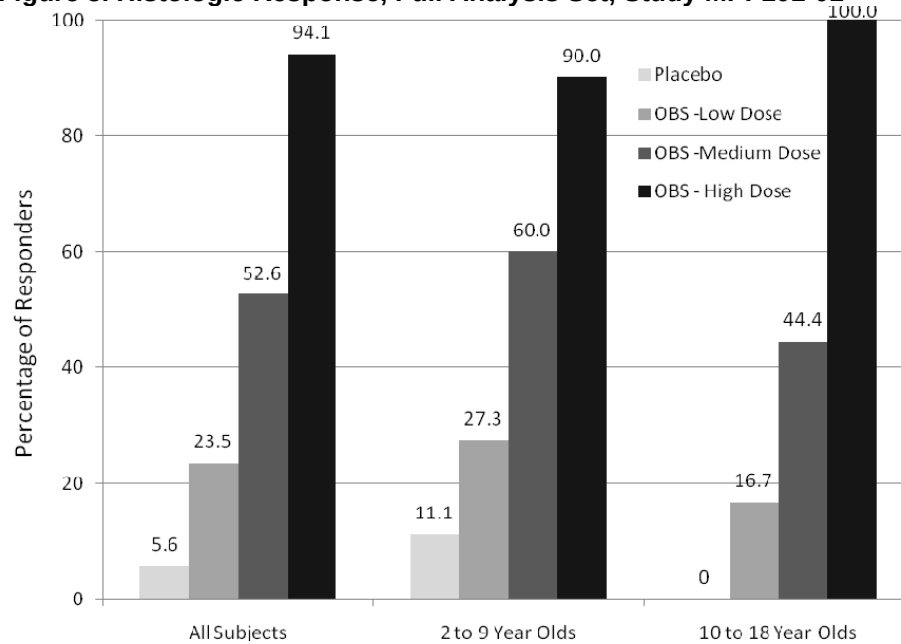


Source: Study MPI 101-01 CSR, Table 14.2.1.1, Table 14.2.4.1, and Table 14.2.2.1

* p < 0.02 for the comparison of OBS (oral budesonide suspension/budesonide oral suspension [BOS]) and placebo for each endpoint

Abbreviation: OBS, oral budesonide solution

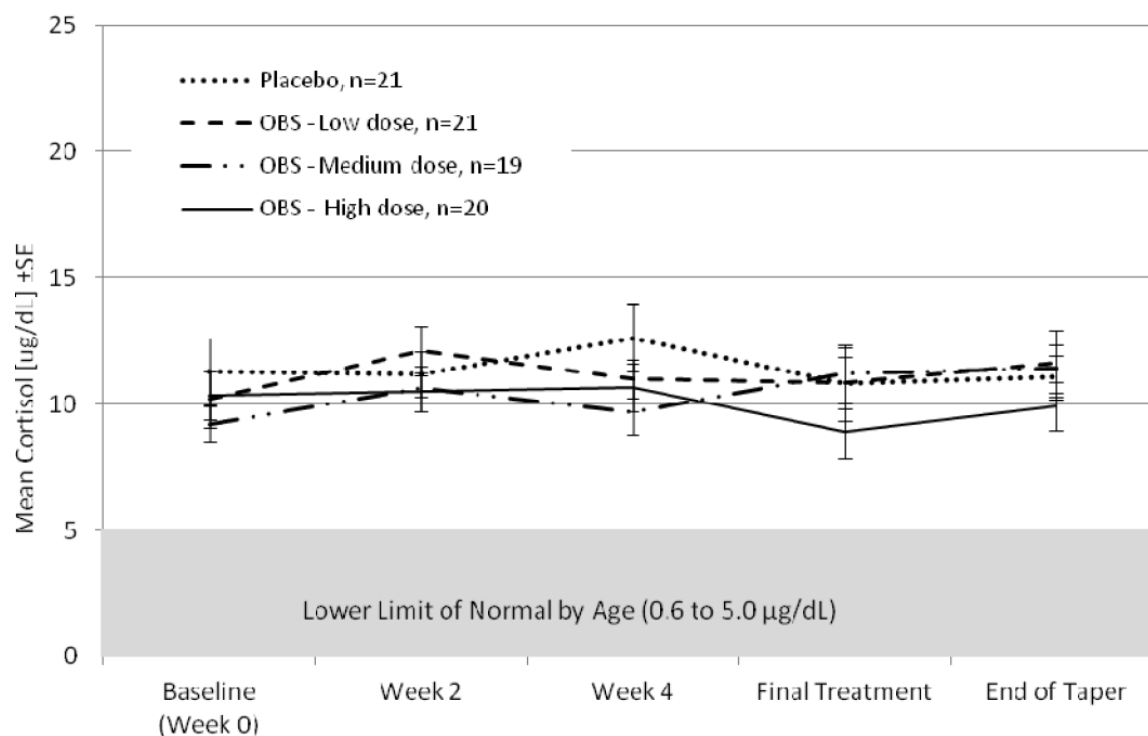
Figure 3. Histologic Response, Full Analysis Set, Study MPI-101-01



Source: Study MPI 101-01 CSR, Table 14.2.1.1, Table 14.2.4.1, and Table 14.2.2.1

Abbreviation: OBS, oral budesonide solution

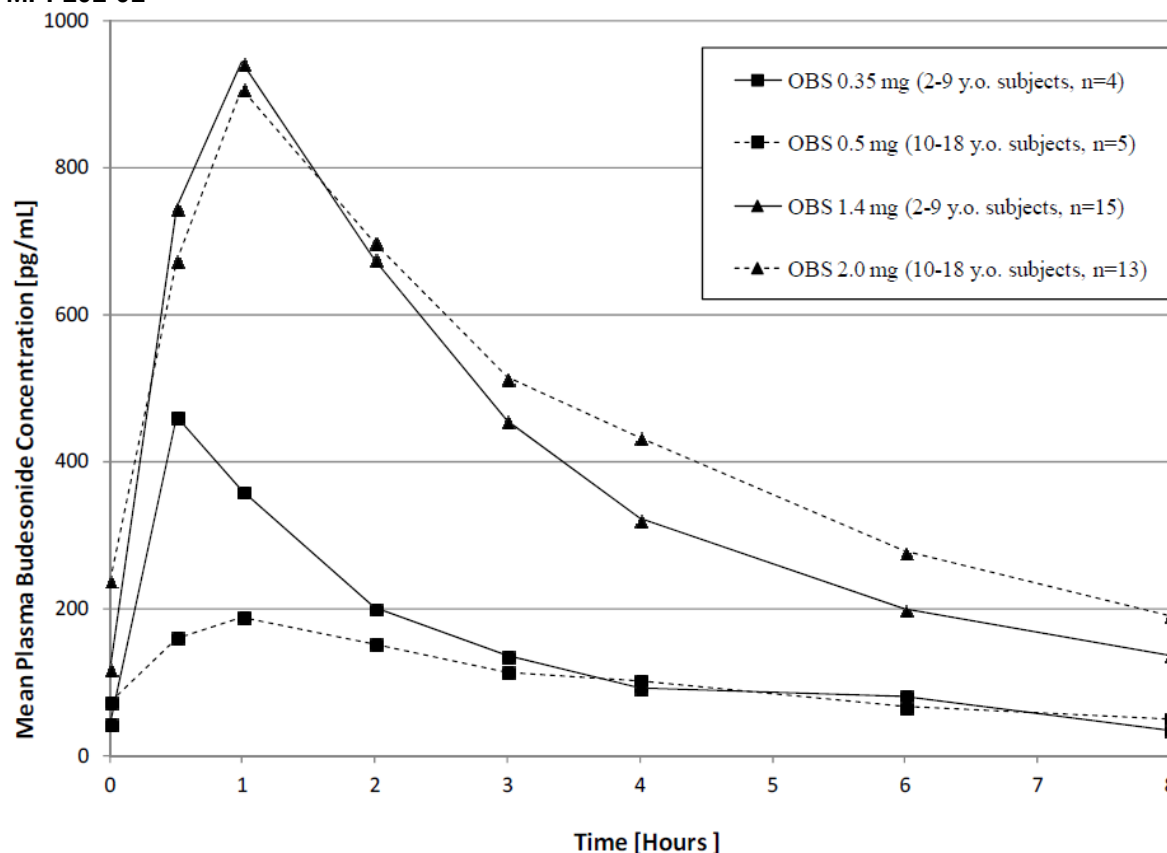
Figure 4. Mean Morning Cortisol Levels by Treatment Group, Study MPI-101-01



Source: Study MPI-101-01 CSR, Figure 8. [\CDSESUB1\evsprod\nda213976\0002\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\eosinophilic-esophagitis\5351-stud-rep-contr\mpi-101-01\mpi-101-01-csr-legacy.pdf](#)

Abbreviation: OBS, oral budesonide solution

Figure 5. Budesonide Plasma Concentration-Time Profiles by Treatment at Steady State, Study MPI-101-01



Source: Study MPI 101-01 CSR, Appendix 16.2, Listing 16.2.3.1 and post hoc PK figures (Section 14).
Abbreviation: OBS, oral budesonide solution

Table 9. Budesonide PK Parameters at Steady State from Dose Ranging Study, Study MP101-01

Parameter	OBS 0.35 mg (n=4)	OBS 0.50 mg (n=5)	OBS 1.4 mg (n=15)	OBS 2.0 mg (n=13)
Patients' age (years old)	2-9	10-18	2-9	10-18
AUC _{0-last} (hr·pg/mL)				
Mean (SD)	1139.5 (800.84)	743.8 (425.26)	3259.3 (2109.37)	3636.9 (1769.88)
Median	1026.0	551.0	2580.0	2700.0
Min, max	286, 2220	328, 1390	320, 8270	1730, 7240
C _{max} (pg/mL)				
Mean (SD)	492.0 (417.81)	195.0 (64.37)	1019.5 (670.18)	958.4 (527.64)
Median	402.0	191.0	812.0	708.0
Min, max	104, 1060	139, 296	70, 2550	359, 2210
T _{max} (hours)				
Mean (SD)	0.68 (0.360)	1.20 (0.447)	0.93 (0.372)	1.12 (0.546)
Median	0.50	1.00	1.00	1.00
Min, max	0.5, 1.22	1, 2	0.5, 2	0.5, 2
T _{1/2} (hours)				
Mean (SD)	3.288 (0.8265)	3.398 (0.7841)	3.472 (2.6753)	3.528 (1.0223)
Median	3.220	3.515	2.700	3.560
Min, max	2.36, 4.35	2.34, 4.22	1.85, 12.7	2.05, 5.11

Source: Study MPI-101-01 CSR, Table 18. [\CDSESUB1\evsprod\nda213976\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\eosinophilic-esophagitis\5351-stud-rep-contr\mpi-101-01\mpi-101-01-csr-legacy.pdf](#)

Abbreviations: AUC_{0-last}, area under the plasma concentration-time curve from time zero to time of last measurable concentration; C_{max}, maximum (peak) plasma drug concentration; OBS, oral budesonide suspension; PK, pharmacokinetic; SD, standard deviation; T_{max}, time to reach maximum (peak) plasma concentration following drug administration; T_{1/2}, elimination half-life

It should be noted that out of 60 subjects who received budesonide in the study, only 37 subjects had plasma samples that were evaluated for PK analysis. Further, there were only four subjects with available data for the lowest BOS dose (0.35 mg). One subject in the low dose 0.35 mg BOS group with unexplained high C_{max} (a 3-year-old subject had a C_{max} that was 2 to 4 times greater than the C_{max} of the other three subjects who received the 0.35 mg BOS dose) led to the disparity between concentration-time curves and PK parameter estimates for the 0.35 mg and 0.5 mg BOS doses. No explanation was provided by the Applicant for this high C_{max} .

Conclusion

A response to therapy was achieved in 5.6%, 11.8%, 52.6% and 47.1% of subjects in the placebo, low, medium, and high BOS dose groups, respectively ([Figure 2](#)). The dose-response relationship for the efficacy endpoint was largely driven by the histologic response (i.e., peak eosinophil count ≤ 6 /high-power field [HPF]). Histologic response 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, with a statistically significant difference in histologic response observed between the medium- and high-dose BOS groups ($p=0.019$) ([Figure 2](#)). In contrast, the EoE Clinical Symptom Score, as reported by the physician investigator, failed to detect a significant change in symptoms between placebo and any of the BOS treatment groups. The Applicant attributed this to the lack of sensitivity of a physician-reported versus a patient-reported outcome measures as was used in MPI 101-06 (see eCTD Module 2.7.3, Section 1.6.2). Dose-dependent responses were also observed in the secondary endpoints of the rate of histologic remission (i.e., peak eosinophil count ≤ 1 /HPF) and improvement in gross endoscopic findings (i.e., total endoscopy score). Further, efficacy outcome based on histologic response rate were generally similar for subjects 2 to 9 years of age and subjects 10 to 18 years of age ([Figure 3](#)).

Mean cortisol values were within normal limits at each study time point and were similar among all BOS dose groups and placebo ([Figure 4](#)). In addition, there were no abnormal values during the taper period.

The C_{max} and AUC values at steady state increased in a dose proportional manner from the low dose (0.35 to 0.5 mg/day) to the medium (1.4 to 2.0 mg/day) and high dose (2.8 to 4.0 mg/day) groups. There were no apparent dose effects on the PK parameters of budesonide. Mean T_{max} and elimination half-life values were similar across the dose and age groups.

Based on result of this dose-ranging phase 2 study, high dose 2 mg twice daily dose was selected for further clinical evaluation.

Phase 2 Study in Adolescents and Adults (11 to 40 Years, Inclusive) (MPI-101-06)

Study Design

Study MPI 101-06 was a phase 2, randomized, double blind, placebo-controlled, parallel-arm study in adolescents and adults (11 to 40 years, inclusive) with EoE and symptoms of dysphagia. The objectives of the study were to evaluate the efficacy, safety, and tolerability of BOS (MB-9 formulation) 2 mg twice daily (qAM, pc, and at bedtime [hs]) during a 12-week double-blind treatment period.

After screening, eligible subjects entered a 4-week, single-blind, placebo baseline period and were dispensed the study drug (placebo). After completing the placebo baseline period, eligible

subjects were randomized to OBS 2 mg BID or placebo (ratio 1:1, stratified by center) for 12 weeks of double-blind treatment (treatment period; Weeks 4 to 16). Subjects returned to the study center for assessments every 4 weeks (Weeks 8, 12, and 16, final evaluation for the treatment period). The study also included an evaluation of the safety and tolerability of BOS 2 mg once daily, hs, during 24 weeks of open-label extension (OLE) treatment.

A total of 93 subjects were randomized and received at least 1 dose of investigational product (IP) during the double-blind treatment period; 51 (adolescents; 18, adults; 33) and 42 (adolescents; 17, adults; 25) subjects received BOS and placebo, respectively.

Results

Pharmacokinetic data were not collected in this study. A greater proportion of subjects in the budesonide treated group (38.8% subjects) demonstrated a peak eosinophil count ≤ 6 /HPF across all esophageal levels (one of the coprimary efficacy endpoint) than the placebo group (2.6% subjects) at the final treatment evaluation (Week 16).

Further, unstimulated mean cortisol levels at baseline were similar across both treatment groups (10.87 $\mu\text{g/dL}$ in placebo; 10.41 $\mu\text{g/dL}$ in BOS) and did not change significantly after 12 weeks of treatment for both treatment group (mean change from baseline to final treatment value was 0.39 $\mu\text{g/dL}$ in placebo and -0.73 $\mu\text{g/dL}$ in BOS) ([Table 10](#)).

Table 10. Morning Cortisol Levels During 12-Weeks Double Blinded Treatment Period, Study MPI 101-06

Morning Cortisol ($\mu\text{g/dL}$)	Placebo (N=42)	OBS 2 mg BID (N=51)
Baseline ^[1]	n=42	n=49
Mean (SD)	10.87 (4.2)	10.41 (3.8)
Median (min, max)	10.10 (4.1, 21.9)	9.50 (4.8, 20.7)
Below the lower limit of the normal range, n (%)	0	0
Change from baseline to the final evaluation (Week 16)	n=42	n=51
Mean (SD)	0.39 (4.2)	-0.73 (4.4)
Median (min, max)	0.30 (-8.3 , 9.9)	0.10 (-12.6 , 7.0)
Below the lower limit of the normal range, n (%)	2 (4.8)	3 (5.9)

Source: Table 41, Module 5.3.5.1, MPI 101-06 Clinical Study Report Amendment 1. [\CDSESUB1\evsprod\nda213976\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\eosinophilic-esophagitis\5351-stud-rep-contr\mpi-101-06\mpi-101-06-clinical-study-report-amendment-1.pdf](#)

^[1] Baseline was defined as the last nonmissing value prior to the first dose of double-blind study drug.

Note: Percentage of subjects with a morning cortisol level below the lower limit of the normal range was based on the number of subjects with a nonmissing value at the given visit

Abbreviations: BID, twice daily; SD, standard deviation

After 24-weeks of OLE, mean changes in morning cortisol value from OLE baseline (defined as the value before the first dose of double-blind study drug) was similar to the values observed during the double blinded treatment period (0.33 $\mu\text{g/dL}$ for all subjects, 0.16 $\mu\text{g/dL}$, placebo/OBS; 0.47 $\mu\text{g/dL}$, OBS/OBS, [Table 11](#)).

Table 11. Morning Cortisol Level During 24-Week OLE Period, Study MPI 101-06

	Placebo/OBS		
	2 mg QD (N=37)	OBS/OBS 2 mg QD (N=45)	All Subjects (N=82)
Morning Cortisol (µg/dL)			
OLE baseline ^[1]	n=35	n=43	n=78
Mean (SD)	10.63 (4.493)	10.41 (3.889)	10.51 (4.144)
Median (min, max)	9.90 (4.1, 21.9)	9.50 (4.8, 20.7)	9.70 (4.1, 21.9)
Below the lower limit of the normal range, n (%)	0	0	0
Change from OLE baseline-final ^[2]	n=35	n=42	n=78
Mean (SD)	0.16 (4.837)	0.47 (4.339)	0.33 (4.544)
Median (min, max)	1.10 (-12.1, 8.9)	-0.10 (-9.0, 12.1)	0.20 (-12.1, 12.1)
Below the lower limit of the normal range, n (%)	0	3 (7.0)	3 (3.8)

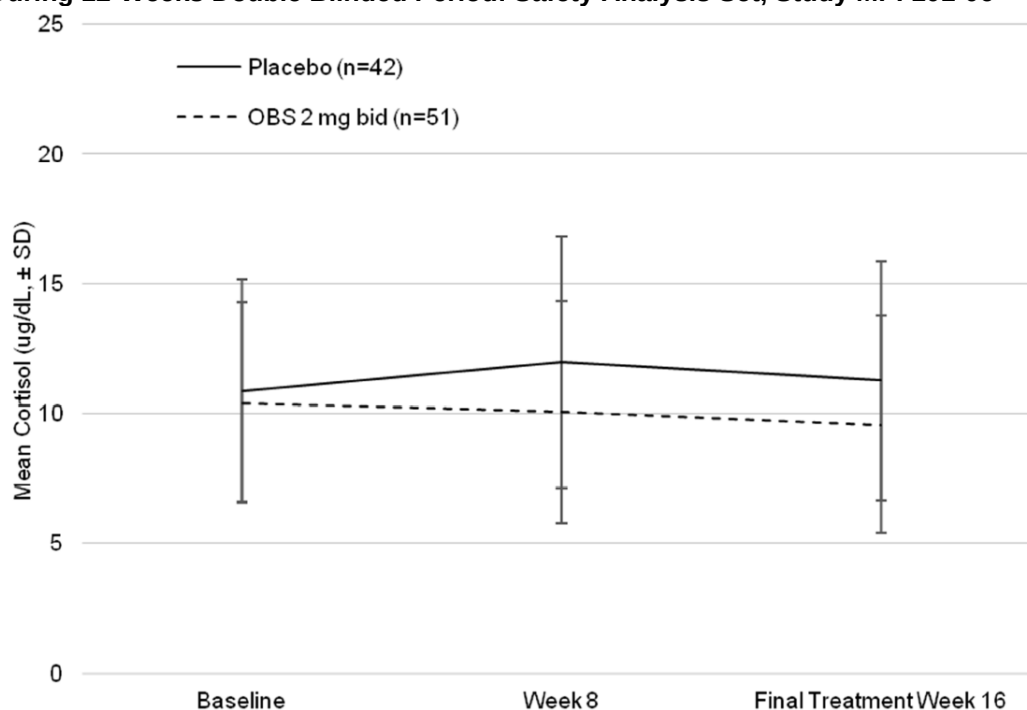
Source: Table 42, Module 5.3.5.1, MPI 101-06 Clinical Study Report Amendment 1. [\CDSESUB1\evsprod\nda213976\0002\m5\53-clin-stud-rep\535-rep-efic-safety-stud\eosinophilic-esophagitis\5351-stud-rep-contr\mpi-101-06\mpi-101-06-clinical-study-report-amendment-1.pdf](#)

^[1] OLE baseline was defined as the last nonmissing value prior to the first dose of double-blind study drug.

