CLINICAL STUDY PROTOCOL

NCT Number: NCT02605837

Study Title: Oral Budesonide Suspension (OBS) in Adolescent and Adult Subjects (11 to 55 Years of Age, Inclusive) with Eosinophilic Esophagitis: A Phase 3 Randomized, Double-blind, Placebo-controlled Study

Study Number: SHP621-301

Protocol Version and Date:

Original Protocol: 31 Aug 2015
Protocol Amendment 1: 17 Dec 2015
Protocol Amendment 2: 26 Jan 2018

PROTOCOL: SHP621-301

TITLE:	Oral Budesonide Suspension (OBS) in Adolescent and Adult Subjects (11 to 55 Years of Age, Inclusive) with Eosinophilic Esophagitis: A Phase 3 Randomized, Double-blind, Placebo-controlled Study
DRUG:	SHP621, oral budesonide suspension (OBS)
IND:	103,173
EUDRACT NO.:	Non-EUDRACT
SPONSOR:	Shire ViroPharma, Incorporated (Shire) 300 Shire Way, Lexington, MA 02421 USA [redacted]
PROTOCOL HISTORY:	Original Protocol: 31 Aug 2015

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [redacted]	**Date: 31 Aug 2015**
[redacted], MD, PhD [redacted] Clinical Development	

Acknowledgement
I have read this protocol for Shire Study SHP621-301.

Title: Oral budesonide suspension (OBS) in Adolescent and Adult Subjects (11 to 55 years of age, inclusive) with Eosinophilic Esophagitis: A Phase 3 Randomized, Double-blind, Placebo-Controlled Study

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)	_____ _____ _____

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

In the event of an SAE, the investigator must fax or e-mail the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol within 24 hours to the Shire Global Pharmacovigilance and Risk Management Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover). A copy of the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol must also be sent to the CRO medical monitor by fax or e-mail using the details below.

[redacted], MD

Email: [redacted]

Fax: [redacted]

For protocol- or safety-related issues <u>during normal business hours (8am to 5 pm Eastern Standard Time)</u>, the investigator must contact the CRO medical monitor:

[redacted], MD

Phone: [redacted]

Mobile: [redacted]

Email: [redacted]

Fax: [redacted]

For protocol- or safety-related issues <u>outside of normal business hours</u>, the investigator must contact the CRO medical monitor:

[redacted], MD

Mobile: [redacted]

Email: [redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 8.

Please use the information below as applicable to report the Product Quality Complaint:

Origin of Product Quality Complaint	E-mail Address
North and South America	[redacted]
European Union and Rest of World	[redacted]

Telephone numbers (provided for reference if needed):

Shire, Lexington, MA (USA)
[redacted] or [redacted]

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ABBREVIATIONS

ACTH	adrenocorticotropic hormone
AE	adverse event
ANCOVA	analysis of covariance
Auc_{tau}	area under the curve for the defined interval between doses
β-hCG	beta-human chorionic gonadotropin
BID	twice daily
BMD	bone mineral density
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum concentration occurring at t_{max}
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CYP450 3A4	cytochrome P450 3A4
DSG1	desmoglein 1
DSQ	Dysphagia Symptom Questionnaire
DXA (DEXA)	dual-energy X-ray absorptiometry
EC	ethics committee
EGD	esophagogastroduodenoscopy
EIS	external independent statistical
EMA	European Medicines Agency
EoE	eosinophilic esophagitis
EoE-QoL-A	Adult Eosinophilic Esophagitis Quality of Life
ePRO	electronic patient-reported outcome
EQ-5D-3L	EuroQol-5 Dimensions 3-level
EQ-5D	EuroQol
EQ-5D-Y	EuroQol 5 Dimensions Youth
EREFS	EoE Endoscopic Reference Score
ET	early termination
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice

HIPAA	Health Insurance Portability and Accountability Act
HPF	high-powered field
HRQoL	health-related quality of life
hs	at bedtime
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web-based response system
Med ID	medication information
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
OBS	oral budesonide suspension
pc	after meals
PedsQL-EoE	Pediatric Quality of Life Inventory – EoE
PGA	Physician Global Assessment
PGI-S	Patient Global Impression of Severity
PP	per-protocol
PPI	proton pump inhibitor
PT	preferred term
qAM	every morning
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	statistical analysis system
SOC	system organ class
TEAE	treatment-emergent adverse event
t_{max}	time of maximum observed concentration sampled during a dosing interval
UK	United Kingdom
US	United States

STUDY SYNOPSIS

Protocol number: SHP621-301	**Drug:** SHP621, oral budesonide suspension (OBS)
Title of the study: Oral Budesonide Suspension (OBS) in Adolescent and Adult Subjects (11 to 55 Years of Age, Inclusive) with Eosinophilic Esophagitis: A Phase 3 Randomized, Double-blind, Placebo-controlled Study	
Number of subjects (total and for each treatment arm): Approximately 300 subjects will be enrolled into the placebo lead-in period to allow for 228 subjects (approximately 152 and 76 per OBS and placebo treatment group, respectively) to be randomized into the double-blind treatment period.	
Investigator(s): Multicenter study	
Site(s) and Region(s): Approximately 60 sites in North America	
Study period (planned): Oct 2015 to July 2018	**Clinical phase:** 3

Objectives

Co-primary:

To demonstrate in a placebo-controlled trial that:

- OBS induces a histologic response (eosinophilic count ≤6/high-powered field [HPF]) in adolescent and adult subjects with eosinophilic esophagitis (EoE) over a 12-week course of therapy.
- OBS reduces dysphagia, as measured by the Dysphagia Symptom Questionnaire (DSQ), by at least 30% from baseline in adolescent and adult subjects with EoE over a 12-week course of therapy.

Key Secondary:

- OBS reduces dysphagia, as measured by the DSQ score from baseline to the final treatment period evaluation (Visit 4).

Secondary:

- To assess the response of endoscopically identified esophageal features to OBS as compared to placebo as measured by the EoE Endoscopic Reference Score (EREFS)
- To explore other responding criteria based on histology and DSQ
- To assess the impact of OBS on pain, as measured by the DSQ
- To evaluate the safety and tolerability of OBS over a 12-week course of therapy
- To obtain OBS pharmacokinetic data in adult subjects with EoE

Exploratory:

[redacted]

Rationale:

Currently there is no approved medication for the treatment of EoE. This study is being conducted in order to provide safety and efficacy data demonstrating histologic response (as measured by eosinophilic count ≤6/HPF) and improvement in dysphagia symptoms (as measured by the DSQ) following 12 weeks of treatment with OBS in adolescent and adult subjects with EoE.

Investigational product, dose, and mode of administration

OBS will be administered in 10 mL at a concentration of 0.2 mg/mL (2 mg dose), twice daily (in the morning [qAM] after meals [breakfast, pc] and at bedtime [hs]). The 0.2 mg/mL concentration of OBS and dosing regimens were selected for use in this Phase 3 study based on the results of Study MPI 101-06, a Phase 2 study in 93 adolescents and adult subjects with EoE and symptoms of dysphagia. Subjects were treated in Study MPI 101-06 with 2 mg OBS twice daily to investigate the co-primary endpoints of histologic response (defined as ≤6 eosinophils/HPF) and reduction in DSQ score from baseline to Week 12 of treatment. For the current study, the investigational product will be supplied in amber glass, multi-dose bottles with child-resistant caps. Each bottle will contain 210 mL of suspension with a budesonide concentration of 0.2 mg/mL, or 0.00 mg/mL (matching placebo).

After the screening period, eligible subjects will enter a 4-week single-blind placebo lead-in period and will receive 10 mL of OBS placebo twice daily (qAM, pc, and hs). At the end of the placebo lead-in period, eligible subjects will enter a 12-week double-blind treatment period (baseline visit, Visit 1) and will be randomized to 1 of 2 treatment groups in a 2:1 ratio (approximately 152 and 76 subjects for OBS and placebo twice daily treatment groups, respectively). Subjects will receive oral administration of 10 mL of 2 mg investigational product twice daily (qAM, pc, and hs; 4 mg/day total), with no ingestion of food or liquids permitted for 30 minutes after study drug administration:

- Placebo twice daily group: placebo qAM (pc) and hs
- OBS twice daily group: OBS 10 mL of 0.2 mg/mL (2 mg total) qAM (pc) and hs

The total daily dose of budesonide will be 0 mg for each subject in the placebo group and 4 mg for each subject in the OBS treatment group (Table 1).

Table 1: Total Daily Dose of OBS

Dose Group	OBS Concentration (mg/mL)	Volume per Dose	Morning Dose (qAM, pc)	Evening Dose (hs)	Total Dose/Day (mg/day)
Placebo	0.0	10 mL	0.0 mg	0.0 mg	0.0
OBS	0.2	10 mL	2.0 mg	2.0 mg	4.0

Abbreviations: hs=at bedtime; OBS=oral budesonide suspension; pc=after meals; qAM=every morning

At the end of the 12-week double-blind treatment period (Visit 4), subjects who complete the study will have the opportunity to enroll in the treatment extension study. These subjects will continue on the blinded assigned treatment for 2-4 weeks as part of the screening prior to enrolling into the treatment extension study.

Methodology:

This is a Phase 3, randomized, double-blind, multicenter, parallel-group, placebo-controlled study to evaluate the efficacy, safety, and tolerability of twice daily administration of OBS (qAM, pc, and hs) in adolescents and adults aged 11-55 years, inclusive, with EoE and dysphagia.

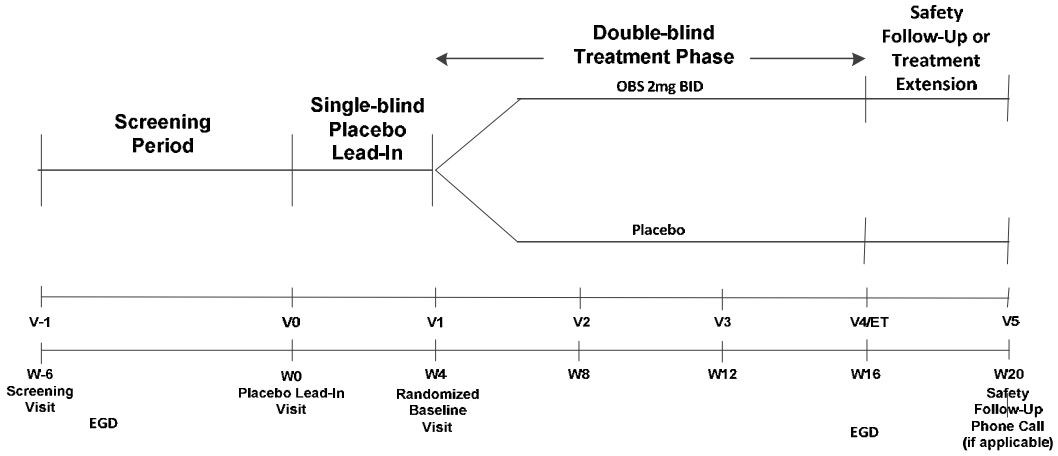
This study will comprise 3 periods: a 3- to 6-week screening period, 4-week single-blind placebo

lead-in period, and 12-week double-blind treatment period (Figure 1). Approximately 300 subjects will be enrolled into the placebo lead-in period to allow for approximately 228 subjects to be randomized in a 2:1 ratio (approximately 152 and 76 per OBS and placebo treatment group, respectively) into the double-blind treatment period. A minimum of 40 randomized subjects will be aged 11-17 years, inclusive.

Subjects who sign informed consent (or assent as applicable for subjects <18 years) will be screened (Visit -1). Subjects who meet eligibility criteria at the screening visit (Visit -1) and at the placebo lead-in visit (Visit 0) will enter the 4-week placebo lead-in period to assess their ability to comply with twice daily medication administration and assess whether there is a placebo response. Upon completion of the placebo lead-in period, subjects will return for the baseline visit (Visit 1) to confirm eligibility. Eligible subjects will be randomized 2:1 into the double-blind treatment period and will be evaluated for efficacy and safety at Weeks 8, 12, and 16 (Visits 2-4). Subjects who fail to meet all eligibility criteria at Visits -1, 0, or 1 will be considered screen failures. Subjects cannot be rescreened once they have been designated as a screen failure unless due solely to the use of a concomitant medication which can be stopped prior to rescreening. Subjects who discontinue will not be replaced.

Subjects will be required to visit the site up to 6 times over up to a 22-week period. A safety follow-up phone call will occur 4 weeks following the last dose of investigational product for subjects who discontinue prematurely during the double-blind treatment period or who do not enroll in the treatment extension study.

Figure 1: Study Design Flow Chart



Abbreviations: BID=twice daily; EGD=esophagogastroduodenoscopy; ET=early termination; OBS=oral budesonide suspension

Inclusion and exclusion criteria:

Inclusion Criteria:

The subject will not be considered eligible for the study without meeting all of the following criteria (including test results):

1. Subject is able to provide written informed consent (subject, parent or legal guardian and, as appropriate, subject assent) to participate in the study before completing any study-related procedures.
2. Subject is male or female aged 11-55 years, inclusive, at time of consent.
3. Subject has histologic evidence of EoE with a peak eosinophil count of ≥15/HPF, from 2 of 3 (proximal, mid-, and/or distal) levels of the esophagus at the screening endoscopy.
4. Subject has a history of clinical symptoms of esophageal dysfunction (eg, eating problems, abdominal pain, heartburn, dysphagia, vomiting, food impaction, weight loss) intermittently or continuously at screening (Visit -1).
5. Subject must have experienced dysphagia (response of "yes" to question 2 on DSQ) on a minimum of 4 days and completed the DSQ on ≥70% of days in any 2 consecutive weeks of the screening period and in the 2 weeks prior to the baseline visit (Visit 1).
6. Subject must not have proton pump inhibitor (PPI)–responsive EoE based on esophageal biopsies performed after the patient 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).
7. Subject will be on a stable (no changes) diet ≥3 months prior to the screening visit (Visit -1).
8. 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.
9. All female subjects must have a negative serum pregnancy test (beta-human chorionic gonadotropin [β-hCG]) prior to enrollment into the study. Females of childbearing potential must agree to continue acceptable birth control measures (eg, abstinence, stable oral contraceptives, or double-barrier methods) throughout study participation.
10. Subject is willing and has an understanding and ability to fully comply with study procedures and restrictions defined in this protocol.

Exclusion Criteria:

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Subject has any condition or abnormality (including laboratory abnormalities), current or past, that, in the opinion of the principal investigator or medical monitor, would compromise the safety of the subject or interfere with or complicate the assessment of signs or symptoms of EoE. Such conditions may include psychiatric problems; neurologic deficits or disease; developmental delay; cardiovascular, metabolic, or pulmonary disease; or previous gastroesophageal surgery. These should be discussed with the medical monitor.
2. 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 (eg, Rituxan) within 3 months of the qualifying EGD

should be reviewed with the medical monitor.

3. 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.
4. Subject has been on inhaled or intranasal steroids and not on stable treatment for ≥3 months prior to screening visit (Visit -1). Subjects on intranasal or inhaled steroids need to stay on stable treatment during study participation.
5. 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 EGD and baseline visit (Visit 1), or anticipates changes in the use of such medications during the treatment period.
6. Subject has been using cytochrome P450 3A4 inhibitors (eg, ketoconazole, grapefruit juice) within the 2 weeks prior to the baseline visit (Visit 1) or within 5 half-lives (whichever is greater) or anticipates using such medications during the treatment period.
7. 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 (eg, with an insertion tube diameter of >9 mm).
8. Subject is on a pure liquid diet or the 6-food elimination diet.
9. Subject has had an esophageal dilation within the 3 months prior to screening (Visit -1).
10. Subject has presence of esophageal varices at the screening endoscopy.
11. 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.
12. Subject has other diseases causing or associated with EoE, including hypereosinophilic syndrome, collagen vascular disease, vasculitis, achalasia, or parasitic infection.
13. Subject has current evidence of oropharyngeal or esophageal candidiasis.
14. 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.
15. 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).
16. Subject has evidence of active infection with *Helicobacter pylori.*
17. 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).
18. Subject is female and pregnant or nursing.
19. Subject has a history of intolerance, hypersensitivity, or idiosyncratic reaction to budesonide (or any other corticosteroids) or to any other ingredients of the investigational product.
20. Subject has taken part in an investigational study within 6 months prior to the screening visit (Visit -1).
21. Subject has a history or high risk of noncompliance with treatment or regular clinic visits.
22. Subject has previously completed, discontinued, or withdrawn from this study.

23. Subject has participated in a previous clinical study involving OBS (SHP621).

Maximum duration of subject involvement in the study:

- Planned duration of screening period: 3-6 weeks
- Planned duration of placebo lead-in period: 4 weeks
- Planned duration of treatment period: 12 weeks
- Planned duration of safety follow-up period: 4 weeks

Endpoints and statistical analysis:

Subject Populations

- The **safety set** will include all subjects who receive at least 1 dose of any double-blind investigational product.
- The **intent-to-treat (ITT) set** will include all randomized subjects. Subjects will be analyzed according to their assigned treatment, regardless of the treatment actually received.
- The **full analysis set (FAS)** will include all randomized subjects who received at least 1 dose of a double-blind investigational product and have both an evaluable post-baseline biopsy in the treatment period (ie, peak eosinophil count is reported for at least 2 esophageal levels) and a post-baseline DSQ score.
- The **per-protocol (PP) set** will include all subjects in the FAS excluding subjects with protocol violations. The PP set will be identified prior to unblinding the treatment assignments by a team consisting of, at a minimum, a physician and a statistician from Shire.
- The **pharmacokinetic set** will include all subjects in the safety set for whom the primary pharmacokinetic data are considered sufficient and interpretable.

Primary Efficacy Endpoints

The co-primary efficacy endpoints are the following:

- Histologic response, defined as a peak eosinophil count of ≤6/HPF across all available esophageal levels at the final treatment period evaluation (Visit 4)
- Dysphagia symptom response, defined as ≥30% reduction in the DSQ combined score (questions 2+3) from baseline to the final treatment period evaluation (Visit 4)

Key Secondary Efficacy Endpoint

- Change in DSQ combined score (questions 2+3) from baseline to the final treatment period evaluation (Visit 4)

Secondary Efficacy Endpoints

- Change in total endoscopy score, as measured by the EREFS classification, from baseline to the final treatment period evaluation (Visit 4)
- Peak eosinophil count <15/HPF across all available esophagus levels at the final treatment period evaluation (Visit 4)
- Peak eosinophil count ≤1/HPF across all available esophagus levels at the final treatment period evaluation (Visit 4)
- Change from baseline in the peak eosinophil count to the final treatment period evaluation (Visit 4) for each available esophageal level (proximal, mid-, and distal)

- Change from baseline in the histopathologic epithelial features combined total score (grade and stage) to the final treatment period evaluation (Visit 4)
- Dysphagia symptom response (binary response), defined as a ≥50% reduction in the DSQ combined score (questions 2+3), from baseline to the final treatment period evaluation (Visit 4)
- Change from baseline in the DSQ combined score (questions 2+3) over time including post-baseline visits
- Cumulative distribution function curves for the change and the percent change in the DSQ score from baseline to the final treatment period evaluation (Visit 4)
- Overall binary response I, defined as a reduction in the DSQ score of ≥30% from baseline to the final treatment period evaluation (Visit 4) and a peak eosinophil count of ≤6/HPF across all esophageal levels at the final treatment period evaluation (Visit 4)
- Overall binary response II, defined as a reduction in the DSQ score of ≥50% from baseline to the final treatment period evaluation (Visit 4) and a peak eosinophil count of ≤6/HPF across all esophageal levels at the final treatment period evaluation (Visit 4)
- Symptom response on DSQ + pain score (binary response), defined as ≥30% and 50% reductions in the DSQ combined score (questions 2+3+4) from baseline to the final treatment period evaluation (Visit 4)
- Symptom response on DSQ pain score (binary response), defined as a ≥30% and 50% reduction in the DSQ score (question 4), from baseline to the final treatment period evaluation (Visit 4)

Exploratory Efficacy Endpoint

[redacted]

Safety Endpoints

Safety parameters will include monitoring of AEs, physical examinations, stadiometry, vital signs (temperature, systolic and diastolic blood pressure, pulse, and respiratory rate), weight and height assessments, dual-energy X-ray absorptiometry (DXA) scans for bone mineral density (BMD) measurements (for adolescents aged 11-17 years, inclusive), clinical laboratory tests (hematology, chemistry, urinalysis; serum pregnancy test, if appropriate), and adrenocorticotropic hormone (ACTH) stimulation tests. To account for the effects of puberty in adolescent subjects (11-17 years, inclusive), BMD z-scores will be adjusted for height z-scores using the Bone Mineral Density in Childhood Study calculator (http://www.bmdcspublic.com).

Health Economics and Outcomes Research Endpoints

- Change in Adult Eosinophilic Esophagitis Quality of Life (EoE-QoL-A) score from baseline to the final treatment period evaluation (Visit 4)
- Change in EuroQol (EQ-5D; EuroQol-5 Dimensions 3-level [EQ-5D-3L] or EuroQol-5 Dimensions Youth [EQ-5D-Y], according to subject's age) score from baseline to the final treatment period evaluation (Visit 4)
- Change in Pediatric Quality of Life Inventory – EoE (PedsQL-EoE) score from baseline to the final treatment period evaluation (Visit 4)

Pharmacokinetic Endpoints

Pharmacokinetic parameters will be determined from the plasma concentration-time data for budesonide by non-compartmental analysis. The pharmacokinetic parameters will include, but not be limited to:

AUC_{tau}	Area under the curve for the defined interval between doses
C_{max}	Maximum concentration occurring at t_{max}
t_{max}	Time of maximum observed concentration sampled during a dosing interval

Statistical Methodology for Primary Efficacy Endpoint

The co-primary efficacy endpoints will be analyzed based on the ITT set. Each of the co-primary efficacy endpoints is a binary response (ie, responders vs non-responders); the endpoint will be analyzed using a logistic regression model with the effects of the treatment group, the age group (either <18 years or ≥18 years), and their interaction. The main-effect model will be considered the final definitive model if the interaction between the treatment and age group is not statistically significant at the 10% level. The odds ratio of being a responder on each of the co-primary endpoints for the OBS 2 mg twice daily group vs placebo group and associated 95% confidence interval (CI) will be estimated from the final model. Subjects who withdraw without providing efficacy data at the final treatment period evaluation (Visit 4, Week 16) will be classified as non-responders in the primary efficacy analysis.

Additionally, the proportion of responders based on each of the co-primary endpoints for each treatment group will be summarized and their respective 95% CI will be reported. The difference in the proportion of responders between the 2 treatment groups and the corresponding 95% CI will also be summarized.

The following sensitivity and supportive analyses will be performed for the co-primary to evaluate the robustness of the results from the primary analysis methods:

- Analyses will be repeated using the FAS and the PP set.
- Analyses will be repeated by considering subjects who withdraw without providing efficacy data at the final treatment period evaluation (Visit 4) will be classified as responders.

Statistical Methodology for Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is defined as the change in the DSQ combined score (questions 2+3) from baseline to the final treatment period evaluation (Visit 4). The change from baseline DSQ score at the final treatment period evaluation (Visit 4) will be analyzed using an analysis of covariance (ANCOVA) model with treatment group and age group as factors and the baseline DSQ score as a continuous covariate.

Statistical Methodology for Secondary Efficacy Endpoints

Secondary subjective efficacy endpoints that are defined as:

- Binary response endpoints will be analyzed using the same logistic model as the co-primary efficacy endpoints.
- Continuous endpoints will be analyzed as a change from baseline using an ANCOVA model that includes treatment group and age group as factors and baseline score as a continuous covariate.

The analyses for all secondary efficacy endpoints (including the key secondary efficacy endpoint) will be carried out using 2-sided tests at the 5% level of significance. For each of the secondary efficacy endpoints, the treatment difference, corresponding 95% CI for the difference, and treatment comparison p-value for testing the null hypothesis of zero treatment effect based on the final statistical model (ie, either logistic regression model or ANCOVA model) will be provided.

Statistical Methodology for Safety Endpoints

All safety measures, including AEs, physical examination, stadiometry, vital signs (temperature, systolic and diastolic blood pressure, pulse, and respiratory rate), weight and height assessments, DXA scans for BMD measurements (for adolescents aged 11-17 years, inclusive), clinical laboratory results

(hematology, chemistry, urinalysis; serum pregnancy test, if appropriate), and ACTH stimulation will be descriptively summarized by treatment group at baseline and for each post-baseline visit.

The number and percent of subjects with TEAEs will be presented. TEAEs are defined as AEs that start or deteriorate on or after the date of the first dose of investigational product and no later than 3 days following the last dose of investigational product. However, for any subjects who die during the study (ie, the date of death is between the date of first dose of investigational product and the date of study discontinuation entered by the site, inclusive), all AEs (including those resulting in death) that occur during the study will be considered as TEAEs irrespective of the last dose and will be included in the TEAE summaries.

Statistical Methodology for Pharmacokinetic Endpoint(s)

Summary statistics (number of observations, mean, standard deviation, coefficient of variation, median, maximum, minimum, and geometric mean) will be determined for all pharmacokinetic parameters by overall and by week. Plasma concentrations at each nominal sampling time will also be summarized using descriptive statistics.

Sample Size Justification

Based on at least a 30-percentage-point reduction in DSQ score, there is an expected difference between treatment response proportions of 69% and 45% in the OBS 2 mg twice daily (qAM, pc, and hs) and placebo groups, respectively. A total of 228 subjects (152 subjects randomized to OBS and 76 subjects randomized to placebo) are required to achieve 90% power at the significance level of 0.0499 (2-sided) using a 2-group chi-square test with unequal allocation 2:1 to treatment groups (OBS 2 mg twice daily and placebo). With the specified number of subjects per treatment group, the study will be powered at 99% assuming histological response proportions of 40% and 3% in the OBS 2 mg twice daily and placebo groups, respectively. The overall study power for the co-primary endpoints will be at least 85%. Therefore, approximately 228 (approximately 152:76 OBS and placebo subjects, respectively) will be randomized to the study to allow for a loss of approximately 5% of subjects due to dropouts or invalid data.

STUDY SCHEDULE(S)

Table 1-1: Schedule of Assessments

Procedures	Screening	Placebo Lead-in	Treatment Phase				Safety Follow-up Telephone Contact[p]
	Visit -1	Visit 0	Randomization Baseline/Visit 1	Visit 2	Visit 3	Visit 4 or ET[o]	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 assessment	X	X	X	X	X	X	
EGD with endoscopy score (EREFS) and biopsy[c]	X					X	
DSQ training and issue of handset	X						
Retrieval of DSQ handset						X	
DSQ compliance assessment		X	X	X	X	X	
EQ-5D[d]			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	

Table 1-1: Schedule of Assessments

Procedures	Screening	Placebo Lead-in	Treatment Phase				Safety Follow-up Telephone Contact[p]
	Visit -1	Visit 0	Randomization Baseline/Visit 1	Visit 2	Visit 3	Visit 4 or ET[o]	Visit 5
Week	**-6**	**0**	**4**	**8**	**12**	**16**	**20**
Window	**≤6 weeks**	**--**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**
Physical examination	X	X	X	X	X	X	
Tanner Staging Assessment[e]	X					X	
Clinical laboratory tests[f]	X	X	X	X	X	X	
Urinalysis[g]	X	X	X	X	X	X	
Pregnancy test[h]	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)[i]				X	X		
DXA Scan for BMD (subjects 11-17 years of age, inclusive)[j]		X				X	
Randomization[k]			X				
Investigational product supplied		X	X	X	X	X[l]	
Investigational product administration[m]		Twice-daily administration of investigational product					
Investigational product compliance assessment			X	X	X	X	
Concomitant medications and procedures	X	X	X	X	X	X	X

Table 1-1: Schedule of Assessments

Procedures	Screening	Placebo Lead-in	Treatment Phase				Safety Follow-up Telephone Contact[p]
	Visit -1	Visit 0	Randomization Baseline/Visit 1	Visit 2	Visit 3	Visit 4 or ET[o]	Visit 5
Week	**-6**	**0**	**4**	**8**	**12**	**16**	**20**
Window	**≤6 weeks**	**--**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**
recorded							
Review of adverse events[n]		X	X	X	X	X	X

Abbreviations: ACTH=adrenocorticotropic hormone; BMD=bone mineral density; 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 will be assessed after the subject has been in a supine position for at least 5 minutes immediately prior to the assessment and will include blood pressure (systolic and diastolic), heart rate, respirations, and temperature.

[b] Height to be collected at screening visit (Visit -1) and Visit 4 for all subjects. Stadiometers are required for subjects 11-17 years of age, inclusive, and will be used at Visit 1 and 4.

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

[d] Subjects 11-17 years of age, inclusive, will complete the EQ-5D-Y; subjects ≥18 years of age will complete the EQ-5D-3L.

[e] Tanner staging assessments will be performed for all subjects aged ≥11 years until investigator confirms subject is post puberty.

[f] Clinical laboratory tests will include the following: alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, total protein, albumin, glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, carbon dioxide, hemoglobin, hematocrit, mean corpuscular

Table 1-1: Schedule of Assessments

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Week	**-6**	**0**	**4**	**8**	**12**	**16**	**20**
Window	**≤6 weeks**	**--**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**

hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, erythrocyte count, leukocyte count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count. All subjects must fast overnight prior to collection.

[g] Urinalysis parameters will include glucose, protein, specific gravity, pH, nitrite, bilirubin, ketones, hemoglobin, urobilinogen, and leukocyte esterase.

[h] The serum pregnancy test will be performed for all female subjects at the screening visit (Visit -1) and final treatment evaluation (Visit 4). Urine pregnancy tests will be performed at all other visits.

[i] Blood samples for pharmacokinetic analysis will be taken from adult subjects (aged ≥18 years). Subjects who do not participate in pharmacokinetic sampling will not be discontinued from the study and lack of participation will not be a considered protocol deviation. Blood samples for pharmacokinetic analysis will be obtained at the Week 8 or Week 12 visit at the following time points: pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, and 12 hours post-dose.

[j] The baseline DXA scan may be performed any time during the placebo lead-in period after the subject has met all screening criteria and prior to blinded-treatment randomization. Baseline and post-treatment DXA scans should be performed using the same machine and software. Post-treatment DXA scan should occur at or within 7 days of the scheduled visit.

[k] Randomization will occur via IWRS at the baseline visit (Visit 1) once the subject's eligibility for study entry is confirmed.

[l] Investigational product will be dispensed at Visit 4 to subjects who consent to enroll in the treatment extension study.

[m] Subjects will receive oral administration of 10 mL of investigational product twice daily (qAM, pc, and hs), with no ingestion of food or liquids permitted for 30 minutes after study drug administration.

[n] AE assessments at each visit and physical examination must include specific assessments for signs of glucocorticoid excess (eg, moon facies, acne, hirsutism, mood swings, insomnia, and depression).

Table 1-1: Schedule of Assessments

Procedures	Screening	Placebo Lead-in	Treatment Phase				Safety Follow-up Telephone Contact[p]
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Week	**-6**	**0**	**4**	**8**	**12**	**16**	**20**
Window	**≤6 weeks**	**--**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**

[o] If subject discontinues study prematurely, the evaluations listed for Visit 4 are to be performed as completely as possible.

[p] For subjects who withdraw from the study or do not continue into treatment extension study, a safety follow-up contact by phone will be performed 4 weeks following the last dose of investigational product.

1. BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

Eosinophilic esophagitis (EoE) is defined as "a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation" (Liacouras et al., 2011). Clinical symptoms of EoE often vary by age: Infants and toddlers present with feeding difficulties; school-aged children are more likely to present with vomiting or pain; and adolescents and adults present with dysphagia and food impaction. When these symptoms are present, the diagnosis is confirmed by finding eosinophilic inflammation of ≥15 eosinophils/high-powered field (HPF) on at least 1 esophageal biopsy and when other causes such as proton pump inhibitor (PPI)-responsive esophageal eosinophilia are excluded (Dellon et al., 2014a; Furuta et al., 2007). The standards of care are diet therapies and off-label use of glucocorticosteroids. Esophageal dilation is used to temporarily relieve symptoms but does not address underlying inflammation. Given the clinical outcomes associated with EoE, including severe dysphagia, esophageal stricture, food impaction, and esophageal perforation (Hirano and Aceves, 2014; Liacouras et al., 2011) and the fact that there are currently no FDA-approved treatments, there is a clear unmet medical need for a novel treatment for this disease.

1.2 Product Background and Clinical Information

Oral budesonide suspension (OBS) consists of budesonide formulated in a viscous suspension that is designed to increase the residence time of budesonide on the surface of the esophagus after swallowing compared to a non-viscous suspension. Shire is developing OBS as a first-line therapy for EoE in adolescents and adults.

The nonclinical pharmacology, pharmacokinetics, and toxicity and the clinical pharmacology, pharmacokinetics, and safety of budesonide are well studied because budesonide is present in several US FDA-approved drug products. Budesonide is currently marketed for the management of Crohn's disease, for asthma maintenance, for the treatment of allergic rhinitis, and for induction of remission in patients with active, mild to moderate ulcerative colitis. Budesonide has strong glucocorticoid receptor affinity and is subject to considerable first pass metabolism by the liver with a short half-life. These attributes permit budesonide to act rapidly and locally in the gut mucosa for treatment of inflammatory disorders such as Crohn's disease and ulcerative colitis. Once absorbed into the systemic circulation, budesonide is rapidly metabolized in the liver and inactivated (FDA, 2011).

The efficacy of OBS for the treatment of EoE has been demonstrated in two Phase 2 studies in the OBS clinical development program. Studies MPI 101-01 and MPI 101-06 evaluated the efficacy of OBS in the treatment of EoE in children and adolescents aged 2-18 years and in adolescents and adults aged 11-40 years, respectively, by measuring histological response (defined as mean peak eosinophil count ≤6/HPF after treatment). Study MPI 101-06 also

evaluated symptom response as measured by the Dysphagia Symptom Questionnaire (DSQ). The DSQ contains 4 questions related to consumption of solid food, the presence of dysphagia and its severity, as well as pain. The DSQ score is calculated only from responses to the questions related to dysphagia, and this clinical outcome assessment was considered to be fit for purpose as a result of the MPI 101-06 study. Results from Study MPI 101-01 demonstrated a statistically significant histologic response (eosinophil count ≤6/HPF) and remission (eosinophil count ≤1/HPF) in the medium-dose (1.4-2.0 mg daily) and high-dose (2.8-4.0 mg daily) OBS groups compared to placebo following 12 weeks of treatment.

In Study MPI 101-06, a significant treatment effect for OBS vs placebo was shown for both the co-primary efficacy endpoints of histologic response and change from baseline in dysphagia symptoms. Following 12 weeks of twice daily treatment (once in the morning after meals [qAM, pc] and at bedtime [hs]), OBS-treated subjects demonstrated a highly consistent reduction from baseline values for cellular (mean peak eosinophil count and histopathology features), organ (endoscopy score), and holistic measures (Physician Global Assessment [PGA] and DSQ scores); these results were independent of the type of rater/reviewer (central pathologist, physician at the study site, or subject).

Always refer to the latest version of the SHP621 investigator's brochure for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics, efficacy, and safety of SHP621.

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

Currently there is no approved medication for the treatment of EoE. This study is being conducted in order to provide safety and efficacy data demonstrating histologic response (as measured by eosinophilic count ≤6/HPF) and improvement in dysphagia symptoms (as measured by the DSQ) following 12 weeks of treatment with OBS in adolescent and adult subjects with EoE.

2.2 Study Objectives

2.2.1 Primary Objectives

The co-primary objectives of the study are to demonstrate in a placebo-controlled trial that:

- OBS induces a histologic response (eosinophilic count ≤6/HPF) in adolescent and adult subjects with EoE over a 12-week course of therapy.
- OBS reduces dysphagia, as measured by the DSQ, by at least 30% from baseline in adolescent and adult subjects with EoE over a 12-week course of therapy.

2.2.2 Secondary Objectives

The key secondary objective of this study is:

- OBS reduces dysphagia, as measured by the DSQ score from baseline to the final treatment period evaluation (Visit 4).

Additional secondary objectives of the study are:

- To assess the response of endoscopically identified esophageal features to OBS as compared to placebo as measured by the EoE Endoscopic Reference Score (EREFS)
- To explore other responding criteria based on histology and DSQ
- To assess the impact of OBS on pain, as measured by the DSQ
- To evaluate the safety and tolerability of OBS over a 12-week course of therapy
- To obtain OBS pharmacokinetic data in adult subjects with EoE

2.2.3 Exploratory Objective

The exploratory objective of this study is:

[redacted]

3. STUDY DESIGN

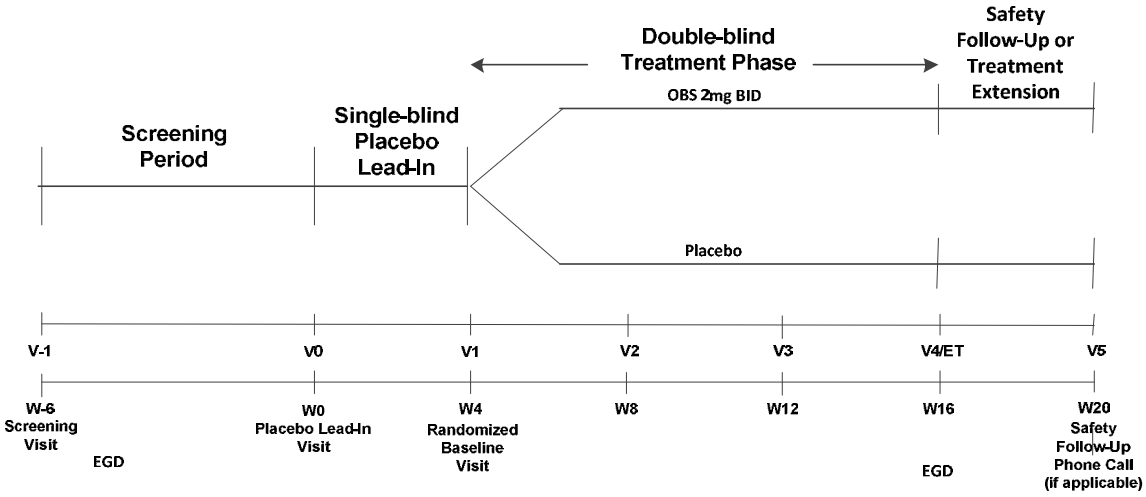
3.1 Study Design and Flow Chart

This is a Phase 3, randomized, multicenter, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of OBS treatment administered twice daily (qAM, pc, and hs) for 12 weeks. The study will be conducted in adolescents and adults, aged 11-55 years, inclusive, with EoE and dysphagia.

Approximately 300 subjects will be enrolled in the placebo lead-in period to allow for approximately 228 subjects to be randomized into the double-blind treatment period. A minimum of 40 randomized subjects will be aged 11-17 years, inclusive. Subjects will be randomized 2:1 (approximately 152 and 76 per OBS and placebo treatment group, respectively) to receive either OBS 2 mg twice daily (qAM, pc, and hs) or placebo twice daily (qAM, pc, and hs).

This study will consist 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 (see Figure 1).

Figure 1: Study Design Flow Chart



Abbreviations: BID=twice daily; EGD=esophagogastroduodenoscopy; ET=end of treatment; OBS=oral budesonide suspension

The upper limit of 55 years, inclusive, was selected for this study population based on the low prevalence of EoE in older patients (Dellon et al., 2014a) and the fact that the type of EoE that develops in older patients is not amenable to anti-inflammatory treatment alone (Dellon et al., 2014b). A natural history study demonstrated that for every decade of life, the odds of developing the fibrostenotic phenotype of EoE more than doubles (Dellon et al., 2014b). By age 55, fibrostenotic EoE occurs in approximately 80% of patients. Fibrostenotic disease is treated with dilatation and is not amenable to anti-inflammatory treatment alone. Therefore, budesonide is not expected to be an effective treatment for the majority of patients above age 55.

Subjects will be required to visit the site up to 6 times over up to a 22-week period. Following completion of the screening and placebo lead-in visits, subjects will be evaluated for eligibility and safety at Week 4 (Visit 1). Subjects who are eligible and randomized will be evaluated for efficacy and safety at Weeks 8, 12, and 16 (Visits 2-4) and additionally for safety at follow-up at Week 20 (Visit 5; telephone contact). Subjects who fail to meet all eligibility criteria at Visits -1, 0, or 1 will be considered screen failures. Subjects cannot be rescreened once they have been designated as a screen failure unless due solely to the use of a concomitant medication which can be stopped prior to rescreening. Subjects who discontinue will not be replaced.

The screening period will start when subjects sign informed consent (or assent as applicable for subjects <18 years of age; screening visit [Visit -1]) and will be approximately 3-6 weeks in duration. During the screening period, all subjects will receive an upper endoscopy with histologic analysis of biopsy specimens to confirm the diagnosis of EoE (eosinophil count of ≥15/HPF from 2 of 3 [proximal, mid-, and/or distal] levels of the esophagus). In addition,

subjects must complete the DSQ daily during the screening period (3-6 weeks) and have at least 4 reported days with symptoms of dysphagia and completed the DSQ on ≥70% of days in any 2 consecutive weeks. At the screening visit (Visit -1), subjects who are on a PPI must remain on the same dose of the PPI throughout the study; if they are not taking a PPI, they must remain off of a PPI for the remainder of the study. After the screening period, eligible subjects will enter a 4-week single-blind placebo lead-in period and will receive 10 mL of OBS placebo twice daily (in the morning after meals/breakfast [qAM, pc] and at bedtime [hs]). The placebo lead-in period will enable assessment of the subject's ability to comply with twice daily medication administration and assess whether the subject experiences a placebo response.

At the end of the placebo lead-in period, subjects will return for the baseline visit (Visit 1) to confirm eligibility. Subjects who continue to meet all eligibility criteria (those with at least 4 reported dysphagia days and who completed the DSQ on ≥70% of days in the 2 weeks prior to randomization per daily DSQ completion) will be randomized to receive either OBS or placebo during the 12-week double-blind treatment period.

OBS will be administered in 10 mL at a concentration of 0.2 mg/mL (2 mg dose), twice daily. The 0.2 mg/mL concentration of OBS and dosing regimens were selected for use in this Phase 3 study based on the results of Study MPI 101-06, a Phase 2 study in 93 adolescent and adult subjects with EoE and symptoms of dysphagia. Subjects were treated in Study MPI 101-06 with 2 mg OBS twice daily to investigate the co-primary endpoints of histologic response (defined as ≤6 eosinophils/HPF) and reduction in DSQ score from baseline to Week 12 of treatment. For the current study, the investigational product will be supplied in amber glass, multi-dose bottles with child-resistant caps. Each bottle will contain 210 mL of suspension with a budesonide concentration of 0.2 mg/mL, or 0.00 mg/mL (matching placebo).

At the end of the 12-week double-blind treatment period (Visit 4, Week 16), subjects who complete the study will have the opportunity to enroll in the treatment extension study. These subjects will continue on the blinded assigned treatment for 2-4 weeks as part of the screening prior to enrolling into the treatment extension study. Subjects who do not enroll in the treatment extension study or who discontinue at any time during the SHP621-301 (Induction) study will receive a follow-up phone call 4 weeks post last dose of investigational product (Visit 5).

3.2 Duration and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 26 weeks, depending on the 3- to 6-week screening period.

The study will be completed in approximately 32 months.

The Study Completion Date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment. Please note that this includes the follow-up visit or

contact, whichever is later. The Study Completion Date is used to ascertain timing for study results posting and reporting.

A completer is a subject who completes all procedures and assessments up to and including Visit 4 (Week 16), inclusive of the final treatment evaluation EGD. Subjects who do not enroll in the treatment extension study or who discontinue prematurely at any time during the SHP621-301 (Induction) study will receive a follow-up phone call 4 weeks post last dose of the investigational product to which they were randomized.

3.3 Sites and Regions

Approximately 60 sites in North America will participate.

4. STUDY POPULATION

Each subject must participate in the informed consent process and provide written informed consent/assent before any procedures specified in the protocol are performed.

4.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the following criteria (including test results):

1. Subject is able to provide written informed consent (subject, parent or legal guardian, and, as appropriate, subject assent) to participate in the study before completing any study-related procedures.
2. Subject is male or female aged 11-55 years, inclusive, at time of consent.
3. Subject has histologic evidence of EoE with a peak eosinophil count of ≥15/HPF, from 2 of 3 (proximal, mid-, and/or distal) levels of the esophagus at the screening endoscopy.
4. Subject has a history of clinical symptoms of esophageal dysfunction (eg, eating problems, abdominal pain, heartburn, dysphagia, vomiting, food impaction, weight loss) intermittently or continuously at screening (Visit -1).
5. Subject must have experienced dysphagia (response of "yes" to question 2 on DSQ) on a minimum of 4 days and completed the DSQ on ≥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).
6. Subject must not have PPI-responsive EoE based on esophageal biopsies performed after the patient 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 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).

7. Subject will be on a stable (no changes) diet ≥3 months prior to the screening visit (Visit -1).
8. 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.
9. All female subjects must have a negative serum pregnancy test (beta-human chorionic gonadotropin [β-hCG]) prior to enrollment into the study. Females of childbearing potential must agree to continue acceptable birth control measures (eg, abstinence, stable oral contraceptives, or double-barrier methods) throughout study participation.
10. Subject is willing and has an understanding and ability to fully comply with study procedures and restrictions defined in this protocol.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Subject has any condition or abnormality (including laboratory abnormalities), current or past, that, in the opinion of the principal investigator or medical monitor, would compromise the safety of the subject or interfere with or complicate the assessment of signs or symptoms of EoE. Such conditions may include psychiatric problems; neurologic deficits or disease; developmental delay; cardiovascular, metabolic, or pulmonary disease; or previous gastroesophageal surgery. These should be discussed with the medical monitor.
2. 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 (eg, Rituxan) within 3 months of the qualifying EGD should be reviewed with the medical monitor.
3. 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.
4. 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.

5. 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 (EGD) and baseline visit (Visit 1), or anticipates changes in the use of such medications during the treatment period.
6. Subject has been using cytochrome P450 3A4 (CYP450 3A4) inhibitors (eg, ketoconazole, grapefruit juice) within the 2 weeks prior to the baseline visit (Visit 1) or within 5 half-lives (whichever is greater) or anticipates using such medications during the treatment period.
7. 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 (eg, with an insertion tube diameter of >9 mm).
8. Subject is on a pure liquid diet or the 6-food elimination diet.
9. Subject has had an esophageal dilation within the 3 months prior to screening (Visit -1).
10. Subject has presence of esophageal varices at the screening endoscopy.
11. 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.
12. Subject has other diseases causing or associated with EoE, including hypereosinophilic syndrome, collagen vascular disease, vasculitis, achalasia, or parasitic infection.
13. Subject has current evidence of oropharyngeal or esophageal candidiasis.
14. 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.
15. 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).
16. Subject has evidence of active infection with *Helicobacter pylori.*
17. 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).
18. Subject is female and pregnant or nursing.
19. Subject has a history of intolerance, hypersensitivity, or idiosyncratic reaction to budesonide (or any other corticosteroids) or to any other ingredients of the investigational product.
20. Subject has taken part in an investigational study within 6 months prior to the screening visit (Visit -1).
21. Subject has a history or high risk of noncompliance with treatment or regular clinic visits.

22. Subject has previously completed, discontinued, or withdrawn from this study.
23. Subject has participated in a previous clinical study involving OBS (SHP621).

4.3 Restrictions

Subjects must adhere to the following restrictions for the duration of the study:

- No change in exercise
- No change in diet (liquid diet for 3 days or less is acceptable.)
- Short course of systemic steroids are permitted to treat, for example, exacerbation of asthma but cannot be used 4 weeks prior to the final EGD.
- No change in PPI use
- No use of CYP450 3A4 inhibitors
- An esophageal dilatation during the trial (Dilatation is considered a treatment failure, and the subject should be withdrawn from the study.)

4.4 Reproductive Potential

4.4.1 Female Contraception

All females must have a negative pregnancy test at the screening visit (Visit -1), placebo lead-in visit (Visit 0), baseline visit (Visit 1), and Visits 1-4. A serum pregnancy test will be performed at the screening visit (Visit -1) and final treatment evaluation (Visit 4). Urine pregnancy tests will be performed at all other visits.

Female subjects should be either:

- Pre-menarchal and Tanner Stage 1, or
- Post-menopausal (24 consecutive months of spontaneous amenorrhea and age 51 years or older).
- Be surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 6 weeks post-sterilization, or
- Females of child-bearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception throughout the study period and for 30 days following the last dose of investigational product.
    - Acceptable methods of contraception are:
        - Intrauterine devices plus condoms

- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam)
- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the screening visit (Visit -1), plus condoms. If hormonal contraceptives are used, they should be administered according to the package insert. Note: If subjects become sexually active during the study, they should use one of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

4.5 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject from investigational product with the medical monitor when possible.

If investigational product is discontinued, leading to subject discontinuation from the study, regardless of the reason, the evaluations listed for Visit 4 are to be performed as completely as possible. If investigational product is discontinued due to an AE, the subject may remain on study to allow for completion of study procedures.

Whenever possible, all discontinued subjects should also undergo the protocol-specified follow-up. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for termination, date of stopping investigational product, and total amount of investigational product taken must be recorded in the case report form (CRF) and source documents.

Subjects who discontinue will not be replaced.

4.5.1 Subject Withdrawal Criteria

Medically important events that in the opinion of the investigator or medical monitor would compromise the subject's ability to safely continue in the study, including but not limited to an esophageal stricture requiring dilation and/or worsening signs and symptoms of EoE (eg, weight loss or increased dysphagia), would be considered a treatment failure and result in withdrawal of the subject from the study.

4.5.2 Reasons for Discontinuation

The reason for withdrawal must be determined by the investigator and recorded in the subject's medical record and on the CRF. If a subject is withdrawn for more than 1 reason,

each reason should be documented in the source document and the most clinically relevant reason should be entered on the CRF.

Reasons for discontinuation include but are not limited to:

- Completed
- Death
- AE
- Non-compliance with study drug
- Non-compliance with study procedure
- Withdrawal by subject
- Withdrawal by parent/guardian
- Physician decision
- Study terminated by sponsor
- Site terminated by sponsor
- Lost to follow-up
- Pregnancy
- Trial screen failure
- Placebo responder
- Protocol deviation
- Other

4.5.3 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and return any unused investigational product.

5. PRIOR AND CONCOMITANT TREATMENT

All non-study treatment (including but not limited to herbal treatments, vitamins, behavioral treatment, and non-pharmacological treatment, such as psychotherapy, as appropriate) received within 3 months prior to the screening visit (Visit -1) (or pharmacokinetic equivalent

of 5 half-lives, whichever is longer) and through the final study contact (including protocol-defined follow-up period) must be recorded on the appropriate CRF page.

5.1 Prior Treatment

Prior treatment includes all treatment, including but not limited to herbal treatments, vitamins, and non-pharmacological treatment such as psychotherapy, as appropriate, received within 3 months of the screening visit (Visit -1). Prior treatment information must be recorded on the appropriate CRF page.

5.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product and the end of the follow-up period, inclusive. Concomitant treatment information must be recorded on the appropriate CRF page.

The investigator may prescribe additional medications during the study, as long as the prescribed medication is not prohibited by the protocol. In the event of an emergency, any needed medications may be prescribed without prior approval, but the medical monitor must be notified of the use of any prohibited medications immediately thereafter.

5.2.1 Permitted Treatment

The following medications are allowed during the course of the study if the subject has been on a stable dosing regimen (ie, same dose and frequency in the previous 4 weeks prior to the endoscopy required for entrance to this study) and will continue this dosing regimen throughout study participation. The investigator must contact the medical monitor to discuss any changes to concomitant steroid regimens or for any medications not listed here that could impact the outcome of the study.

1. Inhaled or intranasal steroids for conditions other than EoE; subject must be on stable treatment for ≥3 months prior to screening visit (Visit -1).
2. PPIs
3. H2 antagonists
4. Antacids
5. Antihistamines or antileukotrienes
6. Maintenance immunotherapy (allergy shots)

Influenza and other routine required vaccinations are allowed during the study.

5.2.2 Prohibited Treatment

The following medications and treatments are prohibited throughout the course of the study and prior to treatment, as specified:

1. Immunomodulatory therapy within 8 weeks prior to the qualifying EGD or between the qualifying EGD and baseline visit (Visit 1) or anticipated use of immunomodulatory therapy during the treatment period (except for any ongoing regimen of allergy shots). Use of long-acting immunomodulatory therapy (eg, Rituxan) within 3 months of the qualifying EGD should be reviewed with the medical monitor.
2. 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 anticipated use during the treatment period; any temporary use or initiation of new steroid treatment during study should be documented and discussed with the medical monitor prospectively but cannot occur within the 4 weeks of the final EGD.
3. Inhaled or intranasal steroids if <3 months prior to screening visit (Visit -1)
4. 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 EGD and baseline visit 1, or anticipated changes in the use of such medications during the treatment period.
5. CYP450 3A4 inhibitors (eg, ketoconazole, grapefruit juice) within the 2 weeks prior to the baseline visit (Visit 1) or within 5 half-lives (whichever is greater) or anticipated use of such medications during the treatment period. For an expanded list of CYP3A inhibitors, investigators should refer to the 2012 FDA Draft Guidance on Drug Interactions (FDA Guidance 2012) and use their clinical judgment with respect to specific medications.
6. Esophageal dilation within the 3 months prior to screening (Visit -1)
7. Investigational study treatment within 6 months prior to the screening visit (Visit -1)

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The test product is OBS (oral budesonide suspension, 0.2 mg/mL), which will be provided in multi-dose amber glass bottles, each containing 210 mL. Additional information is provided in the current SHP621 investigator's brochure.

The reference/comparator product is placebo, which will be provided in amber glass bottle form with the same volume.

6.1.1 Blinding the Treatment Assignment

Investigational product will be supplied in amber glass, multi-dose bottles with child-resistant caps. Each bottle contains 210 mL of suspension with a budesonide concentration of 0.2 mg/mL. Inactive ingredients in OBS include dextrose, disodium edetate, citric acid, sodium citrate, potassium sorbate, polysorbate 80, glycerin, sodium benzoate, cherry flavor, Magnasweet 110, acesulfame potassium, and water.

The placebo solution will also be supplied in amber glass multi-dose bottles with child-resistant caps. Placebo consists of all components of the investigational product solution with the exception of budesonide.

6.2 Administration of Investigational Product(s)

All investigational product and supplies (eg, dosing spoons) will be provided by Shire or its designee. At each visit, subjects will be supplied with enough investigational product to last until the subsequent visit. The first dose of investigational product (placebo) for each subject will be administered in the clinic at the placebo lead-in visit (Visit 0). The subject will continue with the evening dosing regimen at home.

OBS and placebo will be supplied in amber glass bottles and must be shaken well prior to administration. The appropriate dose will be dispensed using the graduated dosing spoon provided. For subjects who are minors (<18 years), a parent/guardian will be responsible for ensuring that the subjects take their investigational product appropriately.

Subjects will be instructed not to eat or drink for 30 minutes after taking the investigational product. Activities such as brushing teeth or rinsing the mouth should also be avoided during this time interval. After 30 minutes, it is recommended that the subjects rinse with water and spit.

Please refer to the Investigational Product Administration Manual for additional details.

6.2.1 Interactive Response Technology for Investigational Product Management

An interactive web-based response system (IWRS) will be used for screening and enrolling subjects, recording subject visits, randomization, investigational product supply dispensation and management, inventory management and supply ordering, investigational product expiration tracking and management, return of investigational product, and emergency unmasking. Please refer to the Study Manual for additional details regarding the IWRS.

The investigator or designee will access the IWRS at the screening visit (Visit -1) to record subject-specific information (ie, unique subject number, date of birth, etc.). Subjects will be entered as screen failures or as entering the placebo lead-in period. Subjects cannot be rescreened once they have been designated as a screen failure unless due solely to the use of a

concomitant medication that can be stopped prior to rescreening. For subjects who enter the placebo lead-in period, IWRS will provide the assignment of placebo lead-in period medication to dispense.

At the baseline visit (Visit 1), the investigator or designee will again access the IWRS to either document a screen failure or, if the subject has met all entry criteria, to randomize the subject. Sites will enter eligibility criteria information prior to randomization. For randomized subjects, the IWRS will provide a medication identification (Med ID) number (ie, kit number to dispense for treatment).

The IWRS will also be used for creating, tracking, and confirming investigational product shipments. A user manual with specific functions and instructions for the IWRS will be provided to the site and site personnel will receive training.

The IWRS provider will provide a user manual and training to each site, with detailed instructions on use of the IWRS.

6.2.2 Allocation of Subjects to Treatment

This study consists of a single-blind lead-in period followed by a double-blind placebo-controlled study period. The actual treatment given to individual subjects during the double-blind period is determined by a randomization schedule.

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation.

The randomization number represents a unique number corresponding to investigational product allocated to the subject once eligibility has been determined following the placebo lead-in period.

Individual subject treatment is automatically assigned by the IWRS.

Subjects will be randomized after confirmation of study eligibility in a ratio of 2:1 via a computer-generated randomization schedule to receive OBS 2 mg twice daily (qAM, pc, and hs) or placebo. The randomization will be performed centrally and stratified by age group (2 strata total: <18 years vs ≥18 years). The stratification will ensure a minimum of 40 subjects in the pediatric group (11-17 years, inclusive). Permuted blocks of random sizes will be used to ensure that approximately equal numbers of patients are assigned each treatment within strata.

6.2.3 Dosing

During the 4-week single-blind placebo lead-in period, all subjects will receive 10 mL of placebo twice daily (qAM, pc, and hs). During the 12-week double-blind treatment period, oral administration of 10 mL of investigational product will occur twice daily (qAM, pc, and hs), with no ingestion of food or liquids permitted for 30 minutes after study drug administration. Subjects randomized to OBS will receive 10 mL of 0.2 mg/mL of OBS (2 mg) twice daily for a total daily dose of 4 mg.

Investigational product doses that are required to be administered at the clinic include the first dose of placebo administered at the placebo lead-in visit (Visit 0), the first dose of randomized investigational product (OBS or placebo) administered at the baseline visit (Visit 1) and all morning doses of investigational product administered at Visits 2-4. Subjects will Subjects will be required to eat breakfast at the clinic prior to self-administering these doses. Subjects can self-administer all other doses of placebo and investigational product at home.

During the visit where the pharmacokinetic blood samples are collected (Visit 2 or Visit 3), subjects will be required to eat a moderate-fat breakfast on-site and will be instructed to take their morning dose at a set time to establish the schedule for post-dose sample collection.

6.2.4 Unblinding the Treatment Assignment

The treatment assignment must not be broken during the study except in emergency situations where the identification of the investigational product is required for further treatment of the subject. The investigator should contact the medical monitor and the sponsor as soon as possible after the investigator has been unblinded.

In the event that the treatment assignment is broken, the date, the signature of the person who broke the code, and the reason for breaking the code are recorded in the IWRS and the source documents. Upon breaking the blind, the subject is withdrawn from the study but should be followed up for safety purposes. Any code breaks that occur must be reported to the contract research organization (CRO) and sponsor. Code break information is held by the pharmacist/designated person at the site and by the CRO medical monitor for the study or designee.

There will be a provision for unblinding to ensure adequate treatment of the subject in the case of an emergency.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

Labels containing study information and pack identification are applied to the investigational product(s) container.

All investigational product is labeled with a minimum of the protocol number, Med ID, dosage form (including product name and quantity in pack), directions for use, storage conditions, expiry date (if applicable), batch number and/or packaging reference, the statements "For clinical trial use only" and/or "CAUTION: New Drug - Limited by Federal (or US) Law to Investigational Use," "Keep out of reach of children," and the sponsor's name and address. Any additional labeling requirements for participating countries and/or controlled substances will also be included on the label.

Space is allocated on the label so that the site representative can record subject information.

Additional labels (eg, those used when dispensing marketed product) may, on a case-by-case basis, be applied to the investigational product in order to satisfy local or institutional requirements, but must not:

- Contradict the clinical study label.
- Obscure the clinical study label.
- Identify the study subject by name.

Additional labels may not be added without the sponsor's prior full agreement.

6.3.2 Packaging

Investigational product is packaged in the following labeled containers:

The sponsor will supply the following medication to the study sites in a blinded manner: OBS 0.2 mg/mL or placebo in an 8-ounce amber glass bottle for multiple use. Three bottles will be packaged in an appropriately labeled carton.

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.

6.3.3 Storage

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

OBS and placebo must be stored at 2-8ºC (36-46ºF), protected from light.

Investigational products are distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier on the investigational product bottle/carton labels as they are distributed.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), eg, fumigation of a storage room.

6.3.4 Special Handling

The investigational product should be stored under refrigeration at 2-8°C/36-46°F at all times. The investigational product should be protected from light and shaken well immediately prior to each dose.

6.4 Drug Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed-upon number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and

condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for administering/dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will dispense the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All dispensed medication will be documented on the CRFs and/or other investigational product record. The investigator is responsible for assuring the retrieval of all study supplies from subjects. The investigator or his/her designee will enter the unique subject identifier and initials on the investigational product kit labels as they are assigned and dispensed.

No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records provided that the blind of the study is not compromised.

At the end of the study, or as instructed by the sponsor, all unused stock, subject-returned investigational product, and empty/used investigational product packaging are to be sent to a nominated contractor on behalf of the sponsor. Investigational product being returned to the sponsor's designated contractors must be counted and verified by clinical site personnel and the sponsor (or designated CRO). For unused supplies where the original supplied tamper-evident feature is verified as intact, the tamper-evident feature must not be broken, and the labeled amount is to be documented in lieu of counting. Shipment return forms, when used, must be signed prior to shipment from the site. Validated electronic return systems (ie, IWRS) do not require a shipment form. Returned investigational product must be packed in a tamper-evident manner to ensure product integrity. Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

6.5 Subject Compliance

Compliance with investigational product will be assessed at each study visit. Subjects must be instructed to bring their unused investigational product and empty/used investigational product packaging to every visit. Drug accountability must be assessed at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (eg, bottles) or at the individual count level for opened containers/packaging. The pharmacist/nominated person will record details on the drug accountability form.

Visit to visit compliance of investigational product dosing will be assessed by site personnel. Site personnel must review the returned investigational product to assess compliance at every visit prior to dispensing additional investigational product. Any discrepancies should be reconciled with the subject immediately. Subjects who do not return their used and unused investigational product should be reminded to bring all used and unused investigational product at their next visit.

Subjects who have taken 70-130% of the investigational product will be assessed as being compliant with the study protocol. Compliance will be assessed at each treatment visit.

Visit to visit compliance of DSQ completion will also be assessed by site personnel. Protocol deviations will be documented for subjects who fail to complete the DSQ for 3 or more days in a given week.

7. STUDY PROCEDURES

7.1 Study Schedule

The detailed study procedures/assessments to be performed throughout the study are outlined in the Schedule of Assessments (see Table 1-1) and must be referred to in conjunction with the instructions provided in this section.

Prior to performing any study-related procedures (including those related to screening), the investigator or his/her designee must obtain written informed consent from the subject (as per local requirements). There must be documentation of consent (as per local requirements) indicating that the subject is aware of the investigational nature of the study and the required procedures and restrictions, prior to performing any study-related procedures.

7.1.1 Screening Period (Weeks -6 to 0)

The screening period starts when subjects sign informed consent. The screening period will comprise 3-6 weeks, during which all procedures listed for the screening visit (Visit -1) in Table 1-1 shall be completed. The screening period will allow for the determination of

eligibility of each subject's inclusion into the study. A subject should not be instructed to discontinue use of any medication or treatment to participate in this study until informed consent has been obtained. Subjects should not stop permitted medications or treatments that are effective and well tolerated to participate in this study (see Section 5.2.1).

Screening assessments may take place across several days to allow an appropriate time frame in which to complete all procedures and confirm study eligibility.

After the screening period, subjects who meet eligibility criteria at the end of the screening visit (Visit -1) will enter the 4-week single-blind, placebo lead-in period. The placebo lead-in period should not commence until all screening assessments required to confirm initial eligibility have been completed. If the subject does not meet eligibility criteria following completion of screening assessments, the investigator or designee will document the subject as a screen failure in the IWRS.

A screen failure is a subject who has given informed consent and failed to meet the inclusion criteria and/or met at least 1 of the exclusion criteria and has not been randomized or administered randomized investigational product. Screen failures can occur at the screening, placebo lead-in, or baseline visits. Subjects cannot be rescreened once they have been designated as a screen failure unless the screen failure was due to a concomitant medication that can be discontinued; those subjects can be rescreened.

7.1.1.1 Screening Visit (Visit -1)

The screening visit (Visit -1) assessments and procedures, beginning with informed consent, will be performed as outlined in Table 1-1.

The following procedures should be performed first:

- Obtain subject consent (or assent as applicable for subjects <18 years).
- Review eligibility criteria.
- Review medical history.
- Record vital signs (including blood pressure [systolic and diastolic], heart rate, respirations, and temperature), height, and weight.
- Review current use of concomitant medications, including medications taken and procedures completed within 3 months prior to the biopsy required for entrance to this study. Note: Subjects who are on a PPI must remain on the same dose of the PPI throughout the study, and if they are not taking a PPI, they must remain off of a PPI for the remainder of the study.
- Clinical chemistry, hematology, and urinalysis laboratory tests will be performed on all subjects; all subjects must fast overnight prior to collection.

The following order is recommended for the remaining procedures that will be performed at this visit or within the 6-week screening period:

- Dispense the DSQ electronic patient-reported outcome (ePRO) device for nightly completion and train the subject on its use. In order to qualify for study entry, subjects must have experienced dysphagia (response of "yes" to question 2 on DSQ) on a minimum of 4 days and completed the DSQ on ≥70% of days in any 2 consecutive weeks of the screening period.
- Perform a physical examination on all subjects. Adolescents (subjects ≤17 years) will also undergo Tanner Staging Assessment.
- **Serum** pregnancy test will be performed on all female subjects.
- Perform EGD and biopsy; both must be performed within the 6 weeks prior to the Placebo Lead-in Visit either at the investigative site or by a referring physician. Biopsy specimens must be available to be sent to the central pathology lab at least 2 weeks prior to the Placebo Lead-in Visit to allow sufficient time for processing and central review and determination of eligibility.

7.1.2 Placebo Lead-in Period (Weeks 0 to 4)

The placebo lead-in period will comprise 4 weeks, during which all procedures listed for the placebo visit (Visit 0) in Table 1-1 shall be completed.

During the 4-week single-blind placebo lead-in, all eligible subjects will self-administer 10 mL of placebo twice daily (qAM, pc, and hs).

At the end of the placebo lead-in period, eligible subjects (those with at least 4 reported dysphagia days and completion of DSQ on ≥70% of days in the 2 weeks prior to baseline [Visit 1]) will be randomized and enter the 12-week double-blind treatment period (baseline visit). Subjects must be administrated placebo during the placebo lead-in period for 4 weeks (±3 days) prior to Visit 1 (baseline) to be eligible for randomization into the 12-week double-blind treatment period.

7.1.2.1 Placebo Lead-in Visit (Visit 0)

The placebo lead-in visit (Visit 0) assessments and procedures will be performed as outlined in Table 1-1.

The following procedures should be performed first:

- Reassess eligibility according to the inclusion/exclusion criteria and medical history.
- Record vital signs (including blood pressure [systolic and diastolic], heart rate, respirations, and temperature) and weight.

- Perform AE assessments.
- Review concomitant medications and procedures.
- Clinical chemistry, hematology, and urinalysis laboratory tests; all subjects must fast overnight prior to collection.

The following order is recommended for the remaining procedures that will be performed at this visit:

- Review DSQ dysphagia episodes and compliance; re-dispense DSQ device to subject with instruction to continue completion of the DSQ nightly.
- Perform a physical examination and assess any changes since screening.
- **Urine** pregnancy test for female subjects.
- Perform dual-energy X-ray absorptiometry (DXA) scan for bone mineral density (BMD) in subjects aged 11-17 years, inclusive; the DXA scan may be performed any time during the placebo lead-in period, after the subject has met all screening criteria and prior to blinded-treatment randomization. Baseline and post-treatment DXA scans should be performed using the same machine and software.
- Dispense placebo study medication and review administration instructions. Subjects will self-administer the first dose of placebo in the clinic after eating breakfast. Site personnel will record the date and time of the first placebo dose in the source documents. Beginning on the evening of Visit 0, the subject will take their second dose at home and continue with the twice daily (qAM, pc, and hs) dosing regimen.

7.1.3 Double-blind Treatment Period (Visits 1-4): Weeks 4, 8, 12, and 16 (or Early Termination)

The double-blind treatment period will comprise 12 weeks, during which all assessments and procedures listed for Visits 1-4 in Table 1-1 shall be completed.

During this period, a ±3-day visit window will be permitted, unless otherwise specified. Visit windows are calculated based upon the date of the placebo lead-in visit (Visit 0).

Subjects who continue to meet all eligibility criteria will be randomized 2:1 to receive either OBS twice daily (qAM, pc, and hs) or placebo twice daily (qAM, pc, and hs). The investigator or assigned site staff will access the IWRS to randomize the subject and dispense the investigational product. Subjects who fail to meet eligibility criteria at the baseline visit (Visit 1) will be documented as screen failures in the IWRS.

Subjects who complete the 12-week double-blind treatment period will have the opportunity to enroll in the treatment extension study. These subjects will continue on the blinded assigned treatment for 2-4 weeks as part of the screening prior to enrolling into the treatment extension study. Subjects who do not enroll in the treatment extension study or who

discontinue prematurely at any time during the SHP621-301 (Induction) study will receive a follow-up phone call 4-weeks post last dose of investigational product.

7.1.3.1 Baseline Visit (Visit 1): Week 4

Subjects will return to the site for the baseline visit (Visit 1) to confirm eligibility. The baseline visit (Visit 1) assessments and procedures will be performed as outlined in Table 1-1.

The following procedures should be performed first:

- Reassess eligibility according to the inclusion/exclusion criteria and medical history.
- Record vital signs (including blood pressure [systolic and diastolic], heart rate, respirations, and temperature) and weight. Perform stadiometry in subjects aged 11-17 years, inclusive.
- Perform AE assessments, including specific assessments for signs of glucocorticoid excess. Any AE that occurs during this visit will be recorded in the CRF and considered a TEAE.
- Review concomitant medications and procedures.
- Clinical chemistry, hematology, and urinalysis laboratory tests; all subjects must fast overnight prior to collection.
- Morning cortisol (performed between 6:00 and 9:00 AM). Subjects should be instructed not to take the morning dose of investigational product until after the morning cortisol test has been performed.
- Administer adrenocorticotropic hormone (ACTH) stimulation testing; the type of synthetic and route of administration will be per local lab discretion. Additional cortisol samples will be drawn at 30 and 60 minutes following stimulation testing.

The following order is recommended for the remaining procedures that will be performed at this visit:

- Review study medication dosing compliance.
- Review DSQ dysphagia episodes and compliance; re-dispense DSQ device to subject with instruction to continue completion of the DSQ nightly.
- Administer health-related quality-of-life (HRQoL) assessments including the EuroQol (EQ-5D), Pediatric Quality of Life Inventory – EoE (PedsQL-EoE), and Adult Eosinophilic Esophagitis Quality of Life (EoE-QoL-A) as age-appropriate.
- Administer PGI-S of disease assessment.
- Perform a physical examination and assess any changes since screening.
- Re-administer **urine** pregnancy test for female subjects.

- Dispense investigational product (OBS or placebo) according to IWRS randomization and review administration instructions. Subjects will self-administer the first dose of investigational product in the clinic during this visit after breakfast. Site personnel will record the date and time of the first randomized dose in the source documents. Beginning on the evening of Visit 1, the subject will take their first dose at home and continue with the twice daily (morning and evening) dosing regimen. For subjects who are minors (<18 years), a parent/guardian will be responsible for ensuring subject takes their investigational product appropriately.

Following all blood draws, subjects can eat breakfast and take their morning dose of investigational product.

7.1.3.2 Visits 2 and 3 (Weeks 8 and 12)

Subjects will return to the site for Visit 2 (Week 8) and Visit 3 (Week 12). Assessments at these visits will be performed as outlined in Table 1-1.

The following procedures should be performed first:

- Record vital signs (including blood pressure [systolic and diastolic], heart rate, respirations, and temperature) and weight.
- Perform AE assessments, including specific assessments for signs of glucocorticoid excess. Any AE that occurs during this visit will be recorded in the CRF and considered a TEAE.
- Review concomitant medications and procedures.
- Clinical chemistry, hematology, and urinalysis laboratory tests; all subjects must fast overnight prior to collection.
- Morning cortisol (performed between 6:00 and 9:00 AM). Subjects should be instructed not to take the morning dose of study medication until after the morning cortisol test has been performed.
- Collect blood samples for pharmacokinetic analysis for adult subjects. Subjects will be instructed to take their morning dose at a set time to establish the schedule for post-dose sample collection.

The following order is recommended for the remaining procedures that will be performed at this visit:

- Review DSQ dysphagia episodes and compliance; re-dispense DSQ device to subject with instruction to continue completion of the DSQ nightly.
- Administer PGI-S assessment.
- Perform a physical examination and assess any changes since screening.

- Re-administer **urine** pregnancy test for female subjects.
- Dispense investigational product (OBS or placebo) and review investigational product dosing compliance.

Following all blood draws, subjects can eat breakfast and take their morning dose of investigational product.

7.1.3.3 Visit 4 (Week 16)

Subjects will return to the site for Visit 4 (Week 16). Assessments at this visit will be performed as outlined in Table 1-1.

The following order is recommended for the procedures that will be performed at this visit:

- Record vital signs (including blood pressure [systolic and diastolic], heart rate, respirations, and temperature), height, and weight. Perform stadiometry in subjects aged 11-17 years, inclusive.
- Perform AE assessments, including specific assessments for signs of glucocorticoid excess. Any AE that occurs during this visit will be recorded in the CRF and considered a TEAE.
- Review concomitant medications and procedures.
- Clinical chemistry, hematology, and urinalysis laboratory tests; all subjects must fast overnight prior to collection.
- Morning cortisol (performed between 6:00 and 9:00 AM). Subjects should be instructed not to take the morning dose of investigational product until after the morning cortisol test has been performed.
- Administer adrenocorticotropic hormone (ACTH) stimulation testing; the type of synthetic and route of administration will be per local lab discretion. Additional cortisol samples will be drawn at 30 and 60 minutes following stimulation testing.
- Retrieve DSQ handset and review DSQ compliance.
- Administer HRQoL assessments including the EQ-5D, PedsQL-EoE, and EoE-QoL-A as age-appropriate.
- Administer PGI-S assessment.
- Perform a physical examination and assess any changes since screening. Adolescents (subjects ≤17 years) will also undergo Tanner Staging Assessment.
- Re-administer **serum** pregnancy test for female subjects.
- Perform DXA scan for BMD in subjects aged 11-17 years, inclusive. DXA scan should be completed at or within 7 days of this visit. Baseline and post-treatment DXA scans should be performed using the same machine and software.

- Perform EGD and biopsy. EGD should be completed at or within 7 days of the scheduled visit.
- For eligible subjects continuing into the treatment extension study, obtain informed consent for the treatment extension study, dispense investigational product (OBS or placebo) according to IWRS randomization and review investigational product dosing compliance.

Following all blood draws, subjects can eat breakfast and take their morning dose of investigational product if they are continuing in the treatment extension study.

7.1.4 Follow-up Period

The follow-up period for this protocol is 4 weeks from the last dose of investigational product. Subjects who do not enroll in the treatment extension study or who discontinue prematurely at any time during the study will receive a follow-up 4 phone call at Visit 5 (Week 20) to query for SAEs, AEs, and concomitant treatments (Section 7.1.4.1).

7.1.4.1 Safety Follow-up Contact (Visit 5): Week 20

Assessments at this time, as outlined in Table 1-1, will include the following:

- Review concomitant medications and procedures.
- Perform AE assessments, including specific assessments for signs of glucocorticoid excess. Any AE that occurs during this visit will be recorded in the CRF and considered a TEAE; all AEs and SAEs that are not resolved at the time of this contact will be followed to closure.

7.1.5 Additional Care of Subjects after the Study

No after care is planned for this study for those subjects who do not enroll in the treatment extension study.

7.2 Study Evaluations and Procedures

The full title and details about who completes the scales used in this study is included in Appendix 1.

All assessments listed below will be performed by the subject and/or a qualified/trained site staff as indicated in the assessment description. For subject-completed assessments, trained site staff should not assist the subject in completing assessments in such a manner that it would influence their responses. Site staff should review the completed assessment to ensure completeness.

If an answer is marked in error, the subject may correct it by drawing a single line through the error and initialing and dating the change; however, corrections can only be made to scales by the subject during a study visit and changes must not be made to subject-completed scales after the visit has been completed. Assessments are to be performed according to the schedule shown in Table 1-1.

7.2.1 Efficacy

7.2.1.1 Esophagogastroduodenoscopy with Esophageal Biopsy and Histopathologic Evaluation

The EGD with endoscopy score and biopsy will be performed during the study as outlined in Table 1-1.

An EGD with esophageal, gastric and duodenal biopsies will be required for study participation; the peak eosinophil count per HPF from each esophageal level will be used as a primary measure of efficacy. The qualifying/baseline EGD with biopsies must be performed by a physician at the investigative site within the 6 weeks prior to placebo lead-in visit (Visit 1). Biopsy specimens must be available to be sent to the central pathology lab by at least 2 weeks prior to the placebo lead-in visit to allow sufficient time for processing and central review and determination of eligibility.

Multiple specimens (at least 2 biopsies from each of 3 levels, 6 specimens total) will be obtained from the proximal (3 cm below the cricopharyngeus muscle), mid-esophagus (mid-point between the cricopharyngeus muscle and the gastroesophageal junction), and distal (3 cm above the gastroesophageal junction). Biopsy tissue will be placed in 3 separate vials (1 vial for each of the levels) and sent to the central pathology laboratory for processing of tissue into slides. A central pathologist will determine histologic eligibility for study entry. Peak eosinophil counts of ≥15/HPF in specimens from 2 or more levels of the esophagus will be a requirement for study entry, as determined by a central pathologist. Eosinophil counts, histopathologic features, and gross endoscopic findings will be evaluated and scored for each EGD. Eight histopathologic epithelial features (basal layer hyperplasia, eosinophil density, eosinophil microabscesses, eosinophil surface layering, dilated intercellular spaces, surface epithelial alteration, dyskeratotic epithelial cells, lamina propria fibrosis) will be scored on a 4-point scale (0=normal, 3=worst) for both the severity of the abnormality (ie grade) and the amount of tissue affected by the abnormality (ie, stage).

Endoscopic findings with separate evaluations of the proximal and distal esophagus will be recorded with respect to 5 categories by the endoscopist: 1) exudates or plaques (grade 0–2); 2) fixed esophageal rings (grade 0–3); 3) edema (grade 0–1); 4) furrows (grade 0–1); and 5) strictures (grade 0–1). An endoscopy score for each category will be calculated and summed for each anatomic location (proximal and distal). The maximum endoscopy score is 10 points for each location, and a Total Endoscopy Score is the sum of the scores for the proximal and distal locations.

In addition, the general appearance of the stomach and duodenum will be assessed by the endoscopist. Biopsies will be taken from the stomach and duodenum for the screening EGD as follows: gastric body (greater curvature): 2 specimens, gastric antrum: 2 specimens, and duodenum (third part or distal): 2 specimens. Biopsies from the stomach should be submitted in one vial; biopsies from the duodenum should be submitted in a separate vial to the central pathology laboratory for processing of tissue into slides. If the pre-treatment biopsy identifies eosinophilia in the stomach and/or duodenum, the subject will be excluded from the study.

At the Week 16 visit (Visit 4) or at early termination (ET), and EGD with esophageal biopsies (at least 2 biopsies from each of 3 levels [proximal, mid-, and distal]) is required. Endoscopic findings will be recorded by the endoscopist. Biopsies will be sent to the central laboratory for processing. A central pathologist will evaluate the slides. Gastric and duodenal biopsies may be repeated at the discretion of the investigator, but are not required.

7.2.1.2 Dysphagia Symptom Questionnaire

Subjects' dysphagia symptoms will be evaluated using a DSQ ePRO device (Appendix 2).

The questionnaire will be completed by subjects daily for a minimum of 3 weeks during the screening period, during the 4-week placebo lead-in period, and during the 12-week treatment period. Each evening before bedtime, subjects will be asked to indicate if they experienced dysphagia symptoms (eg, food passing slowly or food sticking) during that day. Subject must have experienced dysphagia (response of "yes" to question 2 on DSQ) on a minimum of 4 days total and completed the DSQ on ≥70% of days in any 2 consecutive weeks of the screening period and in the 2 weeks prior to the baseline visit (Visit 1). Subjects must fill out the DSQ at least 5 or more days during a given week in order to be compliant.

Calculations will be performed on daily ePRO entries from the screening period, during a 2-week interval prior to the baseline period, and prior to each study visit during the baseline and treatment periods. The DSQ score for the co-primary endpoint and secondary endpoints will be calculated by summing the scores of responses to questions 2 and 3 only. Questions 1 and 4 will be excluded from the DSQ score:

- DSQ score= $\dfrac{\text{(Sum of points from questions 2+3 in the daily DSQ)}\times 14}{\text{Number of diaries reported with non-missing data}}$

The DSQ + pain score for the secondary endpoints will be calculated by summing the scores of responses to questions 2, 3, and 4. Question 1 will be excluded from the DSQ + pain score.

- DSQ + pain score= $\dfrac{\text{(Sum of points from questions 2+3+4 in the daily DSQ)}\times 14}{\text{Number of diaries reported with non-missing data}}$

The DSQ pain score for the secondary endpoint will be calculated by summing the scores of responses to Question 4 only.

- DSQ pain score=$\frac{(\text{Sum of points from question 4 in the daily DSQ})\times 14}{\text{Number of diaries reported with non-missing data}}$

7.2.2 Safety

The name and address of each third-party vendor (eg, clinical laboratory) used in this study will be maintained in the investigator's and sponsor's files.

7.2.2.1 Medical and Medication History

Medical History

The investigator must record all clinically or medically relevant information regardless of how much time has elapsed since the date of any diagnosis. Medical history will be classified as EoE or non-EoE by the investigator. The EoE medical history must include any prior history of esophageal strictures and esophageal dilations.

Medication History

Refer to Section 5.1 for full details on collection of prior treatment.

Prior treatment information, including any prior treatments for EoE (eg, dietary, medication, or other), must be recorded on the appropriate CRF page.

7.2.2.2 Physical Examination (Including Height and Weight)

Abnormalities identified at the screening visit (Visit -1) will be documented in the subject's source documents and on the medical history CRF. Changes after the screening visit (Visit -1) will be captured as AEs on the AE CRF page, as deemed by the investigator.

Physical examination assessments at each visit should also include specific assessments for signs of glucocorticoid excess (eg, moon faces, acne, hirsutism, mood swings, insomnia, and depression). Physical examination at the screening visit (Visit -1) will also include Tanner Staging Assessments for subjects <18 years of age.

Height will be collected at the screening visit (Visit -1) and Visit 4 for all subjects. Stadiometers will be used to measure height at Visit 1 and Visit 4 for subjects aged 11-17 years, inclusive. Statural height will be measured by trained site staff using a stabilized stadiometer. The same stadiometer should be used for the baseline and post treatment

measurements. Standard measuring procedures should be followed (eg, removal of socks, shoes, and hats; calibration frequency). Please refer to the study manual for additional details.