^[2] Final OLE evaluation was OLE Week 24 or early termination.

Notes: Placebo/OBS received placebo bid during the treatment period and OBS 2 mg once daily during OLE; OBS/OBS received OBS 2 mg bid during the treatment period and OBS 2 mg once daily during OLE; all subjects received OBS 2 mg once daily during OLE. Percentage of subjects with a morning cortisol level below the lower limit of the normal range based on the number of subjects with a nonmissing value at the given visit.

Abbreviations: OBS, oral budesonide suspension; OLE, open-label extension; QD, once daily; SD, standard deviation

Figure 6. Mean Morning Cortisol Values at Baseline, Week 8, and Final Treatment Evaluation During 12-Weeks Double Blinded Period: Safety Analysis Set, Study MPI 101-06

Source: Figure 7, Module 5.3.5.1, MPI 101-06 Clinical Study Report Amendment 1. [\CDSESUB1\evsprod\nda213976\0002\m5\53-clin-stud-rep\535-rep-efic-safety-stud\eosinophilic-esophagitis\5351-stud-rep-contr\mpi-101-06\mpi-101-06-clinical-study-report-amendment-1.pdf](#)

Abbreviations: OBS, oral budesonide solution; SD, standard deviation

Conclusion

A significant treatment effect (38.8% BOS versus 2.6% in placebo) for budesonide treatment was demonstrated for one of the coprimary efficacy endpoints of peak eosinophil count ≤ 6 /HPF across all esophageal levels at the final treatment evaluation (Week 16).

Change in mean morning cortisol from baseline to end of 12-weeks double blinded treatment was greater with budesonide than placebo, i.e., 0.39 for placebo and -0.73 for OBS). However, morning cortisol concentrations after treatment with placebo and 2 mg BID BOS treatment group were overall similar and similar numbers of subjects with a morning cortisol below the lower limit of the normal range at the final treatment evaluation (4.8% in placebo versus 5.9% in OBS) were observed.

Further, mean changes in morning cortisol from OLE baseline (defined as the value before the first dose of the double-blind study drug) to the end of 24 weeks of the OLE period were similar to the values observed during the double blinded treatment period. A low percentage of subjects had a morning cortisol result below the lower limit of the normal range at the final OLE evaluation (3 [3.8%] subjects). These findings indicate no significant effects on cortisol suppression during double-blind treatment and OLE.

Phase 3 Study: Randomized, Double-Blind, Placebo-Controlled Study in Adolescent and Adult Subjects (11 to 55 Years of Age, Inclusive) With Eosinophilic Esophagitis (SHP621-301)

Study Design

This was a phase 3, randomized, double-blind, multicenter, parallel-group, placebo-controlled study to evaluate the efficacy, safety, and tolerability of twice daily administration of BOS (qAM, pc, and hs) in adolescents and adults aged 11 to 55 years, inclusive, with EoE and dysphagia. This study comprised three periods: a 3- to 6-week screening period, a 4-week single-blind placebo lead-in period, and a 12-week double-blind treatment period. Eligible subjects were randomized in a 2:1 ratio to double-blind treatment (BOS 2 mg twice daily or placebo twice daily). Randomization was performed centrally and stratified by age group (2 strata total: <18 years or ≥18 years) to allow for equal distribution of adolescent subjects (11 to 17 years, inclusive) to each treatment group, and by diet restriction for EoE or other health-related conditions (no diet restriction or any diet restriction). A total of 318 subjects were randomized and received at least 1 dose of IP during the double-blind treatment period; 213 and 105 subjects received BOS and placebo, respectively.

Results

Sparse and intensive PK samples were collected in adult subjects. Specifically, blood samples for PK analysis were obtained one time on any day starting 7 days after Week 5 and through Week 16. PK samples were to be drawn at predose, 0.5, and 1 hour postdose, and at additional postdose time points, if feasible (2, 3, 4, 6, 8, and 12 hours postdose).

A population PK analysis was performed for all subjects who received BOS treatment and provided at least one quantifiable plasma concentration of budesonide. A total of 72 unique adult subjects receiving BOS treatment provided at least one PK sample; 49 subjects provided intensive PK samples and were included in the PK parameter set. PK samples were not collected in adolescent subjects.

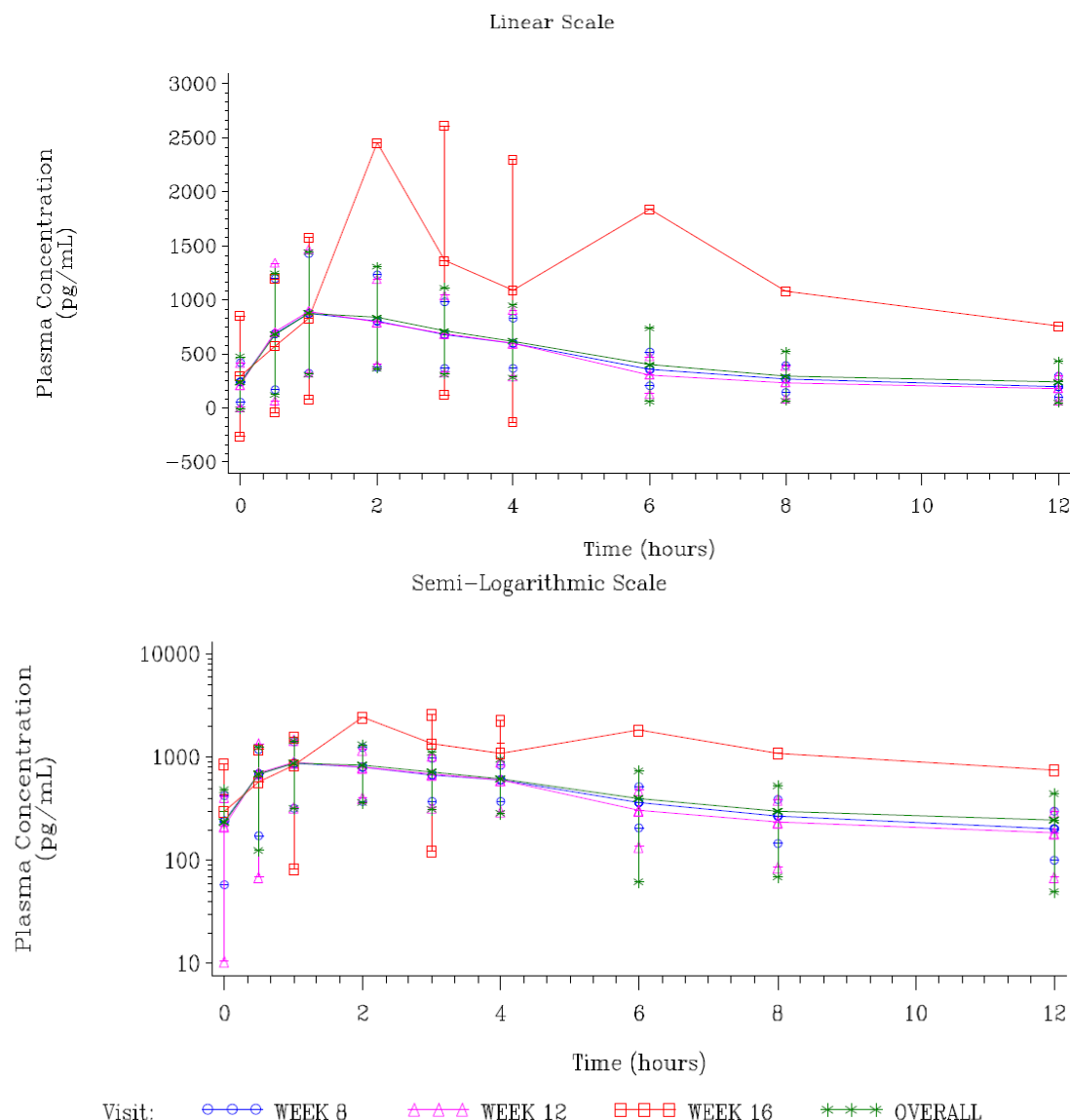
Table 12. Summary of Plasma Budesonide Pharmacokinetic Parameters, PK Parameter Set, Study SHP621-301 in Adult Patients with EoE

Parameter	Summary Statistic	Week 8 ^[1]	Week 12 ^[1]	Week 16 ^[1]	Overall
AUC_{0-tau} (h·pg/mL)					
N		12	11	1	24
GM (%CV)		5056 (49.3)	4526 (53.3)	18310 (NC)	5071 (58.1)
95% CI of GM		3759, 6802	3235, 6334	NC	4038, 6368
C_{max} (pg/mL)					
N		25	19	3	47
GM (%CV)		940.7 (54.2)	909.5 (56.5)	751.7 (158.9)	914.8 (59.2)
95% CI of GM		762.9, 1160	705.8, 1172	46.24, 12220	778.8, 1074
T_{max} (h)					
N		25	19	3	47
Median (min, max)		2.00 (0.50, 4.00)	2.00 (0.50, 4.00)	2.08 (1.00, 2.87)	2.00 (0.50, 4.00)
λ_z (/h)					
N		11	11	1	23
GM (%CV)		0.2058 (18.5)	0.2250 (27.0)	0.1262 (NC)	0.2103 (25.2)
95% CI of GM		0.1819, 0.2329	0.1882, 0.2690	NC	0.1888, 0.2341
t_{1/2} (h)					
N		11	11	1	23
GM (%CV)		3.367 (18.5)	3.081 (27.0)	5.491 (NC)	3.296 (25.2)
95% CI of GM		2.976, 3.810	2.577, 3.682	NC	2.960, 3.670
CL/F (L/h)					
N		12	11	1	24
GM (%CV)		395.5 (49.3)	441.8 (53.3)	109.2 (NC)	394.4 (58.1)
95% CI of GM		294.0, 532.1	315.7, 618.3	NC	314.1, 495.3
V_z/F (L)					
N		11	11	1	23
GM (%CV)		1944 (46.1)	1964 (54.4)	865.3 (NC)	1886 (51.4)
95% CI of GM		1448, 2611	1395, 2764	NC	1530, 2325

Source: SHP621-301 CSR, Section 14, Table 14.2.3.3

^[1] Week 8, Week 12, and Week 16 samples were collected 4, 8, and 12 weeks, respectively, after initiation of double-blind treatment. Note: PK Parameters were only estimated in subjects with at least 4 postdose PK samples. Geometric mean, geometric %CV and 95% CI of geometric mean were set to missing where zero (below lower limits of quantitation; BLQ) values exist. PK parameters from unscheduled visits have been summarized with parameters from the nearest visit. Abbreviations: λ_z, terminal rate constant; AUC_{0-tau}, area under the curve during a dosing interval; CI, confidence interval; CL/F, oral clearance; C_{max}, maximum concentration; CV, coefficient of variation; GM, geometric mean; n, number of subjects with evaluable values; NC, not calculated; PK, pharmacokinetic; T_{max}, time to maximum observed plasma concentration; V_z/F, apparent volume of distribution

Figure 7. Mean ($\pm$ SD) Plasma Concentration-Time Profiles of Budesonide in Adult Patients with EoE, PK Parameter Set, Study SHP621-301



Source: SHP621-301 CSR Section 14, Figure 14.2.4.1

Note: Budesonide concentration-time profiles are only displayed for subjects with at least 4 postdose PK samples.

PK concentrations from unscheduled visits have been summarized with concentrations from the nearest visit. PK concentrations from samples with collection times that deviated from the nominal time by more than ± 5 minutes within the first 4 hours, ± 15 minutes after 4 hours postdose were excluded.

Ns for C_{max} are 25, 19, and 3 for Week 8, 12, and 16, respectively. Sample sizes were smaller for subsequent time points.

Abbreviations: PK, pharmacokinetic; SD, standard deviation

Median morning unstimulated cortisol at baseline, Weeks 4, 8, 12, and 16 was slightly lower for the BOS group than for the placebo group at postbaseline timepoints (i.e., Weeks 8, 12, and 16). Morning unstimulated cortisol did not change significantly from baseline to end of the 12 weeks of treatment for both placebo arm and treatment arm with BOS 2 mg BID (0.15 mcg/dL in placebo versus -1.68 mcg/dL for BOS 2.0 mg BID).

Table 13. Morning Unstimulated Cortisol Levels (mcg/dL) by Treatment Group, Study SHP621-301

Visit Statistic	Placebo (N=105)		BOS 2.0 mg BID (N=213)	
	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Baseline [a]				
n	105		213	
Mean (SD)	12.44 (5.347)		12.96 (5.666)	
Median	12.20		12.00	
Q1, Q3	8.70, 14.90		9.20, 16.00	
Min, Max	0.6, 34.2		1.5, 41.8	
Week 8				
n	102	102	207	207
Mean (SD)	12.88 (6.020)	0.47 (4.517)	11.44 (5.780)	-1.47 (4.799)
Median	12.45	0.60	11.00	-1.20
Q1, Q3	9.10, 16.40	-2.60, 2.90	7.70, 14.20	-4.30, 2.00
Min, Max	1.0, 38.1	-12.7, 16.1	0.5, 33.1	-15.7, 11.6
Week 12				
n	96	96	204	204
Mean (SD)	12.26 (5.462)	-0.24 (4.904)	11.88 (5.823)	-1.11 (5.766)
Median	11.15	-0.55	11.30	-0.75
Q1, Q3	8.60, 15.70	-3.35, 2.15	8.00, 15.10	-3.90, 2.25
Min, Max	0.8, 30.9	-16.2, 23.4	0.5, 33.8	-36.2, 15.8
Week 16				
n	90	90	201	201
Mean (SD)	12.55 (5.388)	0.15 (4.955)	11.32 (5.598)	-1.68 (5.721)
Median	12.60	-0.30	11.10	-1.20
Q1, Q3	7.90, 15.10	-2.50, 2.70	7.20, 14.30	-5.30, 1.90
Min, Max	3.9, 29.0	-18.8, 12.0	0.5, 32.3	-20.1, 14.0

Source: Module 5.3.5.1, CSR SHP621-301, Table 14.3.6.1

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All measurements are done Predose. [a] Baseline is defined as the predose value at Week 4.

Conclusions

Following repeated twice daily administration of BOS 2 mg in adult patients with EoE, estimated geometric mean AUC_{tau} and C_{max} were 5071 h·pg/mL (n=24) and 915 pg/mL (n=47), respectively. These PK parameters were generally comparable after 4 (Week 8) and 8 weeks (Week 12) of double-blind treatment. The C_{max} was attained at approximately 2 hours post dose (median T_{max}); thereafter, plasma concentrations of budesonide declined monoexponentially with a geometric mean half-life ($T_{1/2}$) of 3.3 hours across all visits. Due to the limited PK data (n=1) available at the final treatment evaluation (Week 16), limited comparisons to the Week 8 and 12 data could be made. Further, high intersubject variability of plasma budesonide exposures over the dosing interval was observed across all visits (overall) with geometric mean % CV values of 58.1% and 59.2% for AUC_{tau} and for C_{max} , respectively. Based on a cross-study comparison, mean C_{max} at steady-state in adult patients with EoE were similar to those in healthy subjects after single dose administration of 2 mg (915 pg/mL versus 1092.68 pg/mL, respectively).

Morning unstimulated cortisol did not change significantly from baseline to the end of the 12 weeks of treatment for both placebo arm and treatment arm with BOS 2 mg BID.

2.3. HPA Axis Suppression Assessment

Issue

Is the hypothalamic-pituitary-adrenal (HPA) axis suppression by BOS adequately assessed?

Background

Since budesonide is a glucocorticoid proposed to be used in EOE patient population, adverse events, including hypercortisolism and adrenal axis suppression, a known class effect of long-term glucocorticoid use, was assessed by the Applicant.

Assessment

HPA axis suppression potential of BOS was evaluated by measuring morning cortisol levels in phase 2 and phase 3 studies and conducting adrenocorticotrophic hormone (ACTH) stimulation test in phase 3 studies. As ACTH stimulation test is a more reliable test to assess the HPA axis suppression than the morning cortisol levels are, this review primarily focuses on the results of ACTH stimulation test. This test was conducted by measuring ACTH stimulated levels of cortisol at baseline and after respective treatment periods in individual phase 3 studies. Blood samples were collected just prior to and approximately 30- and 60-minutes following injection (intramuscular or intravenous) of synthetic ACTH (250 µg) to measure the stimulated level of cortisol. Adrenal suppression or normal to abnormal ACTH stimulation serum cortisol shifts were defined as using a threshold defined as peak ACTH stimulated serum cortisol of ≤ 18 µg/dL after a synthetic ACTH injection.

In Trial 301, the BOS and placebo treatment arms had a similar proportion of patients noted to have abnormal response to ACTH stimulation at the baseline at Week 4 (3.8% versus 5.0%). After 12 weeks of treatment (at Week 16), a higher percentage of patients who received BOS 2 mg BID had abnormal ACTH stimulated serum cortisol levels (9.1%) when compared to patients in the placebo group (3.4%) ([Table 14](#)).

Table 14. ACTH Stimulation Test Values, Safety Population, Trial 301

Variable	BOS 2 mg BID	Placebo	Risk Difference (95% CI)
Week 4 screening maximum cortisol post-dose ACTH			
n	211	100	NA
Peak value ≤ 18 mcg/dL ^[1]	8 (3.8)	5 (5.0)	-1.2 (-6.2, 3.8)
Week 16 maximum cortisol post-dose ACTH			
n	198	87	NA
Peak value ≤ 18 mcg/dL ^[1]	18 (9.1)	3 (3.4)	5.7 (0.1, 11.2)

Source: adlb.xpt; Software: R

^[1] Values in "Peak value ≤ 18 mcg/dL" row of the BOS and Placebo columns are expressed as n (%), in which n represents the number of patients with peak value ≤ 18 mcg/dL.

Abbreviations: ACTH, adrenocorticotrophic hormone; BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval

In Trial 302, abnormal ACTH stimulated peak cortisol levels (≤ 18 mcg/dL) were observed at Week 36 for 7.3% of patients in the BOS-BOS group (from 3.1% at Trial 301 baseline and 7.9% at Trial 302 screening), 8.2% of patients in the PBO-BOS group (from 6.5% at Trial 301 baseline and 3.3% at Trial 302 screening), and 11.1% of patients in the BOS-PBO group (from 4.5% at Trial 301 baseline and 8.7% at Trial 302 screening) ([Table 15](#)).

Table 15. ACTH Stimulation Test Values, Safety Population, Trial 302

Variable	BOS-BOS N=131	PBO-BOS N=65	Total ^[1] N=196	BOS-PBO N=23
301 baseline maximum cortisol postdose ACTH				
n	130	62	192	22
Peak value ≤18 mcg/dL ^[2]	4 (3.1)	4 (6.5)	8 (4.2)	1 (4.5)
302 screening maximum cortisol postdose ACTH				
n	127	61	188	23
Peak value ≤18 mcg/dL ^[2]	10 (7.9)	2 (3.3)	12 (6.4)	2 (8.7)
Week 36 maximum cortisol postdose ACTH				
n	96	49	145	18
Peak value ≤18 mcg/dL ^[2]	7 (7.3)	4 (8.2)	11 (7.6)	2 (11.1)

Source: adlb.xpt; Software: R

^[1] Total of BOS-BOS and PBO-BOS^[2] Values in "Peak value ≤18 mcg/dL" are expressed as n (%), in which n represents the number of patients with peak value ≤18 mcg/dL.