7.2.2.3 Adverse Event Collection

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?"). AEs are collected from the time informed consent is signed. (Please refer to Section 8.)

AE assessments at each visit should also include specific assessments for signs of glucocorticoid excess (eg, moon facies, acne, hirsutism, mood swings, insomnia, and depression).

7.2.2.4 Vital Signs

Vital signs will be conducted after the subject has been supine for at least 5 minutes immediately prior to the assessment and will include blood pressure (systolic and diastolic), heart rate, respirations, and temperature. Blood pressure should be determined by cuff (using the same method, the same arm, and in the same position throughout the study). Any clinically significant deviations from baseline (Visit 1) vital signs that are deemed clinically significant in the opinion of the investigator are to be recorded as an AE.

7.2.2.5 Clinical Laboratory Evaluations

All clinical laboratory assays will be performed according to the laboratory's normal procedures. All subjects must fast overnight prior to collection of clinical laboratory tests.

Reference ranges are to be supplied by the laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

The following clinical laboratory assessments will be performed:

Biochemistry

- alkaline phosphatase
- aspartate aminotransferase
- alanine aminotransferase
- blood urea nitrogen
- creatinine
- sodium

- total bilirubin
- total protein
- albumin
- glucose
- potassium
- chloride
- calcium
- carbon dioxide

Hematology

- hemoglobin
- hematocrit
- mean corpuscular hemoglobin
- mean corpuscular hemoglobin concentration
- mean corpuscular volume
- erythrocyte count
- leukocyte count
- neutrophils
- lymphocytes
- monocytes
- eosinophils
- basophils
- platelet count

Urinalysis

- glucose
- protein
- specific gravity
- pH
- nitrite
- bilirubin
- ketones
- hemoglobin
- urobilinogen
- leukocyte esterase

Other tests

- serum pregnancy
- urine pregnancy
- morning cortisol (6:00-9:00 AM collection)
- ACTH stimulation testing

ACTH stimulation testing will be performed by measuring the levels of cortisol in the blood following the injection of a synthetic form of ACTH. The type of synthetic and route of administration will be per local lab discretion. Blood samples will be collected just prior to and approximately 30 and 60 minutes following the injection.

In the event of clinically significant abnormal laboratory test results, follow-up laboratory tests may be conducted. Any clinically significant abnormalities noted in the laboratory tests will be discussed with the medical monitor.

7.2.2.6 Pregnancy Test

A serum β-hCG pregnancy test is performed on all female subjects at the screening visit (Visit -1) and the final treatment evaluation visit (Visit 4) or ET visit. A urine pregnancy test is performed on all female subjects at the placebo lead-in visit (Visit 0), baseline visit (Visit 1), Visit 2, and Visit 3 or if pregnancy is suspected.

7.2.2.7 Dual-energy X-ray Absorptiometry for Bone Mineral Density

DXA (also referred to as DEXA) scans for determination of BMD will be performed in subjects aged 11-17 years, inclusive, as outlined in Table 1-1.

The sites for DXA measurement will be the lumber spine (L1-L4 preferred) and total body less head (Bachrach, 2011; Gordon, 2008; International Society for Clinical Densitometry, 2013). The same DXA machine and software should be used for the baseline and post-treatment scans. The DXA manufacturer, model, and software version should be recorded in the CRF.

7.2.3 Other Assessments

7.2.3.1 Health-related Quality-of-life Assessment

EuroQol-5 Dimensions 3-level Questionnaire

The EuroQol-5D Dimensions 3-level (EQ-5D-3L; for subjects ≥18 years) and the EuroQol-5 Dimensions Youth (EQ-5D-Y; for subjects 11-17 years of age, inclusive) will be performed during the study as outlined in Table 1-1.

The EQ-5D-3L is a standardized measure of health status for use in adult populations that was developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQol Group, 1990). The EQ-5D-3L provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of healthcare as well as in population health surveys. It consists of a 5-item descriptive system that measures 5 dimensions of health, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is represented by a single item with 3 levels of responses. The EQ-5D-3L will be completed by the subject. The EQ-5D-3L should take the subject a few minutes to complete.

The EQ-5D-Y is a self-report version of the EQ-5D that was developed by the EuroQol Group for use in younger populations (Wille et al., 2010). The EQ-5D-Y provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of healthcare as well as in population health surveys. It consists of a 5-item descriptive system that measures 5 dimensions of health, including mobility, looking

after myself, doing usual activities, having pain or discomfort, and feeling worried, sad, or unhappy. Each dimension is represented by a single item with 3 levels of responses. The EQ-5D-Y will be completed by the subject and should take a few minutes to complete.

Pediatric Quality of Life – EoE Questionnaire

The PedsQL-EoE questionnaire will be completed by subjects 11-17 years of age, inclusive, and their parent or legal guardian, as outlined in Table 1-1.

The PedsQL-EoE is a modular, disease-specific instrument designed to measure HRQoL in children and adolescents (2-18 years of age) with EoE (Franciosi, 2013; PROQOLID). The PedsQL-EoE module consists of 33 items for children and teenagers encompassing the following 7 scales: 1) Symptoms I (6 items; chest/throat/stomach pain and nausea/vomiting), 2) Symptoms II (4 items; trouble swallowing), 3) Treatment (5 items; treatment barriers), 4) Worry (6 items; worries about treatment and disease), 5) Communication (5 items; communication with others about EoE), 6) Food and Eating (4 items; food and eating allergies and limitations), and 7) Food Feelings (3 items; emotions associated with food allergies). The PedsQL-EoE should take the subject and parent approximately 10 minutes to complete.

Adult Eosinophilic Esophagitis Quality of Life Questionnaire

The EoE-QoL-A will be performed in subjects ≥18 years of age as outlined in Table 1-1.

The EoE-QoL-A is a disease-specific measure of HRQoL in adult patients (≥18 years of age) with EoE (Taft et al., 2011). The EoE-QoL-A consists of a 37-item test with 5 subscales: eating/diet impact, social impact, emotional impact, disease anxiety, and choking anxiety. The EoE-QoL-A will be completed by the subject and should take the subject approximately 15 minutes to complete.

7.2.3.2 Severity of Disease Assessments

Patient Global Impression of Severity

The PGI-S will be performed in all subjects as outlined in Table 1-1.

The PGI-S is a global index (Appendix 3) that can be used to rate the severity of a specific condition - in this case, dysphagia in EoE. Subjects will be asked to rate the severity of their dysphagia over the last 7 days using a 5-point scale.

7.2.4 Clinical Pharmacology Assessments

Blood samples will be collected from adult subjects (≥18 years of age) as outlined in Table 1-1 to measure plasma concentrations of budesonide. Subjects who do not participate in

pharmacokinetic sampling will not be discontinued from the study, and lack of participation will not be a considered protocol deviation.

Actual pharmacokinetic blood sample collection times vs time of dosing will be monitored. The sponsor's expectation is that the investigator will ensure that every effort will be made to collect all pharmacokinetic blood samples at the precise protocol scheduled time. Pharmacokinetic blood collection must not deviate from the nominal collection time set forth in the protocol by more than ± 5 minutes for samples drawn within 4 hours post-dose or by more than ± 15 minutes for samples drawn after 4 hours post-dose. Samples drawn outside these parameters will be considered a protocol deviation.

Blood samples (4 mL) for pharmacokinetic analysis will be drawn by direct venipuncture into K2EDTA tubes, capped and mixed by inversion (×3), and chilled immediately on crushed ice. The actual blood collection time will be recorded in the subject's source documents and on the appropriate CRF page (24-hour format). After applying a tourniquet, venous blood will be drawn with a disposable needle. If a catheter is used, the first milliliter of blood on each sampling occasion will be discarded. Saline can be used to keep catheters patent.

Within 15 minutes following each sample collection, the blood tubes will be centrifuged at approximately 1500 g (15 minutes, 4°C). The separated plasma will be decanted into appropriately labeled primary and backup polypropylene tubes via a plastic pipette. All samples will be stored nominally at -20°C, and the freezer temperature will be controlled, monitored, and recorded during the storage period until the samples are shipped to the designated bioanalytical laboratory for analysis.

For additional information detailing sample handling, storage, and shipment, see Appendix 4.

7.2.5 Volume of Blood to Be Drawn from Each Subject

Table 7-1: Approximate Volume of Blood to Be Drawn from Each Subject

Assessment		Sample Volume (mL)	Number of Samples	Approximate Total Volume (mL)
Pharmacokinetic samples[a]		5	9	45
Safety	Biochemistry and β-hCG[b]	6	6	36
	ACTH	2	4	8
	Cortisol	2	4	8
	Hematology	2	6	12
Total mL				109

Abbreviations: ACTH=adrenocorticotropic hormone; β-hCG=beta-human chorionic gonadotropin

[a] If a catheter is used, the first mL is to be discarded; then take 4 mL into appropriate tube for pharmacokinetic sample. A total of 5 mL of blood drawn has been used in determination of sample volume.

Table 7-1: Approximate Volume of Blood to Be Drawn from Each Subject			
Assessment	**Sample Volume (mL)**	**Number of Samples**	**Approximate Total Volume (mL)**

[b] β-hCG testing is for females only.

During this study, it is expected that approximately 109 mL of blood will be drawn from all subjects, regardless of sex.

Note: The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment; however, the total volume drawn over the course of the study should be approximately 109 mL. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments may be combined.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An **AE** is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 7.1.4. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the CRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE CRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the

event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate CRF).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as “not related.” Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related” based on the definitions in Table 8-1. The causality assessment must be documented in the source document.

Table 8-1: Adverse Event Relatedness

Term	Relationship Definition
Not Related	Unrelated to study drug.
Possibly Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of study drug, but which could also be explained by concurrent disease or other drugs or chemicals.
Probably Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of study drug, unlikely to be attributable to concurrent disease or other drugs and chemicals and which follows a clinically reasonable response on de-challenge. The association of the clinical event or laboratory abnormality must also have some biologic plausibility, at least on theoretical grounds.
Definitely Related	The event follows a reasonable temporal sequence from administration of the study drug, follows a known or suspected response pattern to the study drug, is confirmed by improvement upon stopping the study drug (de-challenge), and reappears upon repeated exposure (re-challenge). Note that this is not to be construed as requiring re-exposure of the patient to study drug; however, the determination of definitely related can only be used when recurrence of event is observed.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the CRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved With Sequelae
- Recovering/Resolving
- Unknown

8.1.4 Symptoms of the Disease under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE.

8.1.5 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory or vital sign assessment can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory or vital sign values which were not present at the pre-treatment value observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory or vital sign parameter is clinically significant and therefore represents an AE.

8.1.6 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 7.1.4.

Any report of pregnancy for any female study participant must be reported within 24 hours to the Shire Global Pharmacovigilance and Risk Management Department using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO/Shire medical monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days postpartum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β-HCG test or ultrasound result will determine the pregnancy onset date.

8.1.7 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- **Overdose** – Intentional or unintentional intake of a dose of an investigational product exceeding a pre-specified total daily dose of 4 mg of the product.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of the unassigned treatment is/are always reportable as a medication error.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

All investigational product provided to pediatric subjects should be supervised by the parent/legally authorized representative/caregiver.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is the investigator brochure, which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Pharmacovigilance and Risk Management Department and the CRO medical monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.7) unless they result in an SAE.

The investigator must complete, sign, and date the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested) and fax or e-mail the form to the Shire Global Pharmacovigilance and Risk Management Department. A copy of the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol (and any applicable follow-up reports) must also be sent to the CRO medical monitor using the details specified in the emergency contact information section of the protocol.

8.2.3 Serious Adverse Event Definition

A ***Serious Adverse Event*** **(SAE)** is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity

- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.4 and must be reported to the Shire Global Pharmacovigilance and Risk Management Department and the medical monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Global Pharmacovigilance and Risk Management Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, leading up to the onset date of the SAE, or following the resolution date of the SAE must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject's death (ie, the SAE was noted as the primary cause of death) must have "fatal" checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered as not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product).

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The sponsor and the clinical CRO are responsible for notifying the relevant regulatory authorities/US central Institutional Review Boards (IRBs) of related, unexpected SAEs.

In addition, the sponsor and the clinical CRO are responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP621 program.

The investigator is responsible for notifying the local IRB, local ethics committee (EC), or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the CRF. A study monitor will visit each site in accordance with the monitoring plan and review the CRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is randomized, it is expected that site personnel will complete the CRF entry within approximately 3 business days of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the CRO's data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Data Handling Considerations

Data that may potentially unblind the treatment assignment (ie, investigational product serum concentrations, treatment allocation, and investigational product preparation/accountability data) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, prior to unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

9.4 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent. All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC, USA) version 9.1 or higher.

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

In addition to a final SAP for the final analysis, a separate interim SAP for the interim analysis will be finalized prior to unblinding and performing the analysis to preserve the integrity of the statistical analysis and study conclusions. The SAP for the final analysis will be finalized prior to final database lock and performing analysis (ie, unblinding) to preserve the integrity of the statistical analysis and study conclusions.

9.5 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

A planned interim analysis for each of the co-primary endpoints will take place after 50% of all randomized subjects have either completed the study or prematurely withdrawn from the study, whichever comes first. The purpose of the unblinded interim analysis is to reassess the appropriateness of assumptions used for each of co-primary efficacy endpoints when the study was designed. The reassessment of the sample size will utilize the conditional power approach under certain conditions that do not inflate the type I error (Mehta and Pocock, 2011). The planned interim analysis will be conducted by an external independent statistical (EIS) group; the individuals involved in the day-to-day conduct of the trial will not be involved in the interim analysis or have access to the results of the interim analysis. The Sponsor will only be notified by the EIS group if any recommendation of increasing the sample size is needed from the conditional power; this will be detailed in the pre-specified interim SAP including a potential maximum sample size to be increased if deemed necessary.

A very minimal fraction of alpha (0.0001) will be spent at the interim analysis as the trial will not stop due to the interim results. The final analysis will use 4.99% for each of the co-primary endpoints in order to preserve an overall type I error at 5% level.

9.6 Sample Size Calculation and Power Considerations

Based on at least a 30-percentage-point reduction in DSQ score, there is an expected difference between treatment response proportions of 69% and 45% in the OBS 2 mg twice daily (qAM, pc, and hs) and placebo groups, respectively. A total of 228 subjects (152 subjects randomized to OBS and 76 subjects randomized to placebo) are required to achieve 90% power at the significance level of 0.0499 (2-sided) using a 2-group chi-square test with unequal allocation 2:1 to treatment groups (OBS 2 mg twice daily and placebo). With the specified number of subjects per treatment group, the study will be powered at 99% assuming histological response proportions of 40% and 3% in the OBS 2 mg twice daily and placebo groups, respectively. The overall study power for the co-primary endpoints will be at least 85%. Therefore, approximately 228 (approximately 152:76 OBS and placebo subjects, respectively) will be randomized to the study to allow for a loss of approximately 5% of subjects due to dropouts or invalid data.

9.7 Study Population

The **safety set** will include all subjects who receive at least 1 dose of any double-blind investigational product.

The **intent-to-treat (ITT)** set will include all randomized subjects. Subjects will be analyzed according to their assigned treatment, regardless of the treatment actually received.

The **full analysis set (FAS)** will include all randomized subjects who received at least 1 dose of a double-blind investigational product and have both an evaluable post-baseline biopsy in the treatment period (ie, peak eosinophil count is reported for at least 2 esophageal levels) and a post-baseline DSQ score.

The **per-protocol (PP)** set will include all subjects in the FAS excluding subjects with protocol violations. The PP set will be identified prior to unblinding the treatment assignments by a team consisting of, at a minimum, a physician and a statistician from Shire.

The **pharmacokinetic set** will include all subjects in the safety set for whom the primary pharmacokinetic data are considered sufficient and interpretable.

9.8 Efficacy Analyses

The primary, key secondary, and secondary efficacy analyses will be performed on the ITT set and presented by treatment group.

Data collected at the baseline visit (Visit 1) will be used as the baseline for all efficacy analyses.

9.8.1 Primary Efficacy Endpoints

The co-primary efficacy endpoints are the following:

- Histologic response, defined as a peak eosinophil count of ≤6/HPF across all available esophageal levels at the final treatment period evaluation (Visit 4)
- Dysphagia symptom response, defined as ≥30% reduction in the DSQ combined score (questions 2+3) from baseline to the final treatment period evaluation (Visit 4)

The co-primary efficacy endpoints will be analyzed based on the ITT set. Each of the co-primary efficacy endpoints is a binary response (ie, responders vs non-responders); the endpoint will be analyzed using a logistic regression model with effects of treatment group, age group (either <18 years or ≥18 years), and their interaction. The main-effect model will be considered the final definitive model if the interaction between treatment and age group is not statistically significant at the 10% level. The odds ratio of being a responder on each of the co-primary endpoints for the OBS 2 mg twice daily group vs placebo group and associated 95% confidence interval (CI) will be estimated from the final model. Subjects who withdraw without providing efficacy data at the final treatment period evaluation (Visit 4, Week 16) will be classified as non-responders in the primary efficacy analysis.

Additionally, the proportion of responders based on each of the co-primary endpoints for each treatment group will be summarized, and their respective 95% CI will be reported. The difference in the proportion of responders between the 2 treatment groups and the corresponding 95% CI will also be summarized.

The following sensitivity and supportive analyses will be performed for the co-primary to evaluate the robustness of the results from the primary analysis methods:

- Analyses will be repeated using the FAS and the PP set.
- Analyses will be repeated by considering subjects who withdraw without providing efficacy data at the final treatment period evaluation (Visit 4) and will be classified as responders.

9.8.1.1 Missing Data Imputation

Method 1: Distribution-based Imputation

The subjects with missing co-primary efficacy endpoints will be assigned randomly according to the distribution of responders with available data for each of the co-primary endpoints (ie, those with non-missing data) across the 2 treatment groups by strata (see Table 9-1).

Table 9-1: Percentage of Responders for All Available Data (ie, Non-missing Data) by Strata

Strata	No	Yes
<18 years	X0%	X1%
≥18 years	Y0%	Y1%

For instance, if there are N subjects with missing data in strata 1 (age <18 years), then X0%*N subjects will be randomly assigned as non-responders and X1%*N subjects will be randomly assigned as responders.

Conversely, if there are M subjects with missing data in strata 2 (age ≥18 years), the Y0%*M subjects will be randomly assigned as non-responders and Y1%*N subjects will be randomly assigned as responders.

Method 2: Multiple Imputations

Multiple imputation (MI) methods will utilize the SAS procedures PROC MI and PROC MIANALYZE. The MI procedure will involve fitting a logistic regression model with the binary outcome (responders vs non-responders) as the dependent variable and the age group and the treatment group as the independent variables. The MI procedure will generate 10 version datasets with binary outcome imputed from the subjects with complete data. Once the missing values are imputed and each dataset is created, the results will be appropriately pooled across the multiply imputed estimated regression coefficients and their standard errors using PROC MIANALYZE.

Other sensitivity analyses will be explored, and details will be provided in the SAP.

9.8.2 Secondary Efficacy Endpoints

9.8.2.1 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is defined as the change in DSQ combined score (questions 2+3) from baseline to the final treatment period evaluation (Visit 4). The change

from baseline DSQ score at the final treatment period evaluation (Visit 4) will be analyzed using an analysis of covariance (ANCOVA) model with treatment group and age group as factors and the baseline DSQ score as a continuous covariate.

The additional secondary efficacy endpoints are the following:

- Change in total endoscopy score, as measured by the EREFS classification, from baseline to the final treatment period evaluation (Visit 4)
- Peak eosinophil count <15/HPF across all available esophagus levels at the final treatment period evaluation (Visit 4)
- Peak eosinophil count ≤1/HPF across all available esophagus levels at the final treatment period evaluation (Visit 4)
- Change from baseline in the peak eosinophil count to the final treatment period evaluation (Visit 4) for each available esophageal level (proximal, mid-, and distal)
- Change from baseline in the histopathologic epithelial features combined total score (grade and stage) to the final treatment period evaluation (Visit 4)
- Dysphagia symptom response (binary response), defined as a ≥50% reduction in the DSQ combined score (questions 2+3), from baseline to the final treatment period evaluation (Visit 4)
- Change from baseline in the DSQ combined score (questions 2+3) over time including post baseline visits
- Cumulative distribution function curves for the change and the percent change in the DSQ score from baseline to the final treatment period evaluation (Visit 4)
- Overall binary response I, defined as a reduction in the DSQ score of ≥30% from baseline to the final treatment period evaluation (Visit 4) and a peak eosinophil count of ≤6/HPF across all esophageal levels at the final treatment period evaluation (Visit 4)
- Overall binary response II, defined as a reduction in the DSQ score of ≥50% from baseline to the final treatment period evaluation (Visit 4) and a peak eosinophil count of ≤6/HPF across all esophageal levels at the final treatment period evaluation (Visit 4)
- Symptom response on DSQ + pain score (binary response), defined as ≥30% and 50% reductions in the DSQ combined score (questions 2+3+4) from baseline to the final treatment period evaluation (Visit 4)
- Symptom response on DSQ + pain score (binary response), defined as a ≥30% and 50% reduction in the DSQ score (question 4), from baseline to the final treatment period evaluation (Visit 4)

The binary response endpoints will be analyzed using the same logistic model as the co-primary efficacy endpoints.

Continuous endpoints will be analyzed as a change from baseline using an ANCOVA model that includes treatment group and age group as factors and baseline score as a covariate.

The analyses for all secondary efficacy endpoints (including the key secondary efficacy endpoint) will be carried out using 2-sided tests at the 5% level of significance. For each of the secondary efficacy endpoints, the treatment difference, corresponding 95% CI for the difference, and treatment comparison p-value for testing the null hypothesis of zero treatment effect based on the final statistical model (ie, either logistic regression model or ANCOVA model) will be provided.

9.8.3 Exploratory Efficacy Endpoint

The exploratory endpoint that will be explored is the following:

[redacted]

9.9 Safety Analyses

Safety data will be presented for the safety set by treatment group.

The safety data collected at the baseline visit (Visit 1) or the last preceding visit if not collected at Visit 1 will be used as the baseline value for safety analyses.

TEAEs are defined as AEs that start or deteriorate on or after the first dose of investigational product (Visit 1) and no later than 3 days following the last dose of investigational product. However, for any subjects who die during the study (ie, the date of death is between the date of first dose of investigational product and the date of study discontinuation entered by the site, inclusive), all AEs (including those resulting in death) that occur during the study will be considered as TEAEs irrespective of the last dose and will be included in the TEAE summaries.

AEs will be coded using MedDRA. The number of events, incidence, and percentage of TEAEs will be calculated overall by system organ class (SOC), preferred term (PT), and treatment group. TEAEs will be further summarized by severity and relationship to investigational product. AEs related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.

Safety parameters will include monitoring of AEs, physical examinations, stadiometry, vital signs (temperature, systolic and diastolic blood pressure, pulse, and respiratory rate), weight and height assessments, DXA scans for BMD measurements (for adolescents aged 11-17 years, inclusive), clinical laboratory tests (hematology, chemistry, urinalysis; serum pregnancy test, if appropriate), and ACTH stimulation tests. To account for the effects of puberty in adolescent subjects (11-17 years of age, inclusive), BMD z-scores will be adjusted for height z-scores using the Bone Mineral Density in Childhood Study calculator. Safety

parameters will be descriptively summarized by treatment group at baseline and for each post-baseline visit.

9.10 Other Analyses

9.10.1 Health-related Quality-of-life Analyses

The health economics and outcomes research endpoints that will be explored are the following:

- EoE-QoL-A Questionnaire (Taft et al., 2011)
- EQ-5D (EQ-5D-3L or EQ-5D-Y, according to subject's age)
- PedsQL-EoE

The sub-modules of the EoE-QoL-A and PedsQL-EoE will be assessed in addition to the overall score with a focus on emotional and physical elements. For all HRQoL analyses, change from baseline to the final treatment period evaluation (Visit 4) will be assessed.

9.10.2 Pharmacokinetic Analyses

Pharmacokinetic parameters will be determined from the plasma concentration-time data for budesonide by non-compartmental analysis.

The pharmacokinetic endpoints will include but not be limited to those listed in Table 9-2.

Table 9-2: Pharmacokinetic Parameters

Parameter	Definition
$AUC_{0\text{-}tau}$	Area under the curve for the defined interval between doses
C_{max}	Maximum concentration occurring at t_{max}
t_{max}	Time of maximum observed concentration sampled during a dosing interval

Summary statistics (number of observations, mean, standard deviation, coefficient of variation, median, maximum, minimum, and geometric mean) will be determined for all pharmacokinetic parameters by overall and by week. Plasma concentrations at each nominal sampling time will also be summarized using descriptive statistics.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and its updates, and local ethical and legal requirements.

The name and address of each third-party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and CRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied to the CRO as necessary.

10.1.3 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.4 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the community guideline on GCP. This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance.

10.1.5 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study, which has been posted to a designated public website, will be updated accordingly.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub-investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal investigator is appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

Electronic CRFs are supplied by the CRO and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto CRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Case report forms must be completed by the investigator or designee as stated in the site delegation log.

All data will have separate source documentation; no data will be recorded directly onto the CRF.

All data sent to the sponsor must be endorsed by the investigator.

The clinical research associate (CRA)/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include but are not limited to subject's medical file, original clinical laboratory reports, and histology and pathology reports.

All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and have direct access to original source records relevant to this study, regardless of media.

The CRA/study monitor (and auditors, IRB/EC, or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays, etc.).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent (or assent as applicable for subjects <18 years of age) from all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally authorized representative, as applicable, is requested to sign and date the subject's informed consent form or a certified translation, if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

Within the source documents, site personnel should document instruction of and understanding by the parent/legally authorized representative/caregiver of the safe, responsible storage and administration of investigational product to the study subject.

The principal investigator provides the sponsor with a copy of the consent form consent (or assent as applicable for subjects <18 years of age) that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB's/EC's written favorable opinion/approval of these documents must be provided to the sponsor, prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information, and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

For sites within the EU, the applicant for an EC opinion can be the sponsor or the investigator or, for multicenter studies, the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent (or assent as applicable for subjects <18 years of age) documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the CRO has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; for sites within the EU, this can be done by the sponsor or the investigator or, for multicenter studies, the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with HIPAA of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the CRO/sponsor.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market SHP621; national or local regulatory authorities; and the IRBs/ECs which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (eg, to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to and used in other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purposes of any such transfer would include supporting regulatory submissions, conducting new data analyses to publish or present the study results, or answering questions asked by regulatory or health authorities.

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (eg, Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2-4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral, or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish, and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single-site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors current standards. Participation as an investigator does not confer any rights to authorship of publications.

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12. APPENDICES

Appendix 1 Scales and Assessments

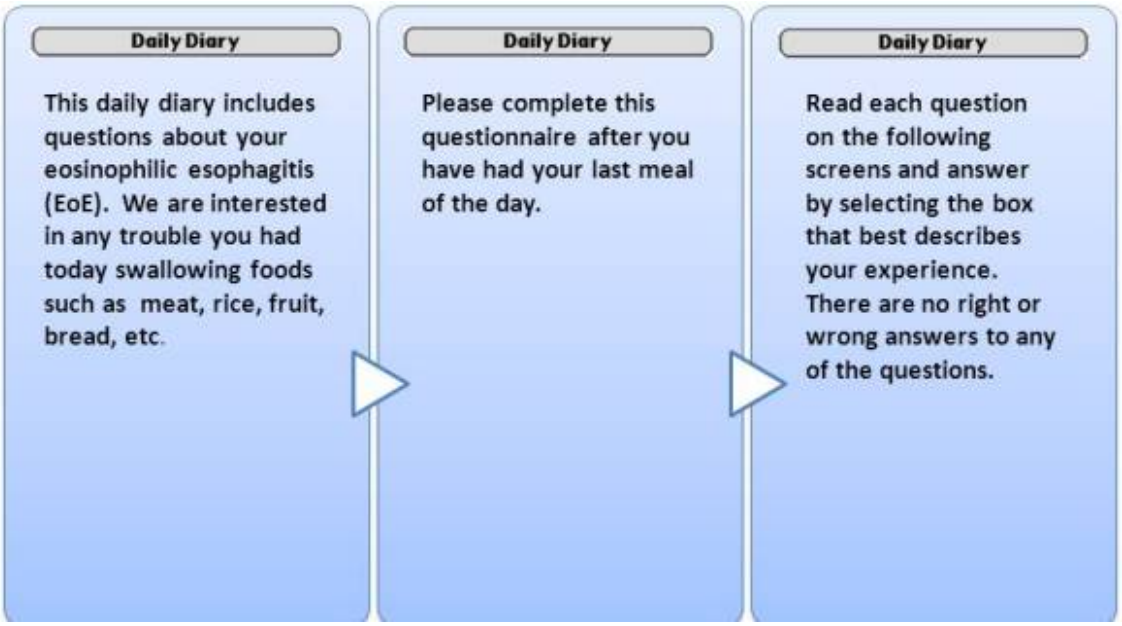
The following scales/assessments will be utilized in this study:

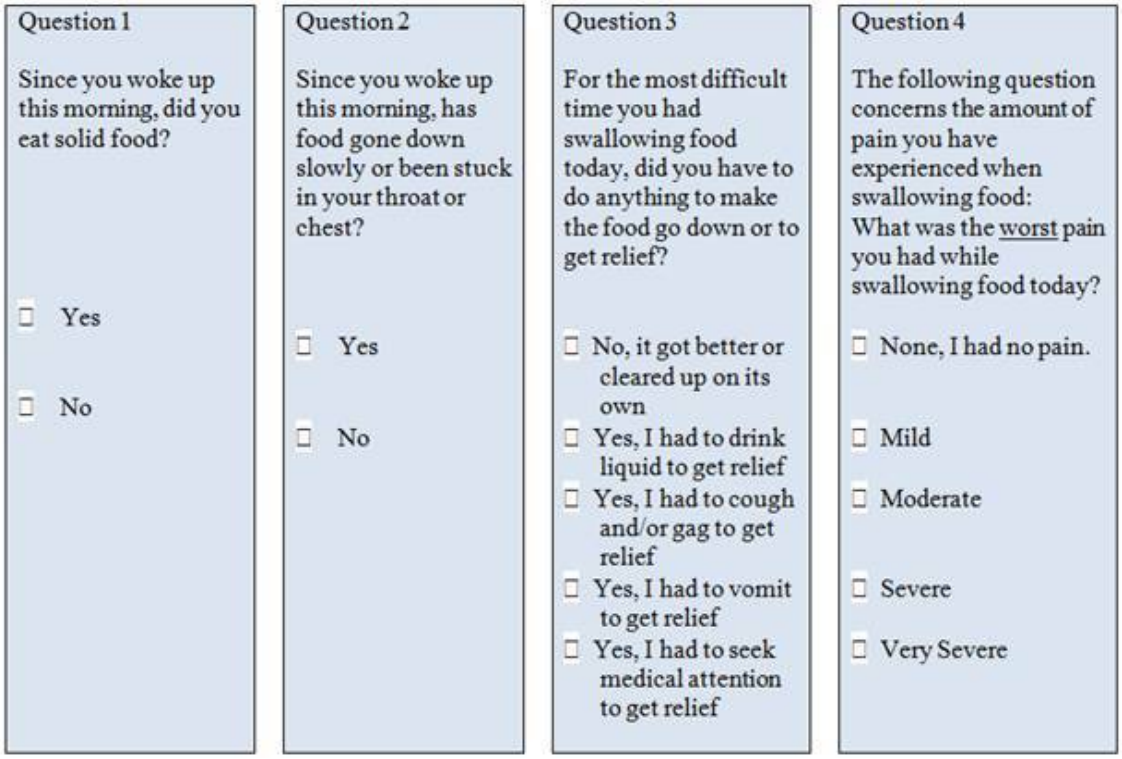
Full Title of Scale/Assessment	Completed By
DSQ	Subject
EQ-5D	Subject
PedsQL-EoE (subjects 11-17 years of age, inclusive)	Subject and parent or legal guardian
EoE-QoL-A (subjects ≥18 years of age)	Subject
PGI-S	Subject
Tanner Staging Assessment	Site
EREFS	Site

Abbreviations: DSQ=Dysphagia Symptom Questionnaire; EoE-QoL-A=Adult Eosinophilic Esophagitis Quality of Life; EQ-5D=EuroQol; EREFS=EoE Endoscopic Reference Score; PedsQL-EoE=Pediatric Quality of Life Inventory – EoE; PGI-S=Patient Global Impression of Severity

A separate master file containing each scale/assessment listed above will be provided to the site. Updates to scales/assessments during the study (if applicable) will be documented in the table above, and a new master file containing the revised scale/assessment will be provided to the site.

Appendix 2 Dysphagia Symptom Questionnaire ePRO for EoE





Appendix 3 Patient Global Impression of Severity

How would you rate the overall severity of your dysphagia (difficulty swallowing) over the past 7 days?

Rating	Description
0	No dysphagia
1	Mild dysphagia
2	Moderate dysphagia
3	Severe dysphagia
4	Very severe dysphagia

Appendix 4 Biosciences Generic Clinical Protocol Insert

Blood Sample Collection

Blood samples will be collected at the times specified in Table 1-1 to measure plasma concentrations of budesonide. Potential metabolites may also be determined as appropriate.

Blood samples 4 mL for pharmacokinetic analysis will be drawn by in-dwelling catheters or direct venipuncture into K2EDTA tubes, capped and mixed by inversion (x3), and chilled immediately on crushed ice. The actual time that the sample was obtained will be recorded in the subject's source document and on the appropriate CRF page. After applying a tourniquet, venous blood will be drawn with a disposable needle. If a catheter is used, the first milliliter of blood on each sampling occasion will be discarded. Saline can be used to keep catheters patent.

1.1 Blood/Plasma Sample Handling

Samples should be kept on crushed ice until plasma is separated as soon as possible after collection within <15 minutes, unless advised otherwise by refrigerated centrifugation (4°C, 1500 rpm 15 minutes). The separated plasma will be decanted into appropriately labeled polypropylene tubes via a plastic pipette. All samples will be stored at approximately -20°C or colder and the freezer temperature will be controlled, monitored, and recorded during the storage period until they are transferred in the frozen state to a designated bioanalytical contract laboratory. Samples will remain frozen at -20°C or colder until analysis.

Plasma sample tubes for bioanalysis must be freezer-safe and identified with freezer-safe labels provided by the central laboratory. The labels will contain the following information:

- Study number
- Subject identifier (randomization number)
- Matrix identifier (plasma)
- Visit
- Nominal time

1.2 Shipment of Plasma Samples

Plasma samples should be double-bagged to contain leaks and packed with a sufficient quantity of dry ice to ensure that they remain frozen for at least 72 hours to allow for delays in shipment. All applicable shipping regulations must be followed. Shipments should be scheduled so that no samples arrive on the weekend and should be shipped Monday to Wednesday only.

Plasma samples, along with the corresponding documentation, will be shipped to:

PPD

2 Tesseneer Drive

Highland Heights, KY 41076, USA

Email: [redacted]

Phone: [redacted] **or** [redacted], [redacted]

Fax: [redacted]

Plasma samples will be stored nominally at -20°C prior to and after analysis at Covance until their disposal is authorized by Shire.

1.3 Assay Methodology

Drug analysis will be performed at Covance under the guidance of the NCE group at Shire. Plasma sample analysis will be performed according to the bioanalytical study plans prepared for the study.

Plasma samples will be analyzed at Covance for budesonide using the most current validated bioanalytical method.

In addition, selected plasma samples may be used to investigate incurred sample reproducibility (full details will be described in the bioanalytical study plan). The presence of other metabolites or artifacts may be monitored or quantified as appropriate.

Raw data will be stored in the archives at Covance.

PROTOCOL: SHP621-301

TITLE:	Oral Budesonide Suspension (OBS) in Adolescent and Adult Subjects (11 to 55 Years of Age, Inclusive) with Eosinophilic Esophagitis: A Phase 3 Randomized, Double-blind, Placebo-controlled Study
DRUG:	SHP621, oral budesonide suspension (OBS)
IND:	103,173
EUDRACT NO.:	Non-EUDRACT
SPONSOR:	Shire ViroPharma, Incorporated (Shire) 300 Shire Way, Lexington, MA 02421 USA [redacted]
PROTOCOL HISTORY:	Original Protocol: 31 Aug 2015 Protocol Amendment 1: 17 Dec 2015

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [redacted]	**Date:** [redacted]
[redacted] MD [redacted] Clinical Development	

Acknowledgement
I have read this protocol for Shire Study SHP621-301.

Title: Oral budesonide suspension (OBS) in Adolescent and Adult Subjects (11 to 55 years of age, inclusive) with Eosinophilic Esophagitis: A Phase 3 Randomized, Double-blind, Placebo-Controlled Study

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)	

Signature: _____ **Date:** _____

SUMMARY OF CHANGES FROM PREVIOUS VERSION

The SHP621-301 protocol is amended to include the addition of safety-related stopping criteria and a diet stratification factor. Additional edits, as captured in the below table, were made to Protocol Amendment 1 to improve the clarity of the protocol and/or correct minor inconsistencies. Note that correction of typos and grammatical errors are not captured in the below table.