Abbreviations: ACTH, adrenocorticotrophic hormone; BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval; PBO, placebo

HPA Suppression Comparison Between Adults (≥18 Yrs) and Adolescents (<18 Yrs):

In Trial 301, the BOS and placebo treatment arms had a similar proportion of patients noted to have abnormal response to ACTH stimulation at the baseline at Week 4 (3.3% versus 4.6% for adults and 7.4% versus 7.7 for adolescents). After 12 weeks of treatment (at Week 16), a higher percentage of adult patients who received BOS 2 mg BID had abnormal ACTH stimulated serum cortisol levels (8.1%) when compared to adult patients in the placebo group (1.4%) ([Table 16](#)). However, similar percentage of adolescent patients who received BOS 2 mg BID had abnormal ACTH stimulated serum cortisol levels (15.4%) when compared to adolescent patients in the placebo group (14.3%) ([Table 16](#)). It should be noted that the number of patients in this subgroup analysis is low. Therefore, these change in percentage of patients based on subgroup analysis may not be interpreted with statistical significance.

Table 16. ACTH Stimulation Test Values by Age, Safety Population, Trial 301

Variable	BOS 2 mg BID		Placebo	
	<18 Years	≥18 Years	<18 Years	≥18 Years
Week 4 screening maximum cortisol postdose ACTH				
n	27	184	13	87
Peak value ≤18 mcg/dL ^[1]	2 (7.4)	6 (3.3)	1 (7.7)	4 (4.6)
Week 16 maximum cortisol postdose ACTH				
n	26	172	14	73
Peak value ≤18 mcg/dL ^[1]	4 (15.4)	14 (8.1)	2 (14.3)	1 (1.4)

Source: adlb.xpt; Software: R

^[1] Values in "Peak value ≤18 mcg/dL" are expressed as n (%), in which n represents the number of patients with peak value ≤18 mcg/dL.

Abbreviations: ACTH, adrenocorticotrophic hormone; BID, twice daily; BOS, budesonide oral suspension; CI, confidence interval

In Trial 302, abnormal ACTH stimulated peak cortisol levels (≤18 mcg/dL) were observed at Week 36 for 7.7% of adolescents patients and 7.2% of adult patient in the BOS-BOS group, 10.0% of adolescent patients and 3.7% of adult patient in the PBO-BOS group, and 50% of adolescent patients and 6.3% of adult patient in the BOS-PBO group ([Table 17](#)). However, similar to above subgroup analysis for trial 301, the number of patients in each subgroup were low. Therefore, a statistically meaningful results may not be interpreted from this data.

Table 17. ACTH Stimulation Test Values by Age, Safety Population, Trial 302

Variable	BOS-BOS N=131		PBO-BOS N=65		Total ^[1] N=196		BOS-PBO N=23	
	<18 Years	≥18 Years	<18 Years	≥18 Years	<18 Years	≥18 Years	<18 Years	≥18 Years
301 baseline maximum cortisol postdose ACTH								
n	16	114	10	52	26	166	3	19
Peak value ≤18 mcg/dL ^[2]	1 (6.3)	3 (2.6)	1(10.0)	3 (5.8)	2 (7.7)	6 (3.6)	0	1 (5.3)
302 screening maximum cortisol postdose ACTH								
n	15	112	11	50	26	162	3	20
Peak value ≤18 mcg/dL ^[2]	2 (13.3)	8 (7.1)	2 (18.2)	0	4 (15.4)	8 (4.9)	1 (33.3)	1 (5.0)
Week 36 maximum cortisol postdose ACTH								
n	13	83	10	39	23	122	2	16
Peak value ≤18 mcg/dL ^[2]	1 (7.7)	6 (7.2)	1 (10.0)	3 (7.7)	2 (8.7)	9 (7.4)	1 (50.0)	1 (6.3)

Source: adlb.xpt; Software: R

^[1] Total = BOS-BOS and PBO-BOS^[2] Values in "Peak value ≤18 mcg/dL" are expressed as n (%), in which n represents the number of patients with peak value ≤18 mcg/dL.

Abbreviation: ACTH, adrenocorticotrophic hormone; BOS, budesonide oral suspension; n, number of patients in age group; PBO, placebo

HPA Suppression Comparison With the Listed Drug, Entocort EC

After 8 weeks of treatment with 9 mg Entocort EC (Elan Pharma International Limited 2016) once daily in pediatric patients aged 8 to 17 years with mild to moderate active Crohn's disease, the proportion of patients with abnormal ACTH stimulated peak cortisol level (≤18 mcg/dL) was 75%, compared to 9.1% of patients with EoE between 11 to 55 years of age after 12 weeks treatment with BOS 2 mg BID in Trial 301. This may be due to lower systemic exposure of budesonide in the BOS formulation compared to Entocort EC ([Figure 1](#)).

Conclusion

Normal to abnormal shifts in ACTH stimulated serum cortisol were higher in the BOS group when compared to the placebo group observed in both phase 3 studies. There was no apparent difference in abnormal shifts in ACTH stimulated serum cortisol between adults and adolescents. Compared to the reference product Entocort EC, BOS appears to have lower potential for HPA axis suppression.

2.4. Pharmacometrics Review

2.4.1. Overall Review Summary

2.4.1.1. Population PK Model

The population PK model was developed by the Applicant to characterize the PK of BOS in adults and adolescents (11 to <18 years old). The Applicant's population PK analysis is acceptable. The goodness-of-fit plots and the visual predictive check indicate that the final population PK model is adequate in characterizing the PK profile of budesonide BOS in adults

and adolescents. The estimated PK parameters appear reasonable. The Applicant's analyses were verified by the reviewer with no significant discordance identified.

2.4.1.2. Simulations

The Applicant simulated PK exposure in adults and adolescents using the final population PK model in order to demonstrate similar exposure for the proposed dose of 2 mg BID. The virtual adult and virtual adolescent populations used for the simulations adequately characterized the proposed target adult and adolescent populations, respectively. The steady-state exposure parameters of AUC_{0-12} , C_{max} , and C_{min} are not expected to differ significantly between adults and adolescents after the proposed dose of 2 mg BID.

2.4.2. Applicant's Population PK Analysis

2.4.2.1. Data

The population PK analyses were based on PK data from three clinical studies. The study design, study population, and timing of samples varied among the 3 studies. Brief descriptions of the studies are presented in [Table 18](#).

Table 18. Summary of Clinical Studies Included in Population PK Analysis

Study	Population and No. Subjects ^a	Formulation	Dose
SHP621-101, Phase 1	Healthy adults No. of subjects: 22	BOS MB-7 and MB-9 (Treatments A, C, D and E ^b)	Single dose - 2 mg (0.2 mg/mL in volumes of 10 mL)
MPI-101-01, Phase 2	Children and adolescents with EoE (2-18 years) No. of subjects: 38	BOS MB-7	Multiple dose -12 weeks treatment Placebo Low dose: 0.35 mg/day (once a day) for 2-9 year 0.5 mg/day (once a day) for 10-18 year Medium dose: 1.4 mg/day (once a day) for 2-9 year 2.0 mg/day (once a day) for 10-18 year High dose: 2.8 mg/day (1.4 mg twice a day) for 2-9 year 4.0 mg/day (2mg twice a day) for 10-18 year
SHP621-301, Phase 3	Adolescents and adults (11-55 years, inclusive) with EoE and dysphagia No. of subjects: 72	BOS MB-9	Multiple dose-2 mg twice a day

^a Actual number of subjects included in population PK analysis.
^b Treatment A=BOS MB-9; Treatment C=BOS MB-7; Treatment D=BOS MB-9 with (b) (4) variant; Treatment E=BOS MB-9 formulation with increased (b) (4) variant
Treatment B (Entocort® EC 9 mg (3 x 3 mg capsules) was excluded from the population PK analysis

Source: Table 3-1 in Applicant's Modeling and Simulation Report
Abbreviations: BOS, budesonide oral suspension; PK, pharmacokinetic

The base model and the interim final covariate model were developed from the "bos-2studies-v1" dataset, which contained 22 healthy adults from the relative bioavailability study (SHP621-101) and 38 subjects between the ages of 2 and 19 years from the phase 2 pediatric dose-finding

study (MPI-101-01). This NONMEM data file contained 1505 PK observations from 60 subjects for analysis.

The initial “bos-2studies-v1” dataset was updated to create the “bos-3studies-v2” dataset, which contained the 1,505 PK observations from the initial dataset in addition to 350 PK observations from 72 patients (1 adolescent and 71 adults) from the pivotal phase 3 study (SHP621-301). The NONMEM data file contained a total of 1,855 PK observations from 132 subjects for analysis. This final dataset was used to develop the final population PK model.

Reviewer Comment:

The initial and final datasets had notable differences in covariate distribution due to the differences in studies that contributed data. In the initial dataset used for development of the base model and interim final model, 36 (60.0%) of subjects were between the ages of 2 and 18 years old. In the final dataset used for development of the final model, 37 (28.0%) of subjects were between the ages of 2 and 18 years. A summary of the baseline covariates for both datasets is provided in [Table 19](#).

Table 19. Summary of Baseline Demographic Covariates for Analysis

Covariate	bos-2studies-v1	bos-3studies-v2
Number of PK samples, n (%)		
Study MPI-101-01	256 (17.0%)	256 (13.8%)
Study SHP621-101	1249 (83.0%)	1249 (67.3%)
Study SHP621-301	0	350 (18.9%)
Total	1505 (100%)	1855 (100%)
Baseline age (years)		
N	60	132
Mean (SD)	20.7 (15.9)	28.3 (14.6)
Median (min, max)	15.8 (2.0, 50.0)	29.5 (2.0, 54.8)
Baseline age category, n (%)		
2 to <11 years	23 (38.3)	23 (17.4)
11 to <18 years	13 (21.7)	14 (10.6)
≥18 years	24 (40.0)	95 (72.0)
Baseline weight (kg)		
N	60	132
Mean (SD)	54.0 (27.7)	70.1 (27.6)
Median (min, max)	55.5 (11.4, 119.7)	76.4 (11.4, 122.5)
Baseline height (cm)		
N	60	132
Mean (SD)	149.2 (27.3)	162.2 (23.1)
Median (min, max)	158.5 (87.0, 184.0)	168.6 (87.0, 198.1)
AST (U/L)		
N	60	132
Mean (SD)	26.3 (7.1)	24.4 (9.2)
Median (min, max)	25.0 (16.0, 43.0)	22.0 (12.0, 82.0)
ALT (U/L)		
N	60	132
Mean (SD)	19.8 (9.0)	24.3 (19.8)
Median (min, max)	17.0 (10.0, 55.0)	19.0 (9.0, 173.0)
Compliance (%)		
N	60	132
Mean (SD)	95.0 (9.5)	97.7 (6.8)
Median (min, max)	100.0 (57.0, 108.0)	100.0 (57.0, 108.0)

Covariate	bos-2studies-v1	bos-3studies-v2
Subject status, n (%)		
Healthy volunteers	22 (36.7)	22 (16.7)
Patients with EoE	38 (63.3)	110 (83.3)
Gender, n (%)		
Male	43 (71.7)	83 (62.9)
Female	17 (28.3)	49 (37.1)
Race, n (%)		
White	57 (95.0)	127 (96.2)
Black or African American	3 (5.0)	4 (3.0)
American Indian or Alaska Native	0 (0)	1 (0.8)
Other	0 (0)	0 (0)
Ethnicity, n (%)		
Not Hispanic or Latino	43 (71.7)	113 (85.6)
Hispanic or Latino	17 (28.3)	19 (14.4)

Source: Reviewer Analysis of Applicant's Datasets

Abbreviations: EoE, eosinophilic esophagitis; PK, pharmacokinetic; SD, standard deviation

2.4.2.2. Base Model

The final base model was a two-compartment PK model with first-order absorption with lag time and first-order elimination from the central compartment. The apparent central volume of distribution (V_c/F) was scaled with body weight at baseline according to the following equation,

$$V_c/F = \exp ([tvV_c/F + \ln (Weight (kg)/70) \times VCWT] + [ETA(V_c)])$$

where the final estimate of the effect of body weight on V_c (VCWT) was 0.558.

2.4.2.3. Covariate Analysis

The covariate parameters of dose, study, baseline age, baseline body weight, race, gender, formulation (MB-7 versus MB-9 with all three MB-9 formulation variants pooled together), subject status (healthy volunteers versus patients with EoE), and hepatic enzymes (aspartate aminotransferase and alanine aminotransferase) were evaluated with the base model.

The interim final model included an effect of the MB-7 formulation which reduced the relative bioavailability (F) and shortened the absorption lag time (ALAG1) compared to the pooled MB-9 formulations. The V_c/F was scaled with body weight at baseline according to the following equation,

$$V_c/F = \exp ([tvV_c/F + \ln (Weight (kg)/70) \times VCWT] + [ETA(V_c)])$$

where the final estimate of VCWT was 0.491.

2.4.2.4. Final Model

The final dataset ("bos-3studies-v2") was used as input to refine the final interim model and create the final model. The covariates of body weight, age, height, body surface area, gender, and subject status were reassessed for parameter effects.

The Applicant's final model was a two-compartment model with first-order absorption with a lag time and first-order elimination from the central compartment. The V_c/F was scaled by baseline body weight according to the following equation,

$$V_c/F = \exp ([tvV_c/F + \ln (Weight (kg)/70) \times VCWT] + [ETA(V_c)])$$

where VCWT was fixed to 1.0.

The MB-7 formulation had a slightly lower relative bioavailability of 0.867 compared to the pooled MB-9 formulations which had relative bioavailability equal to 1.0. The MB-7 formulation also had a slightly shorter typical absorption lag time (0.180 hours) than did the pooled MB-9 formulations (0.211 hours).

Notable changes in structure between the interim final model and the final model include fixing the VCWT allometric scaling multiplier to 1.0 in the final model instead of estimating its value. Additionally, the base model and the interim final model had one proportional residual variability estimate for all subjects.

In the final model, residual variability was described using separate estimates for healthy volunteers and patients with EoE. Residual variability was higher for healthy volunteers (CV=29.51%) than for patients with EoE (CV=16.28%). This is likely due to the differences in number and timing of samples, as healthy volunteers had a greater number of early (<0.25 hours postdose) and late (>12 hours postdose) samples than did patients with EoE.

The parameter estimates for the final covariate model are listed in [Table 20](#). The prediction-corrected visual predictive check (pcVPC) plot for the final model is shown in [Figure 8](#).

Table 20. Parameter Estimates of Final Population PK Model

Parameter	Units	Estimate ^a	%RSE ^b	95% CI ^a	IIV ^c
CL/F	L/hr	415	5.56	372-463	64.9
Vc/F	L	409	12.6	319-523	140
Q/F	L/hr	211	10.6	171-260	74.4
Vp/F	L	1371	7.21	1191-1579	51.1
Ka	hr ⁻¹	0.513	7.20	0.446-0.591	48.0
ALAG	hr	0.211	7.39	0.183-0.244	44.5
Vc/F-Weight	unitless	1.00	-	-	-
F-MB-7	unitless	0.867	1.81	0.836-0.898	-
ALAG-MB-7	unitless	0.851	2.05	0.816-0.885	-
σ^2_{prop} : HV	unitless	0.0872	4.50	0.0795-0.0949	29.5% ^d
σ^2_{prop} : EoE	unitless	0.0264	10.6	0.0209-0.0319	16.2% ^d

^a Back-transformed from natural log scale (except for σ^2)

^b RSE=SE.100 (except for σ^2). RSE for σ^2 =SE(σ^2)/ σ^2 .100

^c CV for IIV calculated as $CV_{IIV} = \sqrt{\omega_p^2} .100$ if $\omega_p^2 \leq 0.15$, else $CV_{IIV} = \sqrt{e^{\omega_p^2} - 1} .100$

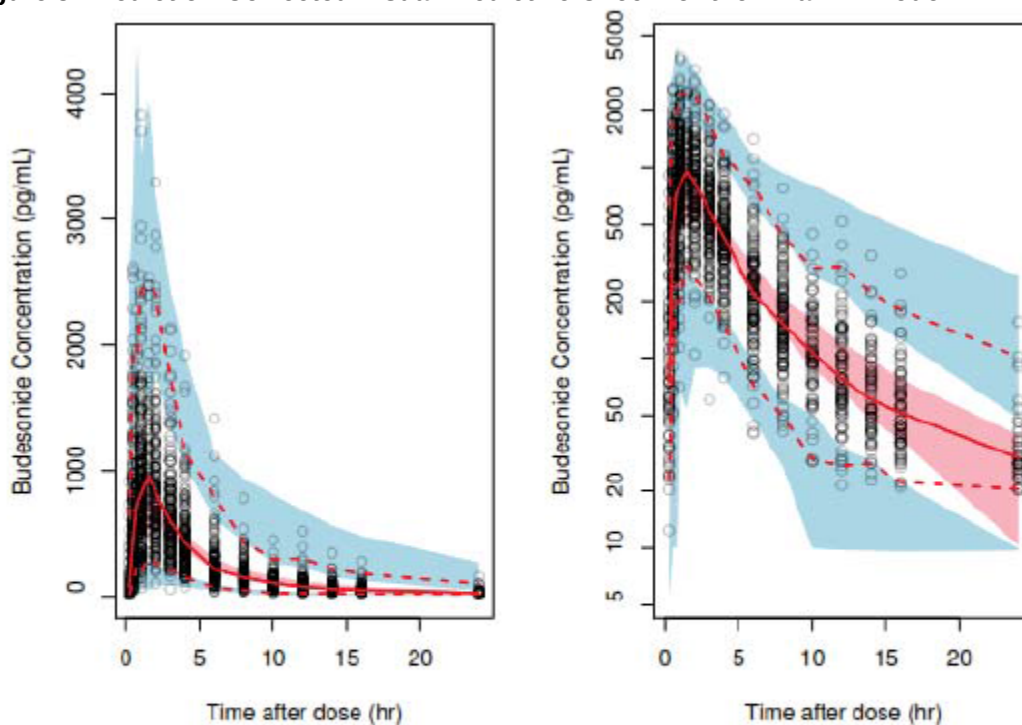
^d Proportional residual error expressed as CV.

HV = Healthy Volunteers. EoE = EoE patients

Source: Table 5-9 in Applicant's Modeling and Simulation Report

Abbreviations: ALAG, absorption lag time; CI, confidence interval; CL, clearance; F, relative bioavailability; IIV, interindividual variability; Ka, absorption rate constant; PK, pharmacokinetic; Q, intercompartmental clearance; RSE, relative standard error; Vc, central volume of distribution; Vp, peripheral volume of distribution

Figure 8. Prediction-Corrected Visual Predictive Check for the Final PK Model



Open Circle: Observed Concentrations; Solid Line: Median of Observed Concentrations; Dashed Lines: 2.5th and 97.5th percentile of observed concentrations. Red Shaded Region: 95% Prediction Interval for Median of Predicted Concentrations; Blue Shaded Regions: 95% Prediction Intervals for the 2.5th and 97.5th percentiles of Predicted Concentrations

Source: Figure 5-6 in Applicant's Modeling and Simulation Report

Reviewer Comment:

The reviewer was able to verify the Applicant's final population PK model. The final estimates, PK predictions, and goodness-of-fit in the reviewer's analysis were consistent with the Applicant's analysis. The Applicant's final population PK model had a condition number of 4528.3 which indicates possible overparameterization. Final parameter estimates for the final model are listed in [Table 21](#). Fixed effect parameter estimates are also listed in [Table 22](#) after back-transforming from a natural log scale if relevant.

Table 21. Parameter Estimates (RSE) and Median (95% CI) for the Final Model

Fixed-Effects Parameters	Estimate	SE	RSE (%)	CI (95%)
LN(tvCL/F)	6.03	0.0555	0.9204	(5.921, 6.139)
LN(tvVc/F)	6.01	0.128	2.13	(5.759, 6.261)
LN(tvQ/F)	5.36	0.129	2.407	(5.107, 5.613)
LN(tvVp/F)	7.22	0.0777	1.076	(7.068, 7.372)
LN(tvKA)	-0.67	0.0728	10.87	(-0.8127, -0.5273)
LN(tvALAG1)	-1.55	0.0742	4.787	(-1.695, -1.405)
VCWT	1 (FIXED)	0	0	(1, 1)
FORM~F	0.867	0.0188	2.168	(0.8302, 0.9038)
FORM~ALAG1	0.849	0.0212	2.497	(0.8074, 0.8906)
tvF	1 (FIXED)	0	0	(1, 1)
Interindividual Variability				
Parameters	Estimate (CV%)	SE	RSE (%)	Shrinkage (%)
ETA(1) (CL)	0.353 (65.1%)	0.0497	14.1	3.1
ETA(2) (Vc)	1.06 (137.3%)	0.27	25.5	13.7
ETA(3) (Q)	0.437 (74.0%)	0.269	61.6	14
ETA(4) (Vp)	0.229 (50.7%)	0.0715	31.2	12.3
ETA(5) (KA)	0.198 (46.8%)	0.0549	27.7	26.8
ETA(6) (ALAG1)	0.182 (44.7%)	0.0571	31.4	28
Intra-Individual Variability				
Parameters	Estimate (CV%)	SE	RSE (%)	Shrinkage (%)
EPS(1) (proportional residual error for healthy volunteers)	0.0871 (29.5%)	0.004	4.592	3.39
EPS(2) (Additive)	0 (FIXED)	N/A	N/A	N/A
EPS(3) (proportional residual error for EoE patients)	0.0265 (16.3%)	0.003	11.17	18.01

Source: Reviewer Analysis

Abbreviations: CI, confidence interval; CV, coefficient of variation; RSE, relative standard error; SE, standard error

Table 22. Fixed Effect Parameter Estimates With 95% CI for the Final Model

Fixed-Effects Parameters	Units	Estimate	CI (95%)
tvCL/F ^[1]	L/hr	415.72	(372.9, 463.5)
tvVc/F ^[1]	L	407.48	(317.1, 523.7)
tvQ/F ^[1]	L/hr	212.72	(165.2, 273.9)
tvVp/F ^[1]	L	1366.5	(1173, 1591)
tvKA ^[1]	1/hr	0.51171	(0.4437, 0.5902)
tvALAG1 ^[1]	hr	0.21225	(0.1835, 0.2455)
VCWT	Unitless	1.0 (FIXED)	(1, 1)
FORM~F	Unitless	0.867	(0.8302, 0.9038)
FORM~ALAG1	Unitless	0.849	(0.8074, 0.8906)
tvF	Proportion	1 (FIXED)	(1, 1)

Source: Reviewer Analysis

^[1] Back-transformed from natural log scale

Abbreviation: CI, confidence interval

Pooling of the three MB-9 variants for the formulation effects on the absorption rate constant (KA) and ALAG1 was acceptable because the relative bioavailability study (Study SHP621-101) did not find significant differences in the resulting C_{max} or AUC values between these variants. The results of the relative bioavailability study also supported the formulation effect on bioavailability in the population PK model, which slightly decreases the relative bioavailability with the MB-7 formulation.

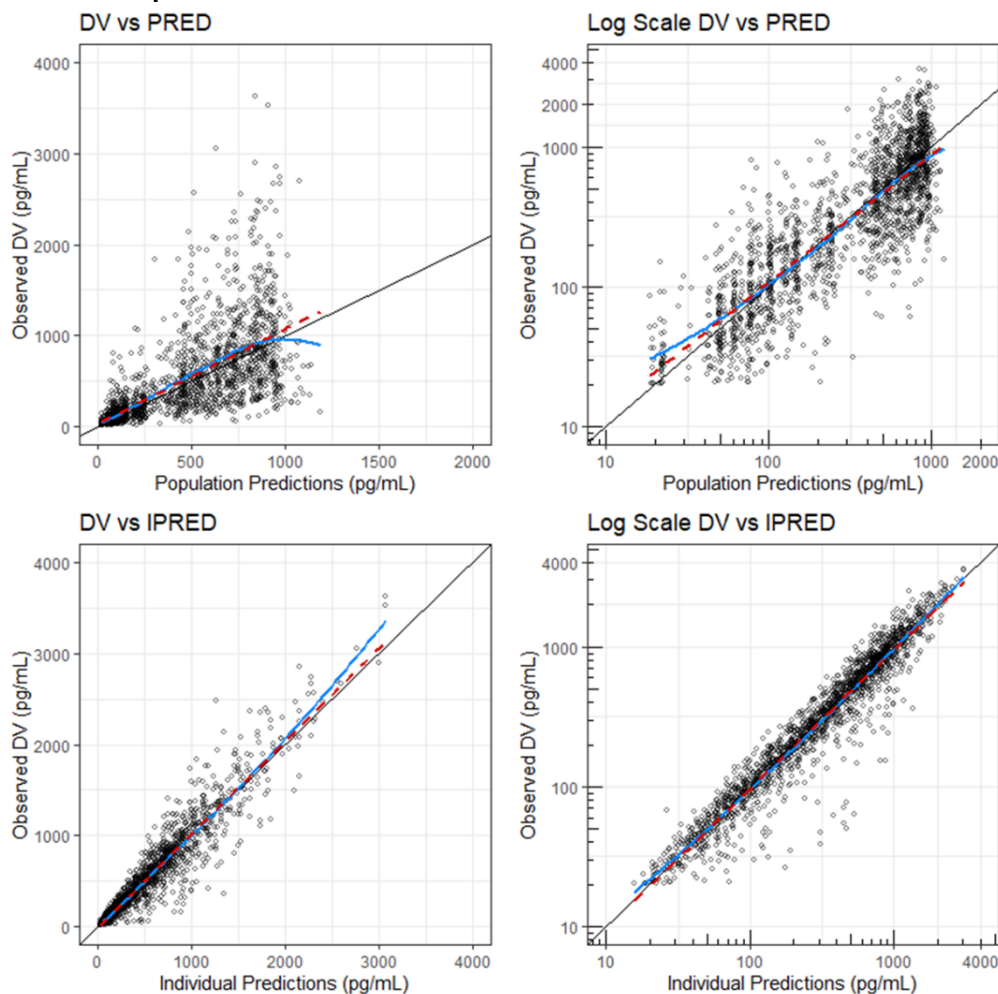
The relative standard error (RSE) for fixed effects parameters in [Table 21](#) differs from [Table 20](#) because the Applicant calculated RSE for fixed effect parameters as the standard error divided

by 100, which is not a true RSE calculation. [Table 21](#) shows that the typical value of KA (tvKA) has the highest RSE (10.87%) among fixed effect parameters.

Among interindividual variability (IIV) parameters, the IIV on Vc has the highest coefficient of variation (CV) at 137.3%. The IIV on clearance of the drug from plasma (CL) and intercompartmental clearance (Q) are also high with CVs of 65.1% and 74.0%, respectively. The shrinkage for IIV parameters was estimated to be between 3.1% and 13.7% for IIV on CL, Vc, Q, and peripheral volume of distribution (Vp). Shrinkage was higher for the IIV on KA (26.8%) and IIV on ALAG1 (28.0%).

Goodness-of-fit plots for the final model are shown in [Figure 9](#) and [Figure 10](#).

Figure 9. Observed Concentrations Versus Population Predictions and Individual Predictions for the Final Population PK Model



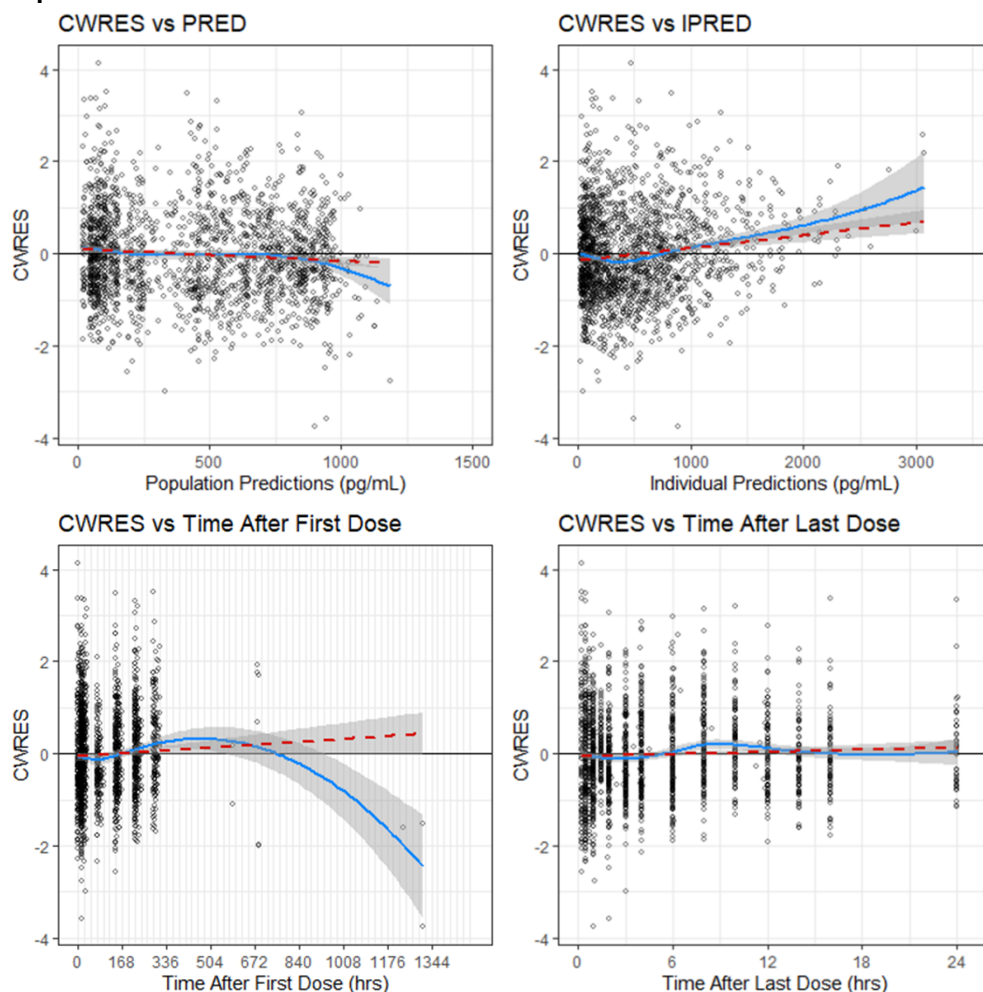
Source: Reviewer Analysis of Applicant's Final Population PK Model

LLOQ = 20 pg/mL

Loess smoothing line is shown as solid blue line. Linear regression is shown as dashed red line.

Abbreviations: LLOQ, lower limit of quantitation; PK, pharmacokinetic

Figure 10. Goodness-of-Fit Plots With Conditional Weighted Residual (CWRES) for the Final Population PK Model



Source: Reviewer Analysis of Applicant's Final Population PK Model
 Loess smoothing line is shown as solid blue line. Linear regression is shown as dashed red line.
 Abbreviation: PK, pharmacokinetic

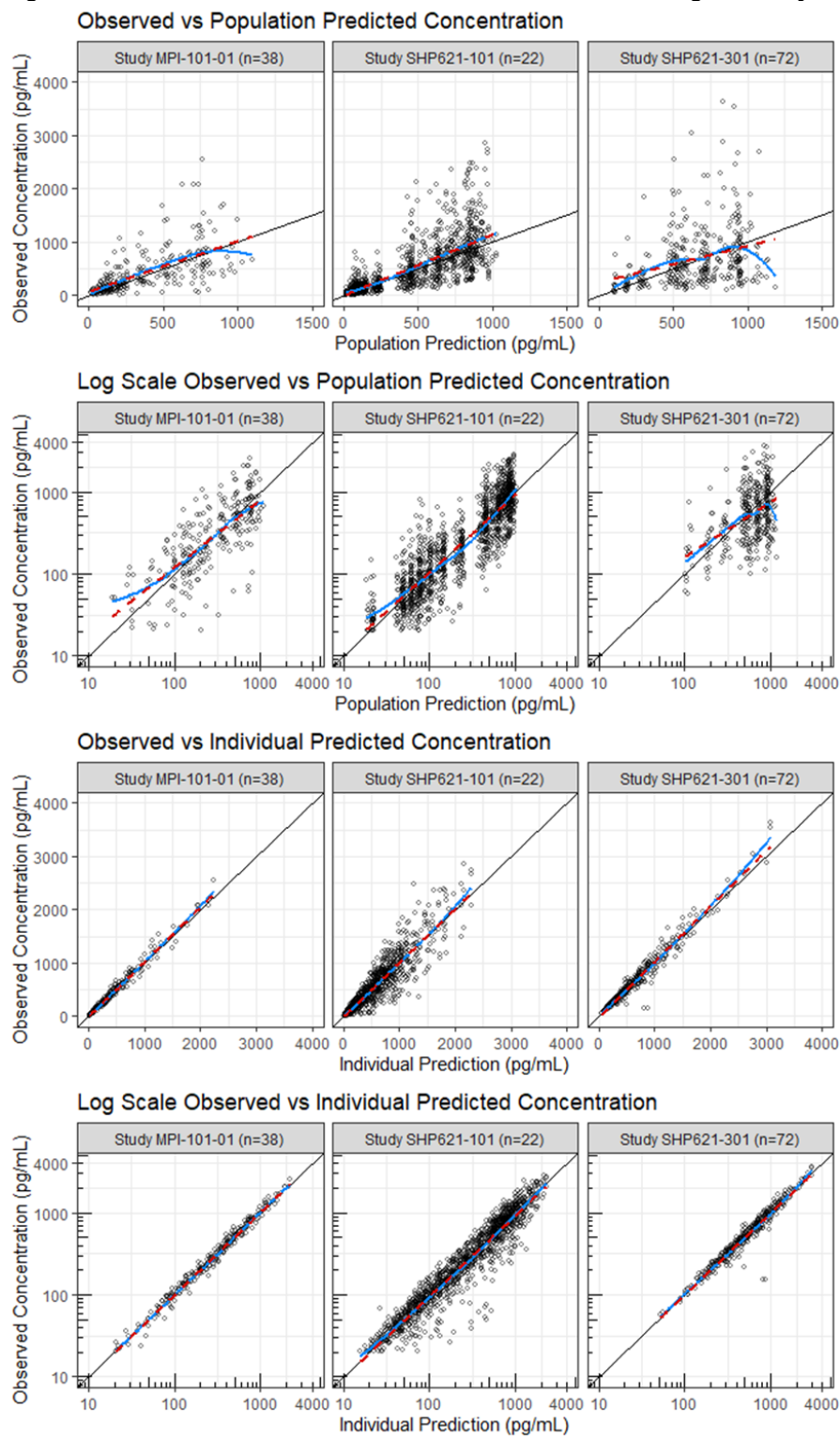
Goodness-of-fit (GOF) plots stratified by study are shown in [Figure 11](#). Both studies of patients with EoE (Study MPI-101-01 and SHP621-301) show a trend of higher absolute conditional weighted residual (CWRES) values at higher individual predicted concentration (IPRED) values. Study SHP621-301 also shows a trend of higher absolute CWRES values at higher population predicted concentration (PRED) values. This is likely related to the fact that the overall and average per-individual number of PK samples was highest for the healthy volunteer study (Study SHP621-101) and lowest for Study SHP621-301. This is reflected in the final model's use of separate residual variability terms for healthy volunteers and patients with EoE.

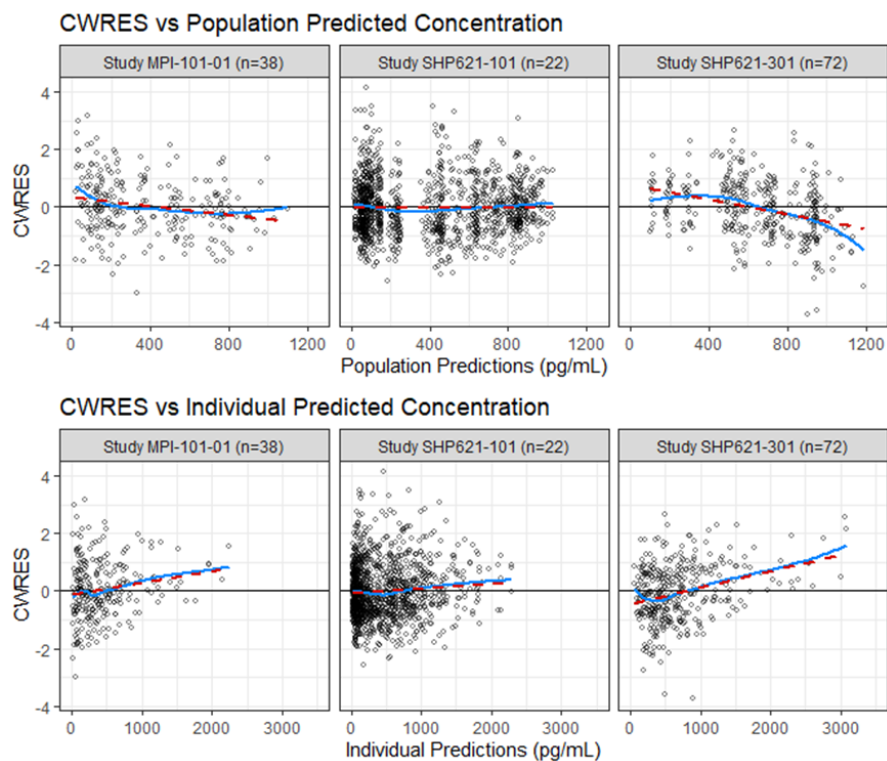
Goodness-of-fit plots stratified by age category are shown in [Figure 12](#). Because 36 out of 37 subjects under the age of 18 years were from Study MPI-101-01, some of the trends by study visible in [Figure 11](#) can be seen reflected in [Figure 12](#).

Overall, based on the GOF plots in [Figure 9](#) and [Figure 10](#), the study-stratified GOF plots in [Figure 11](#), and the age-category-stratified GOF plots in [Figure 12](#), the final population PK model appears adequate in characterizing the PK profile of BOS in adults and adolescents (11 to

<18 years) after 2 mg BID at steady state although the high condition number indicates possible over-parameterization with the model's current input dataset.