New text indicated in bold; deleted text indicated in strikethrough.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date** **16 Dec 2015**	**Global Amendment**
Description of Change		**Section(s) Affected by Change**
Changed from: [redacted], MD, PhD [redacted] [redacted], Clinical Development **To:** **[redacted], MD** **[redacted]** **[redacted], Clinical Development**		Protocol Signature page; Sponsor Medical Monitor
Changed from: [redacted] **To:** [redacted]		Emergency Contact Information Page
"Each bottle contains **approximately** 210 mL of suspension…"		Study Synopsis, Investigational product, dose, and mode of administration; Section 3.1, Study Design; Section 6.1, Identity of Investigational Product
…the investigational product will be supplied in amber glass, multi-dose bottles with child-resistant caps **and refrigerated throughout the study (in the clinic and subject's home).**		Study Synopsis, Investigational product, dose, and mode of administration; Section 3.1, Study Design; Section 6.1.1, Blinding the Treatment Assignment
~~A minimum of 40 randomized subjects will be aged 11-17 years, inclusive.~~ **The randomization will be performed centrally and stratified by age group (2 strata total: <18 years or ≥18 years) and diet restriction for EoE or other health-related conditions (no diet restriction or any diet restriction). The stratification by age will**		Study Synopsis, Methodology; Section

ensure a minimum of 40 subjects in the pediatric group (11-17 years, inclusive). The stratification by age and diet restriction will ensure balance between treatment groups for the respective stratification factors.	
Subjects cannot be rescreened once **it is confirmed they do not meet inclusion/exclusion criteria unless the screen failure was due to a concomitant medication that can be discontinued prior to rescreening; those subjects may be rescreened.** ~~they have been designated as a screen failure unless due solely to the use of a concomitant medication which can be stopped prior to rescreening~~ **Other reasons for rescreening (ie, reasons unrelated to inclusion/exclusion criteria) must be discussed prospectively with the medical monitor.**	Study Synopsis, Methodology; Section; Section 3.1, Study Design; Section 6.2.1, Interactive Response Technology for Investigational Product Management; Section 7.1.1, Screening Period (Weeks -6 to 0)
6. If PPI responsiveness was excluded by a previous EGD and biopsy, the historical EGD and biopsy must have been performed after the patient had been on a minimum of 6 weeks of high-dose PPI therapy. **Rationale:** Inclusion criterion is modified to allow entry of subjects with at least 6 weeks of historical data demonstrating PPI responsiveness since the duration of PPI needed to exclude PPI responsiveness may vary by local standard of care.	Study Synopsis, Inclusion Criteria; Section 4.1, Inclusion Criteria
4. 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 been on intranasal steroids and has not been on stable treatment for a minimum of 4 weeks prior to the qualifying EGD. After the qualifying EGD, subjects with seasonal allergic rhinitis may resume (or discontinue) intranasal corticosteroids based on the subject's usual treatment regimen for allergy season**.	Study Synopsis, Exclusion Criteria; Section 4.2, Exclusion Criteria
5. Subject has initiated, discontinued, or changed dosage regimen of PPIs, H2 antagonists, antacids, ~~antihistamines~~, or leukotriene inhibitors.	Study Synopsis, Exclusion Criteria; Section 4.2, Exclusion Criteria
20. Subject has taken part in an **interventional** ~~investigational~~ study **related to EoE** within 6 months prior to the screening visit (Visit -1), **and or investigational study within 30 days prior to the screening visit (Visit -1).**	Study Synopsis, Exclusion Criteria; Section 4.2, Exclusion Criteria
24. Subject anticipates using sucralfate during the study. **Rationale:** Sucralfate is added as an exclusionary medication since the medication may interfere with oral budesonide esophageal adherence and may potentially impact efficacy.	Study Synopsis, Exclusion Criteria; Section 4.2, Exclusion Criteria

Changed: ~~Symptom response on~~ DSQ + pain score ~~(binary response), defined as ≥30% and 50% reductions in the DSQ combined score~~ (questions 2+3+4) from baseline to the final treatment period evaluation (Visit 4) **To:** **Change in the** DSQ + pain score (questions 2+3+4) from baseline to the final treatment period evaluation (Visit 4) **Rationale:** The binary response criteria in the DSQ (30% and 50%) were intended only for the DSQ combined score (questions 2+3). Therefore, this secondary efficacy endpoint pertaining to DSQ + pain score (questions 2+3+4) has been corrected.	Study Synopsis, Secondary Efficacy Endpoints; Section 9.8.2, Secondary Efficacy Endpoints
Changed: ~~Symptom response on~~ DSQ pain score ~~(binary response), defined as ≥30% and 50% reductions in the DSQ score~~ (question 4) from baseline to the final treatment period evaluation (Visit 4) **To:** **Change in the** DSQ pain score (question 4) from baseline to the final treatment period evaluation (Visit 4) **Rationale:** The binary response criteria in the DSQ (30% and 50%) were intended only for the DSQ combined score (questions 2+3). Therefore, this secondary efficacy endpoint pertaining to DSQ pain score (question 4) has been corrected.	Study Synopsis, Secondary Efficacy Endpoints; Section 9.8.2, Secondary Efficacy Endpoints
"dual-energy X-ray absorptiometry (DXA) scans for bone mineral density (BMD) and **body composition measurements**…"	Study Synopsis, Safety Endpoints, Statistical Methodology for Safety Endpoints; Section 7.1.2.1, Placebo Lead-in Visit (Visit 0);Section 7.1.3.3, Visit 4 (Week 16); Section 7.2.2.7, Dual -energy X-ray Absorptiometry for Bone Mineral Density; Section 9.9, Safety Analyses
"…the endpoint will be analyzed using **the Cochran-Mantel-Haenszel (CMH) test** ~~a logistic regression model with the effects of the treatment group~~ **adjusting for** age group (either < 18 years or ≥18 years) **and diet restriction for EoE or other health-related conditions (no diet restriction or any diet restriction)** ~~and their interaction. The main effect model will be considered the final definitive model if the interactions between the treatment and age group is not statistically significant at the 10% level.~~ The **adjusted** odds ratio of being a responder on each of the co-primary endpoints for the OBS 2 mg twice daily group vs placebo group and associated 95% confidence interval (CI) will be ~~estimated from the final model~~ **provided.**" • **Each of the co-primary efficacy endpoints will be analyzed using a logistic regression with the effects of treatment group, age group (either <18 years or ≥18 years) and diet**	Synopsis, Statistical Methodology for Primary Efficacy Endpoint; Section 9.8.1, Primary Efficacy Endpoints

restriction for EoE or other health-related conditions (no diet restriction or any diet restriction). The odds ratio of being a responder on each of the co-primary endpoints for the OBS 2 mg twice daily group vs placebo group and associated 95% confidence interval (CI) will be estimated from the final model. Subjects who withdraw without providing efficacy data at the final treatment period evaluation (Visit 4, Week 16) will be classified as non-responders in the primary efficacy analysis.	
Expected response and dropout rates are based on observation from the Phase 2 study (MPI 101-06).	Synopsis, Sample Size Justification; Section 9.6, Sample Size Calculation and Power Considerations
Added row for continuous DSQ completion	Schedule of Assessments
• No change in exercise **(other than seasonal changes in sports or activities). Intense exercise should be avoided unless part of an established exercise routine.** • Short course of systemic steroids **(≤7 days)** are permitted to treat… • **Stable treatment with intranasal or inhaled corticosteroids. For subjects with perennial allergic rhinitis and stable asthma, the topical corticosteroid must be maintained at the same dose throughout the study. For subjects with seasonal allergic rhinitis, it is permissible after the qualifying EGD to resume (or discontinue) intranasal corticosteroids based on the subject's usual treatment regimen for allergy season. All topical corticosteroid dosing changes, including those for seasonal allergic rhinitis, should be avoided within 4 weeks prior to the Week 16 EGD. Subjects who require a change in inhaled corticosteroid treatment for an asthma exacerbation should be discussed with the medical monitor.** • **No use of sucralfate during the study as this may interfere with the adherence of OBS.**	Section 4.3, Restrictions
An urgent safety review will be conducted within 7 days by the sponsor if one or more of the following criteria are met: • **Death that is considered related to the study drug** • **Two SAEs of similar type (defined as same or similar Medical Dictionary for Regulatory Activities [MedDRA] higher level group code) and considered related to the study drug** **The urgent review will be performed by a sponsor safety review group, which will include the study Pharmacovigilance and Risk Management (PVRM) physician and the PVRM Therapeutic Area Head. The PVRM Therapeutic Area Head, not the PVRM physician involved in the study, may be unblinded as part of this urgent safety review, if required. Following the sponsor's review of safety data, one of the following actions will be taken with respect to study status:**	Section 4.5.4, Safety-related Stopping Rules

• **Continue study with protocol unchanged** • **Continue study with modifications to the protocol** • **Terminate study** **Subject safety will be monitored on a continuous basis during this study until the last subject completes his or her last scheduled study visit/assessment.** **Rationale:** Safety-related stopping rules are added to provide for an urgent safety review if criteria for related SAEs are met.	
1. Inhaled or intranasal steroids for conditions other than EoE; subject must be on stable treatment for ≥3 months prior to screening visit (Visit -1), **except for seasonal allergic rhinitis, see Section 4.3.**	Section 5.2.1, Permitted Treatment
3. Inhaled ~~or intranasal steroids~~ **if initiated or changed in dose** <3 months prior to screening visit (Visit -1). **(Seasonal nasal corticosteroid use for seasonal allergic rhinitis is permitted; changes within 4 weeks of scheduled EGD should be avoided).** 4. **Initiation or change in dosing frequency of** PPIs, H2 antagonists, antacids, ~~antihistamines,~~ or leukotriene inhibitors… **8. Sucralfate use during the treatment period**	Section 5.2.2, Prohibited Treatment
OBS and placebo should be refrigerated at 2-8ºC (36 46ºF) throughout the study (in the clinic and subject's home). After 30 minutes, ~~it is recommended that the~~ subjects **will be instructed to** rinse with water and spit**, particularly after the bedtime dose.**	Section 6.2, Administration of Investigational Product(s)
The randomization will be performed centrally and stratified by age group (2 strata total: <18 years **or** ~~vs~~ ≥18 years) **and diet restriction for EoE or other health-related conditions (no diet restriction or any diet restriction)**. The stratification **by age** will ensure a minimum of 40 subjects in the pediatric group (11-17 years, inclusive). **The stratification by age and diet restriction will ensure balance between treatment groups for the respective stratification factors. Fixed block randomization** will be used to ensure that approximately equal numbers of patients are assigned each treatment within strata. [redacted] **Rationale:** As the presence of dietary therapy may impact a subject's response to therapy, a stratification factor based on baseline diet is added to ensure balance between treatment groups.	Section 6.2.2, Allocation of Subjects to Treatment
~~Visit to visit compliance of DSQ completion will also be assessed by site personnel. Protocol deviations will be documented for subjects who fail to complete the DSQ for 3 or more days in a given week.~~	Section 6.5, Subject Compliance
Perform stadiometry in subjects aged 11-17 years, inclusive.	Section 7.1.1.1, Screening Visit (Visit -1)
~~Perform stadiometry in subjects aged 11-17 years, inclusive.~~	Section 7.1.3.1, Baseline Visit (Visit 1): Week 4

Endoscopic findings with separate evaluations of the proximal and distal esophagus will be recorded with respect to 5 categories by the endoscopist: 1) exudates or plaques (grade 0-2); 2) fixed esophageal rings (grade 0–3); 3) edema (grade 0-~~2~~**1**); 4) furrows (grade 0–~~2~~**1**)…	Section 7.2.1.1, Esophagogastroduodenoscopy with Esophageal Biopsy and Histopathologic Evaluation
Visit to visit compliance of DSQ completion will also be assessed by site personnel. Protocol deviations will be documented for subjects who fail to complete the DSQ for 3 or more days in a given week. Calculations will be performed on daily ePRO entries ~~from the screening period,~~ during a 2 week interval prior to~~ the baseline period, and prior to~~ each study visit during the ~~baseline and~~ treatment periods.	Section 7.2.1.2, Dysphagia Symptom Questionnaire
Standard measuring procedures should be followed (eg, removal of socks, shoes, and hats~~; calibration frequency~~). **The stadiometer must be calibrated at least once daily, and as feasible, within 4 hours of measurement. All measurements should be recorded to the nearest 10th of a centimeter (1 mm).**	Section 7.2.2.2, Physical Examination (Including Height and Weight)
All subjects with an abnormal ACTH stimulation test or urinary or serum glucose level must be followed closely until resolution. For subjects who discontinue from the treatment period at any time and have an abnormal ACTH stimulation test at the early termination visit, subjects will be scheduled for repeat testing approximately 6 weeks post last dose of investigational product to ensure that ACTH levels have normalized.	Section 7.2.2.5, Clinical Laboratory Evaluations
PedsQL-EoE module consists of ~~33~~ **35** items…	Section 7.2.3.1, Health-related Quality-of-life Assessment, Pediatric Quality of Life – EoE Questionnaire
The EoE-QoL-A consists of a ~~37~~ **30**-item test	Section 7.2.3.1, Health-related Quality-of-life Assessment, Adult Eosinophilic Esophagitis Quality of Life Questionnaire
All data **from the investigator** will have separate source… **The data from the central pathologist will be recorded directly onto paper CRFs.**	Section 10.2.3.1, Case Report Forms
Added protocol history details.	Section 12, Appendix 1 Protocol History
Edited former Appendix 1 to Appendix 2 Specified age groups for EQ-5D-3L, EQ-5D-Y and Tanner Staging assessments.	Section 12, Appendix 2 Scales and Assessments

See Appendix 1 for protocol history, including all amendments.

EMERGENCY CONTACT INFORMATION

In the event of an SAE, the investigator must fax or e-mail the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol within 24 hours to the Shire Global Pharmacovigilance and Risk Management Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover). A copy of the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol must also be sent to the CRO medical monitor by fax or e-mail using the details below.

[redacted], MD

Email: [redacted]

Fax: [redacted]

For protocol- or safety-related issues <u>during normal business hours (8am to 5 pm Eastern Standard Time)</u>, the investigator must contact the CRO medical monitor:

[redacted], MD

Phone: [redacted]

Mobile: [redacted]

Email: [redacted]

Fax: [redacted]

For protocol- or safety-related issues <u>outside of normal business hours</u>, the investigator must contact the CRO medical monitor:

[redacted], MD

Mobile: [redacted]

Email: [redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 8.

Please use the information below as applicable to report the Product Quality Complaint:

Origin of Product Quality Complaint	E-mail Address
North and South America	[redacted]
European Union and Rest of World	[redacted]

Telephone numbers (provided for reference if needed):

Shire, Lexington, MA (USA)
[redacted] or [redacted]

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ABBREVIATIONS

ACTH	adrenocorticotropic hormone
AE	adverse event
ANCOVA	analysis of covariance
Auc_{tau}	area under the curve for the defined interval between doses
β-hCG	beta-human chorionic gonadotropin
BID	twice daily
BMD	bone mineral density
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum concentration occurring at t_{max}
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CYP450 3A4	cytochrome P450 3A4
DSG1	desmoglein 1
DSQ	Dysphagia Symptom Questionnaire
DXA (DEXA)	dual-energy X-ray absorptiometry
EC	ethics committee
EGD	esophagogastroduodenoscopy
EIS	external independent statistical
EMA	European Medicines Agency
EoE	eosinophilic esophagitis
EoE-QoL-A	Adult Eosinophilic Esophagitis Quality of Life
ePRO	electronic patient-reported outcome
EQ-5D-3L	EuroQol-5 Dimensions 3-level
EQ-5D	EuroQol
EQ-5D-Y	EuroQol 5 Dimensions Youth
EREFS	EoE Endoscopic Reference Score
ET	early termination
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice

HIPAA	Health Insurance Portability and Accountability Act
HPF	high-powered field
HRQoL	health-related quality of life
hs	at bedtime
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web-based response system
Med ID	medication information
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
OBS	oral budesonide suspension
pc	after meals
PedsQL-EoE	Pediatric Quality of Life Inventory – EoE
PGA	Physician Global Assessment
PGI-S	Patient Global Impression of Severity
PP	per-protocol
PPI	proton pump inhibitor
PT	preferred term
PVRM	Pharmacovigilance and Risk Management
qAM	every morning
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	statistical analysis system
SOC	system organ class
TEAE	treatment-emergent adverse event
t_{max}	time of maximum observed concentration sampled during a dosing interval
UK	United Kingdom
US	United States

STUDY SYNOPSIS

Protocol number: SHP621-301	**Drug:** SHP621, oral budesonide suspension (OBS)
Title of the study: Oral Budesonide Suspension (OBS) in Adolescent and Adult Subjects (11 to 55 Years of Age, Inclusive) with Eosinophilic Esophagitis: A Phase 3 Randomized, Double-blind, Placebo-controlled Study	
Number of subjects (total and for each treatment arm): Approximately 300 subjects will be enrolled into the placebo lead-in period to allow for 228 subjects (approximately 152 and 76 per OBS and placebo treatment group, respectively) to be randomized into the double-blind treatment period.	
Investigator(s): Multicenter study	
Site(s) and Region(s): Approximately 60 sites in North America	
Study period (planned): Oct 2015 to July 2018	**Clinical phase:** 3

Objectives

Co-primary:

To demonstrate in a placebo-controlled trial that:

- OBS induces a histologic response (eosinophilic count ≤6/high-powered field [HPF]) in adolescent and adult subjects with eosinophilic esophagitis (EoE) over a 12-week course of therapy.
- OBS reduces dysphagia, as measured by the Dysphagia Symptom Questionnaire (DSQ), by at least 30% from baseline in adolescent and adult subjects with EoE over a 12-week course of therapy.

Key Secondary:

- OBS reduces dysphagia, as measured by the DSQ score from baseline to the final treatment period evaluation (Visit 4).

Secondary:

- To assess the response of endoscopically identified esophageal features to OBS as compared to placebo as measured by the EoE Endoscopic Reference Score (EREFS)
- To explore other responding criteria based on histology and DSQ
- To assess the impact of OBS on pain, as measured by the DSQ pain score
- To evaluate the safety and tolerability of OBS over a 12-week course of therapy
- To obtain OBS pharmacokinetic data in adult subjects with EoE

Exploratory:

[redacted]

Rationale:

Currently there is no approved medication for the treatment of EoE. This study is being conducted in order to provide safety and efficacy data demonstrating histologic response (as measured by eosinophilic count ≤6/HPF) and improvement in dysphagia symptoms (as measured by the DSQ) following 12 weeks of treatment with OBS in adolescent and adult subjects with EoE.

Investigational product, dose, and mode of administration

OBS will be administered in 10 mL at a concentration of 0.2 mg/mL (2 mg dose), twice daily (in the morning [qAM] after meals [breakfast, pc] and at bedtime [hs]). The 0.2 mg/mL concentration of OBS and dosing regimens were selected for use in this Phase 3 study based on the results of Study MPI 101-06, a Phase 2 study in 93 adolescents and adult subjects with EoE and symptoms of dysphagia. Subjects were treated in Study MPI 101-06 with 2 mg OBS twice daily to investigate the co-primary endpoints of histologic response (defined as ≤6 eosinophils/HPF) and reduction in DSQ score from baseline to Week 12 of treatment. For the current study, the investigational product will be supplied in amber glass, multi-dose bottles with child-resistant caps and refrigerated throughout the study (in the clinic and subject's home). Each bottle will contain approximately 210 mL of suspension with a budesonide concentration of 0.2 mg/mL, or 0.00 mg/mL (matching placebo).

After the screening period, eligible subjects will enter a 4-week single-blind placebo lead-in period and will receive 10 mL of OBS placebo twice daily (qAM, pc, and hs). At the end of the placebo lead-in period, eligible subjects will enter a 12-week double-blind treatment period (baseline visit, Visit 1) and will be randomized to 1 of 2 treatment groups in a 2:1 ratio (approximately 152 and 76 subjects for OBS and placebo twice daily treatment groups, respectively). Subjects will receive oral administration of 10 mL of 2 mg investigational product twice daily (qAM, pc, and hs; 4 mg/day total), with no ingestion of food or liquids permitted for 30 minutes after study drug administration:

- Placebo twice daily group: placebo qAM (pc) and hs
- OBS twice daily group: OBS 10 mL of 0.2 mg/mL (2 mg total) qAM (pc) and hs

The total daily dose of budesonide will be 0 mg for each subject in the placebo group and 4 mg for each subject in the OBS treatment group (Table 1).

Table 1: Total Daily Dose of OBS

Dose Group	OBS Concentration (mg/mL)	Volume per Dose	Morning Dose (qAM, pc)	Evening Dose (hs)	Total Dose/Day (mg/day)
Placebo	0.0	10 mL	0.0 mg	0.0 mg	0.0
OBS	0.2	10 mL	2.0 mg	2.0 mg	4.0

Abbreviations: hs=at bedtime; OBS=oral budesonide suspension; pc=after meals; qAM=every morning

At the end of the 12-week double-blind treatment period (Visit 4), subjects who complete the study will have the opportunity to enroll in the treatment extension study. These subjects will continue on the blinded assigned treatment for 2-4 weeks as part of the screening prior to enrolling into the treatment extension study.

Methodology:

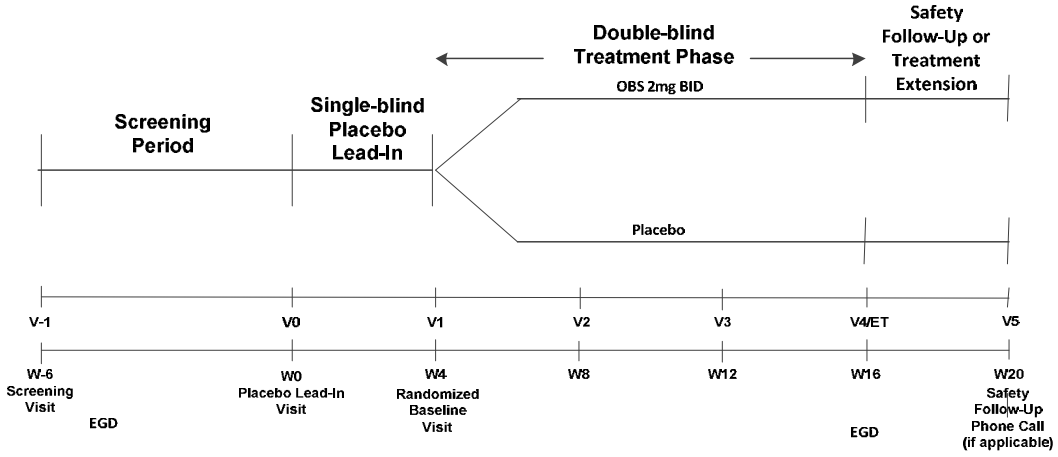
This is a Phase 3, randomized, double-blind, multicenter, parallel-group, placebo-controlled study to evaluate the efficacy, safety, and tolerability of twice daily administration of OBS (qAM, pc, and hs) in adolescents and adults aged 11-55 years, inclusive, with EoE and dysphagia.

This study will comprise 3 periods: a 3- to 6-week screening period, 4-week single-blind placebo lead-in period, and 12-week double-blind treatment period (Figure 1). Approximately 300 subjects will be enrolled into the placebo lead-in period to allow for approximately 228 subjects to be randomized in a 2:1 ratio (approximately 152 and 76 per OBS and placebo treatment group, respectively) into the double-blind treatment period. The randomization will be performed centrally and stratified by age group (2 strata total: <18 years or ≥18 years) and diet restriction for EoE or other health-related conditions (no diet restriction or any diet restriction). The stratification by age will ensure a minimum of 40 subjects in the pediatric group (11-17 years, inclusive). The stratification by age and diet will ensure balance between treatment groups for the respective stratification factors.

Subjects who sign informed consent (or assent as applicable for subjects <18 years) will be screened (Visit -1). Subjects who meet eligibility criteria at the screening visit (Visit -1) and at the placebo lead-in visit (Visit 0) will enter the 4-week placebo lead-in period to assess their ability to comply with twice daily medication administration and assess whether there is a placebo response. Upon completion of the placebo lead-in period, subjects will return for the baseline visit (Visit 1) to confirm eligibility. Eligible subjects will be randomized 2:1 into the double-blind treatment period and will be evaluated for efficacy and safety at Weeks 8, 12, and 16 (Visits 2-4). Subjects who fail to meet all eligibility criteria at Visits -1, 0, or 1 will be considered screen failures. Subjects cannot be rescreened once it is confirmed they do not meet inclusion/exclusion criteria unless the screen failure was due to a concomitant medication that can be discontinued prior to rescreening; those subjects may be rescreened. Other reasons for rescreening (ie, reasons unrelated to inclusion/exclusion criteria) must be discussed prospectively with the medical monitor. Subjects who discontinue will not be replaced.

Subjects will be required to visit the site up to 6 times over up to a 22-week period. A safety follow-up phone call will occur 4 weeks following the last dose of investigational product for subjects who discontinue prematurely during the double-blind treatment period or who do not enroll in the treatment extension study.

Figure 1: Study Design Flow Chart



Abbreviations: BID=twice daily; EGD=esophagogastroduodenoscopy; ET=early termination; OBS=oral budesonide suspension

Inclusion and exclusion criteria:

Inclusion Criteria:

The subject will not be considered eligible for the study without meeting all of the following criteria (including test results):

1. Subject is able to provide written informed consent (subject, parent or legal guardian and, as appropriate, subject assent) to participate in the study before completing any study-related procedures.
2. Subject is male or female aged 11-55 years, inclusive, at time of consent.
3. Subject has histologic evidence of EoE with a peak eosinophil count of ≥15/HPF, from 2 of 3 (proximal, mid-, and/or distal) levels of the esophagus at the screening endoscopy.
4. Subject has a history of clinical symptoms of esophageal dysfunction (eg, eating problems, abdominal pain, heartburn, dysphagia, vomiting, food impaction, weight loss) intermittently or continuously at screening (Visit -1).
5. Subject must have experienced dysphagia (response of "yes" to question 2 on DSQ) on a minimum of 4 days and completed the DSQ on ≥70% of days in any 2 consecutive weeks of the screening period and in the 2 weeks prior to the baseline visit (Visit 1).
6. Subject must not have proton pump inhibitor (PPI)–responsive EoE based on esophageal biopsies performed after the patient 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). If PPI responsiveness was excluded by a previous EGD and biopsy, the historical EGD and biopsy must have been performed after the patient had been on a minimum of 6 weeks of high-dose PPI therapy.
7. Subject will be on a stable (no changes) diet ≥3 months prior to the screening visit (Visit -1).
8. 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.
9. All female subjects must have a negative serum pregnancy test (beta-human chorionic gonadotropin [β-hCG]) prior to enrollment into the study. Females of childbearing potential must agree to continue acceptable birth control measures (eg, abstinence, stable oral contraceptives, or double-barrier methods) throughout study participation.
10. Subject is willing and has an understanding and ability to fully comply with study procedures and restrictions defined in this protocol.

Exclusion Criteria:

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Subject has any condition or abnormality (including laboratory abnormalities), current or past, that, in the opinion of the principal investigator or medical monitor, would compromise the safety of the subject or interfere with or complicate the assessment of signs or symptoms of EoE. Such conditions may include psychiatric problems; neurologic deficits or disease; developmental delay; cardiovascular, metabolic, or pulmonary disease; or previous gastroesophageal surgery. These should be discussed with the medical monitor.
2. 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 (eg, Rituxan) within 3 months of the qualifying EGD should be reviewed with the medical monitor.

3. 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 (≤7 days) 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.
4. Subject has been on inhaled steroids and not on stable treatment for ≥3 months prior to screening visit (Visit -1). Subjects on inhaled steroids need to stay on stable treatment during study participation. Subject has been on intranasal steroids and has not been on stable treatment for a minimum of 4 weeks prior to the qualifying EGD. After the qualifying EGD, subjects with seasonal allergic rhinitis may resume (or discontinue) intranasal corticosteroids based on the subject's usual treatment regimen for allergy season.
5. Subject has initiated, discontinued, or changed dosage regimen of PPIs, H2 antagonists, antacids, 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 EGD and baseline visit (Visit 1), or anticipates changes in the use of such medications during the treatment period.
6. Subject has been using cytochrome P450 3A4 inhibitors (eg, ketoconazole, grapefruit juice) within the 2 weeks prior to the baseline visit (Visit 1) or within 5 half-lives (whichever is greater) or anticipates using such medications during the treatment period.
7. 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 (eg, with an insertion tube diameter of >9 mm).
8. Subject is on a pure liquid diet or the 6-food elimination diet.
9. Subject has had an esophageal dilation within the 3 months prior to screening (Visit -1).
10. Subject has presence of esophageal varices at the screening endoscopy.
11. 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.
12. Subject has other diseases causing or associated with EoE, including hypereosinophilic syndrome, collagen vascular disease, vasculitis, achalasia, or parasitic infection.
13. Subject has current evidence of oropharyngeal or esophageal candidiasis.
14. 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.
15. 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).
16. Subject has evidence of active infection with *Helicobacter pylori.*
17. 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).
18. Subject is female and pregnant or nursing.
19. Subject has a history of intolerance, hypersensitivity, or idiosyncratic reaction to budesonide (or any other corticosteroids) or to any other ingredients of the investigational product.
20. Subject has taken part in an interventional study related to EoE within 6 months prior to the

screening visit (Visit -1), or any investigational study within 30 days prior to the screening visit (Visit -1).

21. Subject has a history or high risk of noncompliance with treatment or regular clinic visits.
22. Subject has previously completed, discontinued, or withdrawn from this study.
23. Subject has participated in a previous clinical study involving OBS (SHP621).
24. Subject anticipates using sucralfate during the study.

Maximum duration of subject involvement in the study:

- Planned duration of screening period: 3-6 weeks
- Planned duration of placebo lead-in period: 4 weeks
- Planned duration of treatment period: 12 weeks
- Planned duration of safety follow-up period: 4 weeks

Endpoints and statistical analysis:

Subject Populations

- The **safety set** will include all subjects who receive at least 1 dose of any double-blind investigational product.
- The **intent-to-treat (ITT) set** will include all randomized subjects. Subjects will be analyzed according to their assigned treatment, regardless of the treatment actually received.
- The **full analysis set (FAS)** will include all randomized subjects who received at least 1 dose of a double-blind investigational product and have both an evaluable post-baseline biopsy in the treatment period (ie, peak eosinophil count is reported for at least 2 esophageal levels) and a post-baseline DSQ score.
- The **per-protocol (PP) set** will include all subjects in the FAS excluding subjects with protocol violations. The PP set will be identified prior to unblinding the treatment assignments by a team consisting of, at a minimum, a physician and a statistician from Shire.
- The **pharmacokinetic set** will include all subjects in the safety set for whom the primary pharmacokinetic data are considered sufficient and interpretable.

Primary Efficacy Endpoints

The co-primary efficacy endpoints are the following:

- Histologic response, defined as a peak eosinophil count of ≤6/HPF across all available esophageal levels at the final treatment period evaluation (Visit 4)
- Dysphagia symptom response, defined as ≥30% reduction in the DSQ combined score (questions 2+3) from baseline to the final treatment period evaluation (Visit 4)

Key Secondary Efficacy Endpoint

- Change in DSQ combined score (questions 2+3) from baseline to the final treatment period evaluation (Visit 4)

Secondary Efficacy Endpoints

- Change in total endoscopy score, as measured by the EREFS classification, from baseline to the final treatment period evaluation (Visit 4)
- Peak eosinophil count <15/HPF across all available esophagus levels at the final treatment period

evaluation (Visit 4)

- Peak eosinophil count ≤1/HPF across all available esophagus levels at the final treatment period evaluation (Visit 4)
- Change from baseline in the peak eosinophil count to the final treatment period evaluation (Visit 4) for each available esophageal level (proximal, mid-, and distal)
- Change from baseline in the histopathologic epithelial features combined total score (grade and stage) to the final treatment period evaluation (Visit 4)
- Dysphagia symptom response (binary response), defined as a ≥50% reduction in the DSQ combined score (questions 2+3), from baseline to the final treatment period evaluation (Visit 4)
- Change from baseline in the DSQ combined score (questions 2+3) over time including post-baseline visits
- Cumulative distribution function curves for the change and the percent change in the DSQ score from baseline to the final treatment period evaluation (Visit 4)
- Overall binary response I, defined as a reduction in the DSQ score of ≥30% from baseline to the final treatment period evaluation (Visit 4) and a peak eosinophil count of ≤6/HPF across all esophageal levels at the final treatment period evaluation (Visit 4)
- Overall binary response II, defined as a reduction in the DSQ score of ≥50% from baseline to the final treatment period evaluation (Visit 4) and a peak eosinophil count of ≤6/HPF across all esophageal levels at the final treatment period evaluation (Visit 4)
- Change in the DSQ + pain score (questions 2 +3+4) from baseline to the final treatment period evaluation (Visit 4)
- Change in the DSQ pain score (question 4) from baseline to the final treatment period evaluation (Visit 4)

Exploratory Efficacy Endpoint

[redacted]

Safety Endpoints

Safety parameters will include monitoring of AEs, physical examinations, stadiometry, vital signs (temperature, systolic and diastolic blood pressure, pulse, and respiratory rate), weight and height assessments, dual-energy X-ray absorptiometry (DXA) scans for bone mineral density (BMD) and body composition measurements (for adolescents aged 11-17 years, inclusive), clinical laboratory tests (hematology, chemistry, urinalysis; serum pregnancy test, if appropriate), and adrenocorticotropic hormone (ACTH) stimulation tests. To account for the effects of puberty in adolescent subjects (11-17 years, inclusive), BMD z-scores will be adjusted for height z-scores using the Bone Mineral Density in Childhood Study calculator (http://www.bmdcspublic.com).

Health Economics and Outcomes Research Endpoints

- Change in Adult Eosinophilic Esophagitis Quality of Life (EoE-QoL-A) score from baseline to the final treatment period evaluation (Visit 4)
- Change in EuroQol (EQ-5D; EuroQol-5 Dimensions 3-level [EQ-5D-3L] or EuroQol-5 Dimensions Youth [EQ-5D-Y], according to subject's age) score from baseline to the final treatment period evaluation (Visit 4)
- Change in Pediatric Quality of Life Inventory – EoE (PedsQL-EoE) score from baseline to the final treatment period evaluation (Visit 4)

Pharmacokinetic Endpoints

Pharmacokinetic parameters will be determined from the plasma concentration-time data for budesonide by non-compartmental analysis. The pharmacokinetic parameters will include, but not be limited to:

AUC_{tau}	Area under the curve for the defined interval between doses
C_{max}	Maximum concentration occurring at t_{max}
t_{max}	Time of maximum observed concentration sampled during a dosing interval

Statistical Methodology for Primary Efficacy Endpoint

The co-primary efficacy endpoints will be analyzed based on the ITT set. Each of the co-primary efficacy endpoints is a binary response (ie, responders vs non-responders); the endpoint will be analyzed using the Cochran-Mantel-Haenszel (CMH) test adjusting for age group (either <18 years or ≥18 years) and diet restriction for EoE or other health-related conditions (no diet restriction or any diet restriction) . The adjusted odds ratio of being a responder on each of the co-primary endpoints for the OBS 2 mg twice daily group vs placebo group and associated 95% confidence interval (CI) will be provided. Subjects who withdraw without providing efficacy data at the final treatment period evaluation (Visit 4, Week 16) will be classified as non-responders in the primary efficacy analysis.

Additionally, the proportion of responders based on each of the co-primary endpoints for each treatment group will be summarized and their respective 95% CI will be reported. The difference in the proportion of responders between the 2 treatment groups and the corresponding 95% CI will also be summarized.

The following sensitivity and supportive analyses will be performed for the co-primary to evaluate the robustness of the results from the primary analysis methods:

- Each of the co-primary efficacy endpoints will be analyzed using a logistic regression with the effects of treatment group, age group (either <18 years or ≥18 years) and diet restriction for EoE or other health-related conditions (no diet restriction or any diet restriction). The odds ratio of being a responder on each of the co-primary endpoints for the OBS 2 mg twice daily group vs placebo group and associated 95% confidence interval (CI) will be estimated from the final model. Subjects who withdraw without providing efficacy data at the final treatment period evaluation (Visit 4, Week 16) will be classified as non-responders in the primary efficacy analysis.
- Analyses will be repeated using the FAS and the PP set.
- Analyses will be repeated by considering subjects who withdraw without providing efficacy data at the final treatment period evaluation (Visit 4) will be classified as responders.

Statistical Methodology for Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is defined as the change in the DSQ combined score (questions 2+3) from baseline to the final treatment period evaluation (Visit 4). The change from baseline DSQ score at the final treatment period evaluation (Visit 4) will be analyzed using an analysis of covariance (ANCOVA) model with treatment group and age group as factors and the baseline DSQ score as a continuous covariate.

Statistical Methodology for Secondary Efficacy Endpoints

Secondary subjective efficacy endpoints that are defined as:

- Binary response endpoints will be analyzed using the same logistic model as the co-primary efficacy endpoints.

- Continuous endpoints will be analyzed as a change from baseline using an ANCOVA model that includes treatment group and age group as factors and baseline score as a continuous covariate.

The analyses for all secondary efficacy endpoints (including the key secondary efficacy endpoint) will be carried out using 2-sided tests at the 5% level of significance. For each of the secondary efficacy endpoints, the treatment difference, corresponding 95% CI for the difference, and treatment comparison p-value for testing the null hypothesis of zero treatment effect based on the final statistical model (ie, either logistic regression model or ANCOVA model) will be provided.

Statistical Methodology for Safety Endpoints

All safety measures, including AEs, physical examination, stadiometry, vital signs (temperature, systolic and diastolic blood pressure, pulse, and respiratory rate), weight and height assessments, DXA scans for BMD and body composition measurements (for adolescents aged 11-17 years, inclusive), clinical laboratory results (hematology, chemistry, urinalysis; serum pregnancy test, if appropriate), and ACTH stimulation will be descriptively summarized by treatment group at baseline and for each post-baseline visit.

The number and percent of subjects with TEAEs will be presented. TEAEs are defined as AEs that start or deteriorate on or after the date of the first dose of investigational product and no later than 3 days following the last dose of investigational product. However, for any subjects who die during the study (ie, the date of death is between the date of first dose of investigational product and the date of study discontinuation entered by the site, inclusive), all AEs (including those resulting in death) that occur during the study will be considered as TEAEs irrespective of the last dose and will be included in the TEAE summaries.

Statistical Methodology for Pharmacokinetic Endpoint(s)

Summary statistics (number of observations, mean, standard deviation, coefficient of variation, median, maximum, minimum, and geometric mean) will be determined for all pharmacokinetic parameters by overall and by week. Plasma concentrations at each nominal sampling time will also be summarized using descriptive statistics.

Sample Size Justification

Based on at least a 30-percentage-point reduction in DSQ score, there is an expected difference between treatment response proportions of 69% and 45% in the OBS 2 mg twice daily (qAM, pc, and hs) and placebo groups, respectively. A total of 228 subjects (152 subjects randomized to OBS and 76 subjects randomized to placebo) are required to achieve 90% power at the significance level of 0.0499 (2-sided) using a 2-group chi-square test with unequal allocation 2:1 to treatment groups (OBS 2 mg twice daily and placebo). With the specified number of subjects per treatment group, the study will be powered at 99% assuming histological response proportions of 40% and 3% in the OBS 2 mg twice daily and placebo groups, respectively. The overall study power for the co-primary endpoints will be at least 85%. Therefore, approximately 228 (approximately 152:76 OBS and placebo subjects, respectively) will be randomized to the study to allow for a loss of approximately 5% of subjects due to dropouts or invalid data. Expected response and dropout rates are based on observation in the Phase 2 study (MPI 101-06).

STUDY SCHEDULE(S)

Table 1-1: Schedule of Assessments

Procedures	Screening	Placebo Lead-in	Treatment Phase				Safety Follow-up Telephone Contact[p]
	Visit -1	Visit 0	Randomization Baseline/Visit 1	Visit 2	Visit 3	Visit 4 or ET[o]	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 assessment	X	X	X	X	X	X	
EGD with endoscopy score (EREFS) and biopsy[c]	X					X	
DSQ training and issue of handset	X						
Retrieval of DSQ handset						X	
DSQ completion	Once daily completion						
DSQ compliance assessment		X	X	X	X	X	
EQ-5D[d]			X			X	
PedsQL-EoE (subjects 11-17 years of age, inclusive)			X			X	

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Procedures	Screening	Placebo Lead-in	Treatment Phase				Safety Follow-up Telephone Contact[p]
	Visit -1	Visit 0	Randomization Baseline/Visit 1	Visit 2	Visit 3	Visit 4 or ET[o]	Visit 5
Week	**-6**	**0**	**4**	**8**	**12**	**16**	**20**
Window	**≤6 weeks**	**--**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**
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[e]	X					X	
Clinical laboratory tests[f]	X	X	X	X	X	X	
Urinalysis[g]	X	X	X	X	X	X	
Pregnancy test[h]	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)[i]				X	X		
DXA Scan (subjects 11-17 years of age, inclusive)[j]		X				X	
Randomization[k]			X				
Investigational product supplied		X	X	X	X	X[l]	
Investigational product administration[m]		Twice-daily administration of investigational product					

Table 1-1: Schedule of Assessments

Procedures	Screening	Placebo Lead-in	Treatment Phase				Safety Follow-up Telephone Contact[p]
	Visit -1	Visit 0	Randomization Baseline/Visit 1	Visit 2	Visit 3	Visit 4 or ET[o]	Visit 5
Week	**-6**	**0**	**4**	**8**	**12**	**16**	**20**
Window	**≤6 weeks**	**--**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**
Investigational product compliance assessment			X	X	X	X	
Concomitant medications and procedures recorded	X	X	X	X	X	X	X
Review of adverse events[n]		X	X	X	X	X	X

Abbreviations: ACTH=adrenocorticotropic 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 will be assessed after the subject has been in a supine position for at least 5 minutes immediately prior to the assessment and will include blood pressure (systolic and diastolic), heart rate, respirations, and temperature.

[b] Height to be collected at screening visit (Visit -1) and Visit 4 for all subjects. Stadiometers are required for subjects 11-17 years of age, inclusive, and will be used at Visit -1 and 4.

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

[d] Subjects 11-17 years of age, inclusive, will complete the EQ-5D-Y; subjects ≥18 years of age will complete the EQ-5D-3L.

[e] Tanner staging assessments will be performed for all subjects aged ≥11 years until investigator confirms subject is post puberty.

[f] Clinical laboratory tests will include the following: alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, total protein, albumin, glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, carbon dioxide, hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, erythrocyte count, leukocyte count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count. All subjects must fast overnight prior to collection.

[g] Urinalysis parameters will include glucose, protein, specific gravity, pH, nitrite, bilirubin, ketones, hemoglobin, urobilinogen, and leukocyte esterase.

[h] The serum pregnancy test will be performed for all female subjects at the screening visit (Visit -1) and final treatment evaluation (Visit 4). Urine pregnancy tests will be performed at all other visits.

[i] Blood samples for pharmacokinetic analysis will be taken from adult subjects (aged ≥18 years). Subjects who do not participate in pharmacokinetic sampling will not be discontinued from the study and lack of participation will not be a considered protocol deviation. Blood samples for pharmacokinetic analysis will be obtained at the Week 8 or Week 12 visit at the following time points: pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, and 12 hours post-dose.

[j] The baseline DXA scan may be performed any time during the placebo lead-in period after the subject has met all screening criteria and prior to blinded-treatment randomization. Baseline and post-treatment DXA scans should be performed using the same machine and software. Post-treatment DXA scan should occur at or within (±) 7 days of the scheduled visit.

[k] Randomization will occur via IWRS at the baseline visit (Visit 1) once the subject's eligibility for study entry is confirmed.

[l] Investigational product will be dispensed at Visit 4 to subjects who consent to enroll in the treatment extension study.

[m] Subjects will receive oral administration of 10 mL of investigational product twice daily (qAM, pc, and hs), with no ingestion of food or liquids permitted for 30 minutes after study drug administration.

[n] AE assessments at each visit and physical examination must include specific assessments for signs of glucocorticoid excess (eg, moon facies, acne, hirsutism, mood swings, insomnia, and depression).

[o] If subject discontinues study prematurely, the evaluations listed for Visit 4 are to be performed as completely as possible.

[p] For subjects who withdraw from the study or do not continue into treatment extension study, a safety follow-up contact by phone will be performed 4 weeks following the last dose of investigational product.

1. BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

Eosinophilic esophagitis (EoE) is defined as "a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation" (Liacouras et al., 2011). Clinical symptoms of EoE often vary by age: Infants and toddlers present with feeding difficulties; school-aged children are more likely to present with vomiting or pain; and adolescents and adults present with dysphagia and food impaction. When these symptoms are present, the diagnosis is confirmed by finding eosinophilic inflammation of ≥15 eosinophils/high-powered field (HPF) on at least 1 esophageal biopsy and when other causes such as proton pump inhibitor (PPI)-responsive esophageal eosinophilia are excluded (Dellon et al., 2014a; Furuta et al., 2007). The standards of care are diet therapies and off-label use of glucocorticosteroids. Esophageal dilation is used to temporarily relieve symptoms but does not address underlying inflammation. Given the clinical outcomes associated with EoE, including severe dysphagia, esophageal stricture, food impaction, and esophageal perforation (Hirano and Aceves, 2014; Liacouras et al., 2011) and the fact that there are currently no FDA-approved treatments, there is a clear unmet medical need for a novel treatment for this disease.

1.2 Product Background and Clinical Information

Oral budesonide suspension (OBS) consists of budesonide formulated in a viscous suspension that is designed to increase the residence time of budesonide on the surface of the esophagus after swallowing compared to a non-viscous suspension. Shire is developing OBS as a first-line therapy for EoE in adolescents and adults.

The nonclinical pharmacology, pharmacokinetics, and toxicity and the clinical pharmacology, pharmacokinetics, and safety of budesonide are well studied because budesonide is present in several US FDA-approved drug products. Budesonide is currently marketed for the management of Crohn's disease, for asthma maintenance, for the treatment of allergic rhinitis, and for induction of remission in patients with active, mild to moderate ulcerative colitis. Budesonide has strong glucocorticoid receptor affinity and is subject to considerable first pass metabolism by the liver with a short half-life. These attributes permit budesonide to act rapidly and locally in the gut mucosa for treatment of inflammatory disorders such as Crohn's disease and ulcerative colitis. Once absorbed into the systemic circulation, budesonide is rapidly metabolized in the liver and inactivated (FDA, 2011).