Figure 11. Goodness-of-Fit Plots for Final Model According to Study





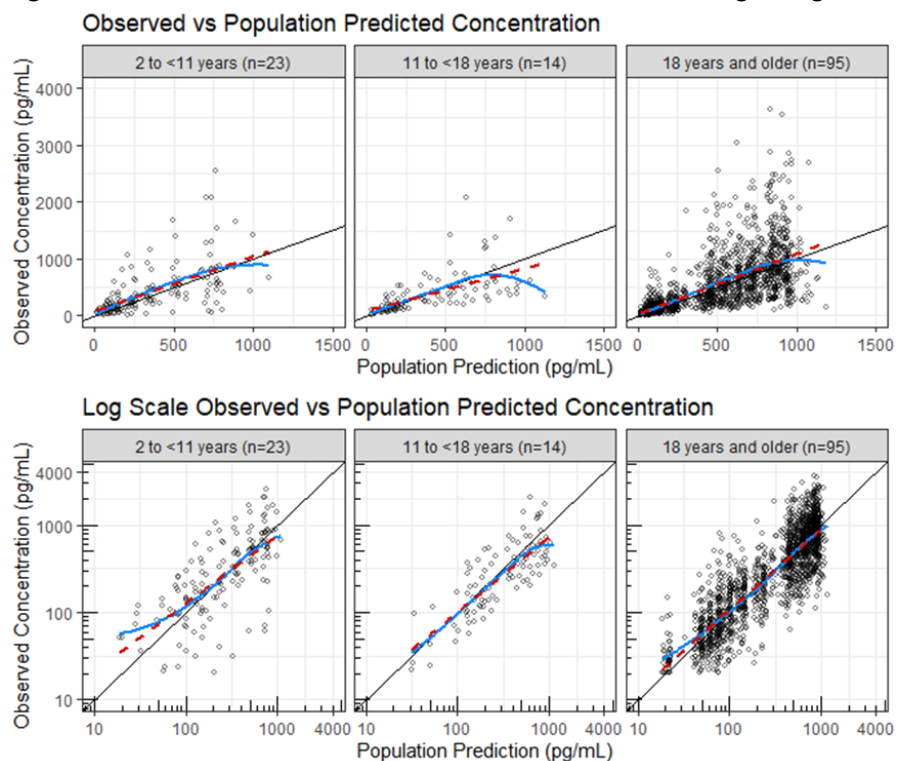
Source: Reviewer Analysis of Applicant's Final Population PK Model

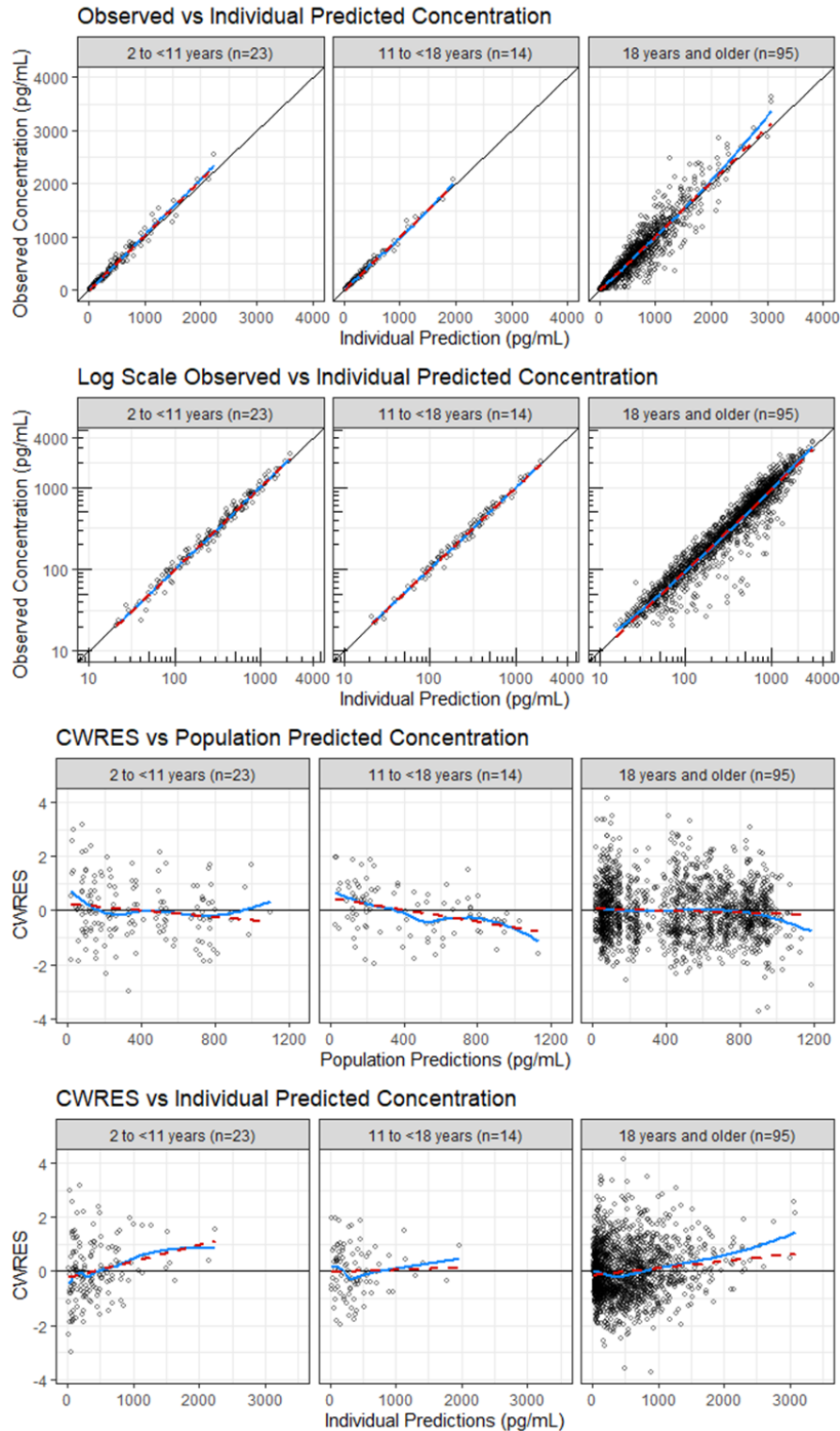
LLOQ = 20 pg/mL

Loess smoothing line is shown as solid blue line. Linear regression is shown as dashed red line.

Abbreviations: CWRES, conditional weighted residuals; LLOQ, lower limit of quantitation

Figure 12. Goodness-of-Fit Plots for Final Model According to Age Category





Source: Reviewer Analysis of Applicant's Final Population PK Model

LLOQ = 20 pg/mL

Loess smoothing line is shown as solid blue line. Linear regression is shown as dashed red line.

Abbreviations: CWRES, conditional weighted residuals; LLOQ, lower limit of quantitation

2.4.2.5. Simulations

Data

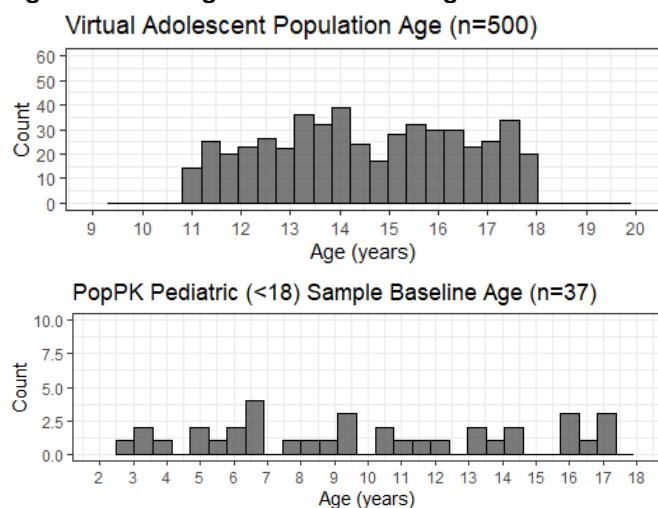
A virtual population of 500 adolescent subjects and a virtual population of 500 adult subjects were created to simulate PK exposure after 2 mg BID at steady-state. PK exposure was also predicted in the dataset of adult patients with PK data in Study SHP621-301 (n=71) after 2 mg BID at steady-state using the individual covariates along with post hoc model parameters for these subjects.

Reviewer Comment:

The virtual adolescent population and the sample of adolescent subjects with PK data do not appear to have significantly different baseline covariates of age or weight, as shown in [Figure 13](#) and [Figure 14](#). The virtual adolescent population appears to adequately represent the target adolescent population in terms of covariates that impact PK.

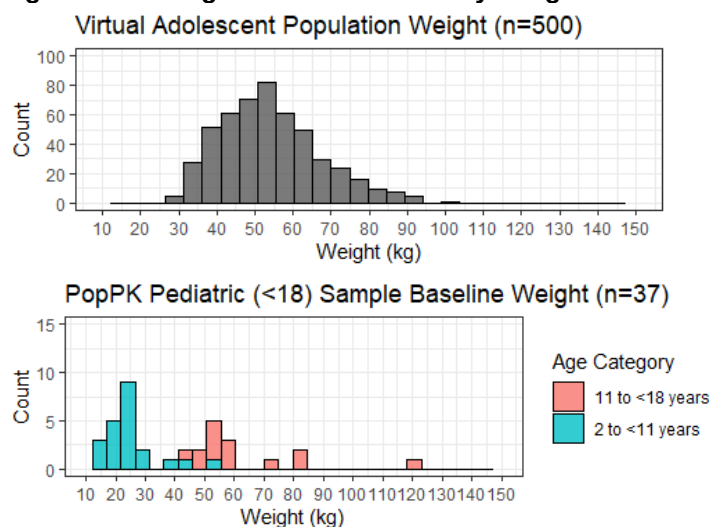
The maximum observed weight among adolescent subjects with PK data was 119.7 kg, followed by the second highest weight of 84.0 kg. The maximum weight in the virtual adolescent population was 99.2 kg. Because the maximum observed weight of 119.7 kg is within the range of body weight in both the adult sample of the population PK dataset (42.1 kg to 122.5 kg) and the virtual adult population (42.7 kg to 120.9 kg), it is acceptable that the adolescent subject with a weight of 119.7 kg was not represented in the virtual adolescent dataset.

Figure 13. Histogram of Baseline Age in Adolescents



Source: Reviewer Analysis

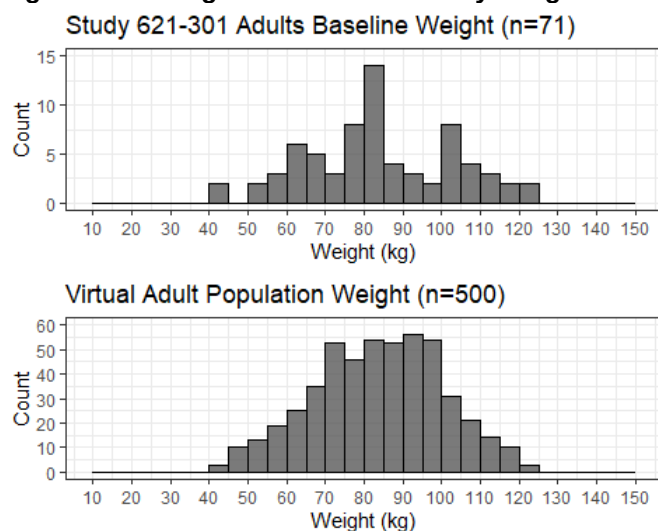
Figure 14. Histogram of Baseline Body Weight in Adolescents



Source: Reviewer Analysis

The virtual adult population and the sample of adult subjects with PK data do not appear to have significantly different baseline weight, as shown in [Figure 15](#). The virtual adult population appears to adequately represent the target adult population in terms of covariates that impact PK.

Figure 15. Histogram of Baseline Body Weight in Adults



Source: Reviewer Analysis

Simulated PK Exposure

The PK exposure after 2 mg BID at steady-state was simulated in the virtual adolescent population (n=500) and the virtual adult population (n=500) with 200 replicates each. The PK exposure parameters of AUC_{0-12} , C_{max} , and C_{min} were calculated from individual predicted concentrations using noncompartmental methods. Virtual populations had parameters summarized by simulation replicate number then by virtual subject ID. The PK exposure parameters were also calculated in the sample of adults with PK data from Study SHP621-301

after 2 mg BID at steady-state using individual covariates and individual post hoc model parameters. A summary of PK exposure parameters is listed in [Table 23](#).

Table 23. Summary of Simulated Steady-State Exposure After 2 mg BID

Parameter	Statistic	Simulated Adolescent Population	Simulated Adult Population	SHP621-301 Adults n=71
AUC ₀₋₁₂ (pg·h/mL)	Geometric mean (CV%)	4828 (65.1)	4819 (64.9)	4544 (58.3)
	95%CI of geometric mean	4583 - 5087	4575 - 5076	3999 - 5165
	90%CI of geometric mean	4622 - 5044	4613 - 5033	4084 - 5057
	Median	4820	4830	4212
	5 th to 95 th Percentile	1795 - 12919	1809 - 12814	2238 - 10757
	10 th to 90 th Percentile	1910 - 12241	1919 - 12161	2412 - 9972
	25 th to 75 th Percentile	2840 - 8233	2838 - 8246	2945 - 7232
C _{max} (pg/mL)	Geometric mean (CV%)	1007 (72.2)	901 (71.1)	858 (65.9)
	95%CI of geometric mean	951 - 1066	852 - 953	744 - 989
	90%CI of geometric mean	960 - 1056	860 - 945	762 - 966
	Median	1013	909	820
	5 th to 95 th Percentile	337 - 2897	308 - 2561	372 - 2220
	10 th to 90 th Percentile	360 - 2724	327 - 2409	392 - 1970
	25 th to 75 th Percentile	563 - 1779	500 - 1612	507 - 1403
C _{min} (pg/mL)	Geometric mean (CV%)	121 (83.3)	134 (83.1)	119 (73.7)
	95%CI of geometric mean	114 - 129	125 - 142	101 - 139
	90%CI of geometric mean	115 - 128	127 - 141	104 - 135
	Median	119	132	106
	5 th to 95 th Percentile	36.9 - 406	40.9 - 450	51.5 - 331
	10 th to 90 th Percentile	39.5 - 380	43.5 - 418	53.9 - 303
	25 th to 75 th Percentile	63.1 - 234	71.5 - 263	68.6 - 215

Source: Table 5-10 in Applicant's Modeling and Simulation Report

CV% corresponds to %CV of geometric mean. For the adolescent and adult populations, the values represent the average from the 200 simulations of 500 subjects.

Abbreviations: AUC₀₋₁₂, area under the plasma concentration-time curve from time 0 to hour 12; BID, twice daily; CI, confidence interval; C_{max}, maximum (peak) plasma drug concentration; C_{min}, minimum plasma drug concentration; CV, coefficient of variation

Neither age nor weight were significant predictors of oral clearance (CL/F) in the final model, so predicted AUC₀₋₁₂ was very similar in adolescents and adults (with median 4820 pg·h/mL and 4830 pg·h/mL, respectively).

The effect of body weight on central volume of distribution in the final model results in a higher predicted C_{max} in adolescents (median 909 pg/mL) compared to adults (median 1013 pg/mL). The predicted difference in C_{max} is not expected to be a clinically significant difference.

Reviewer Comment:

In the reviewer's independent analysis, the virtual adult dataset and virtual adolescent dataset provided by the Applicant were used to simulate PK exposure with the final population PK model. PK exposure was also simulated in the sample of adult subjects with PK data in Study SHP621-301 (n=71) with 500 replicates.

In order to represent the distribution of individual predicted exposure, the PK parameters of AUC₀₋₁₂, C_{max}, and C_{min} after 2 mg BID at steady-state were derived for each replicate of each subject. [Table 24](#) contains a summary of all 100,000 values per parameter for each virtual population and all 35,500 values per parameter for the Study SHP621-301 adult simulation. The predicted AUC₀₋₁₂ and C_{max} are also presented in [Figure 16](#).

The code provided by the Applicant to calculate and summarize exposure parameters revealed that the percentiles reported in [Table 23](#) were equal to the nth percentile of the nth percentile-of-

each-replicate, which resulted in wider reported prediction intervals compared to the respective populations in [Table 24](#). Similarly, [Table 23](#) reports the confidence intervals of the geometric mean per replicate in the virtual adult and virtual adolescent populations. This results in a wider confidence interval than [Table 24](#), which reports the confidence interval of the geometric mean from all 100,000 sets of parameters.

The Study SHP621-301 adult simulation with 500 replicates resulted in higher geometric mean AUC_{0-12} , C_{max} , and C_{min} values compared to Study SHP621-301 adult individual post hoc exposure. However, the simulation's geometric mean exposure (4843 pg·h/mL for AUC_{0-12} , 904 pg/mL for C_{max} , and 134 pg/mL for C_{min}) were all within the 95% confidence interval (CI) of geometric mean for the individual post hoc exposures (4007 to 5153 pg·h/mL for AUC_{0-12} ; 746 to 987 pg/mL for C_{max} ; and 102 to 138 pg/mL for C_{min}).

Table 24. Independent Review Summary of Simulated Steady-State Exposure After 2 mg BID

			SHP621-301	
Parameter Statistic	Virtual Adult Population	Virtual Adolescent Population	Adult Individual Post hoc Exposure	SHP 621-301 Adult Simulation
AUC ₀₋₁₂ (pg·h/mL)				
N	100000	100000	71	35500
Geometric mean (GeoCV%)	4820 (65.07)	4830 (65.35)	4544 (58.26)	4843 (65.33)
95% CI of geometric mean	4803–4838	4812–4848	4007–5153	4825–4860
90% CI of geometric mean	4805–4835	4815–4845	4089–5050	4828–4858
Median	4829	4820	4212	483
5 th to 95 th percentile	1813–12820	1809–12903	2063–11543	1804–12989
10 th to 90 th percentile	2248–10306	2250–10385	2562–9299	2255–10442
25 th to 75 th percentile	3229–7201	3232–7222	3072–6543	3251–7225
C _{max} (pg/mL)				
N	100000	100000	71	35500
Geometric mean (GeoCV%)	902 (71.34)	1007 (72.4)	858 (65.91)	904 (71.59)
95% CI of geometric mean	898–905	1003–1011	746–987	900–908
90% CI of geometric mean	899–905	1004–1011	763–965	901–907
Median	910	1015	820	909
5 th to 95 th percentile	309–2558	341–2885	352–2470	308–2576
10 th to 90 th percentile	392–2044	434–2311	410–1756	393–2064
25 th to 75 th percentile	586–1400	652–1574	539–1285	587–1403
C _{min} (pg/mL)				
N	100000	100000	71	35500
Geometric mean (GeoCV%)	134 (83.49)	121 (83.7)	119 (73.74)	134 (84.01)
95% CI of geometric mean	133–134	120–122	102–138	134–135
90% CI of geometric mean	133–134	121–121	104–135	134–135
Median	133	120	106	133
5 th to 95 th percentile	41–448	37–406	49–360	41–455
10 th to 90 th percentile	53–341	48–310	56–278	53–343
25 th to 75 th percentile	81–217	74–197	73–194	82–219

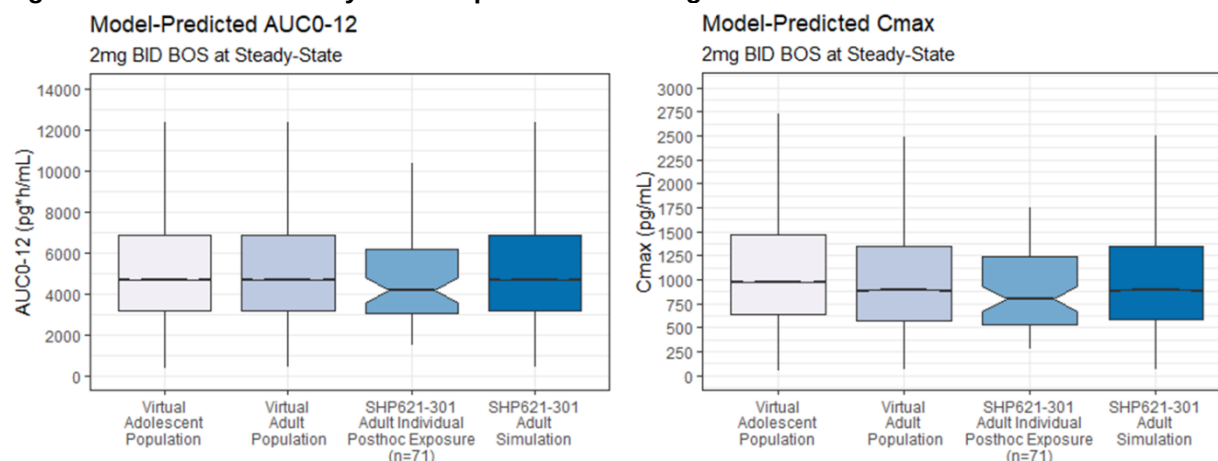
Source: Reviewer Analysis

Virtual adult and virtual adolescent populations each included 500 virtual subjects with 200 replicates.

SHP 621-301 Adult Simulation included 71 subjects with 500 replicates.

Abbreviations: AUC_{0-12} , area under the plasma concentration-time curve from time 0 to hour 12; BID, twice daily; CI, confidence interval; C_{max} , maximum (peak) plasma drug concentration; C_{min} , minimum plasma drug concentration; CV, coefficient of variation

Figure 16. Simulated Steady-State Exposure After 2 mg BID



Source: Reviewer Analysis

Virtual Adult and Virtual Adolescent Populations each included 500 virtual subjects with 200 replicates.