The efficacy of OBS for the treatment of EoE has been demonstrated in two Phase 2 studies in the OBS clinical development program. Studies MPI 101-01 and MPI 101-06 evaluated the efficacy of OBS in the treatment of EoE in children and adolescents aged 2-18 years and in adolescents and adults aged 11-40 years, respectively, by measuring histological response (defined as mean peak eosinophil count ≤6/HPF after treatment). Study MPI 101-06 also

evaluated symptom response as measured by the Dysphagia Symptom Questionnaire (DSQ). The DSQ contains 4 questions related to consumption of solid food, the presence of dysphagia and its severity, as well as pain. The DSQ score is calculated only from responses to the questions related to dysphagia, and this clinical outcome assessment was considered to be fit for purpose as a result of the MPI 101-06 study. Results from Study MPI 101-01 demonstrated a statistically significant histologic response (eosinophil count ≤6/HPF) and remission (eosinophil count ≤1/HPF) in the medium-dose (1.4-2.0 mg daily) and high-dose (2.8-4.0 mg daily) OBS groups compared to placebo following 12 weeks of treatment.

In Study MPI 101-06, a significant treatment effect for OBS vs placebo was shown for both the co-primary efficacy endpoints of histologic response and change from baseline in dysphagia symptoms. Following 12 weeks of twice daily treatment (once in the morning after meals [qAM, pc] and at bedtime [hs]), OBS-treated subjects demonstrated a highly consistent reduction from baseline values for cellular (mean peak eosinophil count and histopathology features), organ (endoscopy score), and holistic measures (Physician Global Assessment [PGA] and DSQ scores); these results were independent of the type of rater/reviewer (central pathologist, physician at the study site, or subject).

Always refer to the latest version of the SHP621 investigator's brochure for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics, efficacy, and safety of SHP621.

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

Currently there is no approved medication for the treatment of EoE. This study is being conducted in order to provide safety and efficacy data demonstrating histologic response (as measured by eosinophilic count ≤6/HPF) and improvement in dysphagia symptoms (as measured by the DSQ) following 12 weeks of treatment with OBS in adolescent and adult subjects with EoE.

2.2 Study Objectives

2.2.1 Primary Objectives

The co-primary objectives of the study are to demonstrate in a placebo-controlled trial that:

- OBS induces a histologic response (eosinophilic count ≤6/HPF) in adolescent and adult subjects with EoE over a 12-week course of therapy.
- OBS reduces dysphagia, as measured by the DSQ, by at least 30% from baseline in adolescent and adult subjects with EoE over a 12-week course of therapy.

2.2.2 Secondary Objectives

The key secondary objective of this study is:

- OBS reduces dysphagia, as measured by the DSQ score from baseline to the final treatment period evaluation (Visit 4).

Additional secondary objectives of the study are:

- To assess the response of endoscopically identified esophageal features to OBS as compared to placebo as measured by the EoE Endoscopic Reference Score (EREFS)
- To explore other responding criteria based on histology and DSQ
- To assess the impact of OBS on pain, as measured by the DSQ pain score
- To evaluate the safety and tolerability of OBS over a 12-week course of therapy
- To obtain OBS pharmacokinetic data in adult subjects with EoE

2.2.3 Exploratory Objective

The exploratory objective of this study is:

[redacted]

3. STUDY DESIGN

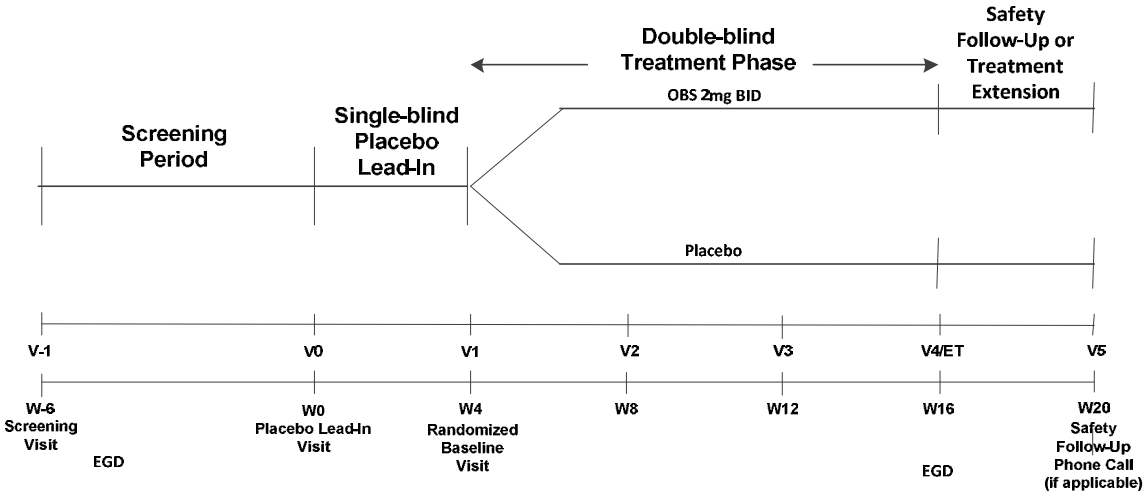
3.1 Study Design and Flow Chart

This is a Phase 3, randomized, multicenter, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of OBS treatment administered twice daily (qAM, pc, and hs) for 12 weeks. The study will be conducted in adolescents and adults, aged 11-55 years, inclusive, with EoE and dysphagia.

Approximately 300 subjects will be enrolled in the placebo lead-in period to allow for approximately 228 subjects to be randomized into the double-blind treatment period. A minimum of 40 randomized subjects will be aged 11-17 years, inclusive. Subjects will be randomized 2:1 (approximately 152 and 76 per OBS and placebo treatment group, respectively) to receive either OBS 2 mg twice daily (qAM, pc, and hs) or placebo twice daily (qAM, pc, and hs).

This study will consist 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 (see Figure 1).

Figure 1: Study Design Flow Chart



Abbreviations: BID=twice daily; EGD=esophagogastroduodenoscopy; ET=end of treatment; OBS=oral budesonide suspension

The upper limit of 55 years, inclusive, was selected for this study population based on the low prevalence of EoE in older patients (Dellon et al., 2014a) and the fact that the type of EoE that develops in older patients is not amenable to anti-inflammatory treatment alone (Dellon et al., 2014b). A natural history study demonstrated that for every decade of life, the odds of developing the fibrostenotic phenotype of EoE more than doubles (Dellon et al., 2014b). By age 55, fibrostenotic EoE occurs in approximately 80% of patients. Fibrostenotic disease is treated with dilatation and is not amenable to anti-inflammatory treatment alone. Therefore, budesonide is not expected to be an effective treatment for the majority of patients above age 55.

Subjects will be required to visit the site up to 6 times over up to a 22-week period. Following completion of the screening and placebo lead-in visits, subjects will be evaluated for eligibility and safety at Week 4 (Visit 1). Subjects who are eligible and randomized will be evaluated for efficacy and safety at Weeks 8, 12, and 16 (Visits 2-4) and additionally for safety at follow-up at Week 20 (Visit 5; telephone contact). Subjects who fail to meet all eligibility criteria at Visits -1, 0, or 1 will be considered screen failures. Subjects cannot be rescreened once it is confirmed they do not meet inclusion/exclusion criteria unless the screen failure was due to a concomitant medication that can be discontinued prior to rescreening; those subjects may be rescreened. Other reasons for rescreening (ie, reasons unrelated to inclusion/exclusion criteria) must be discussed prospectively with the medical monitor. Subjects who discontinue will not be replaced.

The screening period will start when subjects sign informed consent (or assent as applicable for subjects <18 years of age; screening visit [Visit -1]) and will be approximately 3-6 weeks in duration. During the screening period, all subjects will receive an upper endoscopy with histologic analysis of biopsy specimens to confirm the diagnosis of EoE (eosinophil count of

≥15/HPF from 2 of 3 [proximal, mid-, and/or distal] levels of the esophagus). In addition, subjects must complete the DSQ daily during the screening period (3-6 weeks) and have at least 4 reported days with symptoms of dysphagia and completed the DSQ on ≥70% of days in any 2 consecutive weeks. At the screening visit (Visit -1), subjects who are on a PPI must remain on the same dose of the PPI throughout the study; if they are not taking a PPI, they must remain off of a PPI for the remainder of the study. After the screening period, eligible subjects will enter a 4-week single-blind placebo lead-in period and will receive 10 mL of OBS placebo twice daily (in the morning after meals/breakfast [qAM, pc] and at bedtime [hs]). The placebo lead-in period will enable assessment of the subject's ability to comply with twice daily medication administration and assess whether the subject experiences a placebo response.

At the end of the placebo lead-in period, subjects will return for the baseline visit (Visit 1) to confirm eligibility. Subjects who continue to meet all eligibility criteria (those with at least 4 reported dysphagia days and who completed the DSQ on ≥70% of days in the 2 weeks prior to randomization per daily DSQ completion) will be randomized to receive either OBS or placebo during the 12-week double-blind treatment period.

OBS will be administered in 10 mL at a concentration of 0.2 mg/mL (2 mg dose), twice daily. The 0.2 mg/mL concentration of OBS and dosing regimens were selected for use in this Phase 3 study based on the results of Study MPI 101-06, a Phase 2 study in 93 adolescent and adult subjects with EoE and symptoms of dysphagia. Subjects were treated in Study MPI 101-06 with 2 mg OBS twice daily to investigate the co-primary endpoints of histologic response (defined as ≤6 eosinophils/HPF) and reduction in DSQ score from baseline to Week 12 of treatment. For the current study, the investigational product will be supplied in amber glass, multi-dose bottles with child-resistant caps and refrigerated throughout the study (in the clinic and subject's home). Each bottle will contain approximately 210 mL of suspension with a budesonide concentration of 0.2 mg/mL, or 0.00 mg/mL (matching placebo).

At the end of the 12-week double-blind treatment period (Visit 4, Week 16), subjects who complete the study will have the opportunity to enroll in the treatment extension study. These subjects will continue on the blinded assigned treatment for 2-4 weeks as part of the screening prior to enrolling into the treatment extension study. Subjects who do not enroll in the treatment extension study or who discontinue at any time during the SHP621-301 (Induction) study will receive a follow-up phone call 4 weeks post last dose of investigational product (Visit 5).

3.2 Duration and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 26 weeks, depending on the 3- to 6-week screening period.

The study will be completed in approximately 32 months.

The Study Completion Date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment. Please note that this includes the follow-up visit or contact, whichever is later. The Study Completion Date is used to ascertain timing for study results posting and reporting.

A completer is a subject who completes all procedures and assessments up to and including Visit 4 (Week 16), inclusive of the final treatment evaluation EGD. Subjects who do not enroll in the treatment extension study or who discontinue prematurely at any time during the SHP621-301 (Induction) study will receive a follow-up phone call 4 weeks post last dose of the investigational product to which they were randomized.

3.3 Sites and Regions

Approximately 60 sites in North America will participate.

4. STUDY POPULATION

Each subject must participate in the informed consent process and provide written informed consent/assent before any procedures specified in the protocol are performed.

4.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the following criteria (including test results):

1. Subject is able to provide written informed consent (subject, parent or legal guardian, and, as appropriate, subject assent) to participate in the study before completing any study-related procedures.
2. Subject is male or female aged 11-55 years, inclusive, at time of consent.
3. Subject has histologic evidence of EoE with a peak eosinophil count of ≥15/HPF, from 2 of 3 (proximal, mid-, and/or distal) levels of the esophagus at the screening endoscopy.
4. Subject has a history of clinical symptoms of esophageal dysfunction (eg, eating problems, abdominal pain, heartburn, dysphagia, vomiting, food impaction, weight loss) intermittently or continuously at screening (Visit -1).
5. Subject must have experienced dysphagia (response of "yes" to question 2 on DSQ) on a minimum of 4 days and completed the DSQ on ≥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).
6. Subject must not have PPI-responsive EoE based on esophageal biopsies performed after the patient 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 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). If PPI responsiveness was excluded by a previous EGD and biopsy, the historical EGD and biopsy must have been performed after the patient had been on a minimum of 6 weeks of high-dose PPI therapy.

7. Subject will be on a stable (no changes) diet ≥3 months prior to the screening visit (Visit -1).
8. 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.
9. All female subjects must have a negative serum pregnancy test (beta-human chorionic gonadotropin [β-hCG]) prior to enrollment into the study. Females of childbearing potential must agree to continue acceptable birth control measures (eg, abstinence, stable oral contraceptives, or double-barrier methods) throughout study participation.
10. Subject is willing and has an understanding and ability to fully comply with study procedures and restrictions defined in this protocol.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Subject has any condition or abnormality (including laboratory abnormalities), current or past, that, in the opinion of the principal investigator or medical monitor, would compromise the safety of the subject or interfere with or complicate the assessment of signs or symptoms of EoE. Such conditions may include psychiatric problems; neurologic deficits or disease; developmental delay; cardiovascular, metabolic, or pulmonary disease; or previous gastroesophageal surgery. These should be discussed with the medical monitor.
2. 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 (eg, Rituxan) within 3 months of the qualifying EGD should be reviewed with the medical monitor.
3. 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 (≤7 days) 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.
4. Subject has been on inhaled steroids and has not been on stable treatment for ≥3 months prior to screening visit (Visit -1). Subjects on inhaled steroids need to stay on a stable

treatment during study participation. Subject has been on intranasal steroids and has not been on stable treatment for a minimum of 4 weeks prior to the qualifying EGD. After the qualifying EGD, subjects with seasonal allergic rhinitis may resume (or discontinue) intranasal corticosteroids based on the subject's usual treatment regimen for allergy season.

5. Subject has initiated, discontinued, or changed dosage regimen of PPIs, H2 antagonists, antacids, 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 (EGD) and baseline visit (Visit 1), or anticipates changes in the use of such medications during the treatment period.
6. Subject has been using cytochrome P450 3A4 (CYP450 3A4) inhibitors (eg, ketoconazole, grapefruit juice) within the 2 weeks prior to the baseline visit (Visit 1) or within 5 half-lives (whichever is greater) or anticipates using such medications during the treatment period.
7. 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 (eg, with an insertion tube diameter of >9 mm).
8. Subject is on a pure liquid diet or the 6-food elimination diet.
9. Subject has had an esophageal dilation within the 3 months prior to screening (Visit -1).
10. Subject has presence of esophageal varices at the screening endoscopy.
11. 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.
12. Subject has other diseases causing or associated with EoE, including hypereosinophilic syndrome, collagen vascular disease, vasculitis, achalasia, or parasitic infection.
13. Subject has current evidence of oropharyngeal or esophageal candidiasis.
14. 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.
15. 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).
16. Subject has evidence of active infection with *Helicobacter pylori.*
17. 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).
18. Subject is female and pregnant or nursing.
19. Subject has a history of intolerance, hypersensitivity, or idiosyncratic reaction to budesonide (or any other corticosteroids) or to any other ingredients of the investigational product.

20. Subject has taken part in an interventional study related to EoE within 6 months prior to the screening visit (Visit -1), or any investigational study within 30 days prior to the screening visit (Visit -1).
21. Subject has a history or high risk of noncompliance with treatment or regular clinic visits.
22. Subject has previously completed, discontinued, or withdrawn from this study.
23. Subject has participated in a previous clinical study involving OBS (SHP621).
24. Subject anticipates using sucralfate during the study.

4.3 Restrictions

Subjects must adhere to the following restrictions for the duration of the study:

- No change in exercise (other than seasonal changes in sports or activities). Intense exercise should be avoided unless part of an established exercise routine.
- No change in diet (liquid diet for 3 days or less is acceptable).
- Short course of systemic steroids (≤7 days) are permitted to treat, for example, exacerbation of asthma but cannot be used 4 weeks prior to the final EGD.
- Stable treatment with intranasal or inhaled corticosteroids. For subjects with perennial allergic rhinitis and stable asthma, the topical corticosteroid must be maintained at the same dose throughout the study. For subjects with seasonal allergic rhinitis, it is permissible after the qualifying EGD to resume (or discontinue) intranasal corticosteroids based on the subject's usual treatment regimen for allergy season. All topical corticosteroid dosing changes, including those for seasonal allergic rhinitis, should be avoided within 4 weeks prior to the Week 16 EGD. Subjects who require a change in inhaled corticosteroid treatment for an asthma exacerbation should be discussed with the medical monitor.
- No change in PPI use
- No use of CYP450 3A4 inhibitors
- No use of sucralfate during the study as this may interfere with the adherence of OBS
- An esophageal dilatation during the trial (Dilatation is considered a treatment failure, and the subject should be withdrawn from the study.)

4.4 Reproductive Potential

4.4.1 Female Contraception

All females must have a negative pregnancy test at the screening visit (Visit -1), placebo lead-in visit (Visit 0), baseline visit (Visit 1), and Visits 1-4. A serum pregnancy test will be

performed at the screening visit (Visit -1) and final treatment evaluation (Visit 4). Urine pregnancy tests will be performed at all other visits.

Female subjects should be either:

- Pre-menarchal and Tanner Stage 1, or
- Post-menopausal (24 consecutive months of spontaneous amenorrhea and age 51 years or older).
- Be surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 6 weeks post-sterilization, or
- Females of child-bearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception throughout the study period and for 30 days following the last dose of investigational product.
    - Acceptable methods of contraception are:
        - Intrauterine devices plus condoms
        - Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam)
        - Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the screening visit (Visit -1), plus condoms. If hormonal contraceptives are used, they should be administered according to the package insert. Note: If subjects become sexually active during the study, they should use one of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

4.5 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject from investigational product with the medical monitor when possible.

If investigational product is discontinued, leading to subject discontinuation from the study, regardless of the reason, the evaluations listed for Visit 4 are to be performed as completely as possible. If investigational product is discontinued due to an AE, the subject may remain on study to allow for completion of study procedures.

Whenever possible, all discontinued subjects should also undergo the protocol-specified follow-up. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for termination, date of stopping investigational

product, and total amount of investigational product taken must be recorded in the case report form (CRF) and source documents.

Subjects who discontinue will not be replaced.

4.5.1 Subject Withdrawal Criteria

Medically important events that in the opinion of the investigator or medical monitor would compromise the subject's ability to safely continue in the study, including but not limited to an esophageal stricture requiring dilation and/or worsening signs and symptoms of EoE (eg, weight loss or increased dysphagia), would be considered a treatment failure and result in withdrawal of the subject from the study.

4.5.2 Reasons for Discontinuation

The reason for withdrawal must be determined by the investigator and recorded in the subject's medical record and on the CRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the CRF.

Reasons for discontinuation include but are not limited to:

- Completed
- Death
- AE
- Non-compliance with study drug
- Non-compliance with study procedure
- Withdrawal by subject
- Withdrawal by parent/guardian
- Physician decision
- Study terminated by sponsor
- Site terminated by sponsor
- Lost to follow-up
- Pregnancy
- Trial screen failure
- Protocol deviation
- Other

4.5.3 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and return any unused investigational product.

4.5.4 Safety-related Stopping Rules

An urgent safety review will be conducted within 7 days by the sponsor if one or more of the following criteria are met:

- Death that is considered related to the study drug
- Two SAEs of similar type (defined as same or similar Medical Dictionary for Regulatory Activities [MedDRA] higher level group code) and considered related to the study drug

The urgent review will be performed by a sponsor safety review group, which will include the study Pharmacovigilance and Risk Management (PVRM) physician and the PVRM Therapeutic Area Head. The PVRM Therapeutic Area Head, not the PVRM physician involved in the study, may be unblinded as part of this urgent safety review, if required. Following the sponsor's review of safety data, one of the following actions will be taken with respect to study status:

- Continue study with protocol unchanged
- Continue study with modifications to the protocol
- Terminate study

Subject safety will be monitored on a continuous basis during this study until the last subject completes his or her last scheduled study visit/assessment.

5. PRIOR AND CONCOMITANT TREATMENT

All non-study treatment (including but not limited to herbal treatments, vitamins, behavioral treatment, and non-pharmacological treatment, such as psychotherapy, as appropriate) received within 3 months prior to the screening visit (Visit -1) (or pharmacokinetic equivalent of 5 half-lives, whichever is longer) and through the final study contact (including protocol-defined follow-up period) must be recorded on the appropriate CRF page.

5.1 Prior Treatment

Prior treatment includes all treatment, including but not limited to herbal treatments, vitamins, and non-pharmacological treatment such as psychotherapy, as appropriate, received within 3 months of the screening visit (Visit -1). Prior treatment information must be recorded on the appropriate CRF page.

5.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product and the end of the follow-up period, inclusive. Concomitant treatment information must be recorded on the appropriate CRF page.

The investigator may prescribe additional medications during the study, as long as the prescribed medication is not prohibited by the protocol. In the event of an emergency, any needed medications may be prescribed without prior approval, but the medical monitor must be notified of the use of any prohibited medications immediately thereafter.

5.2.1 Permitted Treatment

The following medications are allowed during the course of the study if the subject has been on a stable dosing regimen (ie, same dose and frequency in the previous 4 weeks prior to the endoscopy required for entrance to this study) and will continue this dosing regimen throughout study participation. The investigator must contact the medical monitor to discuss any changes to concomitant steroid regimens or for any medications not listed here that could impact the outcome of the study.

1. Inhaled or intranasal steroids for conditions other than EoE; subject must be on stable treatment for ≥3 months prior to screening visit (Visit -1), except for seasonal allergic rhinitis, see Section 4.3.
2. PPIs
3. H2 antagonists
4. Antacids

5. Antihistamines or antileukotrienes
6. Maintenance immunotherapy (allergy shots)

Influenza and other routine required vaccinations are allowed during the study.

5.2.2 Prohibited Treatment

The following medications and treatments are prohibited throughout the course of the study and prior to treatment, as specified:

1. Immunomodulatory therapy within 8 weeks prior to the qualifying EGD or between the qualifying EGD and baseline visit (Visit 1) or anticipated use of immunomodulatory therapy during the treatment period (except for any ongoing regimen of allergy shots). Use of long-acting immunomodulatory therapy (eg, Rituxan) within 3 months of the qualifying EGD should be reviewed with the medical monitor.
2. 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 anticipated use during the treatment period; any temporary use (≤7 days) or initiation of new steroid treatment during study should be documented and discussed with the medical monitor prospectively but cannot occur within the 4 weeks of the final EGD.
3. Inhaled steroids if initiated or changed in dose <3 months prior to screening visit (Visit -1). (**Seasonal nasal corticosteroid use for seasonal allergic rhinitis is permitted; changes within 4 weeks of scheduled EGD should be avoided).**
4. Initiation or change in dosing frequency of PPIs, H2 antagonists, antacids, 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 EGD and baseline visit 1, or anticipated changes in the use of such medications during the treatment period.
5. CYP450 3A4 inhibitors (eg, ketoconazole, grapefruit juice) within the 2 weeks prior to the baseline visit (Visit 1) or within 5 half-lives (whichever is greater) or anticipated use of such medications during the treatment period. For an expanded list of CYP3A inhibitors, investigators should refer to the 2012 FDA Draft Guidance on Drug Interactions (FDA Guidance 2012) and use their clinical judgment with respect to specific medications.
6. Esophageal dilation within the 3 months prior to screening (Visit -1)
7. Investigational study treatment within 6 months prior to the screening visit (Visit -1)
8. Sucralfate use during the treatment period

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The test product is OBS (oral budesonide suspension, 0.2 mg/mL), which will be provided in multi-dose amber glass bottles, each containing approximately 210 mL. Additional information is provided in the current SHP621 investigator's brochure.

The reference/comparator product is placebo, which will be provided in amber glass bottle form with the same volume.

6.1.1 Blinding the Treatment Assignment

Investigational product will be supplied in amber glass, multi-dose bottles with child-resistant caps and refrigerated throughout the study (in the clinic and subject's home). Each bottle contains approximately 210 mL of suspension with a budesonide concentration of 0.2 mg/mL. Inactive ingredients in OBS include dextrose, disodium edetate, citric acid, sodium citrate, potassium sorbate, polysorbate 80, glycerin, sodium benzoate, cherry flavor, Magnasweet 110, acesulfame potassium, and water.

The placebo solution will also be supplied in amber glass multi-dose bottles with child-resistant caps. Placebo consists of all components of the investigational product solution with the exception of budesonide.

6.2 Administration of Investigational Product(s)

All investigational product and supplies (eg, dosing spoons) will be provided by Shire or its designee. At each visit, subjects will be supplied with enough investigational product to last until the subsequent visit. The first dose of investigational product (placebo) for each subject will be administered in the clinic at the placebo lead-in visit (Visit 0). The subject will continue with the evening dosing regimen at home.

OBS and placebo will be supplied in amber glass bottles and must be shaken well prior to administration. OBS and placebo should be refrigerated at 2-8ºC (36-46ºF) throughout the study (in the clinic and subject's home). The appropriate dose will be dispensed using the graduated dosing spoon provided. For subjects who are minors (<18 years), a parent/guardian will be responsible for ensuring that the subjects take their investigational product appropriately.

Subjects will be instructed not to eat or drink for 30 minutes after taking the investigational product. Activities such as brushing teeth or rinsing the mouth should also be avoided during this time interval. After 30 minutes, subjects will be instructed to rinse with water and spit, particularly after the bedtime dose.

Please refer to the Investigational Product Administration Manual for additional details.

6.2.1 Interactive Response Technology for Investigational Product Management

An interactive web-based response system (IWRS) will be used for screening and enrolling subjects, recording subject visits, randomization, investigational product supply dispensation and management, inventory management and supply ordering, investigational product expiration tracking and management, return of investigational product, and emergency unmasking. Please refer to the Study Manual for additional details regarding the IWRS.

The investigator or designee will access the IWRS at the screening visit (Visit -1) to record subject-specific information (ie, unique subject number, date of birth, etc.). Subjects will be entered as screen failures or as entering the placebo lead-in period. Subjects cannot be rescreened once it is confirmed they do not meet inclusion/exclusion criteria unless the screen failure was due to a concomitant medication that can be discontinued prior to rescreening; those subjects may be rescreened. Other reasons for rescreening (ie, reasons unrelated to inclusion/exclusion criteria) must be discussed prospectively with the medical monitor. For subjects who enter the placebo lead-in period, IWRS will provide the assignment of placebo lead-in period medication to dispense.

At the baseline visit (Visit 1), the investigator or designee will again access the IWRS to either document a screen failure or, if the subject has met all entry criteria, to randomize the subject. Sites will enter eligibility criteria information prior to randomization. For randomized subjects, the IWRS will provide a medication identification (Med ID) number (ie, kit number to dispense for treatment).

The IWRS will also be used for creating, tracking, and confirming investigational product shipments. A user manual with specific functions and instructions for the IWRS will be provided to the site and site personnel will receive training.

The IWRS provider will provide a user manual and training to each site, with detailed instructions on use of the IWRS.

6.2.2 Allocation of Subjects to Treatment

This study consists of a single-blind lead-in period followed by a double-blind placebo-controlled study period. The actual treatment given to individual subjects during the double-blind period is determined by a randomization schedule.

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation.

The randomization number represents a unique number corresponding to investigational product allocated to the subject once eligibility has been determined following the placebo lead-in period.

Individual subject treatment is automatically assigned by the IWRS.

Subjects will be randomized after confirmation of study eligibility in a ratio of 2:1 via a computer-generated randomization schedule to receive OBS 2 mg twice daily (qAM, pc, and hs) or placebo. The randomization will be performed centrally and stratified by age group (2 strata total: <18 years or ≥18 years) and diet restriction for EoE or other health-related conditions (no diet restriction or any diet restriction). The stratification by age will ensure a minimum of 40 subjects in the pediatric group (11-17 years, inclusive). The stratification by age and diet restriction will ensure balance between treatment groups for the respective stratification factors. Fixed block randomization will be used to ensure that approximately equal numbers of patients are assigned each treatment within strata. [redacted]

6.2.3 Dosing

During the 4-week single-blind placebo lead-in period, all subjects will receive 10 mL of placebo twice daily (qAM, pc, and hs). During the 12-week double-blind treatment period, oral administration of 10 mL of investigational product will occur twice daily (qAM, pc, and hs), with no ingestion of food or liquids permitted for 30 minutes after study drug administration. Subjects randomized to OBS will receive 10 mL of 0.2 mg/mL of OBS (2 mg) twice daily for a total daily dose of 4 mg.

Investigational product doses that are required to be administered at the clinic include the first dose of placebo administered at the placebo lead-in visit (Visit 0), the first dose of randomized investigational product (OBS or placebo) administered at the baseline visit (Visit 1) and all morning doses of investigational product administered at Visits 2-4. Subjects will Subjects will be required to eat breakfast at the clinic prior to self-administering these doses. Subjects can self-administer all other doses of placebo and investigational product at home.

During the visit where the pharmacokinetic blood samples are collected (Visit 2 or Visit 3), subjects will be required to eat a moderate-fat breakfast on-site and will be instructed to take their morning dose at a set time to establish the schedule for post-dose sample collection.

6.2.4 Unblinding the Treatment Assignment

The treatment assignment must not be broken during the study except in emergency situations where the identification of the investigational product is required for further treatment of the

subject. The investigator should contact the medical monitor and the sponsor as soon as possible after the investigator has been unblinded.

In the event that the treatment assignment is broken, the date, the signature of the person who broke the code, and the reason for breaking the code are recorded in the IWRS and the source documents. Upon breaking the blind, the subject is withdrawn from the study but should be followed up for safety purposes. Any code breaks that occur must be reported to the contract research organization (CRO) and sponsor. Code break information is held by the pharmacist/designated person at the site and by the CRO medical monitor for the study or designee.

There will be a provision for unblinding to ensure adequate treatment of the subject in the case of an emergency.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

Labels containing study information and pack identification are applied to the investigational product(s) container.

All investigational product is labeled with a minimum of the protocol number, Med ID, dosage form (including product name and quantity in pack), directions for use, storage conditions, expiry date (if applicable), batch number and/or packaging reference, the statements “For clinical trial use only” and/or “CAUTION: New Drug - Limited by Federal (or US) Law to Investigational Use,” “Keep out of reach of children,” and the sponsor’s name and address. Any additional labeling requirements for participating countries and/or controlled substances will also be included on the label.

Space is allocated on the label so that the site representative can record subject information.

Additional labels (eg, those used when dispensing marketed product) may, on a case-by-case basis, be applied to the investigational product in order to satisfy local or institutional requirements, but must not:

- Contradict the clinical study label.
- Obscure the clinical study label.
- Identify the study subject by name.

Additional labels may not be added without the sponsor’s prior full agreement.

6.3.2 Packaging

Investigational product is packaged in the following labeled containers:

The sponsor will supply the following medication to the study sites in a blinded manner: OBS 0.2 mg/mL or placebo in an 8-ounce amber glass bottle for multiple use. Three bottles will be packaged in an appropriately labeled carton.

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.

6.3.3 Storage

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

OBS and placebo must be stored at 2-8ºC (36-46ºF), protected from light.

Investigational products are distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier on the investigational product bottle/carton labels as they are distributed.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), eg, fumigation of a storage room.

6.3.4 Special Handling

The investigational product should be stored under refrigeration at 2-8°C/36-46°F at all times. The investigational product should be protected from light and shaken well immediately prior to each dose.

6.4 Drug Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed-upon number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for administering/dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will dispense the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All dispensed medication will be documented on the CRFs and/or other investigational product record. The investigator is responsible for assuring the retrieval of all study supplies from subjects. The investigator or his/her designee will enter the unique subject identifier and initials on the investigational product kit labels as they are assigned and dispensed.

No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records provided that the blind of the study is not compromised.

At the end of the study, or as instructed by the sponsor, all unused stock, subject-returned investigational product, and empty/used investigational product packaging are to be sent to a nominated contractor on behalf of the sponsor. Investigational product being returned to the sponsor's designated contractors must be counted and verified by clinical site personnel and the sponsor (or designated CRO). For unused supplies where the original supplied tamper-evident feature is verified as intact, the tamper-evident feature must not be broken, and the labeled amount is to be documented in lieu of counting. Shipment return forms, when used, must be signed prior to shipment from the site. Validated electronic return systems (ie,

IWRS) do not require a shipment form. Returned investigational product must be packed in a tamper-evident manner to ensure product integrity. Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

6.5 Subject Compliance

Compliance with investigational product will be assessed at each study visit. Subjects must be instructed to bring their unused investigational product and empty/used investigational product packaging to every visit. Drug accountability must be assessed at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (eg, bottles) or at the individual count level for opened containers/packaging. The pharmacist/nominated person will record details on the drug accountability form.

Visit to visit compliance of investigational product dosing will be assessed by site personnel. Site personnel must review the returned investigational product to assess compliance at every visit prior to dispensing additional investigational product. Any discrepancies should be reconciled with the subject immediately. Subjects who do not return their used and unused investigational product should be reminded to bring all used and unused investigational product at their next visit.

Subjects who have taken 70-130% of the investigational product will be assessed as being compliant with the study protocol. Compliance will be assessed at each treatment visit.

7. STUDY PROCEDURES

7.1 Study Schedule

The detailed study procedures/assessments to be performed throughout the study are outlined in the Schedule of Assessments (see Table 1-1) and must be referred to in conjunction with the instructions provided in this section.

Prior to performing any study-related procedures (including those related to screening), the investigator or his/her designee must obtain written informed consent from the subject (as per local requirements). There must be documentation of consent (as per local requirements) indicating that the subject is aware of the investigational nature of the study and the required procedures and restrictions, prior to performing any study-related procedures.

7.1.1 Screening Period (Weeks -6 to 0)

The screening period starts when subjects sign informed consent. The screening period will comprise 3-6 weeks, during which all procedures listed for the screening visit (Visit -1) in Table 1-1 shall be completed. The screening period will allow for the determination of eligibility of each subject's inclusion into the study. A subject should not be instructed to discontinue use of any medication or treatment to participate in this study until informed consent has been obtained. Subjects should not stop permitted medications or treatments that are effective and well tolerated to participate in this study (see Section 5.2.1).

Screening assessments may take place across several days to allow an appropriate time frame in which to complete all procedures and confirm study eligibility.

After the screening period, subjects who meet eligibility criteria at the end of the screening visit (Visit -1) will enter the 4-week single-blind, placebo lead-in period. The placebo lead-in period should not commence until all screening assessments required to confirm initial eligibility have been completed. If the subject does not meet eligibility criteria following completion of screening assessments, the investigator or designee will document the subject as a screen failure in the IWRS.

A screen failure is a subject who has given informed consent and failed to meet the inclusion criteria and/or met at least 1 of the exclusion criteria and has not been randomized or administered randomized investigational product. Screen failures can occur at the screening, placebo lead-in, or baseline visits. Subjects cannot be rescreened once it is confirmed they do not meet inclusion/exclusion criteria unless the screen failure was due to a concomitant medication that can be discontinued prior to rescreening; those subjects may be rescreened. Other reasons for rescreening (ie, reasons unrelated to inclusion/exclusion criteria) must be discussed prospectively with the medical monitor.

7.1.1.1 Screening Visit (Visit -1)

The screening visit (Visit -1) assessments and procedures, beginning with informed consent, will be performed as outlined in Table 1-1.

The following procedures should be performed first:

- Obtain subject consent (or assent as applicable for subjects <18 years).
- Review eligibility criteria.
- Review medical history.
- Record vital signs (including blood pressure [systolic and diastolic], heart rate, respirations, and temperature), height, and weight. Perform stadiometry in subjects aged 11-17 years, inclusive.
- Review current use of concomitant medications, including medications taken and

procedures completed within 3 months prior to the biopsy required for entrance to this study. Note: Subjects who are on a PPI must remain on the same dose of the PPI throughout the study, and if they are not taking a PPI, they must remain off of a PPI for the remainder of the study.

- Clinical chemistry, hematology, and urinalysis laboratory tests will be performed on all subjects; all subjects must fast overnight prior to collection.

The following order is recommended for the remaining procedures that will be performed at this visit or within the 6-week screening period:

- Dispense the DSQ electronic patient-reported outcome (ePRO) device for nightly completion and train the subject on its use. In order to qualify for study entry, subjects must have experienced dysphagia (response of "yes" to question 2 on DSQ) on a minimum of 4 days and completed the DSQ on ≥70% of days in any 2 consecutive weeks of the screening period.
- Perform a physical examination on all subjects. Adolescents (subjects ≤17 years) will also undergo Tanner Staging Assessment.
- **Serum** pregnancy test will be performed on all female subjects.
- Perform EGD and biopsy; both must be performed within the 6 weeks prior to the Placebo Lead-in Visit either at the investigative site or by a referring physician. Biopsy specimens must be available to be sent to the central pathology lab at least 2 weeks prior to the Placebo Lead-in Visit to allow sufficient time for processing and central review and determination of eligibility.

7.1.2 Placebo Lead-in Period (Weeks 0 to 4)

The placebo lead-in period will comprise 4 weeks, during which all procedures listed for the placebo visit (Visit 0) in Table 1-1 shall be completed.

During the 4-week single-blind placebo lead-in, all eligible subjects will self-administer 10 mL of placebo twice daily (qAM, pc, and hs).

At the end of the placebo lead-in period, eligible subjects (those with at least 4 reported dysphagia days and completion of DSQ on ≥70% of days in the 2 weeks prior to baseline [Visit 1]) will be randomized and enter the 12-week double-blind treatment period (baseline visit). Subjects must be administrated placebo during the placebo lead-in period for 4 weeks (±3 days) prior to Visit 1 (baseline) to be eligible for randomization into the 12-week double-blind treatment period.

7.1.2.1 Placebo Lead-in Visit (Visit 0)

The placebo lead-in visit (Visit 0) assessments and procedures will be performed as outlined in Table 1-1.

The following procedures should be performed first:

- Reassess eligibility according to the inclusion/exclusion criteria and medical history.
- Record vital signs (including blood pressure [systolic and diastolic], heart rate, respirations, and temperature) and weight.
- Perform AE assessments.
- Review concomitant medications and procedures.
- Clinical chemistry, hematology, and urinalysis laboratory tests; all subjects must fast overnight prior to collection.

The following order is recommended for the remaining procedures that will be performed at this visit:

- Review DSQ dysphagia episodes and compliance; re-dispense DSQ device to subject with instruction to continue completion of the DSQ nightly.
- Perform a physical examination and assess any changes since screening.
- **Urine** pregnancy test for female subjects.
- Perform dual-energy X-ray absorptiometry (DXA) scan for bone mineral density (BMD) and body composition in subjects aged 11-17 years, inclusive; the DXA scan may be performed any time during the placebo lead-in period, after the subject has met all screening criteria and prior to blinded-treatment randomization. Baseline and post-treatment DXA scans should be performed using the same machine and software.
- Dispense placebo study medication and review administration instructions. Subjects will self-administer the first dose of placebo in the clinic after eating breakfast. Site personnel will record the date and time of the first placebo dose in the source documents. Beginning on the evening of Visit 0, the subject will take their second dose at home and continue with the twice daily (qAM, pc, and hs) dosing regimen.

7.1.3 Double-blind Treatment Period (Visits 1-4): Weeks 4, 8, 12, and 16 (or Early Termination)

The double-blind treatment period will comprise 12 weeks, during which all assessments and procedures listed for Visits 1-4 in Table 1-1 shall be completed.

During this period, a ±3-day visit window will be permitted, unless otherwise specified. Visit windows are calculated based upon the date of the placebo lead-in visit (Visit 0).

Subjects who continue to meet all eligibility criteria will be randomized 2:1 to receive either OBS twice daily (qAM, pc, and hs) or placebo twice daily (qAM, pc, and hs). The investigator or assigned site staff will access the IWRS to randomize the subject and dispense the investigational product. Subjects who fail to meet eligibility criteria at the baseline visit (Visit 1) will be documented as screen failures in the IWRS.

Subjects who complete the 12-week double-blind treatment period will have the opportunity to enroll in the treatment extension study. These subjects will continue on the blinded assigned treatment for 2-4 weeks as part of the screening prior to enrolling into the treatment extension study. Subjects who do not enroll in the treatment extension study or who discontinue prematurely at any time during the SHP621-301 (Induction) study will receive a follow-up phone call 4-weeks post last dose of investigational product.

7.1.3.1 Baseline Visit (Visit 1): Week 4

Subjects will return to the site for the baseline visit (Visit 1) to confirm eligibility. The baseline visit (Visit 1) assessments and procedures will be performed as outlined in Table 1-1.

The following procedures should be performed first:

- Reassess eligibility according to the inclusion/exclusion criteria and medical history.
- Record vital signs (including blood pressure [systolic and diastolic], heart rate, respirations, and temperature) and weight.
- Perform AE assessments, including specific assessments for signs of glucocorticoid excess. Any AE that occurs during this visit will be recorded in the CRF and considered a TEAE.
- Review concomitant medications and procedures.
- Clinical chemistry, hematology, and urinalysis laboratory tests; all subjects must fast overnight prior to collection.
- Morning cortisol (performed between 6:00 and 9:00 AM). Subjects should be instructed not to take the morning dose of investigational product until after the morning cortisol test has been performed.
- Administer adrenocorticotropic hormone (ACTH) stimulation testing; the type of synthetic and route of administration will be per local lab discretion. Additional cortisol samples will be drawn at 30 and 60 minutes following stimulation testing.

The following order is recommended for the remaining procedures that will be performed at this visit:

- Review study medication dosing compliance.
- Review DSQ dysphagia episodes and compliance; re-dispense DSQ device to subject with instruction to continue completion of the DSQ nightly.
- Administer health-related quality-of-life (HRQoL) assessments including the EuroQol (EQ-5D), Pediatric Quality of Life Inventory – EoE (PedsQL-EoE), and Adult Eosinophilic Esophagitis Quality of Life (EoE-QoL-A) as age-appropriate.
- Administer PGI-S of disease assessment.

- Perform a physical examination and assess any changes since screening.
- Re-administer **urine** pregnancy test for female subjects.
- Dispense investigational product (OBS or placebo) according to IWRS randomization and review administration instructions. Subjects will self-administer the first dose of investigational product in the clinic during this visit after breakfast. Site personnel will record the date and time of the first randomized dose in the source documents. Beginning on the evening of Visit 1, the subject will take their first dose at home and continue with the twice daily (morning and evening) dosing regimen. For subjects who are minors (<18 years), a parent/guardian will be responsible for ensuring subject takes their investigational product appropriately.

Following all blood draws, subjects can eat breakfast and take their morning dose of investigational product.

7.1.3.2 Visits 2 and 3 (Weeks 8 and 12)

Subjects will return to the site for Visit 2 (Week 8) and Visit 3 (Week 12). Assessments at these visits will be performed as outlined in Table 1-1.

The following procedures should be performed first:

- Record vital signs (including blood pressure [systolic and diastolic], heart rate, respirations, and temperature) and weight.
- Perform AE assessments, including specific assessments for signs of glucocorticoid excess. Any AE that occurs during this visit will be recorded in the CRF and considered a TEAE.
- Review concomitant medications and procedures.
- Clinical chemistry, hematology, and urinalysis laboratory tests; all subjects must fast overnight prior to collection.
- Morning cortisol (performed between 6:00 and 9:00 AM). Subjects should be instructed not to take the morning dose of study medication until after the morning cortisol test has been performed.
- Collect blood samples for pharmacokinetic analysis for adult subjects. Subjects will be instructed to take their morning dose at a set time to establish the schedule for post-dose sample collection.

The following order is recommended for the remaining procedures that will be performed at this visit:

- Review DSQ dysphagia episodes and compliance; re-dispense DSQ device to subject with instruction to continue completion of the DSQ nightly.
- Administer PGI-S assessment.

- Perform a physical examination and assess any changes since screening.
- Re-administer **urine** pregnancy test for female subjects.
- Dispense investigational product (OBS or placebo) and review investigational product dosing compliance.

Following all blood draws, subjects can eat breakfast and take their morning dose of investigational product.

7.1.3.3 Visit 4 (Week 16)

Subjects will return to the site for Visit 4 (Week 16). Assessments at this visit will be performed as outlined in Table 1-1.

The following order is recommended for the procedures that will be performed at this visit:

- Record vital signs (including blood pressure [systolic and diastolic], heart rate, respirations, and temperature), height, and weight. Perform stadiometry in subjects aged 11-17 years, inclusive.
- Perform AE assessments, including specific assessments for signs of glucocorticoid excess. Any AE that occurs during this visit will be recorded in the CRF and considered a TEAE.
- Review concomitant medications and procedures.
- Clinical chemistry, hematology, and urinalysis laboratory tests; all subjects must fast overnight prior to collection.
- Morning cortisol (performed between 6:00 and 9:00 AM). Subjects should be instructed not to take the morning dose of investigational product until after the morning cortisol test has been performed.
- Administer adrenocorticotropic hormone (ACTH) stimulation testing; the type of synthetic and route of administration will be per local lab discretion. Additional cortisol samples will be drawn at 30 and 60 minutes following stimulation testing.
- Retrieve DSQ handset and review DSQ compliance.
- Administer HRQoL assessments including the EQ-5D, PedsQL-EoE, and EoE-QoL-A as age-appropriate.
- Administer PGI-S assessment.
- Perform a physical examination and assess any changes since screening. Adolescents (subjects ≤17 years) will also undergo Tanner Staging Assessment.
- Re-administer **serum** pregnancy test for female subjects.
- Perform DXA scan for BMD and body composition in subjects aged 11-17 years, inclusive. DXA scan should be completed at or within (±) 7 days of this visit. Baseline

and post-treatment DXA scans should be performed using the same machine and software.

- Perform EGD and biopsy. EGD should be completed at or within (±) 7 days of the scheduled visit.
- For eligible subjects continuing into the treatment extension study, obtain informed consent for the treatment extension study, dispense investigational product (OBS or placebo) according to IWRS randomization and review investigational product dosing compliance.

Following all blood draws, subjects can eat breakfast and take their morning dose of investigational product if they are continuing in the treatment extension study.

7.1.4 Follow-up Period

The follow-up period for this protocol is 4 weeks from the last dose of investigational product. Subjects who do not enroll in the treatment extension study or who discontinue prematurely at any time during the study will receive a follow-up 4 phone call at Visit 5 (Week 20) to query for SAEs, AEs, and concomitant treatments (Section 7.1.4.1).

7.1.4.1 Safety Follow-up Contact (Visit 5): Week 20

Assessments at this time, as outlined in Table 1-1, will include the following:

- Review concomitant medications and procedures.
- Perform AE assessments, including specific assessments for signs of glucocorticoid excess. Any AE that occurs during this visit will be recorded in the CRF and considered a TEAE; all AEs and SAEs that are not resolved at the time of this contact will be followed to closure.

7.1.5 Additional Care of Subjects after the Study

No after care is planned for this study for those subjects who do not enroll in the treatment extension study.

7.2 Study Evaluations and Procedures

The full title and details about who completes the scales used in this study is included in Appendix 1.

All assessments listed below will be performed by the subject and/or a qualified/trained site staff as indicated in the assessment description. For subject-completed assessments, trained site staff should not assist the subject in completing assessments in such a manner that it

would influence their responses. Site staff should review the completed assessment to ensure completeness.

If an answer is marked in error, the subject may correct it by drawing a single line through the error and initialing and dating the change; however, corrections can only be made to scales by the subject during a study visit and changes must not be made to subject-completed scales after the visit has been completed. Assessments are to be performed according to the schedule shown in Table 1-1.

7.2.1 Efficacy

7.2.1.1 Esophagogastroduodenoscopy with Esophageal Biopsy and Histopathologic Evaluation

The EGD with endoscopy score and biopsy will be performed during the study as outlined in Table 1-1.

An EGD with esophageal, gastric and duodenal biopsies will be required for study participation; the peak eosinophil count per HPF from each esophageal level will be used as a primary measure of efficacy. The qualifying/baseline EGD with biopsies must be performed by a physician at the investigative site within the 6 weeks prior to placebo lead-in visit (Visit 1). Biopsy specimens must be available to be sent to the central pathology lab by at least 2 weeks prior to the placebo lead-in visit to allow sufficient time for processing and central review and determination of eligibility.

Multiple specimens (at least 2 biopsies from each of 3 levels, 6 specimens total) will be obtained from the proximal (3 cm below the cricopharyngeus muscle), mid-esophagus (mid-point between the cricopharyngeus muscle and the gastroesophageal junction), and distal (3 cm above the gastroesophageal junction). Biopsy tissue will be placed in 3 separate vials (1 vial for each of the levels) and sent to the central pathology laboratory for processing of tissue into slides. A central pathologist will determine histologic eligibility for study entry. Peak eosinophil counts of ≥15/HPF in specimens from 2 or more levels of the esophagus will be a requirement for study entry, as determined by a central pathologist. Eosinophil counts, histopathologic features, and gross endoscopic findings will be evaluated and scored for each EGD. Eight histopathologic epithelial features (basal layer hyperplasia, eosinophil density, eosinophil microabscesses, eosinophil surface layering, dilated intercellular spaces, surface epithelial alteration, dyskeratotic epithelial cells, lamina propria fibrosis) will be scored on a 4-point scale (0=normal, 3=worst) for both the severity of the abnormality (ie, grade) and the amount of tissue affected by the abnormality (ie, stage).

Endoscopic findings with separate evaluations of the proximal and distal esophagus will be recorded with respect to 5 categories by the endoscopist: 1) exudates or plaques (grade 0–2); 2) fixed esophageal rings (grade 0–3); 3) edema (grade 0–2); 4) furrows (grade 0–2); and 5) strictures (grade 0–1). An endoscopy score for each category will be calculated and summed

for each anatomic location (proximal and distal). The maximum endoscopy score is 10 points for each location, and a Total Endoscopy Score is the sum of the scores for the proximal and distal locations.

In addition, the general appearance of the stomach and duodenum will be assessed by the endoscopist. Biopsies will be taken from the stomach and duodenum for the screening EGD as follows: gastric body (greater curvature): 2 specimens, gastric antrum: 2 specimens, and duodenum (third part or distal): 2 specimens. Biopsies from the stomach should be submitted in one vial; biopsies from the duodenum should be submitted in a separate vial to the central pathology laboratory for processing of tissue into slides. If the pre-treatment biopsy identifies eosinophilia in the stomach and/or duodenum, the subject will be excluded from the study.

At the Week 16 visit (Visit 4) or at early termination (ET), and EGD with esophageal biopsies (at least 2 biopsies from each of 3 levels [proximal, mid-, and distal]) is required. Endoscopic findings will be recorded by the endoscopist. Biopsies will be sent to the central laboratory for processing. A central pathologist will evaluate the slides. Gastric and duodenal biopsies may be repeated at the discretion of the investigator, but are not required.

7.2.1.2 Dysphagia Symptom Questionnaire

Subjects' dysphagia symptoms will be evaluated using a DSQ ePRO device (Appendix 3).

The questionnaire will be completed by subjects daily for a minimum of 3 weeks during the screening period, during the 4-week placebo lead-in period, and during the 12-week treatment period. Each evening before bedtime, subjects will be asked to indicate if they experienced dysphagia symptoms (eg, food passing slowly or food sticking) during that day. Subject must have experienced dysphagia (response of "yes" to question 2 on DSQ) on a minimum of 4 days total and completed the DSQ on ≥70% of days in any 2 consecutive weeks of the screening period and in the 2 weeks prior to the baseline visit (Visit 1). Subjects must fill out the DSQ at least 5 or more days during a given week in order to be compliant.

Visit to visit compliance of DSQ completion will also be assessed by site personnel. Protocol deviations will be documented for subjects who fail to complete the DSQ for 3 or more days in a given week.

Calculations will be performed on daily ePRO entries during a 2-week interval prior to each study visit during the treatment periods. The DSQ score for the co-primary endpoint and secondary endpoints will be calculated by summing the scores of responses to questions 2 and 3 only. Questions 1 and 4 will be excluded from the DSQ score:

- DSQ score= $\frac{\text{(Sum of points from questions 2+3 in the daily DSQ)}\times 14}{\text{Number of diaries reported with non-missing data}}$

The DSQ + pain score for the secondary endpoints will be calculated by summing the scores of responses to questions 2, 3, and 4. Question 1 will be excluded from the DSQ + pain score.

- DSQ + pain score= $\frac{\text{(Sum of points from questions 2+3+4 in the daily DSQ)}\times 14}{\text{Number of diaries reported with non-missing data}}$

The DSQ pain score for the secondary endpoint will be calculated by summing the scores of responses to Question 4 only.

- DSQ pain score=$\frac{\text{(Sum of points from question 4 in the daily DSQ)}\times 14}{\text{Number of diaries reported with non-missing data}}$

7.2.2 Safety

The name and address of each third-party vendor (eg, clinical laboratory) used in this study will be maintained in the investigator's and sponsor's files.

7.2.2.1 Medical and Medication History

Medical History

The investigator must record all clinically or medically relevant information regardless of how much time has elapsed since the date of any diagnosis. Medical history will be classified as EoE or non-EoE by the investigator. The EoE medical history must include any prior history of esophageal strictures and esophageal dilations.

Medication History

Refer to Section 5.1 for full details on collection of prior treatment.

Prior treatment information, including any prior treatments for EoE (eg, dietary, medication, or other), must be recorded on the appropriate CRF page.

7.2.2.2 Physical Examination (Including Height and Weight)

Abnormalities identified at the screening visit (Visit -1) will be documented in the subject's source documents and on the medical history CRF. Changes after the screening visit (Visit -1) will be captured as AEs on the AE CRF page, as deemed by the investigator.

Physical examination assessments at each visit should also include specific assessments for signs of glucocorticoid excess (eg, moon faces, acne, hirsutism, mood swings, insomnia, and

depression). Physical examination at the screening visit (Visit -1) will also include Tanner Staging Assessments for subjects <18 years of age.

Height will be collected at the screening visit (Visit -1) and Visit 4 for all subjects. Stadiometers will be used to measure height at Visit -1 and Visit 4 for subjects aged 11-17 years, inclusive. Statural height will be measured by trained site staff using a stabilized stadiometer. The same stadiometer should be used for the baseline and post treatment measurements. Standard measuring procedures should be followed (eg, removal of socks, shoes, and hats). The stadiometer must be calibrated at least once daily, and as feasible, within 4 hours of measurement. All measurements should be recorded to the nearest 10th of a centimeter (1 mm). Please refer to the study manual for additional details.

7.2.2.3 Adverse Event Collection

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?"). AEs are collected from the time informed consent is signed. (Please refer to Section 8.)

AE assessments at each visit should also include specific assessments for signs of glucocorticoid excess (eg, moon facies, acne, hirsutism, mood swings, insomnia, and depression).

7.2.2.4 Vital Signs

Vital signs will be conducted after the subject has been supine for at least 5 minutes immediately prior to the assessment and will include blood pressure (systolic and diastolic), heart rate, respirations, and temperature. Blood pressure should be determined by cuff (using the same method, the same arm, and in the same position throughout the study). Any clinically significant deviations from baseline (Visit 1) vital signs that are deemed clinically significant in the opinion of the investigator are to be recorded as an AE.

7.2.2.5 Clinical Laboratory Evaluations

All clinical laboratory assays will be performed according to the laboratory's normal procedures. All subjects must fast overnight prior to collection of clinical laboratory tests.

Reference ranges are to be supplied by the laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

The following clinical laboratory assessments will be performed:

Biochemistry

- alkaline phosphatase
- aspartate aminotransferase
- alanine aminotransferase
- total bilirubin
- total protein
- albumin
- glucose
- blood urea nitrogen
- creatinine
- sodium
- potassium
- chloride
- calcium
- carbon dioxide

Hematology

- hemoglobin
- hematocrit
- mean corpuscular hemoglobin
- mean corpuscular hemoglobin concentration
- mean corpuscular volume
- erythrocyte count
- leukocyte count
- neutrophils
- lymphocytes
- monocytes
- eosinophils
- basophils
- platelet count

Urinalysis

- glucose
- protein
- specific gravity
- pH
- nitrite
- bilirubin
- ketones
- hemoglobin
- urobilinogen
- leukocyte esterase

Other tests

- serum pregnancy
- urine pregnancy
- morning cortisol (6:00-9:00 AM collection)
- ACTH stimulation testing

ACTH stimulation testing will be performed by measuring the levels of cortisol in the blood following the injection of a synthetic form of ACTH. The type of synthetic and route of administration will be per local lab discretion. Blood samples will be collected just prior to and approximately 30 and 60 minutes following the injection.

In the event of clinically significant abnormal laboratory test results, follow-up laboratory tests may be conducted. All subjects with an abnormal ACTH stimulation test or urinary or serum glucose level must be followed closely until resolution. For subjects who discontinue from the treatment period at any time and have an abnormal ACTH stimulation test at the early termination visit, subjects will be scheduled for repeat testing approximately 6 weeks post last dose of investigational product to ensure that ACTH levels have normalized. Any clinically significant abnormalities noted in the laboratory tests will be discussed with the medical monitor.

7.2.2.6 Pregnancy Test

A serum β-hCG pregnancy test is performed on all female subjects at the screening visit (Visit -1) and the final treatment evaluation visit (Visit 4) or ET visit. A urine pregnancy test is performed on all female subjects at the placebo lead-in visit (Visit 0), baseline visit (Visit 1), Visit 2, and Visit 3 or if pregnancy is suspected.

7.2.2.7 Dual-energy X-ray Absorptiometry for Bone Mineral Density

DXA (also referred to as DEXA) scans for determination of BMD and body composition will be performed in subjects aged 11-17 years, inclusive, as outlined in Table 1-1.

The sites for DXA measurement will be the lumber spine (L1-L4 preferred) and total body less head (Bachrach, 2011; Gordon, 2008; International Society for Clinical Densitometry, 2013). The same DXA machine and software should be used for the baseline and post-treatment scans. The DXA manufacturer, model, and software version should be recorded in the CRF.

7.2.3 Other Assessments

7.2.3.1 Health-related Quality-of-life Assessment

EuroQol-5 Dimensions 3-level Questionnaire

The EuroQol-5D Dimensions 3-level (EQ-5D-3L; for subjects ≥18 years) and the EuroQol-5 Dimensions Youth (EQ-5D-Y; for subjects 11-17 years of age, inclusive) will be performed during the study as outlined in Table 1-1.

The EQ-5D-3L is a standardized measure of health status for use in adult populations that was developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQol Group, 1990). The EQ-5D-3L provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of healthcare as well as in population health surveys. It consists of a 5-item descriptive system that measures 5 dimensions of health, including mobility, self-care,

usual activities, pain/discomfort, and anxiety/depression. Each dimension is represented by a single item with 3 levels of responses. The EQ-5D-3L will be completed by the subject. The EQ-5D-3L should take the subject a few minutes to complete.

The EQ-5D-Y is a self-report version of the EQ-5D that was developed by the EuroQol Group for use in younger populations (Wille et al., 2010). The EQ-5D-Y provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of healthcare as well as in population health surveys. It consists of a 5-item descriptive system that measures 5 dimensions of health, including mobility, looking after myself, doing usual activities, having pain or discomfort, and feeling worried, sad, or unhappy. Each dimension is represented by a single item with 3 levels of responses. The EQ-5D-Y will be completed by the subject and should take a few minutes to complete.

Pediatric Quality of Life – EoE Questionnaire

The PedsQL-EoE questionnaire will be completed by subjects 11-17 years of age, inclusive, and their parent or legal guardian, as outlined in Table 1-1.

The PedsQL-EoE is a modular, disease-specific instrument designed to measure HRQoL in children and adolescents (2-18 years of age) with EoE (Franciosi, 2013; PROQOLID). The PedsQL-EoE module consists of 35 items for children and teenagers encompassing the following 7 scales: 1) Symptoms I (6 items; chest/throat/stomach pain and nausea/vomiting), 2) Symptoms II (4 items; trouble swallowing), 3) Treatment (5 items; treatment barriers), 4) Worry (6 items; worries about treatment and disease), 5) Communication (5 items; communication with others about EoE), 6) Food and Eating (4 items; food and eating allergies and limitations), and 7) Food Feelings (3 items; emotions associated with food allergies). The PedsQL-EoE should take the subject and parent approximately 10 minutes to complete.

Adult Eosinophilic Esophagitis Quality of Life Questionnaire

The EoE-QoL-A will be performed in subjects ≥18 years of age as outlined in Table 1-1.

The EoE-QoL-A is a disease-specific measure of HRQoL in adult patients (≥18 years of age) with EoE (Taft et al., 2011). The EoE-QoL-A consists of a 30-item test with 5 subscales: eating/diet impact, social impact, emotional impact, disease anxiety, and choking anxiety. The EoE-QoL-A will be completed by the subject and should take the subject approximately 15 minutes to complete.

7.2.3.2 Severity of Disease Assessments

Patient Global Impression of Severity

The PGI-S will be performed in all subjects as outlined in Table 1-1.

The PGI-S is a global index (Appendix 4) that can be used to rate the severity of a specific condition - in this case, dysphagia in EoE. Subjects will be asked to rate the severity of their dysphagia over the last 7 days using a 5-point scale.

7.2.4 Clinical Pharmacology Assessments

Blood samples will be collected from adult subjects (≥18 years of age) as outlined in Table 1-1 to measure plasma concentrations of budesonide. Subjects who do not participate in pharmacokinetic sampling will not be discontinued from the study, and lack of participation will not be a considered protocol deviation.

Actual pharmacokinetic blood sample collection times vs time of dosing will be monitored. The sponsor's expectation is that the investigator will ensure that every effort will be made to collect all pharmacokinetic blood samples at the precise protocol scheduled time. Pharmacokinetic blood collection must not deviate from the nominal collection time set forth in the protocol by more than ± 5 minutes for samples drawn within 4 hours post-dose or by more than ± 15 minutes for samples drawn after 4 hours post-dose. Samples drawn outside these parameters will be considered a protocol deviation.

Blood samples (4 mL) for pharmacokinetic analysis will be drawn by direct venipuncture into K2EDTA tubes, capped and mixed by inversion (×3), and chilled immediately on crushed ice. The actual blood collection time will be recorded in the subject's source documents and on the appropriate CRF page (24-hour format). After applying a tourniquet, venous blood will be drawn with a disposable needle. If a catheter is used, the first milliliter of blood on each sampling occasion will be discarded. Saline can be used to keep catheters patent.

Within 15 minutes following each sample collection, the blood tubes will be centrifuged at approximately 1500 g (15 minutes, 4°C). The separated plasma will be decanted into appropriately labeled primary and backup polypropylene tubes via a plastic pipette. All samples will be stored nominally at -20°C, and the freezer temperature will be controlled, monitored, and recorded during the storage period until the samples are shipped to the designated bioanalytical laboratory for analysis.

For additional information detailing sample handling, storage, and shipment, see Appendix 5.

7.2.5 Volume of Blood to Be Drawn from Each Subject

Table 7-1: Approximate Volume of Blood to Be Drawn from Each Subject

Assessment		Sample Volume (mL)	Number of Samples	Approximate Total Volume (mL)
Pharmacokinetic samples[a]		5	9	45
Safety	Biochemistry and β-hCG[b]	6	6	36
	ACTH	2	4	8
	Cortisol	2	4	8
	Hematology	2	6	12
Total mL				109

Abbreviations: ACTH=adrenocorticotropic hormone; β-hCG=beta-human chorionic gonadotropin

[a] If a catheter is used, the first mL is to be discarded; then take 4 mL into appropriate tube for pharmacokinetic sample. A total of 5 mL of blood drawn has been used in determination of sample volume.

[b] β-hCG testing is for females only.

During this study, it is expected that approximately 109 mL of blood will be drawn from all subjects, regardless of sex.

Note: The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment; however, the total volume drawn over the course of the study should be approximately 109 mL. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments may be combined.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An **AE** is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 7.1.4. This includes events occurring during the screening phase of

the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the CRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE CRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate CRF).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related." Otherwise, if there is any valid reason, even if undetermined or untested, for

suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related" based on the definitions in Table 8-1. The causality assessment must be documented in the source document.

Table 8-1: Adverse Event Relatedness

Term	Relationship Definition
Not Related	Unrelated to study drug.
Possibly Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of study drug, but which could also be explained by concurrent disease or other drugs or chemicals.
Probably Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of study drug, unlikely to be attributable to concurrent disease or other drugs and chemicals and which follows a clinically reasonable response on de-challenge. The association of the clinical event or laboratory abnormality must also have some biologic plausibility, at least on theoretical grounds.
Definitely Related	The event follows a reasonable temporal sequence from administration of the study drug, follows a known or suspected response pattern to the study drug, is confirmed by improvement upon stopping the study drug (de-challenge), and reappears upon repeated exposure (re-challenge). Note that this is not to be construed as requiring re-exposure of the patient to study drug; however, the determination of definitely related can only be used when recurrence of event is observed.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the CRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved With Sequelae
- Recovering/Resolving
- Unknown

8.1.4 Symptoms of the Disease under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE.

8.1.5 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory or vital sign assessment can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory or vital sign values which were not present at the pre-treatment value observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory or vital sign parameter is clinically significant and therefore represents an AE.

8.1.6 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 7.1.4.

Any report of pregnancy for any female study participant must be reported within 24 hours to the Shire Global PVRM Department using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO/Shire medical monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days postpartum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β-HCG test or ultrasound result will determine the pregnancy onset date.

8.1.7 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- **Overdose** – Intentional or unintentional intake of a dose of an investigational product exceeding a pre-specified total daily dose of 4 mg of the product.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of the unassigned treatment is/are always reportable as a medication error.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

All investigational product provided to pediatric subjects should be supervised by the parent/legally authorized representative/caregiver.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is the investigator brochure, which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global PVRM Department and the CRO medical monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.7) unless they result in an SAE.

The investigator must complete, sign, and date the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested) and fax or e-mail the form to the Shire Global PVRM Department. A copy of the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol (and any applicable follow-up reports) must also be sent to the CRO medical monitor using the details specified in the emergency contact information section of the protocol.

8.2.3 Serious Adverse Event Definition

A ***Serious Adverse Event*** **(SAE)** is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect

- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.4 and must be reported to the Shire Global PVRM Department and the medical monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Global PVRM Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, leading up to the onset date of the SAE, or following the resolution date of the SAE must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject's death (ie, the SAE was noted as the primary cause of death) must have "fatal" checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered as not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product).

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The sponsor and the clinical CRO are responsible for notifying the relevant regulatory authorities/US central Institutional Review Boards (IRBs) of related, unexpected SAEs.

In addition, the sponsor and the clinical CRO are responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP621 program.

The investigator is responsible for notifying the local IRB, local ethics committee (EC), or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the CRF. A study monitor will visit each site in accordance with the monitoring plan and review the CRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is randomized, it is expected that site personnel will complete the CRF entry within approximately 3 business days of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the CRO's data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Data Handling Considerations

Data that may potentially unblind the treatment assignment (ie, investigational product serum concentrations, treatment allocation, and investigational product preparation/accountability

data) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, prior to unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

9.4 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent. All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC, USA) version 9.1 or higher.

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

In addition to a final SAP for the final analysis, a separate interim SAP for the interim analysis will be finalized prior to unblinding and performing the analysis. The SAP for the final analysis will be finalized prior to final database lock and performing analysis (ie, unblinding) to preserve the integrity of the statistical analysis and study conclusions.

9.5 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

A planned interim analysis for each of the co-primary endpoints will take place after 50% of all randomized subjects have either completed the study or prematurely withdrawn from the study, whichever comes first. The purpose of the unblinded interim analysis is to reassess the appropriateness of assumptions used for each of co-primary efficacy endpoints when the study was designed. The reassessment of the sample size will utilize the conditional power approach under certain conditions that do not inflate the type I error (Mehta and Pocock, 2011). The planned interim analysis will be conducted by an external independent statistical (EIS) group; the individuals involved in the day-to-day conduct of the trial will not be involved in the interim analysis or have access to the results of the interim analysis. The Sponsor will only be notified by the EIS group if any recommendation of increasing the sample size is needed from the conditional power; this will be detailed in the pre-specified interim SAP including a potential maximum sample size to be increased if deemed necessary.

A very minimal fraction of alpha (0.0001) will be spent at the interim analysis as the trial will not stop due to the interim results. The final analysis will use 4.99% for each of the co-primary endpoints in order to preserve an overall type I error at 5% level.

9.6 Sample Size Calculation and Power Considerations

Based on at least a 30-percentage-point reduction in DSQ score, there is an expected difference between treatment response proportions of 69% and 45% in the OBS 2 mg twice daily (qAM, pc, and hs) and placebo groups, respectively. A total of 228 subjects (152 subjects randomized to OBS and 76 subjects randomized to placebo) are required to achieve 90% power at the significance level of 0.0499 (2-sided) using a 2-group chi-square test with unequal allocation 2:1 to treatment groups (OBS 2 mg twice daily and placebo). With the specified number of subjects per treatment group, the study will be powered at 99% assuming histological response proportions of 40% and 3% in the OBS 2 mg twice daily and placebo groups, respectively. The overall study power for the co-primary endpoints will be at least 85%. Therefore, approximately 228 (approximately 152:76 OBS and placebo subjects, respectively) will be randomized to the study to allow for a loss of approximately 5% of subjects due to dropouts or invalid data. Expected response and dropout rates are based on observation from the Phase 2 study (MPI 101-06).

9.7 Study Population

The **safety set** will include all subjects who receive at least 1 dose of any double-blind investigational product.

The **intent-to-treat (ITT)** set will include all randomized subjects. Subjects will be analyzed according to their assigned treatment, regardless of the treatment actually received.

The **full analysis set (FAS)** will include all randomized subjects who received at least 1 dose of a double-blind investigational product and have both an evaluable post-baseline biopsy in the treatment period (ie, peak eosinophil count is reported for at least 2 esophageal levels) and a post-baseline DSQ score.

The **per-protocol (PP)** set will include all subjects in the FAS excluding subjects with protocol violations. The PP set will be identified prior to unblinding the treatment assignments by a team consisting of, at a minimum, a physician and a statistician from Shire.

The **pharmacokinetic set** will include all subjects in the safety set for whom the primary pharmacokinetic data are considered sufficient and interpretable.

9.8 Efficacy Analyses

The primary, key secondary, and secondary efficacy analyses will be performed on the ITT set and presented by treatment group.

Data collected at the baseline visit (Visit 1) will be used as the baseline for all efficacy analyses.

9.8.1 Primary Efficacy Endpoints

The co-primary efficacy endpoints are the following:

- Histologic response, defined as a peak eosinophil count of ≤6/HPF across all available esophageal levels at the final treatment period evaluation (Visit 4)
- Dysphagia symptom response, defined as ≥30% reduction in the DSQ combined score (questions 2+3) from baseline to the final treatment period evaluation (Visit 4)

The co-primary efficacy endpoints will be analyzed based on the ITT set. Each of the co-primary efficacy endpoints is a binary response (ie, responders vs non-responders); the endpoint will be analyzed using the Cochran-Mantel-Haenszel (CMH) test adjusting for age group (either <18 years or ≥18 years) and diet restriction for EoE or other health-related conditions (no diet restriction or any diet restriction). The adjusted odds ratio of being a responder on each of the co-primary endpoints for the OBS 2 mg twice daily group vs placebo group and associated 95% confidence interval (CI) will be provided. Subjects who withdraw without providing efficacy data at the final treatment period evaluation (Visit 4, Week 16) will be classified as non-responders in the primary efficacy analysis.

Additionally, the proportion of responders based on each of the co-primary endpoints for each treatment group will be summarized, and their respective 95% CI will be reported. The difference in the proportion of responders between the 2 treatment groups and the corresponding 95% CI will also be summarized.

The following sensitivity and supportive analyses will be performed for the co-primary to evaluate the robustness of the results from the primary analysis methods:

- Each of the co-primary efficacy endpoints will be analyzed using a logistic regression with the effects of treatment group, age group (either <18 years or ≥18 years) and diet restriction for EoE or other health-related conditions (no diet restriction or any diet restriction). The odds ratio of being a responder on each of the co-primary endpoints for the OBS 2 mg twice daily group vs placebo group and associated 95% confidence interval (CI) will be estimated from the final model. Subjects who withdraw without providing efficacy data at the final treatment period evaluation (Visit 4, Week 16) will be classified as non-responders in the primary efficacy analysis.

- Analyses will be repeated using the FAS and the PP set.

- Analyses will be repeated by considering subjects who withdraw without providing efficacy data at the final treatment period evaluation (Visit 4) and will be classified as responders.

9.8.1.1 Missing Data Imputation

Method 1: Distribution-based Imputation

The subjects with missing co-primary efficacy endpoints will be assigned randomly according to the distribution of responders with available data for each of the co-primary endpoints (ie, those with non-missing data) across the 2 treatment groups by strata (see Table 9-1).

Table 9-1: Percentage of Responders for All Available Data (ie, Non-missing Data) by Strata

Strata	No	Yes
<18 years	X0%	X1%
≥18 years	Y0%	Y1%

For instance, if there are N subjects with missing data in strata 1 (age <18 years), then X0%*N subjects will be randomly assigned as non-responders and X1%*N subjects will be randomly assigned as responders.

Conversely, if there are M subjects with missing data in strata 2 (age ≥18 years), the Y0%*M subjects will be randomly assigned as non-responders and Y1%*N subjects will be randomly assigned as responders.

Method 2: Multiple Imputations

Multiple imputation (MI) methods will utilize the SAS procedures PROC MI and PROC MIANALYZE. The MI procedure will involve fitting a logistic regression model with the binary outcome (responders vs non-responders) as the dependent variable and the age group and the treatment group as the independent variables. The MI procedure will generate 10 version datasets with binary outcome imputed from the subjects with complete data. Once the missing values are imputed and each dataset is created, the results will be appropriately pooled across the multiply imputed estimated regression coefficients and their standard errors using PROC MIANALYZE.

Other sensitivity analyses will be explored, and details will be provided in the SAP.

9.8.2 Secondary Efficacy Endpoints

9.8.2.1 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is defined as the change in DSQ combined score (questions 2+3) from baseline to the final treatment period evaluation (Visit 4). The change

from baseline DSQ score at the final treatment period evaluation (Visit 4) will be analyzed using an analysis of covariance (ANCOVA) model with treatment group and age group as factors and the baseline DSQ score as a continuous covariate.

The additional secondary efficacy endpoints are the following:

- Change in total endoscopy score, as measured by the EREFS classification, from baseline to the final treatment period evaluation (Visit 4)
- Peak eosinophil count <15/HPF across all available esophagus levels at the final treatment period evaluation (Visit 4)
- Peak eosinophil count ≤1/HPF across all available esophagus levels at the final treatment period evaluation (Visit 4)
- Change from baseline in the peak eosinophil count to the final treatment period evaluation (Visit 4) for each available esophageal level (proximal, mid-, and distal)
- Change from baseline in the histopathologic epithelial features combined total score (grade and stage) to the final treatment period evaluation (Visit 4)
- Dysphagia symptom response (binary response), defined as a ≥50% reduction in the DSQ combined score (questions 2+3), from baseline to the final treatment period evaluation (Visit 4)
- Change from baseline in the DSQ combined score (questions 2+3) over time including post baseline visits
- Cumulative distribution function curves for the change and the percent change in the DSQ score from baseline to the final treatment period evaluation (Visit 4)
- Overall binary response I, defined as a reduction in the DSQ score of ≥30% from baseline to the final treatment period evaluation (Visit 4) and a peak eosinophil count of ≤6/HPF across all esophageal levels at the final treatment period evaluation (Visit 4)
- Overall binary response II, defined as a reduction in the DSQ score of ≥50% from baseline to the final treatment period evaluation (Visit 4) and a peak eosinophil count of ≤6/HPF across all esophageal levels at the final treatment period evaluation (Visit 4)
- Change in the DSQ + pain score (questions 2+3+4) from baseline to the final treatment period evaluation (Visit 4)
- Change in the DSQ pain score (question 4) from baseline to the final treatment period evaluation (Visit 4)

The binary response endpoints will be analyzed using the same logistic model as the co-primary efficacy endpoints.

Continuous endpoints will be analyzed as a change from baseline using an ANCOVA model that includes treatment group and age group as factors and baseline score as a covariate.

The analyses for all secondary efficacy endpoints (including the key secondary efficacy endpoint) will be carried out using 2-sided tests at the 5% level of significance. For each of the secondary efficacy endpoints, the treatment difference, corresponding 95% CI for the difference, and treatment comparison p-value for testing the null hypothesis of zero treatment effect based on the final statistical model (ie, either logistic regression model or ANCOVA model) will be provided.

9.8.3 Exploratory Efficacy Endpoint

The exploratory endpoint that will be explored is the following:

[redacted]

9.9 Safety Analyses

Safety data will be presented for the safety set by treatment group.

The safety data collected at the baseline visit (Visit 1) or the last preceding visit if not collected at Visit 1 will be used as the baseline value for safety analyses.

TEAEs are defined as AEs that start or deteriorate on or after the first dose of investigational product (Visit 1) and no later than 3 days following the last dose of investigational product. However, for any subjects who die during the study (ie, the date of death is between the date of first dose of investigational product and the date of study discontinuation entered by the site, inclusive), all AEs (including those resulting in death) that occur during the study will be considered as TEAEs irrespective of the last dose and will be included in the TEAE summaries.

AEs will be coded using MedDRA. The number of events, incidence, and percentage of TEAEs will be calculated overall by system organ class (SOC), preferred term (PT), and treatment group. TEAEs will be further summarized by severity and relationship to investigational product. AEs related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.

Safety parameters will include monitoring of AEs, physical examinations, stadiometry, vital signs (temperature, systolic and diastolic blood pressure, pulse, and respiratory rate), weight and height assessments, DXA scans for BMD and body composition measurements (for adolescents aged 11-17 years, inclusive), clinical laboratory tests (hematology, chemistry, urinalysis; serum pregnancy test, if appropriate), and ACTH stimulation tests. To account for the effects of puberty in adolescent subjects (11-17 years of age, inclusive), BMD z-scores will be adjusted for height z-scores using the Bone Mineral Density in Childhood Study calculator (http://www.bmdcspublic.com). Safety parameters will be descriptively summarized by treatment group at baseline and for each post-baseline visit.

9.10 Other Analyses

9.10.1 Health-related Quality-of-life Analyses

The health economics and outcomes research endpoints that will be explored are the following:

- EoE-QoL-A Questionnaire (Taft et al., 2011)
- EQ-5D (EQ-5D-3L or EQ-5D-Y, according to subject's age)
- PedsQL-EoE

The sub-modules of the EoE-QoL-A and PedsQL-EoE will be assessed in addition to the overall score with a focus on emotional and physical elements. For all HRQoL analyses, change from baseline to the final treatment period evaluation (Visit 4) will be assessed.

9.10.2 Pharmacokinetic Analyses

Pharmacokinetic parameters will be determined from the plasma concentration-time data for budesonide by non-compartmental analysis.

The pharmacokinetic endpoints will include but not be limited to those listed in Table 9-2.

Table 9-2: Pharmacokinetic Parameters

Parameter	Definition
$AUC_{0\text{-}tau}$	Area under the curve for the defined interval between doses
C_{max}	Maximum concentration occurring at t_{max}
t_{max}	Time of maximum observed concentration sampled during a dosing interval

Summary statistics (number of observations, mean, standard deviation, coefficient of variation, median, maximum, minimum, and geometric mean) will be determined for all pharmacokinetic parameters by overall and by week. Plasma concentrations at each nominal sampling time will also be summarized using descriptive statistics.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and its updates, and local ethical and legal requirements.

The name and address of each third-party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and CRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied to the CRO as necessary.

10.1.3 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.4 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the community guideline on GCP. This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance.

10.1.5 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study, which has been posted to a designated public website, will be updated accordingly.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub-investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal investigator is appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

Electronic CRFs are supplied by the CRO and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto CRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Case report forms must be completed by the investigator or designee as stated in the site delegation log.

All data from the investigator will have separate source documentation; no data will be recorded directly onto the CRF.

All data sent to the sponsor must be endorsed by the investigator.

The data from the central pathologist will be recorded directly onto paper CRFs.

The clinical research associate (CRA)/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include but are not limited to subject's medical file, original clinical laboratory reports, and histology and pathology reports.

All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and have direct access to original source records relevant to this study, regardless of media.

The CRA/study monitor (and auditors, IRB/EC, or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays, etc.).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent (or assent as applicable for subjects <18 years of age) from all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally authorized representative, as applicable, is requested to sign and date the subject's informed consent form or a certified translation, if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

Within the source documents, site personnel should document instruction of and understanding by the parent/legally authorized representative/caregiver of the safe, responsible storage and administration of investigational product to the study subject.

The principal investigator provides the sponsor with a copy of the consent form consent (or assent as applicable for subjects <18 years of age) that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB's/EC's written favorable opinion/approval of these documents must be provided to the sponsor, prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information, and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

For sites within the EU, the applicant for an EC opinion can be the sponsor or the investigator or, for multicenter studies, the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent (or assent as applicable for subjects <18 years of age) documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the CRO has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; for sites within the EU, this can be done by the sponsor or the investigator or, for multicenter studies, the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with HIPAA of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the CRO/sponsor.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market SHP621; national or local regulatory authorities; and the IRBs/ECs which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (eg, to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to and used in other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purposes of any such transfer would include supporting regulatory submissions, conducting new data analyses to publish or present the study results, or answering questions asked by regulatory or health authorities.

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (eg, Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2-4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral, or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish, and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single-site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors current standards. Participation as an investigator does not confer any rights to authorship of publications.