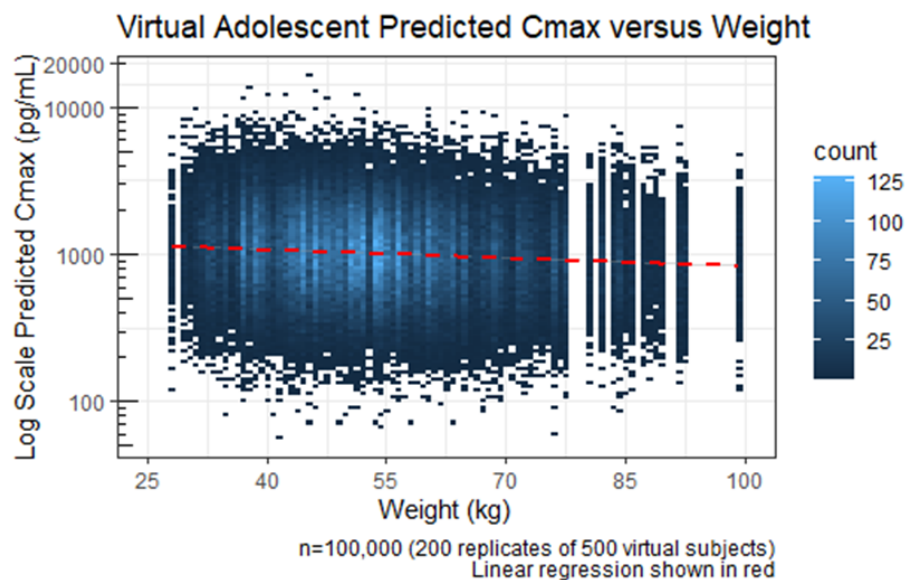
SHP 621-301 Adult Simulation included 71 subjects with 500 replicates.

Abbreviation: AUC₀₋₁₂, area under the plasma concentration-time curve from time 0 to hour 12; BID, twice daily; BOS, budesonide oral suspension; C_{max}, maximum (peak) plasma drug concentration

Body weight is expected to impact C_{max} due to the effect of weight on central volume of distribution. In order to assess the potential PK difference in adolescents with low body weight, the individual predicted C_{max} after 2 mg BID at steady-state from all 200 replicates of the 500 virtual adolescent subjects was plotted against body weight, as shown in [Figure 17](#).

The predicted C_{max} appears to be consistent across body weight ranged from 28.0 kg to 99.2 kg in the virtual adolescent population. The median C_{max} for the virtual adolescent with the lowest weight was 1252 pg/mL (95% prediction interval = 299 to 3807 pg/mL), while the median C_{max} for the virtual adolescent with the highest weight was 855 pg/mL (95% prediction interval = 255 to 3292 pg/mL), which easily fall within the range of observed C_{max} values reported in the subset of adolescents in Study MPI-101-01 who received either 2 mg once daily or 2 mg twice daily (≥ 11 years of age, $n=10$). This subset of ten adolescent subjects had a median observed C_{max} of 675.0 pg/mL and a C_{max} range of 359 pg/mL to 2210 pg/mL. Overall, the differences in C_{max} between low weight adolescents and high weight adolescents after 2 mg BID are not expected to be clinically significant.

Figure 17. Virtual Predicted C_{max} Versus Body Weight



Source: Reviewer Analysis

2.4.3. Reviewer's Independent Analysis to Verify the Population PK Model

Introduction

The reviewer conducted additional sensitivity analyses based on the Applicant's final population PK model in order to verify the final population PK model and covariate evaluation.

Methods

Dataset handling and generation of diagnostics and other plots were conducted using R version 4.0.2. NONMEM version 7.3 was used for population PK analysis. The dataset ("bos-3studies-v2", n=132) was provided as a csv file by the Applicant and submitted to NONMEM without edit. This dataset was used for all additional models. Additional models were developed by editing the final population PK model control file provided by the Applicant.

Results

Additional population PK models were tested using the Applicant's final model as a reference. Key models in the analyses are summarized in [Table 25](#), and any changes from the reference model structure are in the model description.

Table 25. Summary of Reviewer's Sensitivity Analyses

Run Number	Model Description	Condition Number	OFV	dOFV	Comments
220	Applicant's final model	4528.3	18833.2	Reference	Final listing file provided by Applicant (220-res.txt)
001	Proportional shift SubjStatus effect on CL; no separate RSD terms	17924.5	18938.0	+104.8	Applicant tested SubjStatus (healthy vs. EoE) effect on CL with separate RSD terms for each subject status category EoE status had significant (95% CI) negative effect on CL but fit did not improve, OFV increased, condition increased
002	Proportional shift SubjStatus effect on Vc; no separate RSD terms	6215.7	18933.1	+99.9	Applicant tested SubjStatus effect on Vc with separate RSD terms for each subject status category EoE status had significant (95% CI) positive effect on Vc but fit worsened, OFV increased, condition increased
003	No separate RSD terms	8805.5	18956.8	+123.6	Final EPS(1) estimated as 27.2% (CV%)
004	Removal of ALAG1, ETA(6), and FORM~ALAG effect	2436.5	19298.8	+465.6	RSE% on ETA(3) (Q) decreased from 61.6% to 20.7% Final EPS(1) increased from 29.5% (CV%) to 35.4% (CV%), but shrinkage on EPS(1) (healthy) decreased from 3.4% to 2.6% Final EPS(3) increased from 16.3% (CV%) to 20.5% (CV%), but RSE% on EPS(3) decreased from 11.2% to 7.7% AND shrinkage on EPS(3) decreased from 18% to 17% DV vs. IPRED fit appears slightly worse than run220; Slightly better CWRES vs. TAFD for time-after-first-dose above 500h
006	Estimated effect of weight on Vc (VCWT) changed to POWER effect	41931.0	18834.7	+1.5	Final estimate for VCWT was 0.156 (95% CI 0.051 to 0.261) ETA(2) (Vc) decreased from 137.3% (CV%) to 104.9% (CV%) AND RSE% on ETA(2) decreased from 61.6% to 30.1%
008	Removal of ALAG1 term; added estimated FORMKA	2427.0	19298.8	+465.6	No notable improvement over run 004

Run Number	Model Description	Condition Number	OFV	dOFV	Comments
009	Keep ALAG1; Remove ETA(6) for ALAG1	1219.9	18925.2	+92.0	RSE% on ALAG1 decreased from 4.8% to 0.3% RSE% on ETA(3) (Q) decreased from 61.6% to 42.3% but shrinkage on ETA(3) (Q) increased from 14% to 24.4% RSE% on ETA(4) (Vp) increased from 31.2% to 37.6% RSE% on EPS(3) decreased slightly from 11.2% to 8.1% GOF plots appear very similar to run220
010	Remove ETA(5) on KA; remove ETA(6) on ALAG1	286.6	18972.6	+139.4	RSE% on KA increased slightly from 10.9% to 12.7% RSE% on ALAG1 decreased from 4.8% to 0.3% ETA(2) (Vc) estimate increased from 137.3% (CV%) to 203.8% (CV%) RSE% on ETA(2) (Vc) decreased from 25.5% to 16.2% AND shrinkage on ETA(2) decreased from 13.7% to 6.9% ETA(3) (Q) estimate increased from 0.437 to 0.574 but RSE% on ETA(3) decreased from 61.6% to 20.9% CWRES vs. PRED fit appears slightly better than run220; other basic GOF appear similar to run 220
011	Diagonal ETA estimates only	17.17	19000.1	+166.9	RSE% on ALAG~FORM decreased from 2.5% to 0.1% RSE% decreased slightly on ETA(3) (Q) RSE% increased a lot on ETA(4) (Vp) and shrinkage increased a lot on ETA(4) (Vp) Shrinkage increased on ETA(3), ETA(4), ETA(5), and ETA(6) Very similar GOF plots to run 220

Source: Reviewer Analysis

Abbreviations: ALAG1, absorption lag time; CI, confidence interval; CL, clearance; CV, coefficient of variation; CWRES, conditional weighted residual; dOFV, difference in objective function values; EoE, eosinophilic esophagitis; FORM, formulation; GOF, goodness-of-fit; IPRED, individual predicted concentration; KA, absorption rate constant; OFV, objective function; PRED, population predicted concentration; Q, intercompartmental clearance; RSD, relative standard deviation; RSE, relative standard error; TAFD, time after first dose; Vc, central volume of distribution; Vp, peripheral volume of distribution.

Independent analysis demonstrated the benefits of including ALAG1 in the model even though the final estimate is short (0.179 hours for the MB-7 formulation and 0.211 hours for the pooled MB-9 formulations). Removal of ALAG1, along with removal of the IIV on ALAG1 and effect of formulation of ALAG1, was investigated in run 004. The OFV increased significantly and the residual variability increased for both healthy volunteers and patients with EoE. Adding an effect

of formulation on the remaining estimated absorption parameter of KA in run 008 did not improve the fit from run 004. Inclusion of lag time may improve the model prediction of $C_{\max}$ and/or $T_{\max}$, which improves the model GOF overall.

When the IIV on ALAG1 was removed from the final population model structure for model run 009, there were multiple small improvements to the model. Most notably, condition number decreased significantly from 4528.3 to 1219.9. When the IIV terms on both KA and ALAG1 were removed for run 010, there were still multiple small improvements and the resulting condition number decreased to 286.6, indicating a more acceptable stability. Goodness-of-fit plots appeared similar to those of the final population model. The significant decrease in condition number indicates that these models may be more stable and may better characterize the data for the Applicant's final model. This may justify the +92.0 and +139.4 increases in OFV with run 009 and run 010, respectively.

Reviewer-independent model runs 009 and 010 offer potential alternative models that may have improved stability compared to the Applicant's final population model, though no clinically relevant impact is expected. For simulation purposes, the Applicant's final model is acceptable while model runs 009 and run 010 will likely generate similar output and results. If the model is to be used with an updated dataset, it may be beneficial to investigate removal of IIV on KA and/or ALAG1 for an improvement in model stability.

2.4.4. Listing of Reviewer Analyses Codes and Output Files

Table 26. Listing of Reviewer Analyses Codes and Output Files

File.Name	Description	Location in \\cdsnas\pharmacometrics\
"PPK and Simulation Dataset Analysis.rmd" and "PPK-and-Simulation-Dataset-Analysis.docx"	R markdown file and Word document output containing code for analyzing popPK and simulation datasets; code for Figure 13 , Figure 14 , and Figure 15	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Budesonide Oral Suspension_NDA213976_REK\FDA_Reviews\PPK_Review
"Population_PK_Review_Template_NDA213976.rmd" and "Population_PK_Review_Template_NDA213976.docx"	R markdown file and Word document output containing code for generating Figure 9 , Figure 10 , Figure 11 , Figure 12 , Table 21 , and Table 22	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Budesonide Oral Suspension_NDA213976_REK\FDA_Reviews\PPK_Review
"Simulated-Exposure-Results-Analysis.rmd" and "Simulated-Exposure-Results-Analysis.docx"	R markdown file and Word document output containing code for analyzing simulation output; code for Table 24 , Figure 16 , and Figure 17	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Budesonide Oral Suspension_NDA213976_REK\FDA_Reviews\PPK_Review\Simulation_Review
run220.mod and run220.lst	Reviewer's NONMEM control file and output file for final population PK model	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Budesonide Oral Suspension_NDA213976_REK\PPK_Analysis\Final_model_for_xpose4
RK_run1.mod and RK_run1.lst	Reviewer's simulation for virtual adolescent population	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Budesonide Oral Suspension_NDA213976_REK\PPK_Analysis\Simulations\Virtual Adolescent Simulation

File.Name	Description	Location in \\cdsnas\pharmacometrics\
RK_run3.mod and RK_run3.lst	Reviewer's simulation for virtual adult population	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Budesonide Oral Suspension_NDA213976_REK\PPK_Analysis\Simulations\Virtual Adult Simulation
RK_simrun1.mod and RK_simrun1.lst	Reviewer's simulation for Study SHP621-301 adults with 500 replicates	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Budesonide Oral Suspension_NDA213976_REK\PPK_Analysis\Simulations\Study 621301 Adult Sim 500replicates
.mod and.lst files for run 001 - run 011	Reviewer's Independent Analysis run 001 – run 011	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Budesonide Oral Suspension_NDA213976_REK\FDA_Reviews\PPK_Review\Indep_review_edits_to_final_model\

2.5. Summary of Bioanalytical Method Validation and Performance

The review team reviewed the bioanalytical method validation reports and sample analysis reports for the quantitation of budesonide in human plasma. Method validation and sample analysis were acceptable. Validation results for bioanalytical methods are summarized in below [Table 27](#).

Table 27. Bioanalytical Method Validation for the Determination of Budesonide in Human Plasma

Method	(b) (4) Study Number: 42-1709	(b) (4) Study No. CN51830PLVAL
Bioanalytical method validation report name, study number supported, and hyperlinks	(b) (4) Study Number: 42-1709 (for SHP621-101 (pivotal BA/BE study) and SHP621-301 studies) 42-1709-SHP621 meth val rep	(b) (4) Study No. CN51830PLVAL (for MPI 101-01 study, dose ranging Phase 2 study) CN51830plval-shp621 meth val rep
Method description	Liquid -liquid extraction followed by LC-MS/MS	Method 2 Solid phase extraction followed by LC-MS/MS
Stability in human plasma	189 Days at -20°C 370 Days at -70C 20 Hours at Ambient Temperature	Method 3 Solid phase extraction followed by LC-MS/MS 33 days at -20°C 129 days at -70°C 6 hrs. at room temp
Processed extract stability		
Standard calibration curve performance during accuracy and precision runs		
LLOQ	20 pg/mL	50 pg/mL
Validated range	20–5000 pg/mL	50–2000 pg/mL
Within-run precision (%CV)	≤15%	≤15%
Between-run precision (%CV)	≤15%	≤15%

Source: FDA Reviewer's table

Abbreviations: CV, coefficient of variation; LLOQ, lower limit of quantitation; LC-MS/MS, Liquid chromatography–mass spectrometry

Reviewer Comment:

The bioanalytical method validation (CN51830plval-shp621 meth val rep) used for phase 2 study (MPI 101-01) has several issues as below

- The method validation has three different validations done as three individual methods were developed for bioanalysis.
- Only method 2 and method 3 were used for final PK sample analysis, but no cross validation was performed for these two methods.
- All validation runs had issues related to random contamination as well as high relative errors for the low QCs samples.
- One major and common issue for these two method validations was that the blank samples showed peaks with an average area response greater than 20% of the average area response of the lowest plasma standard for budesonide (20 pg/mL). Based on the overall amount found in the blanks in the validation and the lower limit of quantitation (LLOQ) quality control (QC) evaluations, LLOQ was raised to 50 pg/mL. However, the method validation report states that since an LLOQ of 20 pg/mL was required, the **blank acceptance criteria were raised to no greater than 75% of the average area response of the lowest acceptable standard.**
- An information request was sent (March 10, 2021) to the Applicant for justification of using above modified bioanalytical method validation (CN51830PLVAL) for the bioanalysis of phase 2 study (MPI 101-01) PK samples. The Applicant responded on March 15, 2021, with a detailed response stating that out of total of 11 analytical runs for this study, only runs #3 to #5 used this bioanalytical method (V02). The analysis from these runs showed that only six reported concentrations from these runs were below the adjusted LLOQ of 50 pg/mL

Table 28. Listing Budesonide Concentrations of <50 pg/mL From Runs #3 to 5 From Bioanalysis Report (CN51830)

Subject ID	Age Strat ^[1]	Treatment ^[1]	Timepoint	Conc (pg/mL)	Analysis Run Set	Included in NCA in MPI 101-01?	Included in PopPK?
(b) (6)	10-18 yr	BOS low dose	PK-PRE	28.0	3	Yes	Yes
	10-18 yr	BOS low dose	PK 6HR	43.3	3	Yes	Yes
	10-18 yr	BOS low dose	PK 8HR	21.9	3	Yes	Yes
	2-9 yr	BOS low dose	PK 30M	20.8	4	No	Yes
	2-9 yr	BOS low dose	PK 4HR	21.0	5	No	Yes
	2-9 yr	Placebo	PK 6HR	23.2	5	No	No

Source: Budesonide in Human Plasma by Liquid Chromatography With Mass Spectrometry (LC-MS) Sample Analysis Report (b) (4) 2010)

^[1] BOS low dose (MPI 101-01): 0.35 mg and 0.5 mg QD in subjects 2-9 years of age and 10-18 years of age, respectively. Abbreviations: BOS, budesonide oral suspension; NCA, noncompartmental analysis; popPK, population pharmacokinetics

The Applicant stated that Subject # (b) (6) (2 to 9 years, had reported concentrations at only two time points) and Subject # (b) (6) (2 to 9 years, received placebo) were not included the PK data analysis presented for Study MPI 101-01. Although data from Subject # (b) (6) were included in the PK data analysis for Study MPI 101-01, this subject received the low dose (0.5 mg once daily [QD]), which is different from the proposed therapeutic dose of 2 mg BID. The concentrations data from Subject # (b) (6) and Subject # (b) (6) in Table 28 were included in the population PK analysis. However, as a total of 2,110 concentrations from 132 subjects were included in the

population PK analysis, the Applicant does not anticipate the small number of concentrations outside the assay acceptance range (n=5) would affect the model parameter estimates of the final population PK model. The Applicant concluded that given the small number of concentrations data outside the acceptance range (n=5) in subjects who received a low dose that is different from the proposed therapeutic dose (high dose), there is limited impact of these bioanalysis outside the assay acceptance range on the PK results. The reviewer agrees with the Applicant's provided justification and concurs that no changes to the PK conclusions, as presented in the NDA for adults and adolescents, will be expected due to inadequate bioanalytical method validation (CN51830PLVAL).

- It should be noted that all three methods provided sufficient accuracy and precision for the analysis of budesonide samples in human plasma. The validated target concentration range for the final method was determined to be 50 to 3000 pg/mL in human plasma using a 200-μL sample.
- This bioanalytical method (from (b) (4)) was only used to measure budesonide plasma concentration in the dose-finding study (MPI 101-01) where based on the efficacy data, the Applicant decided to select the 2 mg BID dose in pivotal study (SHP621-101). The pivotal study used another bioanalytical method (from (b) (4)) where method validation (42-1709-SHP621 meth val rep) was adequately performed and has no issues.

3. References

(b) (4)

Elan Pharma International Limited, 2016, Prescribing Information: Entocort EC, accessed February 10, 2021,
https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021324s012s013lbl.pdf.

FDA, 2016, Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers, Table 1-2: Examples of in vitro selective inhibitors for P450-mediated metabolism.

Guidance for Industry, Clinical Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions (January 2020a)

Guidance for Industry, In Vitro Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions (January 2020b)

Takeda Pharmaceuticals, Table 1. In Vivo Projections Based on In Vitro DDI Studies

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA ASSESSMENT AND EVALUATION

Application Number*: 213976
Supporting Document Number/s: 1 and 4
CDER Receipt Date: October 15, 2020
Sponsor: Takeda Pharmaceuticals U.S.A. Inc.
Product: Budesonide (Eohilia)
Pharmacologic Class: Corticosteroid
Indication: For the treatment of eosinophilic
esophagitis (EoE), (b) (4)
(b) (4)
in adult and adolescent patients 11 years
and older
Therapeutic area: Gastroenterology
Clinical Review Division: Division of Gastroenterology (DG)
Pharm/Tox Division: Division of Pharm/Tox for Immunology and
Inflammation (DPT-II)
Reviewer: Yolanda Branch, Ph.D.
Supervisor/Team Leader: Sushanta Chakder, Ph.D.
Project Manager: Ben Vali, M.S.
Purpose of Review: Other
NDA Review
Reviewer Completion Date: March 18, 2021

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Executive Summary (Clinical Relevance)

Budesonide is a synthetic corticosteroid and has a high glucocorticoid activity and a weak mineralocorticoid activity. The affinity of budesonide to glucocorticoid receptors is about 200-fold higher than that of cortisol and 15-fold higher than prednisolone. The nonclinical evidence of the effectiveness of budesonide (BOS) in EoE comes from the reference listed drug and published pharmacodynamic (PD) studies using *in vitro* and *in vivo* animal models of inflammation. Although the effectiveness of BOS has not been directly tested in models of EoE, the anti-inflammatory effects of BOS were tested in various nonclinical models of inflammation.