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12. APPENDICES

Appendix 1 Protocol History

Document	Date	Global/Country/Site Specific
Protocol Amendment 1	16 Dec 2015	Global
Original Protocol	31 Aug 2015	Global

Appendix 2 Scales and Assessments

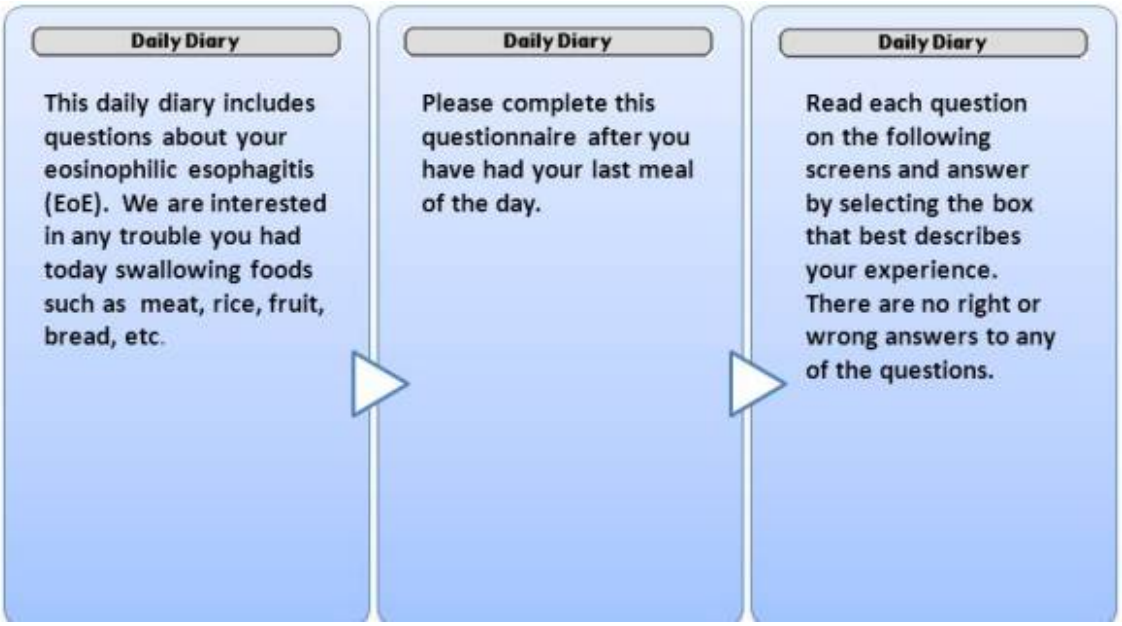
The following scales/assessments will be utilized in this study:

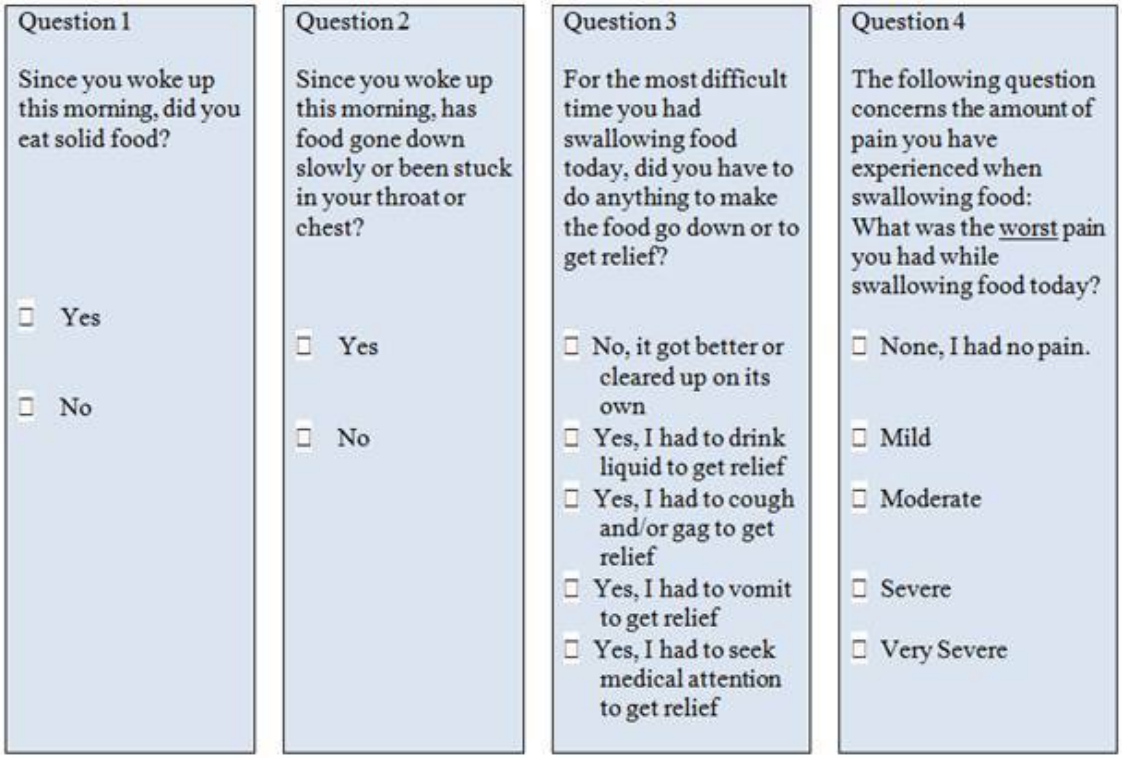
Full Title of Scale/Assessment	Completed By
DSQ	Subject
EQ-5D-3L (for subjects ≥18 years) EQ-5D-Y (for subjects 11-17 years of age, inclusive)	Subject
PedsQL-EoE (subjects 11-17 years of age, inclusive)	Subject and parent or legal guardian
EoE-QoL-A (subjects ≥18 years of age)	Subject
PGI-S	Subject
Tanner Staging Assessment (for subjects 11-17 years of age, inclusive)	Site
EREFS	Site

Abbreviations: DSQ=Dysphagia Symptom Questionnaire; EoE-QoL-A=Adult Eosinophilic Esophagitis Quality of Life; EQ-5D=EuroQol; EREFS=EoE Endoscopic Reference Score; PedsQL-EoE=Pediatric Quality of Life Inventory – EoE; PGI-S=Patient Global Impression of Severity

A separate master file containing each scale/assessment listed above will be provided to the site. Updates to scales/assessments during the study (if applicable) will be documented in the table above, and a new master file containing the revised scale/assessment will be provided to the site.

Appendix 3 Dysphagia Symptom Questionnaire ePRO for EoE





Appendix 4 Patient Global Impression of Severity

How would you rate the overall severity of your dysphagia (difficulty swallowing) over the past 7 days?

Rating	Description
0	No dysphagia
1	Mild dysphagia
2	Moderate dysphagia
3	Severe dysphagia
4	Very severe dysphagia

Appendix 5 Biosciences Generic Clinical Protocol Insert

Blood Sample Collection

Blood samples will be collected at the times specified in Table 1-1 to measure plasma concentrations of budesonide. Potential metabolites may also be determined as appropriate.

Blood samples 4 mL for pharmacokinetic analysis will be drawn by in-dwelling catheters or direct venipuncture into K2EDTA tubes, capped and mixed by inversion (x3), and chilled immediately on crushed ice. The actual time that the sample was obtained will be recorded in the subject's source document and on the appropriate CRF page. After applying a tourniquet, venous blood will be drawn with a disposable needle. If a catheter is used, the first milliliter of blood on each sampling occasion will be discarded. Saline can be used to keep catheters patent.

1.1 Blood/Plasma Sample Handling

Samples should be kept on crushed ice until plasma is separated as soon as possible after collection within <15 minutes, unless advised otherwise by refrigerated centrifugation (4°C, 1500 rpm 15 minutes). The separated plasma will be decanted into appropriately labeled polypropylene tubes via a plastic pipette. All samples will be stored at approximately -20°C or colder and the freezer temperature will be controlled, monitored, and recorded during the storage period until they are transferred in the frozen state to a designated bioanalytical contract laboratory. Samples will remain frozen at -20°C or colder until analysis.

Plasma sample tubes for bioanalysis must be freezer-safe and identified with freezer-safe labels provided by the central laboratory. The labels will contain the following information:

- Study number
- Subject identifier (randomization number)
- Matrix identifier (plasma)
- Visit
- Nominal time

1.2 Shipment of Plasma Samples

Plasma samples should be double-bagged to contain leaks and packed with a sufficient quantity of dry ice to ensure that they remain frozen for at least 72 hours to allow for delays in shipment. All applicable shipping regulations must be followed. Shipments should be scheduled so that no samples arrive on the weekend and should be shipped Monday to Wednesday only.

Plasma samples, along with the corresponding documentation, will be shipped to:

PPD

2 Tesseneer Drive

Highland Heights, KY 41076, USA

Email: [redacted]

Phone: [redacted] **or** [redacted], [redacted]

Fax: [redacted]

Plasma samples will be stored nominally at -20°C prior to and after analysis at Covance until their disposal is authorized by Shire.

1.3 Assay Methodology

Drug analysis will be performed at Covance under the guidance of the NCE group at Shire. Plasma sample analysis will be performed according to the bioanalytical study plans prepared for the study.

Plasma samples will be analyzed at Covance for budesonide using the most current validated bioanalytical method.

In addition, selected plasma samples may be used to investigate incurred sample reproducibility (full details will be described in the bioanalytical study plan). The presence of other metabolites or artifacts may be monitored or quantified as appropriate.

Raw data will be stored in the archives at Covance.

PROTOCOL: SHP621-301

TITLE:	Oral Budesonide Suspension (OBS) in Adolescent and Adult Subjects (11 to 55 Years of Age, Inclusive) with Eosinophilic Esophagitis: A Phase 3 Randomized, Double-blind, Placebo-controlled Study
DRUG:	SHP621, oral budesonide suspension (OBS)
IND:	103,173
EUDRACT NO.:	Non-EUDRACT
SPONSOR:	Shire ViroPharma, Incorporated (Shire) 300 Shire Way, Lexington, MA 02421 USA [redacted]
PROTOCOL HISTORY:	Original Protocol: 31 Aug 2015 Protocol Amendment 1: 17 Dec 2015 Protocol Amendment 2: 26 Jan 2018

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature:	Date:
[redacted] MD [redacted] Clinical Development	

Acknowledgement
I have read this protocol for Shire Study SHP621-301.

Title: Oral Budesonide Suspension (OBS) in Adolescent and Adult Subjects (11 to 55 Years of Age, Inclusive) with Eosinophilic Esophagitis: A Phase 3 Randomized, Double-blind, Placebo-controlled Study

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: _____
(please hand print or type) _____
_____
_____

Signature: _____ **Date:** _____

SUMMARY OF CHANGES FROM PREVIOUS VERSION

The SHP621-301 protocol is amended to address the following items:

- Increase the number of enrolled subjects to allow an adequate number of subjects to enroll in the treatment extension study (SHP621-302).
- Administrative changes issued since Protocol Amendment 1.

Additional edits, as captured in the below table, were made to Protocol Amendment 2 to improve the clarity of the protocol and/or correct minor inconsistencies. Note that correction of typos and grammatical errors are not captured in the below table.

New text indicated in bold; deleted text indicated in strikethrough.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date** **26 Jan 2018**	**Global Amendment**
Description of Change		**Section(s) Affected by Change**
Revised text to reflect increased enrollment of subjects in this study (from 300 to 420) to allow an adequate number of subjects to enroll in the treatment extension study. Updated number of subjects to be randomized (from 152 to 204 for OBS; from 76 to 102 for placebo) to reflect increase enrollment of subjects in this study.		Study Synopsis: Number of subjects Section 3.1: Study Design and Flow Chart
Approximately ~~60~~ **70** sites in North America		Study Synopsis: Sites and Region(s) Section 3.3; Sites and Regions
Oct 2015 to ~~July 2018~~ **Nov 2018**		Study Synopsis: Study Period (Planned)
14. Subject has **a potentially serious** acute or chronic viral infection or immunodeficiency condition, including tuberculosis, fungal, bacterial, viral/parasite infection, ocular herpes simplex, herpes esophagitis, or chicken pox/measles.		Study Synopsis: Exclusion Criteria; Section 4.2: Exclusion Criteria
20. Subject has taken part **and received intervention** in an interventional study related to EoE **(except for an interventional study for a topical swallowed steroid)** within 6 months prior to the screening visit (Visit -1), or any investigational study within 30 days prior to the screening visit (Visit -1). **An investigational topical swallowed steroid must have been discontinued at least 30 days prior to the screening visit (Visit -1).**		Study Synopsis: Exclusion Criteria; Section 4.2: Exclusion Criteria
Pharmacokinetic parameters will be determined from the plasma concentration-time data for budesonide by non-compartmental analysis~~.~~ **for subjects who provide sufficient numbers of intensive PK samples**. **For all subjects who provide PK samples (ie, limited or intensive samples) population PK analysis will be conducted.** **A report for the population PK analysis will be provided**		Study Synopsis: Endpoints and Statistical Analysis; Pharmacokinetic Endpoints Section 9.10.2: Pharmacokinetic Analysis Section 9.10.2: Pharmacokinetic

separately from the clinical study report (CSR).	Analysis
Height measurements for adolescent subjects 11-17 years of age, inclusive, should be measured in triplicate.	Table 1-1; Schedule of Assessments, footnote b Section 7.2.2.2; Physical Examination (Including Height and Weight)
Weight measurements for adolescent subjects (11-17 years, inclusive) should be measured in duplicate.	Table 1-1; Schedule of Assessments, footnote c Section 7.2.2.2; Physical Examination (Including Height and Weight)
DSQ assessment includes completion of reports on DSQ handset (ie, eligibility reports and visit confirmations).	Table 1-1; Schedule of Assessments, footnote e
Blood samples for pharmacokinetic analysis ~~will~~ **can** be obtained ~~at the~~ **one time on any day starting 7 days after Visit 1** (Week ~~8 or~~ **5) and through Visit 4** (Week ~~12 visit~~ **16**). **PK samples should be drawn, ideally, at pre-dose, 0.5 and 1 hour post-dose, and** at ~~the following~~ **additional post-dose** time points: ~~pre-dose and at 0.5, 1~~**, if feasible** (2, 3, 4, 6, 8, and 12 hours post-dose).	Table 1-1, Schedule of Assessments, footnote k Section 7.1.3.2; Visits 2 and 3 (Weeks 8 and 12) Section 7.1.3.3; Visit 4 (Week 16)
Subjects cannot be rescreened once it is confirmed they do not meet inclusion/exclusion criteria unless the screen failure was due to a **temporary condition or incomplete information at the time of consent (Visit -1) that would make rescreening at a later date appropriate (eg,** concomitant medication that can be discontinued prior to rescreening; ~~those subjects may be rescreened~~. ~~Other,~~ **review of subject medical records provides new information with respect to the date of a prior esophageal dilation or diet change, or subject has a minor illness such as an upper respiratory or urinary tract infection). All** reasons for rescreening (ie, reasons unrelated to inclusion/exclusion criteria) must be discussed **and approved** prospectively with the medical monitor. Subjects who discontinue will not be replaced.	Section 3.1: Study Design and Flow Chart Section 7.1.1; Screening Period (Weeks -6 to 0)
• **Abstinence** • **Surgically sterile male partner** • **Stable oral contraceptives**	Section 4.4.1; Female Contraception
Medically important events that in the opinion of the investigator or medical monitor would compromise the subject's ability to safely continue in the study, including but not limited to **severe signs and symptoms of EoE, such as an** esophageal stricture requiring dilation ~~and/or worsening signs and symptoms of EoE (eg,~~ weight loss ~~or increased~~ **due to severe** dysphagia~~)~~, **and/or upper GI bleed** would be considered a treatment failure and result in withdrawal of the subject from the study.	Section 4.5.1; Subject Withdrawal Criteria
6. Maintenance immunotherapy (allergy shots **or sublingual immunotherapy**)	Section 5.2.1; Permitted Treatment
During the ~~visit~~ **day** where the pharmacokinetic blood samples are collected ~~(Visit 2 or Visit 3)~~, subjects will be required to eat a moderate-fat breakfast on-site	Section 6.2.3; Dosing
• ~~Review~~ **Confirm** DSQ dysphagia episodes and compliance **by completing baseline screening eligibility report on DSQ device**;	Section 7.1.2.1; Placebo Lead-in Visit (Visit 0) Section 7.1.3.1; Baseline Visit

	(Visit 1)
• Review DSQ ~~dysphagia episodes~~compliance **and complete visit confirmation on the DSQ device**;	Section 7.1.3.2; Visits 2 and 3 (Weeks 8 and 12) Section 7.1.3.3; Visit 4 (Week 16)
• **If an esophageal dilatation is performed at Visit 4 (treatment failure), subjects will not be eligible to participate in the treatment extension study.** Following all **safety** blood draws, subjects can eat breakfast and take their morning dose of investigational product if they are continuing in the treatment extension study **or staying in clinic for PK sampling (to be performed as described in Section 7.1.3.2 above).**	Section 7.1.3.3; Visit 4 (Week 16)
Subjects must fill out the DSQ at least ~~5~~ **4** or more days during a given week in order to be compliant. Protocol deviations will be documented for subjects who fail to complete the DSQ for ~~3~~ **4** or more days in a given week.	Section 7.2.1.2; Dysphagia Symptom Questionnaire
The original protocol noted that a total of 228 subjects (152 subjects randomized to OBS and 76 subjects randomized to placebo) are required to achieve 90% power at the significance level of 0.0499 (2-sided)… The overall study power for the co-primary endpoints ~~**will**~~ **was estimated to** be at least 85%. Therefore, approximately 228 (approximately 152:76 OBS and placebo subjects, respectively) ~~will~~ **were to** be randomized ~~to~~ **in** the study to allow for a loss of approximately 5% of subjects due to dropouts or invalid data. **In this protocol amendment, in order to ensure that a sufficient number of subjects will complete this study and enroll in the treatment extension study, up to approximately 420 subjects will be enrolled in the placebo lead-in period to allow for approximately 306 subjects to be randomized into the double blind period of this study (approximately 204:102 OBS and placebo subjects, respectively). With a total of 306 randomized subjects in this study, using the same assumptions for the co-primary endpoints and the dropout rate, the overall study power for the co-primary endpoints is estimated to be at least 95%.** **Rationale:** The sample size is increased to ensure that a sufficient number of subjects complete this study and enroll in the treatment extension study (SHP621-302). Approximately 200 subjects (65%) who are randomized in the SHP621-301 study are estimated to complete the SHP621-301 study and enroll in the treatment extension study.	Section 9.6; Sample Size and Power Considerations
Added text to clarify the retention period for laboratory samples (blood and urine).	Section 10.2.3.2; Recording, Access, and Retention of Source Data and Study Documents

See Appendix 1 for protocol history, including all amendments.

EMERGENCY CONTACT INFORMATION

In the event of an SAE, the investigator must fax or e-mail the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol within 24 hours to the Shire Global Drug Safety Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover). A copy of the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol must also be sent to the CRO medical monitor by fax or e-mail using the details below.

[redacted], MD

Email: [redacted]

Fax: [redacted]7

For protocol- or safety-related issues <u>during normal business hours (8am to 5 pm Eastern Standard Time)</u>, the investigator must contact the CRO medical monitor:

[redacted], MD

Phone: [redacted]

Mobile: [redacted]

Email: [redacted]

Fax: [redacted]

For protocol- or safety-related issues <u>outside of normal business hours</u>, the investigator must contact the CRO medical monitor:

[redacted], MD

Mobile: [redacted]

Email: [redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 8.

Please use the information below as applicable to report the Product Quality Complaint:

Origin of Product Quality Complaint	E-mail Address
North and South America	[redacted]
European Union and Rest of World	[redacted]

Telephone numbers (provided for reference if needed):

Shire, Lexington, MA (USA)
[redacted] or [redacted]

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ABBREVIATIONS

ACTH	adrenocorticotropic hormone
AE	adverse event
ANCOVA	analysis of covariance
Auc_{tau}	area under the curve for the defined interval between doses
β-hCG	beta-human chorionic gonadotropin
BMD	bone mineral density
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum concentration occurring at t_{max}
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CYP450 3A4	cytochrome P450 3A4
DSQ	Dysphagia Symptom Questionnaire
DXA (DEXA)	dual-energy X-ray absorptiometry
EC	ethics committee
EGD	esophagogastroduodenoscopy
EIS	external independent statistical
EMA	European Medicines Agency
EoE	eosinophilic esophagitis
EoE-QoL-A	Adult Eosinophilic Esophagitis Quality of Life
ePRO	electronic patient-reported outcome
EQ-5D-3L	EuroQol-5 Dimensions 3-level
EQ-5D	EuroQol
EQ-5D-Y	EuroQol 5 Dimensions Youth
EREFS	EoE Endoscopic Reference Score
ET	early termination
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDS	Global Drug Safety
HIPAA	Health Insurance Portability and Accountability Act

HPF	high-powered field
HRQoL	health-related quality of life
hs	at bedtime
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web-based response system
Med ID	medication identification
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
OBS	oral budesonide suspension
pc	after meals
PedsQL-EoE	Pediatric Quality of Life Inventory – EoE
PGI-S	Patient Global Impression of Severity
PP	per-protocol
PPI	proton pump inhibitor
PT	preferred term
qAM	every morning
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	statistical analysis system
SOC	system organ class
TEAE	treatment emergent adverse event
t_{max}	time of maximum observed concentration sampled during a dosing interval
UK	United Kingdom
US	United States

STUDY SYNOPSIS

Protocol number: SHP621-301	**Drug:** SHP621, oral budesonide suspension (OBS)
Title of the study: Oral Budesonide Suspension (OBS) in Adolescent and Adult Subjects (11 to 55 Years of Age, Inclusive) with Eosinophilic Esophagitis: A Phase 3 Randomized, Double-blind, Placebo-controlled Study	
Number of subjects (total and for each treatment arm): Approximately up to approximately 420 subjects will be enrolled into the placebo lead-in period to allow for approximately 306 subjects (approximately 204 and 102 per OBS and placebo treatment group, respectively) to be randomized into the double-blind treatment period.	
Investigator(s): Multicenter study	
Site(s) and Region(s): Approximately 70 sites in North America	
Study period (planned): Oct 2015 to Nov 2018	**Clinical phase:** 3

Objectives

Co-primary:

To demonstrate in a placebo-controlled trial that:

- OBS induces a histologic response (eosinophilic count ≤6/high-powered field [HPF]) in adolescent and adult subjects with eosinophilic esophagitis (EoE) over a 12-week course of therapy.
- OBS reduces dysphagia, as measured by the Dysphagia Symptom Questionnaire (DSQ), by at least 30% from baseline in adolescent and adult subjects with EoE over a 12-week course of therapy.

Key Secondary:

- OBS reduces dysphagia, as measured by the DSQ score from baseline to the final treatment period evaluation (Visit 4).

Secondary:

- To assess the response of endoscopically identified esophageal features to OBS as compared to placebo as measured by the EoE Endoscopic Reference Score (EREFS)
- To explore other responding criteria based on histology and DSQ
- To assess the impact of OBS on pain, as measured by the DSQ pain score
- To evaluate the safety and tolerability of OBS over a 12-week course of therapy
- To obtain OBS pharmacokinetic data in adult subjects with EoE

Exploratory:

Rationale:

Currently there is no approved medication for the treatment of EoE. This study is being conducted in order to provide safety and efficacy data demonstrating histologic response (as measured by eosinophilic count ≤6/HPF) and improvement in dysphagia symptoms (as measured by the DSQ) following 12 weeks of treatment with OBS in adolescent and adult subjects with EoE.

Investigational product, dose, and mode of administration

OBS will be administered in 10 mL at a concentration of 0.2 mg/mL (2 mg dose), twice daily (every morning [qAM] after meals [breakfast, pc] and at bedtime [hs]). The 0.2 mg/mL concentration of OBS and dosing regimens were selected for use in this Phase 3 study based on the results of Study MPI 101-06, a Phase 2 study in 93 adolescents and adult subjects with EoE and symptoms of dysphagia. Subjects were treated in Study MPI 101-06 with 2 mg OBS twice daily to investigate the co-primary endpoints of histologic response (defined as ≤6 eosinophils/HPF) and reduction in DSQ score from baseline to Week 12 of treatment. For the current study, the investigational product will be supplied in amber glass, multi-dose bottles with child-resistant caps and refrigerated throughout the study (in the clinic and subject's home). Each bottle will contain approximately 210 mL of suspension with a budesonide concentration of 0.2 mg/mL, or 0.00 mg/mL (matching placebo).

After the screening period, eligible subjects will enter a 4-week single-blind placebo lead-in period and will receive 10 mL of OBS placebo twice daily (qAM, pc, and hs). At the end of the placebo lead-in period, eligible subjects will enter a 12-week double-blind treatment period (baseline visit, Visit 1) and will be randomized to 1 of 2 treatment groups in a 2:1 ratio (approximately 152 and 76 subjects for OBS and placebo twice daily treatment groups, respectively). Subjects will receive oral administration of 10 mL of 2 mg investigational product twice daily (qAM, pc, and hs; 4 mg/day total), with no ingestion of food or liquids permitted for 30 minutes after study drug administration:

- Placebo twice daily group: placebo qAM (pc) and hs
- OBS twice daily group: OBS 10 mL of 0.2 mg/mL (2 mg total) qAM (pc) and hs

The total daily dose of budesonide will be 0 mg for each subject in the placebo group and 4 mg for each subject in the OBS treatment group (Table 1).

Table 1: Total Daily Dose of OBS

Dose Group	OBS Concentration (mg/mL)	Volume per Dose	Morning Dose (qAM, pc)	Evening Dose (hs)	Total Dose/Day (mg/day)
Placebo	0.0	10 mL	0.0 mg	0.0 mg	0.0
OBS	0.2	10 mL	2.0 mg	2.0 mg	4.0

hs=at bedtime; OBS=oral budesonide suspension; pc=after meals; qAM=every morning

At the end of the 12-week double-blind treatment period (Visit 4), subjects who complete the study will have the opportunity to enroll in the treatment extension study. These subjects will continue on the blinded assigned treatment for 2-4 weeks as part of the screening prior to enrolling into the treatment extension study.

Methodology:

This is a Phase 3, randomized, double-blind, multicenter, parallel-group, placebo-controlled study to evaluate the efficacy, safety, and tolerability of twice daily administration of OBS (qAM, pc, and hs) in adolescents and adults aged 11-55 years, inclusive, with EoE and dysphagia.

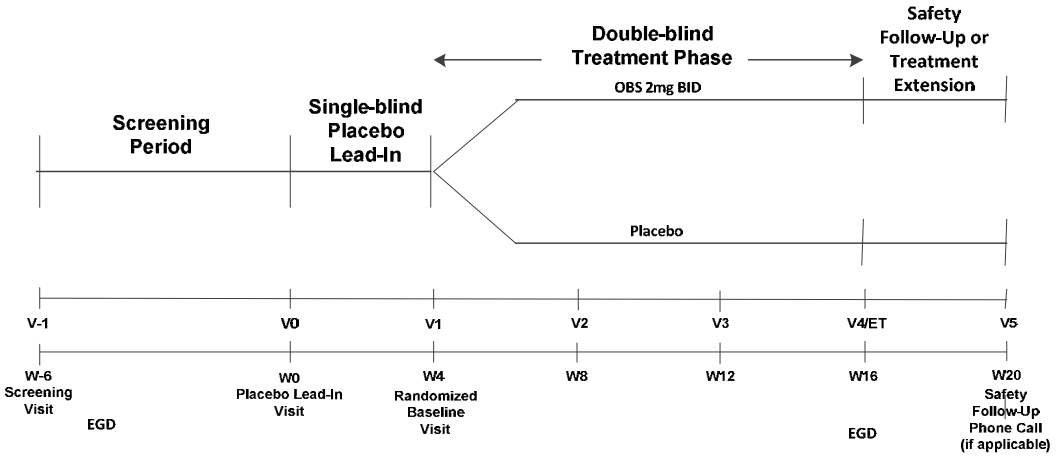
This study will comprise 3 periods: a 3- to 6-week screening period, 4-week single-blind placebo lead-in period, and 12-week double-blind treatment period (Figure 1). The original protocol (dated 31 Aug 2015) planned for approximately 300 subjects to be enrolled into the placebo lead-in period to

allow for approximately 228 subjects to be randomized in a 2:1 ratio (approximately 152 and 76 per OBS and placebo treatment group, respectively) into the double-blind treatment period. Under this protocol amendment, up to 420 subjects will be enrolled in the double-blind period to allow for approximately 306 subjects to be randomized 2:1 in the double blind period (approximately 204 and 102 per OBS and placebo group, respectively), in order to provide for at least 200 subjects who complete this study and enroll in the successive treatment extension study (SHP621-302). The randomization will be performed centrally and stratified by age group (2 strata total: <18 years or ≥18 years) and diet restriction for EoE or other health-related conditions (no diet restriction or any diet restriction). The stratification by age will ensure a minimum of 40 subjects in the pediatric group (11-17 years, inclusive). The stratification by age and diet will ensure balance between treatment groups for the respective stratification factors.

Subjects who sign informed consent (or assent as applicable for subjects <18 years) will be screened (Visit -1). Subjects who meet eligibility criteria at the screening visit (Visit -1) and at the placebo lead-in visit (Visit 0) will enter the 4-week placebo lead-in period to assess their ability to comply with twice daily medication administration and assess whether there is a placebo response. Upon completion of the placebo lead-in period, subjects will return for the baseline visit (Visit 1) to confirm eligibility. Eligible subjects will be randomized 2:1 into the double-blind treatment period and will be evaluated for efficacy and safety at Weeks 8, 12, and 16 (Visits 2-4). Subjects who fail to meet all eligibility criteria at Visits -1, 0, or 1 will be considered screen failures. Subjects cannot be rescreened once it is confirmed they do not meet inclusion/exclusion criteria unless the screen failure was due to a temporary condition or incomplete information at the time of consent (Visit -1) that would make rescreening at a later date appropriate (eg, concomitant medication that can be discontinued prior to rescreening, review of subject medical records provides new information with respect to the date of a prior esophageal dilation of diet change, or subject has a minor illness such as an upper respiratory or urinary tract infection). All reasons for rescreening (ie, reasons unrelated to inclusion/exclusion criteria) must be discussed and approved prospectively with the medical monitor. Subjects who discontinue will not be replaced.

Subjects will be required to visit the site up to 6 times over up to a 22-week period. A safety follow-up phone call will occur 4 weeks following the last dose of investigational product for subjects who discontinue prematurely during the double-blind treatment period or who do not enroll in the treatment extension study.

Figure 1: Study Design Flow Chart



BID=twice daily; EGD=esophagogastroduodenoscopy; ET=early termination; OBS=oral budesonide suspension

Inclusion and exclusion criteria:

Inclusion Criteria:

The subject will not be considered eligible for the study without meeting all of the following criteria (including test results):

1. Subject is able to provide written informed consent (subject, parent or legal guardian and, as appropriate, subject assent) to participate in the study before completing any study-related procedures.
2. Subject is male or female aged 11-55 years, inclusive, at time of consent.
3. Subject has histologic evidence of EoE with a peak eosinophil count of ≥15/HPF, from 2 of 3 (proximal, mid-, and/or distal) levels of the esophagus at the screening endoscopy.
4. Subject has a history of clinical symptoms of esophageal dysfunction (eg, eating problems, abdominal pain, heartburn, dysphagia, vomiting, food impaction, weight loss) intermittently or continuously at screening (Visit -1).
5. Subject must have experienced dysphagia (response of "yes" to question 2 on DSQ) on a minimum of 4 days and completed the DSQ on ≥70% of days in any 2 consecutive weeks of the screening period and in the 2 weeks prior to the baseline visit (Visit 1).
6. Subject must not have proton pump inhibitor (PPI)–responsive EoE based on esophageal biopsies performed after the patient 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). If PPI responsiveness was excluded by a previous EGD and biopsy, the historical EGD and biopsy must have been performed after the patient had been on a minimum of 6 weeks of high-dose PPI therapy.
7. Subject will be on a stable (no changes) diet ≥3 months prior to the screening visit (Visit -1).
8. 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.
9. All female subjects must have a negative serum pregnancy test (beta-human chorionic gonadotropin [β-hCG]) prior to enrollment into the study. Females of childbearing potential must agree to continue acceptable birth control measures (eg, abstinence, stable oral contraceptives, or double-barrier methods) throughout study participation.
10. Subject is willing and has an understanding and ability to fully comply with study procedures and restrictions defined in this protocol.

Exclusion Criteria:

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Subject has any condition or abnormality (including laboratory abnormalities), current or past, that, in the opinion of the principal investigator or medical monitor, would compromise the safety of the subject or interfere with or complicate the assessment of signs or symptoms of EoE. Such conditions may include psychiatric problems; neurologic deficits or disease; developmental delay; cardiovascular, metabolic, or pulmonary disease; or previous gastroesophageal surgery. These should be discussed with the medical monitor.
2. 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 (eg, Rituxan) within 3 months of the qualifying EGD should be reviewed with the medical monitor.
3. 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 (≤7 days) 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.

4. Subject has been on inhaled steroids and not on stable treatment for ≥3 months prior to screening visit (Visit -1). Subjects on inhaled steroids need to stay on stable treatment during study participation. Subject has been on intranasal steroids and has not been on stable treatment for a minimum of 4 weeks prior to the qualifying EGD. After the qualifying EGD, subjects with seasonal allergic rhinitis may resume (or discontinue) intranasal corticosteroids based on the subject's usual treatment regimen for allergy season.
5. Subject has initiated, discontinued, or changed dosage regimen of PPIs, H2 antagonists, antacids, 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 EGD and baseline visit (Visit 1), or anticipates changes in the use of such medications during the treatment period.
6. Subject has been using cytochrome P450 3A4 inhibitors (eg, ketoconazole, grapefruit juice) within the 2 weeks prior to the baseline visit (Visit 1) or within 5 half-lives (whichever is greater) or anticipates using such medications during the treatment period.
7. 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 (eg, with an insertion tube diameter of >9 mm).
8. Subject is on a pure liquid diet or the 6-food elimination diet.
9. Subject has had an esophageal dilation within the 3 months prior to screening (Visit -1).
10. Subject has presence of esophageal varices at the screening endoscopy.
11. 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.
12. Subject has other diseases causing or associated with EoE, including hypereosinophilic syndrome, collagen vascular disease, vasculitis, achalasia, or parasitic infection.
13. Subject has current evidence of oropharyngeal or esophageal candidiasis.
14. Subject has a potentially serious acute or chronic viral infection or immunodeficiency condition, including tuberculosis, fungal, bacterial, viral/parasite infection, ocular herpes simplex, herpes esophagitis, or chicken pox/measles.
15. 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).
16. Subject has evidence of active infection with *Helicobacter pylori.*
17. 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).
18. Subject is female and pregnant or nursing.
19. Subject has a history of intolerance, hypersensitivity, or idiosyncratic reaction to budesonide (or any other corticosteroids) or to any other ingredients of the investigational product.
20. Subject has taken part and received intervention in an interventional study related to EoE (except for an interventional study for a topical swallowed steroid) within 6 months prior to the screening visit (Visit -1), or any investigational study within 30 days prior to the screening visit (Visit -1). An investigational topical swallowed steroid must have been discontinued at least 30 days prior to the screening visit (Visit -1).

21. Subject has a history or high risk of noncompliance with treatment or regular clinic visits.
22. Subject has previously completed, discontinued, or withdrawn from this study.
23. Subject has participated in a previous clinical study involving OBS (SHP621).
24. Subject anticipates using sucralfate during the study.

Maximum duration of subject involvement in the study:

- Planned duration of screening period: 3-6 weeks
- Planned duration of placebo lead-in period: 4 weeks
- Planned duration of treatment period: 12 weeks
- Planned duration of safety follow-up period: 4 weeks

Endpoints and statistical analysis:

Subject Populations

- The **safety set** will include all subjects who receive at least 1 dose of any double-blind investigational product.
- The **intent-to-treat (ITT) set** will include all randomized subjects. Subjects will be analyzed according to their assigned treatment, regardless of the treatment actually received.
- The **full analysis set (FAS)** will include all randomized subjects who received at least 1 dose of a double-blind investigational product and have both an evaluable post-baseline biopsy in the treatment period (ie, peak eosinophil count is reported for at least 2 esophageal levels) and a post-baseline DSQ score.
- The **per-protocol (PP) set** will include all subjects in the FAS excluding subjects with protocol violations. The PP set will be identified prior to unblinding the treatment assignments by a team consisting of, at a minimum, a physician and a statistician from Shire.
- The **pharmacokinetic set** will include all subjects in the safety set for whom the primary pharmacokinetic data are considered sufficient and interpretable.

Primary Efficacy Endpoints

The co-primary efficacy endpoints are the following:

- Histologic response, defined as a peak eosinophil count of ≤6/HPF across all available esophageal levels at the final treatment period evaluation (Visit 4)
- Dysphagia symptom response, defined as ≥30% reduction in the DSQ combined score (questions 2+3) from baseline to the final treatment period evaluation (Visit 4)

Key Secondary Efficacy Endpoint

- Change in DSQ combined score (questions 2+3) from baseline to the final treatment period evaluation (Visit 4)

Secondary Efficacy Endpoints

- Change in total endoscopy score, as measured by the EREFS classification, from baseline to the final treatment period evaluation (Visit 4)
- Peak eosinophil count <15/HPF across all available esophagus levels at the final treatment period evaluation (Visit 4)
- Peak eosinophil count ≤1/HPF across all available esophagus levels at the final treatment period evaluation (Visit 4)

- Change from baseline in the peak eosinophil count to the final treatment period evaluation (Visit 4) for each available esophageal level (proximal, mid-, and distal)
- Change from baseline in the histopathologic epithelial features combined total score (grade and stage) to the final treatment period evaluation (Visit 4)
- Dysphagia symptom response (binary response), defined as a ≥50% reduction in the DSQ combined score (questions 2+3), from baseline to the final treatment period evaluation (Visit 4)
- Change from baseline in the DSQ combined score (questions 2+3) over time including post-baseline visits
- Cumulative distribution function curves for the change and the percent change in the DSQ score from baseline to the final treatment period evaluation (Visit 4)
- Overall binary response I, defined as a reduction in the DSQ score of ≥30% from baseline to the final treatment period evaluation (Visit 4) and a peak eosinophil count of ≤6/HPF across all esophageal levels at the final treatment period evaluation (Visit 4)
- Overall binary response II, defined as a reduction in the DSQ score of ≥50% from baseline to the final treatment period evaluation (Visit 4) and a peak eosinophil count of ≤6/HPF across all esophageal levels at the final treatment period evaluation (Visit 4)
- Change in the DSQ + pain score (questions 2 +3+4) from baseline to the final treatment period evaluation (Visit 4)
- Change in the DSQ pain score (question 4) from baseline to the final treatment period evaluation (Visit 4)

Exploratory Efficacy Endpoint

[redacted]

Safety Endpoints

Safety parameters will include monitoring of adverse events (AEs), physical examinations, stadiometry, vital signs (temperature, systolic and diastolic blood pressure, pulse, and respiratory rate), weight and height assessments, dual-energy X-ray absorptiometry (DXA) scans for bone mineral density (BMD) and body composition measurements (for adolescents aged 11-17 years, inclusive), clinical laboratory tests (hematology, chemistry, urinalysis; serum pregnancy test, if appropriate), and adrenocorticotropic hormone (ACTH) stimulation tests. To account for the effects of puberty in adolescent subjects (11-17 years, inclusive), BMD z-scores will be adjusted for height z-scores using the Bone Mineral Density in Childhood Study calculator (BMDCS 2015) (http://www.bmdcspublic.com).

Health Economics and Outcomes Research Endpoints

- Change in Adult Eosinophilic Esophagitis Quality of Life (EoE-QoL-A) score from baseline to the final treatment period evaluation (Visit 4)
- Change in EuroQol (EQ-5D; EuroQol-5 Dimensions 3-level [EQ-5D-3L] or EuroQol-5 Dimensions Youth [EQ-5D-Y], according to subject's age) score from baseline to the final treatment period evaluation (Visit 4)
- Change in Pediatric Quality of Life Inventory – EoE (PedsQL-EoE) score from baseline to the final treatment period evaluation (Visit 4)

Pharmacokinetic Endpoints

Pharmacokinetic parameters will be determined from the plasma concentration-time data for budesonide by non-compartmental analysis for subjects who provide sufficient numbers of intensive

PK samples. For all subjects who provide PK samples (ie, limited or intensive samples) population PK analysis will be conducted. The pharmacokinetic parameters will include, but not be limited to:

AUC_{tau}	Area under the curve for the defined interval between doses
C_{max}	Maximum concentration occurring at t_{max}
t_{max}	Time of maximum observed concentration sampled during a dosing interval

Statistical Methodology for Primary Efficacy Endpoint

The co-primary efficacy endpoints will be analyzed based on the ITT set. Each of the co-primary efficacy endpoints is a binary response (ie, responders vs non-responders); the endpoint will be analyzed using the Cochran-Mantel-Haenszel (CMH) test adjusting for age group (either <18 years or ≥18 years) and diet restriction for EoE or other health-related conditions (no diet restriction or any diet restriction) . The adjusted odds ratio of being a responder on each of the co-primary endpoints for the OBS 2 mg twice daily group vs placebo group and associated 95% confidence interval (CI) will be provided. Subjects who withdraw without providing efficacy data at the final treatment period evaluation (Visit 4, Week 16) will be classified as non-responders in the primary efficacy analysis.

Additionally, the proportion of responders based on each of the co-primary endpoints for each treatment group will be summarized and their respective 95% CI will be reported. The difference in the proportion of responders between the 2 treatment groups and the corresponding 95% CI will also be summarized.

The following sensitivity and supportive analyses will be performed for the co-primary to evaluate the robustness of the results from the primary analysis methods:

- Each of the co-primary efficacy endpoints will be analyzed using a logistic regression with the effects of treatment group, age group (either <18 years or ≥18 years) and diet restriction for EoE or other health-related conditions (no diet restriction or any diet restriction). The odds ratio of being a responder on each of the co-primary endpoints for the OBS 2 mg twice daily group vs placebo group and associated 95% CI will be estimated from the final model. Subjects who withdraw without providing efficacy data at the final treatment period evaluation (Visit 4, Week 16) will be classified as non-responders in the primary efficacy analysis.
- Analyses will be repeated using the FAS and the PP set.
- Analyses will be repeated by considering subjects who withdraw without providing efficacy data at the final treatment period evaluation (Visit 4) will be classified as responders.

Statistical Methodology for Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is defined as the change in the DSQ combined score (questions 2+3) from baseline to the final treatment period evaluation (Visit 4). The change from baseline DSQ score at the final treatment period evaluation (Visit 4) will be analyzed using an analysis of covariance (ANCOVA) model with treatment group and age group as factors and the baseline DSQ score as a continuous covariate.

Statistical Methodology for Secondary Efficacy Endpoints

Secondary subjective efficacy endpoints that are defined as:

- Binary response endpoints will be analyzed using the same logistic model as the co-primary efficacy endpoints.
- Continuous endpoints will be analyzed as a change from baseline using an ANCOVA model that includes treatment group and age group as factors and baseline score as a continuous covariate.

The analyses for all secondary efficacy endpoints (including the key secondary efficacy endpoint) will be carried out using 2-sided tests at the 5% level of significance. For each of the secondary efficacy

endpoints, the treatment difference, corresponding 95% CI for the difference, and treatment comparison p-value for testing the null hypothesis of zero treatment effect based on the final statistical model (ie, either logistic regression model or ANCOVA model) will be provided.