In an *in vitro* model of inflammation of cultured T-84 epithelial monolayers, budesonide dose-dependently inhibited T-84 abnormalities and prevented epithelial dysfunction in this model by inhibiting activation of T-cells and monocytes (DM McKay et al, 1996, J Pharmacol Exp Ther., 277(1): 408-410. In cultured adherent blood monocytes and alveolar macrophages, stimulated with lipopolysaccharide, budesonide caused a partial suppression of IL-1 β and IL-6. In contrast, the stimulation of granulocyte macrophage colony stimulating factor (GM-CSF) was almost completely stimulated in the culture (MLinden and R Brattsand, 1994, Pulmonary Pharmacol, 7: 43-47).

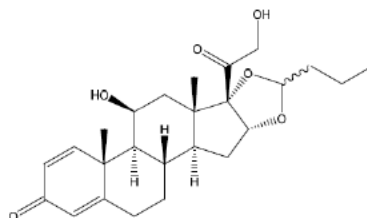
In a L2-IL5OXA EoE mouse model, the role of GM-CSF in esophageal inflammation was assessed by analyses of the expression of GM-CSF mRNA and protein. Significantly increased levels of esophageal GM-CSF expression, predominantly in the esophageal eosinophils, was detected in the L2-IL5OXA mouse EoE model during active inflammation. GM-CSF neutralization in L2-IL5OXA EoE mice resulted in a significant diminution of epithelial eosinophilia in addition to basal cell hyperplasia and vascular remodeling (EN McNamee et al, 2017, Allergy, 72: 1232-1242).

Nonclinical Summary

Drug Information⁺

Type of Product:	Oral Suspension
Code/ Generic Name:	Codes: 21100M1 and 21100MC/Budesonide
Chemical Name (optional):	(RS)-11 β ,16 α ,17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde
	16 α ,17-[(1RS)- butylidenebis(oxy)]-11 β ,21-dihydroxypregna-1,4-diene-3,20-dione
CAS# or UNII (if available):	CAS:51333-22-3

Structure or Biochemical Description:



Molecular Formula/ Molecular Weight:	430.53
Comment on Excipients:	None

Comment on Impurities:

(b) (4)

The nonclinical safety profile of budesonide has been evaluated in comprehensive pharmacology, pharmacokinetic, and toxicology studies to support the approval of currently marketed budesonide containing products (summary basis of approval) and published literature. In addition, supplemental studies were conducted with the new formulation of BOS to support the EoE indication in the proposed patient population. The nonclinical studies submitted to the NDA for BOS consisted of juvenile animal toxicity studies in rats and dogs to support dosing in pediatric patients and a series of genotoxicity studies to qualify an impurity (b) (4). The toxicity of BOS was evaluated in juvenile rats and dogs for 91-days following oral administration. All observed effects were expected pharmacological effects following administration of a potent glucocorticoid, with no novel toxicities identified. The degradation impurity (b) (4) was mutagenic in the Ames assay, however, it did not induce

mutagenicity in the 28-day rat Pig-A assay. There were no significant safety concerns identified in the toxicology studies conducted following oral administration of BOS in rats and dogs.

In a 91-day juvenile toxicity study in rats (PND22), daily administration of BOS at doses of 0.05, 0.2, 0.6 and 1.5 mg/kg/day was generally well tolerated. Seven unscheduled deaths were observed in this study. The deaths were attributed to urogenital inflammation (secondary to immunosuppression) and dosing error. There were significant reductions in body weight and food consumption in a dose dependent manner. Classic effects of glucocorticoids, including lymphocyte and leukocytic changes, clinical chemistry changes consistent with glucocorticoid administration, adrenal atrophy, lymphoid depletion in the thymus, lymph nodes, Peyer's patch and spleen, decreased cellularity in bone marrow, hyperostosis and physeal atrophy, and atrophy of the stomach were noted, with decreasing bone length of the tibia and femur. The effects noted following BOS administration were related to pharmacological actions of glucocorticoids. The no-observed-adverse-effect-levels (NOAEL) for daily administration of BOS for 91 days in juvenile rats was 0.05 mg/kg/day.

In the 91-day juvenile toxicity study in dogs (6 weeks), BOS was administered at 0.05, 0.2, and 0.6 mg/kg/day. Gross and histopathology assessments showed expected glucocorticoid related changes. There were ten unscheduled deaths following BOS administration, which was attributed to pharmacologically-mediated immunosuppression and/or inguinal hernias. Cushing disease like changes and steroid hepatopathy were noted at ≥ 0.2 mg/kg/day. The test article related effects observed were decreased body weight gain, decreased food consumption, leukocytic/lymphocyte changes, adrenal cortical atrophy, lymphoid depletion in lymphoid organs, decreased cellularity in bone marrow, hyperostosis and physeal atrophy, and suppression of long bone growth. No apparent unexpected or adverse toxicity was observed with BOS at the doses tested, outside of the expected pharmacologic actions of this class of compound.

The Applicant did not conduct any reproductive toxicology studies with BOS. Studies previously conducted by the innovator showed adverse reproductive findings in rats and rabbits. In the Segment I fertility and early embryonic developmental toxicity study in rats, there was a significant reduction in maternal body weight gain, prenatal viability, and the viability of the pups at birth and during lactation at 20 $\mu\text{g/kg/day}$. These findings were more pronounced at the high dose, 80 $\mu\text{g/kg/day}$. Budesonide had no effect on fertility at doses up to 80 $\mu\text{g/kg/day}$.

In the embryofetal developmental toxicity study in pregnant rats, there was a decrease in food consumption and body weight gain in the budesonide treated animals. at a dose of 100 $\mu\text{g/kg/day}$, there was increased fetal loss and fetal abnormalities. Fetal abnormalities (i.e. umbilical eventration and reduced ossification of skull bones along with sternebral or vertebral defects) were observed at 500 $\mu\text{g/kg/day}$. In the embryofetal developmental toxicity study in rabbits following subcutaneous administration of budesonide, there was a decrease in food consumption and body weight gains at 25 and 125 $\mu\text{g/kg/day}$. There was an increase in visceral abnormalities at 2 and 25 $\mu\text{g/kg/day}$. Skeletal anomalies (skull and vertebral defects) were increased at 25 $\mu\text{g/kg/day}$. There was an increase in maternal

abortion, effects on fetal development, and a reduction in litter weights at doses up to approximately 25 µg/kg/day.

In Segment III pre- and post-natal development study in rats, a slight prolongation of gestational period was noted. In the mid and high dose dams, there was a decrease in body weight gain. Offspring survival was reduced and surviving offspring had decreased mean body weights at birth and during lactation at ≥20 µg/kg/day.

In the standard *in vitro* and *in vivo* genotoxicity tests, budesonide was not mutagenic. (b) (4) was mutagenic in the Ames assay, and was negative in the *Pig-A* gene mutation assay at doses up to and including 0.50 mg/kg/day in males and 0.20 mg/kg/day in females.

In the 2-year oral carcinogenicity study in rats, there was a statistically significant increase in incidences of gliomas in the 50 µg/kg males and primary hepatocellular tumors in the ≥25 µg/kg males. There were no tumor findings in the female rats. In an additional 2-year carcinogenicity study in rats, the only tumor findings were increased incidences of hepatocellular tumors at an oral dose of 50 µg/kg. Budesonide was not carcinogenic in mice at doses up to 200 µg/kg/day.

5 Pharmacokinetics/ADME/Toxicokinetics

No pharmacokinetics studies were conducted.

6 General Toxicology

6.2.1 Study Title: An Oral 28-Day Range Finding Toxicity Study in Juvenile Rats with Recovery

Study no.:	R8559M-SHP621
Study report location:	4.2.3.5.4
Conducting laboratory and location:	 (b) (4)
Duration:	28
Duration Units:	Days
GLP compliance:	No
Drug, lot #, and % purity:	Budesonide, Lot #017K1779, purity 101%

In the 28-day dose range finding study, juvenile rats (PND 22) were orally administered BOS (M-7 formulation) at 0.1, 0.5, 2.5 and 5 mg/kg/day for 28 days. Following the oral administration of BOS, there was a dose-dependent increase in mortality with the highest incidence of mortality at the 5 mg/kg/day dose. The cause of death was attributed to exaggerated pharmacology related effects toxic effects associated with corticosteroid administration, including inflammation and/or septicemia which were the most frequent causes of treatment related deaths at 5 mg/kg/day. In the budesonide treatment groups, statistically significant decreased body weights were observed in a dose responsive manner. The decreased body weights correlated with significant reductions in food consumption. In the males given ≥ 0.05 mg/kg/day, there was a statistically significant increase in the touch response on Week 6 when compared to the controls. At 12 weeks and at 18 weeks, there were no statistically significant changes in this parameter in the males as compared to controls. On Week 12, the activity/arousal was significantly increased in the males at 0.05, 0.2 and 0.6 mg/kg/day doses. In the 1.5 mg/kg/day animals, decreased forelimb grip strength was significantly reduced on Week 6 with no effects observed on Weeks 12 and 18. Hindlimb splay was significantly reduced in the 0.6 mg/kg/day animals and the high dose males on Week 12. Treatment related microscopic findings were decreased cellularity in the bone marrow (≥ 0.1 mg/kg/day), lymphoid depletion of the lymph nodes (≥ 0.1 mg/kg/day), thymus (≥ 0.1 mg/kg/day), spleen (5 mg/kg/day) and Peyer's patch (5 mg/kg/day), atrophy of the stomach (0.1 mg/kg/day), physeal atrophy, skin alopecia (≥ 0.1 mg/kg/day), and mucification of the vagina/uterus (5 mg/kg/day). Hyperostosis of the bone femur and sternum were observed in the animals given ≥ 0.5 mg/kg/day. In the ≥ 0.5 mg/kg/day dose groups, histiocytes in

the alveoli of the lungs were observed. This finding was attributed to aspiration of dosing material. Statistically significant decreases in tibia (-3.3% to -26%) and femur (-4.2% to -26.8%) lengths were noted at all treatment levels when compared to the control. At the recovery period, the reduction in bone length was still evident, however at a lesser magnitude.

6.2.2 Study Title: An Oral 28-Day Range Finding Toxicity Study in Juvenile Dogs with Recovery

Study no.:	D8558M-SHP631
Study report location:	4.2.3.5.4
Conducting laboratory and location:	 (b) (4)
Duration:	28
Duration Units:	Days
GLP compliance:	No
Drug, lot #, and % purity:	Budesonide, Lot #017K1779, purity 101%

In the 28-day dose range finding study, juvenile dogs (5 to 6 weeks old) were orally administered BOS (M-7 formulation) at doses of 0.1, 0.3, 1 and 2 mg/kg/day for 28 days. One male at 0.1 mg/kg/day, one female at 0.3 mg/kg/day, five males and three females at 1.0 mg/kg/day, and three males and one female at 2.0 mg/kg/day were euthanized *in extremis*. Clinical signs included decreased activity, loss of skin elasticity, soft watery/mucoid stools, and pale gums. These animals had significant body weight loss (0.1 to 0.5 kg). The cause of death was generally attributed to the exaggerated pharmacological effects of corticosteroid administration (e.g. lymphoid depletion, infection and septicemia). Microscopic findings were adrenal cortical atrophy, hepatocellular vacuolation, lymphoid depletion, decreased bone marrow cellularity, bone physal dysplasia, skeletal muscle atrophy, and skin alopecia/hypotrichosis). In the budesonide treatment groups, statistically significant decreased body weights were noted. The decreased body weights correlated with significant reductions in food consumption. Statistically significant elevation in leukocytes, neutrophils, monocytes, and platelets were noted in the budesonide treated animals. Test article related reductions in reticulocytes, eosinophils, and lymphocytes were observed. At ≥ 1.0 mg/kg/day, there were mild decreases in calcium compared to the control group. Mild decreases in phosphorus were observed at all dose levels. There were also sporadic mild increases in alanine and aspartate aminotransferase, alkaline phosphatase and gamma glutamyltransferase (GGT) in both males and females at multiple doses. At the end of the recovery period, these changes were generally resolved. Treatment related microscopic findings were adrenal cortical atrophy, hepatocellular vacuolation, hepatic subacute/chronic inflammation, gallbladder epithelial vacuolation, lymphoid depletion in lymphoid organs (lymph nodes, Peyer's patch, spleen, thymus), decreased cellularity in bone marrow, skeletal muscle atrophy, and skin alopecia/hypotrichosis. These microscopic findings

were expected effects of corticosteroid administration. Decreases in tibia and femur lengths were noted in all treatment groups when compared to the control. At the end of the recovery period, the reduction in bone length was still evident, however at a slightly lower magnitude. Based on the findings from this study, a maximum dose of 0.6 mg/kg/day was recommended to be used for the 91-day toxicity study in juvenile dogs.

6.2.3 Study Title: An Oral 91-Day Toxicity Study in Juvenile Rats with Recovery

Study no.:	R8561M-SP621
Study report location:	4.2.3.5.4
Conducting laboratory and location:	 (b) (4)
Duration:	91
Duration Units:	Days
GLP compliance:	Yes
Drug, lot #, and % purity:	Budesonide, Lot #1398109, Purity 99.6%

Key Findings:

- Budesonide produced expected dose responsive classic glucocorticoid effects in juvenile rats. The immunosuppressive and metabolic effects related to budesonide resulted in pharmacologically mediated changes at doses ≥ 0.2 mg/kg/day.
- The NOAEL was considered 0.05 mg/kg/day in juvenile rats.

Methods

Doses:	0.05, 0.2, 0.6 and 1.5 mg/kg
Frequency of dosing:	Once Daily on Postnatal Day 22 to 91 From Days 92 to 98, the recovery animals were dosed at a dose volume of 1.875 mL/kg resulting in a dose level of 0.0125, 0.05, 0.15, and 0.375 mg/kg/day to achieve a gradual decrease in dose levels in order to circumvent potential withdrawal symptoms related to the acute stoppage of the corticosteroid, Budesonide. Following completion of the taper period, the recovery animals were maintained for a 28-day non-treatment period.
Number/Sex/Group:	20/sex/group
Dose volume:	7.5 mL/kg mL/kg
Formulation/Vehicle:	Budesonide Suspension (Placebo)
Route of administration:	ORAL GAVAGE
Species:	Rat
Strain:	CD® [CrI:CD®(SD)] Rat

Age at start of experiment: PND22

Observations and Results

Mortality

On Day 115, one animal given 0.2 mg/kg was prematurely euthanized because of a mechanical injury (nasal bone fracture). Four main study and two toxicokinetic animals given 1.5 mg/kg/day were found dead on Days 70, 73, 76, 89, and 90. In the 1.5 mg/kg animal found dead on Day 70, the cause of death was urogenital inflammation. The cause of death of the remaining animals was attributed to dosing error.

Clinical Signs

Drug-related clinical observations included increased activity, dorsiflexed tails, and sparse hair.

Body Weight

On Week 13, statistically significant decreases in body weight (-9 to -46%) were observed for all treatment groups in a dose responsive manner. The significant decreases in body weight correlated with a significant decreased food consumption.

Ophthalmoscopy

There were no BOS treatment-related effects noted.

Hematology

In the 0.05 mg/kg/day dose group, there were no relevant test article-related effects on hematological parameters. Statistically significant reductions in eosinophils, basophils, platelets and lymphocytes were observed at ≥ 0.2 mg/kg/day BOS in a dose responsive manner. BOS-related increases in neutrophils, monocytes, erythrocytes, hemoglobin, and hematocrit were observed at doses of ≥ 0.2 mg/kg/day. The significant reductions in lymphocytes at ≥ 0.6 mg/kg/ were considered adverse. By the end of the recovery period, all the BOS-related changes in hematological parameters were resolved.

Clinical Chemistry

Significant differences in some clinical chemistry values of BOS treated animals:

- Decreased total protein and globulin and an increase in the albumin/globulin ratio in the ≥ 0.2 mg/kg/day animals.
- Increased albumin in the ≥ 0.6 mg/kg/day dose groups
- Increased aspartate transaminase, alanine transaminase and alkaline phosphatase in the ≥ 0.2 mg/kg/day animals. These changes were attributed to hepatobiliary effects, an expected effect of glucocorticoid administration.
- Variable increases in phosphorus were observed in the 0.6 mg/kg/day animals and in 1.5 mg/kg/day females.
- Dose-dependent BOS treatment related decreases in cholesterol were observed at ≥ 0.2 mg/kg/day.
- Statistically significant differences in clinical chemistry parameters (e.g. sodium, chloride, potassium, calcium, triglyceride, and glucose), but they did not pose any clinical significance.

Urinalysis

Treatment related increases in urine ketones were observed in ≥ 0.2 mg/kg/day males.

Sexual Maturation

In the BOS treated males, the preputial separation days were significantly reduced by 2-4 days. There were no BOS treatment related effects noted on vaginal opening.

CNS/ Neurobehavioral Assessment

In the males given ≥ 0.05 mg/kg/day, there was a statistically significant increase in the touch response on Week 6 when compared to the controls. At 12 weeks and at 18 weeks there were no statistically significant changes in this parameter in the males as compared to controls. On Week 12, the activity/arousal was significantly increased in the males at 0.05, 0.2 and 0.6 mg/kg/day dose groups. In the 1.5 mg/kg/day animals, decreased forelimb grip strength was significant on Week 6 with no effects observed on Weeks 12 and 18. Hindlimb splay was significantly reduced in the 0.6 mg/kg/day animals and the high dose males on Week 12. These findings were not considered adverse but attributed to the decreased body weight and muscle mass as a result of pharmacological effects of the test article.

Bone Evaluation

Statistically significant decreases in tibia (-3.6% to -15.5%) and femur (-3.8* to -13.7%) lengths were noted at all treatment levels, except for the 0.05 mg/kg/day males. These findings were still present at the end of the recovery period.

Gross Pathology

Small adrenals (mild to severe) were observed in males at ≥ 0.2 mg/kg/day and in females at 0.2 and 1.5 mg/kg/day, which correlated with microscopic findings of adrenal atrophy. Mild to severe small thymus were observed in males at 0.6 mg/kg/day, and 1.5 mg/kg/day and females at 1.5 mg/kg/day, which correlated with microscopic findings of generalized

thymic lymphoid depletion. At ≥ 0.6 mg/kg/day, minimal to moderate sparse hair was observed with correlating microscopic findings of alopecia/hypotrichosis.

Organ Weights

A dose-dependent, statistically significant decrease in absolute adrenal gland, liver, spleen and thymus weights in the ≥ 0.2 mg/kg/day dose groups when compared to the control.

Histopathology

Adequate Battery: Yes

BOS treatment related microscopic findings were decreased cellularity in the bone marrow (≥ 0.2 mg/kg/day), lymphoid depletion of the lymph nodes (≥ 0.6 mg/kg/day), thymus (≥ 0.2 mg/kg/day), spleen (1.5 mg/kg/day) and Peyer's patch (1.5 mg/kg/day), atrophy of the stomach (1.5 mg/kg/day), physeal atrophy, skin alopecia (≥ 0.6 mg/kg/day), and mucification of the vagina/uterus (≥ 0.2 mg/kg/day). Hyperostosis of the bone femur were observed in the females given ≥ 0.05 mg/kg/day and males given ≥ 0.2 mg/kg/day. In the ≥ 0.2 mg/kg/day dose groups, histiocytes in the alveoli of the lungs were observed. This finding was attributed to aspiration of dosing material.

Toxicokinetics

Following repeat administration of BOS, the systemic exposure (C_{max} and AUC_{∞}) increased in a dose proportional manner. There were no gender related effects on TK parameters. On Day 91, the AUC_{∞} was less than the values on Day 1, suggesting no drug accumulation. The T_{max} ranged from 0.5 h to 2 h.

Day 1 Toxicokinetic Parameters

Gender	Target Dose (mg/kg)	Observed C_{max} (ng/mL)	Observed $C_{max}/Dose$ (kg*ng/mL/mg)	Observed T_{max} (hr)	Terminal Elimination Half-Life (hr)	Apparent Volume of Distribution (mL/kg)	Apparent Clearance (mL/hr/kg)	$AUC_{0-\infty}$ (hr*ng/mL)	AUC_{0-24} (hr*ng/mL)	$AUC_{0-24}/Dose$ (hr*kg*ng/mL/mg)
Male	0.05	1.68	33.6	0.500	NR ^b	NR ^b	NR ^b	3.33	NR ^b	NR ^b
	0.2	5.34	26.7	2.00	ND ^c	ND ^c	ND ^c	14.4	ND ^c	ND ^c
	0.6	14.2	23.7	2.00	2.52	36200	9960	57.8	60.2	100
	1.5	32.2	21.5	1.00	3.13	41400	9180	152	163	109
Female	0.05	1.37	27.4	2.00	ND ^c	ND ^c	ND ^c	4.07	ND ^c	ND ^c
	0.2	5.56	27.8	0.539	2.13	25400	8280	21.9	24.1	121
	0.6	18.9	31.5	1.07	2.50	23100	6390	90.1	93.9	156
	1.5	47.4	31.6	1.08	2.45	27800	7840	184	191	127

a. TK parameters were reported to three significant figures.

b. Not reported due to failure of all acceptance criteria.

c. Not determined due failure to estimate lambda z.

Day 91 Toxicokinetic Parameters

Gender	Target Dose (mg/kg)	Observed C _{max} (ng/mL)	Observed C _{max} /Dose (kg*ng/mL/mg)	Observed T _{max} (hr)	Terminal Elimination Half-Life (hr)	Apparent Volume of Distribution (mL/kg)	Apparent Clearance (mL/hr/kg)	AUC _{last} (hr*ng/mL)	AUC _∞ (hr*ng/mL)	AUC _∞ /Dose (hr*kg*ng/mL/mg)
Male	0.05	ND ^b	ND ^b	ND ^b	ND ^b	ND ^b	ND ^b	ND ^b	ND ^b	ND ^b
	0.2	4.35	21.8	2.00	ND ^c	ND ^c	ND ^c	8.53	ND ^c	ND ^c
	0.6	17.4	29.0	2.00	1.53	19600	8900	64.4	67.4	112
	1.5	23.9	15.9	2.00	1.74	52000	20700	71.7	72.6	48.4
Female	0.05	2.30	46.0	2.00	ND ^c	ND ^c	ND ^c	6.24	ND ^c	ND ^c
	0.2	7.52	37.6	2.00	2.22	28000	8740	21.1	22.9	114
	0.6	18.9	31.5	0.500	NR ^d	NR ^d	NR ^d	49.0	NR ^d	NR ^d
	1.5	19.0	12.7	1.00	2.21	59800	18800	73.1	79.9	53.3

a. TK parameters were reported to three significant figures.

b. Not determined due to lack of time points for analysis.

c. Not determined due failure to estimate lambda z.

d. Not reported due to failure of all acceptance criteria.

6.4.4. Study Title: An Oral 91-Day Toxicity Study in Juvenile Dogs with Recovery

Study no.: D8560M-SHP621

Study report location: 4.2.3.5.4

Conducting laboratory and location:

(b) (4)

Duration: 91

Duration Units: Days

GLP compliance: Yes

Drug, lot #, and % purity: Budesonide, Lot #1398109, purity 99.6%

Key Findings:

- Following the repeat dose administration of MB-7 in juvenile dogs, there were no apparent drug related toxicological findings. The findings noted in the toxicity study were pharmacologically-mediated and consistent with long-term, high level, glucocorticoid/corticosteroid exposure.
- Ten mortalities were observed in this study and were attributed to the pharmacologic effects of corticosteroid administration (immunosuppression).
- Exaggerated pharmacological effects were observed at the lowest tested dose, as dogs are a highly sensitive species to the effects of glucocorticoids. Thus, a NOAEL was not established for this study.

Methods

Doses: Main Study-0.05, 0.2 and 0.6 mg/kg
 TK animals received the vehicle or test article in the same manner and dose levels as the main study groups
 Recovery Group- Day 92 through Day 98, animals designated for recovery were administered the vehicle or test article once daily at a dose volume of 1

mL/kg/day (25% of originally designated dose level).
Frequency of dosing: Once daily
Number/Sex/Group: Main Study-12/sex/group
Recovery-*Up to 6/sex/group were maintained for a 7-day taper period followed by a 28-day recovery period.
Dose volume: 4 mL/kg
Formulation/Vehicle: Budesonide Suspension (Placebo)
Route of administration: ORAL
Species: Dog
Strain: Naïve Beagle Dogs
Age at start of experiment: 6 to 6.5 weeks

Observations and Results

Mortality

Three animals were found dead, which included one male at 0.2 mg/kg/day on Day 80, one male on Day 84, and one female at 0.6 mg/kg/day on Day 22. Two males at 0.6 mg/kg/day on Days 75 and 90, respectively, and five females at 0.6 mg/kg/ on Days 24, 56, 94, 102, and 86, respectively, were euthanized in extremis. The cause of death could not be determined for the 0.2 mg/kg/day animal. Two of the animals (one prematurely euthanized and one found dead) had cardiac findings (heart inflammation/necrosis). These findings were not considered treatment related as they were not observed in any other animals. The other animals moribundity was attributed to lung inflammation or inguinal hernia complications. The pulmonary findings were considered a secondary finding of aspiration of vomit. Animals euthanized in extremis due to inguinal hernias had findings of intestinal torsion, blockage and/or strangulation associated with the hernia. These hernias were generally considered to be due to the cumulative pharmacologic effects of corticosteroid administration.

Clinical Signs

Drug-related clinical observations included distended abdomen and swelling at ≥ 0.2 mg/kg/day. Increased incidences of red discolored feces were observed in all BOS treatment groups. Increased incidences of ocular discharge were observed in the high dose animals when compared to the control.

Body Weight

On Week 13, significant decreases in body weight (-9 to -36%) were observed for all treatment groups. The significant decreases in body weight correlated with a significant decreased food consumption.

ECG

Statistically significant shortening of the QTc intervals were noted at ≥ 0.2 mg/kg/day when compared to the control group. However, the magnitude of the QTc interval change were less than 10%, lacked dose dependency; and therefore, was not considered treatment related. There were no other test article related effects on ECG parameters.

Ophthalmoscopy

The BOS related ocular findings were increased incidences of ocular discharge at ≥ 0.2 mg/kg/day; with protrusion of the nictitating membrane in two of the high dose animals with ocular discharge.

Hematology

In the animals given ≥ 0.05 mg/kg/day, there was a statistically decrease in lymphocytes (-21% to -60%) and eosinophils (-52% to -76%). Platelets (+27% to +30%) and leukocytes (+51% to +72%) were increased at 0.6 mg/kg/day and neutrophils (+65% to +153%) and monocytes (+69% to +159%) were increased at ≥ 0.2 mg/kg/day. There were no test article related effects on coagulation parameters.

Clinical Chemistry

Mild increases in total protein, albumin, and globulin and decreased phosphorus were observed at all dose levels. In ≥ 0.2 mg/kg/day animals, sporadic decreases in urea nitrogen, creatinine and glucose were observed. Mild and sporadic increases in triglyceride, GGT, ALT and SDH levels were observed in animals given ≥ 0.2 mg/kg/day.

Urinalysis

Test article related increases in urine volume (+76% to +79%) were observed at 0.6 mg/kg/day.

CNS/ Neurobehavioral Assessment

There were no significant changes in FOB parameters.

Bone Evaluation

Statistically significant decreases in femur (-12% to -16%) and tibia (-12% to -31%) bone lengths were noted in animals given ≥ 0.2 mg/kg/day when compared to the controls. At the end of the recovery period, bone shortening was still present but to a lesser degree than observed in the study period.

Gross Pathology

The treatment related macroscopic findings were small thymus (≥ 0.05 mg/kg/day), enlarged nictitans glands (0.6 mg/kg/day), abdominal skeletal muscle perforation (0.6 mg/kg/day) and inguinal subcutis hernia and thickening (> 0.2 mg/kg/day).

Organ Weights

Statistically significant decreases in absolute adrenal gland (-40% to -62%), spleen (-6% to -56%), thymus (-1% to 1% to -72%), heart (-4% to -38%) and lung (-18% to -59%) weights in the ≥ 0.05 mg/kg/day dose groups when compared to the control. The liver weights were increased (+6% to +61%) in all BOS treatment groups, except for the females at 0.05 mg/kg/day (-3.5%). The aforementioned changes in liver, adrenal, spleen and thymic weights correlated with microscopic findings of hepatocellular vacuolation,

adrenal cortical atrophy, and generalized lymphoid depletion. There were no heart and lung microscopic correlates.

Histopathology

Adequate Battery: Yes

The test-article related findings were esophageal glandular hypertrophy/hyperplasia (≥ 0.2 mg/kg), nictitans glands hypertrophy/hyperplasia (≥ 0.2 mg/kg), parathyroid gland cellular vacuolation (≥ 0.2 mg/kg), adrenal cortical atrophy (≥ 0.05 mg/kg), hepatocellular vacuolation (≥ 0.05 mg/kg), gallbladder epithelial vacuolation (≥ 0.2 mg/kg), lymphoid depletion at ≥ 0.6 mg/kg (lymph nodes, Peyer's patch, spleen, thymus), decreased cellularity in bone marrow (≥ 0.05 mg/kg), physeal atrophy in bone (≥ 0.05 mg/kg), skeletal muscle atrophy (≥ 0.6 mg/kg) and skin alopecia/hypotrichosis (≥ 0.6 mg/kg).

Toxicokinetics

The systemic exposure for BOS increased in a greater than dose proportional manner with increasing doses. The T_{max} ranged from 0.5 h to 0.83 h. Group mean C_{max} and AUC_{∞} values were similar, within 2-fold, between males and females for a given dose level, except for the AUC_{∞} for the female 0.05 mg/kg group, which was 2.2-fold higher than the males. Following repeat administration of BOS, the clearance values decreased while the elimination half-life increased; thereby resulting in increased AUC_{∞} values from Day 1 to Day 91.

Day 1 TK Parameters ^a							
Dose (mg/kg/day)	Gender	Observed C_{max} (ng/mL)	Observed T_{max} (hr)	Terminal Elimination Half-Life (hr)	Apparent Clearance (mL/hr/kg)	Apparent Volume of Distribution (mL/kg)	AUC_{∞} (hr*ng/mL)
0.05	Male	0.911	0.500	1.84	36000	77100	1.69
	Female	0.902	0.500	1.91	29100	74300	1.97
0.2	Male	3.67	0.500	1.99	29600	69400	7.39
	Female	3.20	0.833	2.21	30600	90400	6.62
0.6	Male	12.6	0.467	1.63	31600	72300	19.9
	Female	17.0	0.500	3.23	21000	92700	30.0
^a TK parameters were reported to three significant figures.							

Day 91 TK Parameters ^a							
Dose (mg/kg/day)	Gender	Observed C_{max} (ng/mL)	Observed T_{max} (hr)	Terminal Elimination Half-Life (hr)	Apparent Clearance (mL/hr/kg)	Apparent Volume of Distribution (mL/kg)	AUC_{∞} (hr*ng/mL)
0.05	Male	0.808	0.667	2.05	28600	70400	2.28
	Female	1.35	0.500	3.10	10700	48000	4.91
0.2	Male	5.92	0.500	3.53	14400	75100	17.0
	Female	3.84	0.500	4.08	11000	64600	18.8
0.6	Male	9.94	0.500	3.79	18800	102000	32.6
	Female	11.4	0.500	3.46	14800	72100	40.7
^a TK parameters were reported to three significant figures.							

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

7.1.1 Study Title: Bacterial Reverse Mutation Assay

Study no.: V7153M-SHP621
Study report location: 4.2.3.7.6
Conducting laboratory and location: (b) (4)
GLP compliance: Yes
Drug, lot #, and % purity: (b) (4) Lot # 072BP077
and 072BP129, 96.2% and 94.6%

Methods

Strains: *Salmonella typhimurium* strains (TA1535, TA1537, TA98, TA100) and *Escherichia coli* strain WP2 *uvrA*

Concentrations in definitive study: 100, 200, 500, 1500 and 5000 µg per plate for tester strains TA98, TA1537 and WP2 *uvrA*

10.0, 30.0, 100, 200, 300, 500, 667 and 1500 µg per plate for tester strains TA100 and TA1535

Retest Assay:
50.0, 100, 200, 500, 1500 and 5000 µg per plate for tester strains TA98, TA1537 and WP2 *uvrA*

10.0, 30.0, 50.0, 100, 200, 300, 400, 500 and 600 µg per plate for tester strains TA100 and TA1535

Basis of concentration selection: Dose levels for the mutagenicity assay were based upon post-treatment toxicity.

Negative control: Dimethylsulfoxide (DMSO)

Positive control: (b) (4)

Formulation/Vehicle: DMSO

Incubation & sampling time: Incubated at 37±2°C for approximately 12 hours before the anticipated time of harvest

Comment on Study Validity: For the study validity, the mean of each positive control must exhibit at least a 3.0-fold increase in the number of revertants over the mean value of the respective vehicle control. The cultures must demonstrate the characteristic mean number of spontaneous revertants in the vehicle controls as stated in the study protocol. A dose level is considered toxic if there was a >50% reduction in the mean number of revertants per plate as compared to the mean vehicle control value and a moderate reduction in the background lawn. The study was considered valid.

Results

Precipitate was observed in the tester strains TA98, TA1535 and WP2 *uvrA* at 5000 µg per plate. Toxicity was observed beginning at 500, 667, 1500 or at 5000 µg per plate with most tester strains. In the tester strain TA100, mutagenic responses were observed (2.9- and 3.9-fold, maximum increases) in the presence and absence of S9 activation. To confirm the results of the definitive mutagenicity assay, a retest mutagenicity assay was performed.

In the retest assay, a positive mutagenic response was observed (2.4-fold, maximum increase) with tester strain TA100 in the presence of S9 activation. In the absence of the S9 activation, there was a 3.3-fold maximum increase observed with TA100. Tester strains TA100 and TA1535 in the absence of S9 activation were not valid data sets, as three non-toxic dose levels were not available. TA98 strain, in the absence and presence of S9 activation, had a 2.1- and 1.9-fold maximum increase which did not meet the criteria for positive evaluation. However, based on the conditions of this study, (b) (4) was considered positive for the induction of mutagenicity in this in vitro assay.

7.2 In Vitro Assays in Mammalian Cells

7.2.1 Study Title: Bacterial Reverse Mutation Assay: (b) (4)

Study no.:	V8711M-SHP621
Study report location:	4 2 3 7 6 (b) (4)
Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Drug, lot #, and % purity:	(b) (4) 08GL085-1 and 08GL08-1, 81.6% and 88.6%

Methods

Strains:	<i>Salmonella typhimurium</i> histidine auxotrophs TA98, TA100, TA1535 and TA1537 and <i>Escherichia coli</i> WP2 <i>uvrA</i>
Concentrations in definitive study:	(b) (4) 5.00, 15.0, 50.0, 150, 500, 1500 and 5000 µg per plate for tester strains TA98 and WP2 <i>uvrA</i> (in the presence and absence of S9 activation) and TA1537 (in the presence of S9 activation) and 0.500, 1.50, 5.00, 15.0, 50.0, 150 and 500 µg per plate for tester strains TA100 and TA1535 (in the presence and absence of S9 activation) and TA1537 (in the absence of S9 activation)
	(b) (4) 10.0, 33.3, 100, 333, 1000, 3333 and 5000 µg per plate for tester strains TA98, TA1537 and WP2 <i>uvrA</i> (in the presence and absence of S9 activation) and 0.333, 1.00, 3.33, 6.67, 10.0, 33.3, 100 and 333 µg per plate for tester strains TA100 and TA1535 (in the presence and absence of S9 activation).
Basis of concentration selection:	Cytotoxicity
Negative control:	DMSO
Positive control:	(b) (4)
Incubation & sampling time:	Incubated at 37±2°C for approximately 12 hours before the anticipated time of harvest
Comment on Study Validity:	Based on historical control data (95% control limits), all tester strain cultures must exhibit characteristic numbers of spontaneous revertants per plate with the vehicle controls. The mean revertants per plate must be within the ranges outlined in the study protocol. The mean of each positive control must exhibit at least a 3.0-fold increase in the number of revertants over the mean value of the respective vehicle control. A minimum of three non-toxic dose levels is required to evaluate assay data. A dose-related increase in the mean revertants per plate of at least one tester strain over a minimum of two increasing concentrations of test article, will be considered positive. All the criteria for

a valid study were met as described in the protocol.

Results

For (b) (4) no positive mutagenic responses were observed with any of the tester strains in either the presence or absence of S9 activation. These results indicate (b) (4) was negative for the ability to induce reverse mutations at selected loci of several strain of *Salmonella typhimurium* and at the tryptophan locus of *Escherichia coli* strain WP2 *uvrA*.

In the presence and absence of S9 activation, positive mutagenic increases were observed with (b) (4) in the tester strain TA98 and with tester strain TA100 in the absence of S9 activation (ranging from 2.9- to 6.6-fold, maximum increase). The increases for tester strain TA100 in the presence of S9 activation was 1.5-fold, a non-dose responsive maximum increase and did not meet the criteria for positive evaluation. Therefore, this condition is considered equivocal.

7.4 Other Genetic Toxicity Studies

Study Title:	A 28-Day Repeat Dose Intravenous Toxicity, <i>Pig-A</i> Analysis and Toxicokinetic Study in Sprague Dawley Rats
Conducting laboratory and location:	(b) (4)
Formulation/Vehicle:	30% PEG 400 in sterile water for injection
GLP compliance:	Yes
QA Statement:	Yes
Drug, lot #, and % purity:	(b) (4) 08GL078-1, and 99.2% purity

Key Study Findings

Based on the conditions of this study, (b) (4) was negative for gene mutation. Statistically significant differences in RET% in males at each dose level, and in females at 0.20 mg/kg/day, indicating bone marrow toxicity.

Methods

Details

Dose and frequency of dosing:	0.010, 0.0625, 0.075, 0.2, 0.25, and 0.5 mg/kg/day Once daily for 26 days (TK cohort) Once daily for 28 days (<i>Pig-A</i> cohort)
Route of administration:	Intravenous
Species/Strain:	Rats/Sprague Dawley
Number/Sex/Group:	8/sex/group

Group	Dose Level - mg/kg/day [Nominal Concentration - mg/mL]		Number of Males/Females	
	Males	Females	<i>Fig.-4</i> Cohort [Repeat*]	TK Cohort
1	0.0 [0.0]	0.0 [0.0]	8/8 [6/0]	3/3
2	N/A	0.01 [0.002]	0/8	0/12
3	0.0625 [0.0125]	N/A	8/0 [6/0]	12/0
4	N/A	0.075 [0.015]	0/8	0/12
5	N/A	0.2 [0.04]	0/8	0/12
6	0.25 [0.05]	N/A	8/0	12/0
7	0.5 [0.1]	N/A	8/0	12/0
Total			32/32 [12/0]	39/39

N/A = Not applicable

* = Repeat *Fig.-4* cohort was added per protocol amendment #8.

Results

On Day 1, one male was found dead following pre-dose blood collection and prior to (b) (4) treatment. A replacement animal was added on Day 1. Statistically significant decreases in body weight were observed for all (b) (4) treatment groups on Days 8, 15, 22 and 29. In the high dose females and (b) (4) treated males, there was a significant decrease in RET%, indicating bone marrow toxicity. There were no statistically significant or dose-dependent increases observed in the RET or RBC frequencies at any (b) (4) dose level compared to the control. Thus, (b) (4) was negative for gene mutation in this in vivo assay. The systemic exposure (C_{max} and AUC₀₋₂₄) of (b) (4) increased generally in a dose proportional manner. Following repeat dose administration for 26 days, there was no evidence of accumulation, with the exception of 0.250 mg/kg/day male rats, where slight accumulation was observed.

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