Statistical Methodology for Safety Endpoints

All safety measures, including AEs, physical examination, stadiometry, vital signs (temperature, systolic and diastolic blood pressure, pulse, and respiratory rate), weight and height assessments, DXA scans for BMD and body composition measurements (for adolescents aged 11-17 years, inclusive), clinical laboratory results (hematology, chemistry, urinalysis; serum pregnancy test, if appropriate), and ACTH stimulation will be descriptively summarized by treatment group at baseline and for each postbaseline visit.

The number and percent of subjects with treatment emergent adverse events (TEAEs) will be presented. TEAEs are defined as AEs that start or deteriorate on or after the date of the first dose of investigational product and no later than 3 days following the last dose of investigational product. However, for any subjects who die during the study (ie, the date of death is between the date of first dose of investigational product and the date of study discontinuation entered by the site, inclusive), all AEs (including those resulting in death) that occur during the study will be considered as TEAEs irrespective of the last dose and will be included in the TEAE summaries.

Statistical Methodology for Pharmacokinetic Endpoint(s)

Summary statistics (number of observations, mean, standard deviation, coefficient of variation, median, maximum, minimum, and geometric mean) will be determined for all pharmacokinetic parameters by overall and by week. Plasma concentrations at each nominal sampling time will also be summarized using descriptive statistics.

Sample Size Justification

Based on at least a 30-percentage-point reduction in DSQ score, there is an expected difference between treatment response proportions of 69% and 45% in the OBS 2 mg twice daily (qAM, pc, and hs) and placebo groups, respectively. The original protocol noted that a total of 228 subjects (152 subjects randomized to OBS and 76 subjects randomized to placebo) are required to achieve 90% power at the significance level of 0.0499 (2-sided) using a 2-group chi-square test with unequal allocation 2:1 to treatment groups (OBS 2 mg twice daily and placebo). With the specified number of subjects per treatment group, the study will be powered at 99% assuming histological response proportions of 40% and 3% in the OBS 2 mg twice daily and placebo groups, respectively. The overall study power for the co-primary endpoints was estimated to be at least 85%. Therefore, approximately 228 (approximately 152:76 OBS and placebo subjects, respectively) were to be randomized in the study to allow for a loss of approximately 5% of subjects due to dropouts or invalid data. Expected response and dropout rates are based on observation in the Phase 2 study (MPI 101-06).

In this protocol amendment, in order to ensure that a sufficient number of subjects will complete this study and enroll in the treatment extension study, up to approximately 420 subjects will be enrolled in the placebo lead-in period to allow for approximately 306 subjects to be randomized into the double blind period of this study (approximately 204:102 OBS and placebo subjects, respectively). With a total of 306 randomized subjects in this study, using the same assumptions for the co-primary endpoints and the dropout rate, the overall study power for the co-primary endpoints is estimated to be at least 95%.

STUDY SCHEDULE(S)

Table 1-1: Schedule of Assessments

Procedures	Screening	Placebo Lead-in	Treatment Phase				Safety Follow-up Telephone Contact[r]
	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	

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	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**
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 (subjects 11-17 years of age, inclusive)[l]		X				X	
Randomization[m]			X				
Investigational product supplied		X	X	X	X	X[l]	
Investigational product administration[o]		Twice-daily administration of investigational product					
Investigational product 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

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Window	**≤6 weeks**	**--**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**

ACTH=adrenocorticotropic 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 will be assessed after the subject has been in a supine position for at least 5 minutes immediately prior to the assessment and will include blood pressure (systolic and diastolic), heart rate, respirations, and temperature.

[b] Height to be collected at screening visit (Visit -1) and Visit 4 for all subjects. Stadiometers are required for subjects 11-17 years of age, inclusive, and will be used at Visit -1 and 4. Height measurements for adolescent subjects (11-17 years of age, inclusive) should be measured in triplicate.

[c] Weight measurements for adolescent subjects (11-17 years, inclusive) should be measured in duplicate.

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

[e] DSQ assessment includes completion of reports on DSQ handset (ie, eligibility reports and visit confirmations).

[f] Subjects 11-17 years of age, inclusive, will complete the EQ-5D-Y; subjects ≥18 years of age will complete the EQ-5D-3L.

[g] Tanner staging assessments will be performed for all subjects aged ≥11 years until investigator confirms subject is post-puberty.

[h] Clinical laboratory tests will include the following: alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, total protein, albumin, glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, carbon dioxide, hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, erythrocyte count, leukocyte count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count. All

Table 1-1: Schedule of Assessments

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	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 must fast overnight prior to collection.

[i] Urinalysis parameters will include glucose, protein, specific gravity, pH, nitrite, bilirubin, ketones, hemoglobin, urobilinogen, and leukocyte esterase.

[j] The serum pregnancy test will be performed for all female subjects at the screening visit (Visit -1) and final treatment evaluation (Visit 4). Urine pregnancy tests will be performed at all other visits.

[k] Blood samples for pharmacokinetic analysis will be taken from adult subjects (aged ≥18 years). Subjects who do not participate in pharmacokinetic sampling will not be discontinued from the study and lack of participation will not be a considered protocol deviation. Blood samples for pharmacokinetic analysis can be obtained one time on any day starting 7 days after Visit 1 (Week 5) and through Visit 4 (Week 16). PK samples should be drawn, ideally, at pre-dose, 0.5 and 1 hour post-dose, and at additional post-dose time points, if feasible (2, 3, 4, 6, 8, and 12 hours post-dose).

[l] The baseline DXA scan may be performed any time during the placebo lead-in period after the subject has met all screening criteria and prior to blinded-treatment randomization. Baseline and post-treatment DXA scans should be performed using the same machine and software. Post-treatment DXA scan should occur at or within (±) 7 days of the scheduled visit.

[m] Randomization will occur via IWRS at the baseline visit (Visit 1) once the subject's eligibility for study entry is confirmed.

[n] Investigational product will be dispensed at Visit 4 to subjects who consent to enroll in the treatment extension study.

[o] Subjects will receive oral administration of 10 mL of investigational product twice daily (qAM, pc, and hs), with no ingestion of food or liquids permitted for 30 minutes after study drug administration.

[p] AE assessments at each visit and physical examination must include specific assessments for signs of glucocorticoid excess (eg, moon facies, acne, hirsutism, mood swings, insomnia, and depression).

[q] If subject discontinues study prematurely, the evaluations listed for Visit 4 are to be performed as completely as possible.

[r] For subjects who withdraw from the study or do not continue into treatment extension study, a safety follow-up contact by phone will be performed 4 weeks following the last dose of investigational product.

1. BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

Eosinophilic esophagitis (EoE) is defined as "a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation" (Liacouras et al., 2011). Clinical symptoms of EoE often vary by age: Infants and toddlers present with feeding difficulties; school-aged children are more likely to present with vomiting or pain; and adolescents and adults present with dysphagia and food impaction. When these symptoms are present, the diagnosis is confirmed by finding eosinophilic inflammation of ≥15 eosinophils/high-powered field (HPF) on at least 1 esophageal biopsy and when other causes such as proton pump inhibitor (PPI)-responsive esophageal eosinophilia are excluded (Dellon et al., 2014a; Furuta et al., 2007). The standards of care are diet therapies and off-label use of glucocorticosteroids. Esophageal dilation is used to temporarily relieve symptoms but does not address underlying inflammation. Given the clinical outcomes associated with EoE, including severe dysphagia, esophageal stricture, food impaction, and esophageal perforation (Hirano and Aceves, 2014; Liacouras et al., 2011) and the fact that there are currently no FDA-approved treatments, there is a clear unmet medical need for a novel treatment for this disease.

1.2 Product Background and Clinical Information

Oral budesonide suspension (OBS) consists of budesonide formulated in a viscous suspension that is designed to increase the residence time of budesonide on the surface of the esophagus after swallowing compared to a non-viscous suspension. Shire is developing OBS as a first-line therapy for EoE in adolescents and adults.

The nonclinical pharmacology, pharmacokinetics, and toxicity and the clinical pharmacology, pharmacokinetics, and safety of budesonide are well studied because budesonide is present in several US FDA-approved drug products. Budesonide is currently marketed for the management of Crohn's disease, for asthma maintenance, for the treatment of allergic rhinitis, and for induction of remission in patients with active, mild to moderate ulcerative colitis. Budesonide has strong glucocorticoid receptor affinity and is subject to considerable first pass metabolism by the liver with a short half-life. These attributes permit budesonide to act rapidly and locally in the gut mucosa for treatment of inflammatory disorders such as Crohn's disease and ulcerative colitis. Once absorbed into the systemic circulation, budesonide is rapidly metabolized in the liver and inactivated (FDA, 2011).

The efficacy of OBS for the treatment of EoE has been demonstrated in two Phase 2 studies in the OBS clinical development program. Studies MPI 101-01 and MPI 101-06 evaluated the efficacy of OBS in the treatment of EoE in children and adolescents aged 2-18 years and in adolescents and adults aged 11-40 years, respectively, by measuring histological response (defined as mean peak eosinophil count ≤6/HPF after treatment). Study MPI 101-06 also evaluated symptom response as measured by the Dysphagia Symptom Questionnaire (DSQ). The DSQ contains 4 questions related to consumption of solid food, the presence of dysphagia and its severity, as well as pain. The DSQ score is calculated only from responses to the questions

related to dysphagia, and this clinical outcome assessment was considered to be fit for purpose as a result of the MPI 101-06 study. Results from Study MPI 101-01 demonstrated a statistically significant histologic response (eosinophil count ≤6/HPF) and remission (eosinophil count ≤1/HPF) in the medium-dose (1.4-2.0 mg daily) and high-dose (2.8-4.0 mg daily) OBS groups compared to placebo following 12 weeks of treatment.

In Study MPI 101-06, a significant treatment effect for OBS vs placebo was shown for both the co-primary efficacy endpoints of histologic response and change from baseline in dysphagia symptoms. Following 12 weeks of twice daily treatment (every morning after meals [qAM, pc] and at bedtime [hs]), OBS-treated subjects demonstrated a highly consistent reduction from baseline values for cellular (mean peak eosinophil count and histopathology features), organ (endoscopy score), and holistic measures (Physician Global Assessment and DSQ scores); these results were independent of the type of rater/reviewer (central pathologist, physician at the study site, or subject).

Always refer to the latest version of the SHP621 investigator's brochure for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics, efficacy, and safety of SHP621.

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

Currently there is no approved medication for the treatment of EoE. This study is being conducted in order to provide safety and efficacy data demonstrating histologic response (as measured by eosinophilic count ≤6/HPF) and improvement in dysphagia symptoms (as measured by the DSQ) following 12 weeks of treatment with OBS in adolescent and adult subjects with EoE.

2.2 Study Objectives

2.2.1 Primary Objectives

The co-primary objectives of the study are to demonstrate in a placebo-controlled trial that:

- OBS induces a histologic response (eosinophilic count ≤6/HPF) in adolescent and adult subjects with EoE over a 12-week course of therapy.
- OBS reduces dysphagia, as measured by the DSQ, by at least 30% from baseline in adolescent and adult subjects with EoE over a 12-week course of therapy.

2.2.2 Secondary Objectives

The key secondary objective of this study is:

- OBS reduces dysphagia, as measured by the DSQ score from baseline to the final treatment period evaluation (Visit 4).

Additional secondary objectives of the study are:

- To assess the response of endoscopically identified esophageal features to OBS as compared to placebo as measured by the EoE Endoscopic Reference Score (EREFS)
- To explore other responding criteria based on histology and DSQ
- To assess the impact of OBS on pain, as measured by the DSQ pain score
- To evaluate the safety and tolerability of OBS over a 12-week course of therapy
- To obtain OBS pharmacokinetic data in adult subjects with EoE

2.2.3 Exploratory Objective

The exploratory objective of this study is:

[redacted]

3. STUDY DESIGN

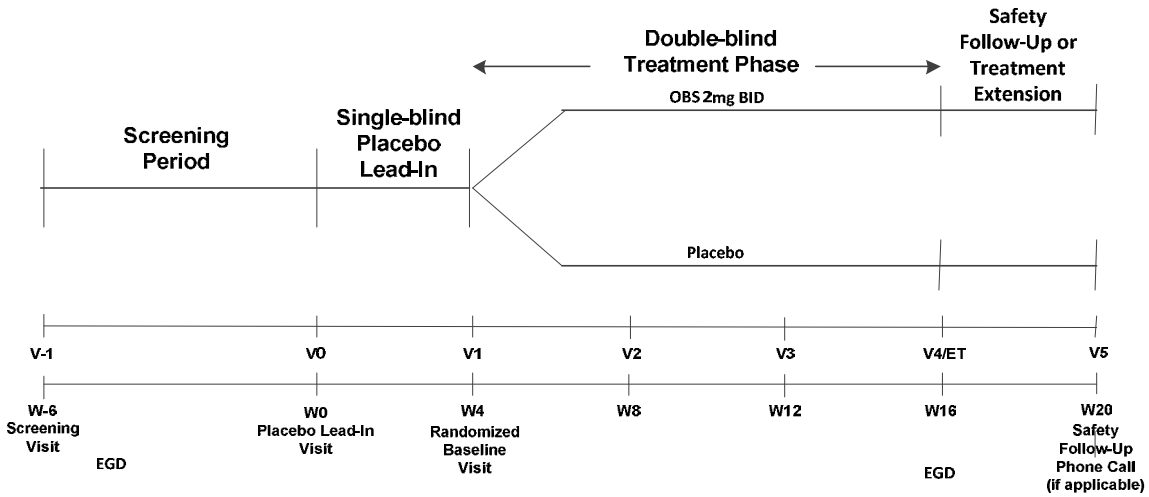
3.1 Study Design and Flow Chart

This is a Phase 3, randomized, multicenter, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of OBS treatment administered twice daily (qAM, pc, and hs) for 12 weeks. The study will be conducted in adolescents and adults, aged 11-55 years, inclusive, with EoE and dysphagia.

The original protocol (dated 31 Aug 2015) planned for approximately 300 subjects to be enrolled in the placebo lead-in period to allow for approximately 228 subjects to be randomized into the double-blind treatment period. Under this protocol amendment, up to approximately 420 subjects will be enrolled in the placebo lead-in period to allow for approximately 306 subjects to be randomized into the double blind period, in order to provide for at least 200 subjects who complete this study and enroll in the successive treatment extension study (SHP621-302). A minimum of 40 randomized subjects will be aged 11-17 years, inclusive. Subjects will be randomized 2:1 (approximately 204 and 102 per OBS and placebo treatment group, respectively) to receive either OBS 2 mg twice daily (qAM, pc, and hs) or placebo twice daily (qAM, pc, and hs).

This study will consist 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 (see Figure 1).

Figure 1: Study Design Flow Chart



BID=twice daily; EGD=esophagogastroduodenoscopy; ET=end of treatment; OBS=oral budesonide suspension

The upper limit of 55 years, inclusive, was selected for this study population based on the low prevalence of EoE in older patients (Dellon et al., 2014a) and the fact that the type of EoE that develops in older patients is not amenable to anti-inflammatory treatment alone (Dellon et al., 2014b). A natural history study demonstrated that for every decade of life, the odds of

developing the fibrostenotic phenotype of EoE more than doubles (Dellon et al., 2014b). By age 55, fibrostenotic EoE occurs in approximately 80% of patients. Fibrostenotic disease is treated with dilatation and is not amenable to anti-inflammatory treatment alone. Therefore, budesonide is not expected to be an effective treatment for the majority of patients above age 55.

Subjects will be required to visit the site up to 6 times over up to a 22-week period. Following completion of the screening and placebo lead-in visits, subjects will be evaluated for eligibility and safety at Week 4 (Visit 1). Subjects who are eligible and randomized will be evaluated for efficacy and safety at Weeks 8, 12, and 16 (Visits 2-4) and additionally for safety at follow-up at Week 20 (Visit 5; telephone contact). Subjects who fail to meet all eligibility criteria at Visits -1, 0, or 1 will be considered screen failures. Subjects cannot be rescreened once it is confirmed they do not meet inclusion/exclusion criteria unless the screen failure was due to a temporary condition or incomplete information at the time of consent (Visit -1) that would make rescreening at a later date appropriate (eg, concomitant medication that can be discontinued prior to rescreening, review of subject medical records provides new information with respect to the date of a prior esophageal dilation or diet change, or subject has a minor illness such as an upper respiratory or urinary tract infection). All reasons for rescreening (ie, reasons unrelated to inclusion/exclusion criteria) must be discussed and approved prospectively with the medical monitor. Subjects who discontinue will not be replaced.

The screening period will start when subjects sign informed consent (or assent as applicable for subjects <18 years of age; screening visit [Visit -1]) and will be approximately 3-6 weeks in duration. During the screening period, all subjects will receive an upper endoscopy with histologic analysis of biopsy specimens to confirm the diagnosis of EoE (eosinophil count of ≥15/HPF from 2 of 3 [proximal, mid-, and/or distal] levels of the esophagus). In addition, subjects must complete the DSQ daily during the screening period (3-6 weeks) and have at least 4 reported days with symptoms of dysphagia and completed the DSQ on ≥70% of days in any 2 consecutive weeks. At the screening visit (Visit -1), subjects who are on a PPI must remain on the same dose of the PPI throughout the study; if they are not taking a PPI, they must remain off of a PPI for the remainder of the study. After the screening period, eligible subjects will enter a 4-week single-blind placebo lead-in period and will receive 10 mL of OBS placebo twice daily (every morning after meals/breakfast [qAM, pc] and at bedtime [hs]). The placebo lead-in period will enable assessment of the subject's ability to comply with twice daily medication administration and assess whether the subject experiences a placebo response.

At the end of the placebo lead-in period, subjects will return for the baseline visit (Visit 1) to confirm eligibility. Subjects who continue to meet all eligibility criteria (those with at least 4 reported dysphagia days and who completed the DSQ on ≥70% of days in the 2 weeks prior to randomization per daily DSQ completion) will be randomized to receive either OBS or placebo during the 12-week double-blind treatment period.

OBS will be administered in 10 mL at a concentration of 0.2 mg/mL (2 mg dose), twice daily. The 0.2 mg/mL concentration of OBS and dosing regimens were selected for use in this Phase 3 study based on the results of Study MPI 101-06, a Phase 2 study in 93 adolescent and adult subjects with EoE and symptoms of dysphagia. Subjects were treated in Study MPI 101-06 with

2 mg OBS twice daily to investigate the co-primary endpoints of histologic response (defined as ≤6 eosinophils/HPF) and reduction in DSQ score from baseline to Week 12 of treatment. For the current study, the investigational product will be supplied in amber glass, multidose bottles with child-resistant caps and refrigerated throughout the study (in the clinic and subject's home). Each bottle will contain approximately 210 mL of suspension with a budesonide concentration of 0.2 mg/mL, or 0.00 mg/mL (matching placebo).

At the end of the 12-week double-blind treatment period (Visit 4, Week 16), subjects who complete the study will have the opportunity to enroll in the treatment extension study. These subjects will continue on the blinded assigned treatment for 2-4 weeks as part of the screening prior to enrolling into the treatment extension study. Subjects who do not enroll in the treatment extension study or who discontinue at any time during the SHP621-301 (Induction) study will receive a follow-up phone call 4 weeks post last dose of investigational product (Visit 5).

3.2 Duration and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 26 weeks, depending on the 3- to 6-week screening period.

The study will be completed in approximately 32 months.

The Study Completion Date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment. Please note that this includes the follow-up visit or contact, whichever is later. The Study Completion Date is used to ascertain timing for study results posting and reporting.

A completer is a subject who completes all procedures and assessments up to and including Visit 4 (Week 16), inclusive of the final treatment evaluation esophagogastroduodenoscopy (EGD). Subjects who do not enroll in the treatment extension study or who discontinue prematurely at any time during the SHP621-301 (Induction) study will receive a follow-up phone call 4 weeks post last dose of the investigational product to which they were randomized.

3.3 Sites and Regions

Approximately 70 sites in North America will participate.

4. STUDY POPULATION

Each subject must participate in the informed consent process and provide written informed consent/assent before any procedures specified in the protocol are performed.

4.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the following criteria (including test results):

1. Subject is able to provide written informed consent (subject, parent or legal guardian, and, as appropriate, subject assent) to participate in the study before completing any study-related procedures.
2. Subject is male or female aged 11-55 years, inclusive, at time of consent.
3. Subject has histologic evidence of EoE with a peak eosinophil count of ≥15/HPF, from 2 of 3 (proximal, mid-, and/or distal) levels of the esophagus at the screening endoscopy.
4. Subject has a history of clinical symptoms of esophageal dysfunction (eg, eating problems, abdominal pain, heartburn, dysphagia, vomiting, food impaction, weight loss) intermittently or continuously at screening (Visit -1).
5. Subject must have experienced dysphagia (response of "yes" to question 2 on DSQ) on a minimum of 4 days and completed the DSQ on ≥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).
6. Subject must not have PPI-responsive EoE based on esophageal biopsies performed after the patient 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 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). If PPI responsiveness was excluded by a previous EGD and biopsy, the historical EGD and biopsy must have been performed after the patient had been on a minimum of 6 weeks of high-dose PPI therapy.
7. Subject will be on a stable (no changes) diet ≥3 months prior to the screening visit (Visit -1).
8. 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.
9. All female subjects must have a negative serum pregnancy test (beta-human chorionic gonadotropin [β-hCG]) prior to enrollment into the study. Females of childbearing potential must agree to continue acceptable birth control measures (eg, abstinence, stable oral contraceptives, or double-barrier methods) throughout study participation.

10. Subject is willing and has an understanding and ability to fully comply with study procedures and restrictions defined in this protocol.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Subject has any condition or abnormality (including laboratory abnormalities), current or past, that, in the opinion of the principal investigator or medical monitor, would compromise the safety of the subject or interfere with or complicate the assessment of signs or symptoms of EoE. Such conditions may include psychiatric problems; neurologic deficits or disease; developmental delay; cardiovascular, metabolic, or pulmonary disease; or previous gastroesophageal surgery. These should be discussed with the medical monitor.
2. 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 (eg, Rituxan) within 3 months of the qualifying EGD should be reviewed with the medical monitor.
3. 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 (≤7 days) 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.
4. Subject has been on inhaled steroids and has not been on stable treatment for ≥3 months prior to screening visit (Visit -1). Subjects on inhaled steroids need to stay on a stable treatment during study participation. Subject has been on intranasal steroids and has not been on stable treatment for a minimum of 4 weeks prior to the qualifying EGD. After the qualifying EGD, subjects with seasonal allergic rhinitis may resume (or discontinue) intranasal corticosteroids based on the subject's usual treatment regimen for allergy season.
5. Subject has initiated, discontinued, or changed dosage regimen of PPIs, H2 antagonists, antacids, 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 EGD and baseline visit (Visit 1), or anticipates changes in the use of such medications during the treatment period.
6. Subject has been using cytochrome P450 3A4 (CYP450 3A4) inhibitors (eg, ketoconazole, grapefruit juice) within the 2 weeks prior to the baseline visit (Visit 1) or within 5 half-lives (whichever is greater) or anticipates using such medications during the treatment period.
7. 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 (eg, with an insertion tube diameter of >9 mm).
8. Subject is on a pure liquid diet or the 6-food elimination diet.

9. Subject has had an esophageal dilation within the 3 months prior to screening (Visit -1).
10. Subject has presence of esophageal varices at the screening endoscopy.
11. 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.
12. Subject has other diseases causing or associated with EoE, including hypereosinophilic syndrome, collagen vascular disease, vasculitis, achalasia, or parasitic infection.
13. Subject has current evidence of oropharyngeal or esophageal candidiasis.
14. Subject has a potentially serious acute or chronic viral infection or immunodeficiency condition, including tuberculosis, fungal, bacterial, viral/parasite infection, ocular herpes simplex, herpes esophagitis, or chicken pox/measles.
15. 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).
16. Subject has evidence of active infection with *Helicobacter pylori.*
17. 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).
18. Subject is female and pregnant or nursing.
19. Subject has a history of intolerance, hypersensitivity, or idiosyncratic reaction to budesonide (or any other corticosteroids) or to any other ingredients of the investigational product.
20. Subject has taken part and received intervention in an interventional study related to EoE (except for an interventional study for a topical swallowed steroid) within 6 months prior to the screening visit (Visit -1), or any investigational study within 30 days prior to the screening visit (Visit -1). An investigational topical swallowed steroid must have been discontinued at least 30 days prior to the screening visit (Visit -1).
21. Subject has a history or high risk of noncompliance with treatment or regular clinic visits.
22. Subject has previously completed, discontinued, or withdrawn from this study.
23. Subject has participated in a previous clinical study involving OBS (SHP621).
24. Subject anticipates using sucralfate during the study.

4.3 Restrictions

Subjects must adhere to the following restrictions for the duration of the study:

- No change in exercise (other than seasonal changes in sports or activities). Intense exercise should be avoided unless part of an established exercise routine.
- No change in diet (liquid diet for 3 days or less is acceptable).
- Short course of systemic steroids (≤7 days) are permitted to treat, for example, exacerbation of asthma but cannot be used 4 weeks prior to the final EGD.

- Stable treatment with intranasal or inhaled corticosteroids. For subjects with perennial allergic rhinitis and stable asthma, the topical corticosteroid must be maintained at the same dose throughout the study. For subjects with seasonal allergic rhinitis, it is permissible after the qualifying EGD to resume (or discontinue) intranasal corticosteroids based on the subject's usual treatment regimen for allergy season. All topical corticosteroid dosing changes, including those for seasonal allergic rhinitis, should be avoided within 4 weeks prior to the Week 16 EGD. Subjects who require a change in inhaled corticosteroid treatment for an asthma exacerbation should be discussed with the medical monitor.
- No change in PPI use
- No use of CYP450 3A4 inhibitors
- No use of sucralfate during the study as this may interfere with the adherence of OBS
- An esophageal dilatation during the trial (Dilatation is considered a treatment failure, and the subject should be withdrawn from the study)

4.4 Reproductive Potential

4.4.1 Female Contraception

All females must have a negative pregnancy test at the screening visit (Visit -1), placebo lead-in visit (Visit 0), baseline visit (Visit 1), and Visits 1-4. A serum pregnancy test will be performed at the screening visit (Visit -1) and final treatment evaluation (Visit 4). Urine pregnancy tests will be performed at all other visits.

Female subjects should be either:

- Premenarchal and Tanner Stage 1, or
- Post-menopausal (24 consecutive months of spontaneous amenorrhea and age 51 years or older).
- Be surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 6 weeks post-sterilization, or
- Females of child-bearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception throughout the study period and for 30 days following the last dose of investigational product.
    - Acceptable methods of contraception are:
        - Abstinence
        - Surgically sterile male partner
        - Stable oral contraceptives
        - Intrauterine devices plus condoms

- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam)
- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the screening visit (Visit -1), plus condoms. If hormonal contraceptives are used, they should be administered according to the package insert. Note: If subjects become sexually active during the study, they should use one of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

4.5 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject from investigational product with the medical monitor when possible.

If investigational product is discontinued, leading to subject discontinuation from the study, regardless of the reason, the evaluations listed for Visit 4 are to be performed as completely as possible. If investigational product is discontinued due to an adverse event (AE), the subject may remain on study to allow for completion of study procedures.

Whenever possible, all discontinued subjects should also undergo the protocol-specified follow-up. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for termination, date of stopping investigational product, and total amount of investigational product taken must be recorded in the case report form (CRF) and source documents.

Subjects who discontinue will not be replaced.

4.5.1 Subject Withdrawal Criteria

Medically important events that in the opinion of the investigator or medical monitor would compromise the subject's ability to safely continue in the study, including but not limited to severe signs and symptoms of EoE, such as an esophageal stricture requiring dilation, weight loss due to severe dysphagia, and/or upper GI bleed would be considered a treatment failure and result in withdrawal of the subject from the study.

4.5.2 Reasons for Discontinuation

The reason for withdrawal must be determined by the investigator and recorded in the subject's medical record and on the CRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the CRF.

Reasons for discontinuation include but are not limited to:

- Completed
- Death
- AE
- Noncompliance with study drug
- Noncompliance with study procedure
- Withdrawal by subject
- Withdrawal by parent/guardian
- Physician decision
- Study terminated by sponsor
- Site terminated by sponsor
- Lost to follow-up
- Pregnancy
- Trial screen failure
- Protocol deviation
- Other

4.5.3 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and return any unused investigational product.

4.5.4 Safety-related Stopping Rules

An urgent safety review will be conducted within 7 days by the sponsor if one or more of the following criteria are met:

- Death that is considered related to the study drug
- Two serious adverse events (SAEs) of similar type (defined as same or similar Medical Dictionary for Regulatory Activities [MedDRA] higher level group code) and considered related to the study drug

The urgent review will be performed by a sponsor safety review group, which will include the study Global Drug Safety (GDS) physician and the GDS Therapeutic Area Head. The GDS Therapeutic Area Head, not the GDS physician involved in the study, may be unblinded as part of this urgent safety review, if required. Following the sponsor's review of safety data, one of the following actions will be taken with respect to study status:

- Continue study with protocol unchanged
- Continue study with modifications to the protocol
- Terminate study

Subject safety will be monitored on a continuous basis during this study until the last subject completes his or her last scheduled study visit/assessment.

5. PRIOR AND CONCOMITANT TREATMENT

All non-study treatment (including but not limited to herbal treatments, vitamins, behavioral treatment, and nonpharmacological treatment, such as psychotherapy, as appropriate) received within 3 months prior to the screening visit (Visit -1) (or pharmacokinetic equivalent of 5 half-lives, whichever is longer) and through the final study contact (including protocol-defined follow-up period) must be recorded on the appropriate CRF page.

5.1 Prior Treatment

Prior treatment includes all treatment, including but not limited to herbal treatments, vitamins, and nonpharmacological treatment such as psychotherapy, as appropriate, received within 3 months of the screening visit (Visit -1). Prior treatment information must be recorded on the appropriate CRF page.

5.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product and the end of the follow-up period, inclusive. Concomitant treatment information must be recorded on the appropriate CRF page.

The investigator may prescribe additional medications during the study, as long as the prescribed medication is not prohibited by the protocol. In the event of an emergency, any needed medications may be prescribed without prior approval, but the medical monitor must be notified of the use of any prohibited medications immediately thereafter.

5.2.1 Permitted Treatment

The following medications are allowed during the course of the study if the subject has been on a stable dosing regimen (ie, same dose and frequency in the previous 4 weeks prior to the endoscopy required for entrance to this study) and will continue this dosing regimen throughout study participation. The investigator must contact the medical monitor to discuss any changes to concomitant steroid regimens or for any medications not listed here that could impact the outcome of the study.

1. Inhaled or intranasal steroids for conditions other than EoE; subject must be on stable treatment for ≥3 months prior to screening visit (Visit -1), except for seasonal allergic rhinitis, see Section 4.3.
2. PPIs
3. H2 antagonists
4. Antacids
5. Antihistamines or anti-leukotrienes
6. Maintenance immunotherapy (allergy shots or sublingual immunotherapy)

Influenza and other routine required vaccinations are allowed during the study.

5.2.2 Prohibited Treatment

The following medications and treatments are prohibited throughout the course of the study and prior to treatment, as specified:

1. Immunomodulatory therapy within 8 weeks prior to the qualifying EGD or between the qualifying EGD and baseline visit (Visit 1) or anticipated use of immunomodulatory therapy during the treatment period (except for any ongoing regimen of allergy shots). Use of long-acting immunomodulatory therapy (eg, Rituxan) within 3 months of the qualifying EGD should be reviewed with the medical monitor.
2. 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 anticipated use during the treatment period; any temporary use (≤7 days) or initiation of new steroid treatment during study should be documented and discussed with the medical monitor prospectively but cannot occur within the 4 weeks of the final EGD.
3. Inhaled steroids if initiated or changed in dose <3 months prior to screening visit (Visit -1). (**Seasonal nasal corticosteroid use for seasonal allergic rhinitis is permitted; changes within 4 weeks of scheduled EGD should be avoided).**
4. Initiation or change in dosing frequency of PPIs, H2 antagonists, antacids, 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 EGD and baseline visit 1, or anticipated changes in the use of such medications during the treatment period.
5. CYP450 3A4 inhibitors (eg, ketoconazole, grapefruit juice) within the 2 weeks prior to the baseline visit (Visit 1) or within 5 half-lives (whichever is greater) or anticipated use of such medications during the treatment period. For an expanded list of CYP3A inhibitors, investigators should refer to the 2012 FDA Draft Guidance on Drug Interactions (FDA Guidance 2012) and use their clinical judgment with respect to specific medications.
6. Esophageal dilation within the 3 months prior to screening (Visit -1)
7. Investigational study treatment within 6 months prior to the screening visit (Visit -1)
8. Sucralfate use during the treatment period

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The test product is OBS (oral budesonide suspension, 0.2 mg/mL), which will be provided in multi-dose amber glass bottles, each containing approximately 210 mL. Additional information is provided in the current SHP621 investigator's brochure.

The reference/comparator product is placebo, which will be provided in amber glass bottle form with the same volume.

6.1.1 Blinding the Treatment Assignment

Investigational product will be supplied in amber glass, multi-dose bottles with child-resistant caps and refrigerated throughout the study (in the clinic and subject's home). Each bottle contains approximately 210 mL of suspension with a budesonide concentration of 0.2 mg/mL. Inactive ingredients in OBS include dextrose, disodium edetate, citric acid, sodium citrate, potassium sorbate, polysorbate 80, glycerin, sodium benzoate, cherry flavor, Magnasweet 110, acesulfame potassium, and water.

The placebo solution will also be supplied in amber glass multi-dose bottles with child-resistant caps. Placebo consists of all components of the investigational product solution with the exception of budesonide.

6.2 Administration of Investigational Product(s)

All investigational product and supplies (eg, dosing spoons) will be provided by Shire or its designee. At each visit, subjects will be supplied with enough investigational product to last until the subsequent visit. The first dose of investigational product (placebo) for each subject will be administered in the clinic at the placebo lead-in visit (Visit 0). The subject will continue with the evening dosing regimen at home.

OBS and placebo will be supplied in amber glass bottles and must be shaken well prior to administration. OBS and placebo should be refrigerated at 2-8ºC (36-46ºF) throughout the study (in the clinic and subject's home). The appropriate dose will be dispensed using the graduated dosing spoon provided. For subjects who are minors (<18 years), a parent/guardian will be responsible for ensuring that the subjects take their investigational product appropriately.

Subjects will be instructed not to eat or drink for 30 minutes after taking the investigational product. Activities such as brushing teeth or rinsing the mouth should also be avoided during this time interval. After 30 minutes, subjects will be instructed to rinse with water and spit, particularly after the bedtime dose.

Please refer to the Investigational Product Administration Manual for additional details.

6.2.1 Interactive Response Technology for Investigational Product Management

An interactive web-based response system (IWRS) will be used for screening and enrolling subjects, recording subject visits, randomization, investigational product supply dispensation and management, inventory management and supply ordering, investigational product expiration tracking and management, return of investigational product, and emergency unmasking. Please refer to the Study Manual for additional details regarding the IWRS.

The investigator or designee will access the IWRS at the screening visit (Visit -1) to record subject-specific information (ie, unique subject number, date of birth, etc.). Subjects will be entered as screen failures or as entering the placebo lead-in period. Subjects cannot be rescreened once it is confirmed they do not meet inclusion/exclusion criteria unless the screen failure was due to a concomitant medication that can be discontinued prior to rescreening; those subjects may be rescreened. Other reasons for rescreening (ie, reasons unrelated to inclusion/exclusion criteria) must be discussed prospectively with the medical monitor. For subjects who enter the placebo lead-in period, IWRS will provide the assignment of placebo lead-in period medication to dispense.

At the baseline visit (Visit 1), the investigator or designee will again access the IWRS to either document a screen failure or, if the subject has met all entry criteria, to randomize the subject. Sites will enter eligibility criteria information prior to randomization. For randomized subjects, the IWRS will provide a medication identification (Med ID) number (ie, kit number to dispense for treatment).

The IWRS will also be used for creating, tracking, and confirming investigational product shipments. A user manual with specific functions and instructions for the IWRS will be provided to the site and site personnel will receive training.

The IWRS provider will provide a user manual and training to each site, with detailed instructions on use of the IWRS.

6.2.2 Allocation of Subjects to Treatment

This study consists of a single-blind lead-in period followed by a double-blind placebo-controlled study period. The actual treatment given to individual subjects during the double-blind period is determined by a randomization schedule.

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation.

The randomization number represents a unique number corresponding to investigational product allocated to the subject once eligibility has been determined following the placebo lead-in period.

Individual subject treatment is automatically assigned by the IWRS.

Subjects will be randomized after confirmation of study eligibility in a ratio of 2:1 via a computer-generated randomization schedule to receive OBS 2 mg twice daily (qAM, pc, and hs) or placebo. The randomization will be performed centrally and stratified by age group (2 strata total: <18 years or ≥18 years) and diet restriction for EoE or other health-related conditions (no diet restriction or any diet restriction). The stratification by age will ensure a minimum of 40 subjects in the pediatric group (11-17 years, inclusive). The stratification by age and diet restriction will ensure balance between treatment groups for the respective stratification factors. Fixed block randomization will be used to ensure that approximately equal numbers of patients are assigned each treatment within strata. [redacted]

6.2.3 Dosing

During the 4-week single-blind placebo lead-in period, all subjects will receive 10 mL of placebo twice daily (qAM, pc, and hs). During the 12-week double-blind treatment period, oral administration of 10 mL of investigational product will occur twice daily (qAM, pc, and hs), with no ingestion of food or liquids permitted for 30 minutes after study drug administration. Subjects randomized to OBS will receive 10 mL of 0.2 mg/mL of OBS (2 mg) twice daily for a total daily dose of 4 mg.

Investigational product doses that are required to be administered at the clinic include the first dose of placebo administered at the placebo lead-in visit (Visit 0), the first dose of randomized investigational product (OBS or placebo) administered at the baseline visit (Visit 1) and all morning doses of investigational product administered at Visits 2-4. Subjects will be required to eat breakfast at the clinic prior to self-administering these doses. Subjects can self-administer all other doses of placebo and investigational product at home.

During the day where the pharmacokinetic blood samples are collected, subjects will be required to eat a moderate-fat breakfast onsite and will be instructed to take their morning dose at a set time to establish the schedule for post-dose sample collection.

6.2.4 Unblinding the Treatment Assignment

The treatment assignment must not be broken during the study except in emergency situations where the identification of the investigational product is required for further treatment of the subject. The investigator should contact the medical monitor and the sponsor as soon as possible after the investigator has been unblinded.

In the event that the treatment assignment is broken, the date, the signature of the person who broke the code, and the reason for breaking the code are recorded in the IWRS and the source documents. Upon breaking the blind, the subject is withdrawn from the study, but should be followed up for safety purposes. Any code breaks that occur must be reported to the contract research organization (CRO) and sponsor. Code-break information is held by the pharmacist/designated person at the site and by the CRO medical monitor for the study or designee.

There will be a provision for unblinding to ensure adequate treatment of the subject in the case of an emergency.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

Labels containing study information and pack identification are applied to the investigational product(s) container.

All investigational product is labeled with a minimum of the protocol number, Med ID, dosage form (including product name and quantity in pack), directions for use, storage conditions, expiry date (if applicable), batch number and/or packaging reference, the statements "For clinical trial use only" and/or "CAUTION: New Drug - Limited by Federal (or US) Law to Investigational Use," "Keep out of reach of children," and the sponsor's name and address. Any additional labeling requirements for participating countries and/or controlled substances will also be included on the label.

Space is allocated on the label so that the site representative can record subject information.

Additional labels (eg, those used when dispensing marketed product) may, on a case-by-case basis, be applied to the investigational product in order to satisfy local or institutional requirements, but must not:

- Contradict the clinical study label.
- Obscure the clinical study label.
- Identify the study subject by name.

Additional labels may not be added without the sponsor's prior full agreement.

6.3.2 Packaging

Investigational product is packaged in the following labeled containers:

The sponsor will supply the following medication to the study sites in a blinded manner: OBS 0.2 mg/mL or placebo in an 8-ounce amber glass bottle for multiple use. Three bottles will be packaged in an appropriately labeled carton.

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.

6.3.3 Storage

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

OBS and placebo must be stored at 2-8ºC (36-46ºF), protected from light.

Investigational products are distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier on the investigational product bottle/carton labels as they are distributed.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), eg, fumigation of a storage room.

6.3.4 Special Handling

The investigational product should be stored under refrigeration at 2-8°C/36-46°F at all times. The investigational product should be protected from light and shaken well immediately prior to each dose.

6.4 Drug Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed-upon number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for administering/dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will dispense the investigational product only to subjects included

in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All dispensed medication will be documented on the CRFs and/or other investigational product record. The investigator is responsible for assuring the retrieval of all study supplies from subjects. The investigator or his/her designee will enter the unique subject identifier and initials on the investigational product kit labels as they are assigned and dispensed.

No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records provided that the blind of the study is not compromised.

At the end of the study, or as instructed by the sponsor, all unused stock, subject-returned investigational product, and empty/used investigational product packaging are to be sent to a nominated contractor on behalf of the sponsor. Investigational product being returned to the sponsor's designated contractors must be counted and verified by clinical site personnel and the sponsor (or designated CRO). For unused supplies where the original supplied tamper-evident feature is verified as intact, the tamper-evident feature must not be broken, and the labeled amount is to be documented in lieu of counting. Shipment return forms, when used, must be signed prior to shipment from the site. Validated electronic return systems (ie, IWRS) do not require a shipment form. Returned investigational product must be packed in a tamper-evident manner to ensure product integrity. Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

6.5 Subject Compliance

Compliance with investigational product will be assessed at each study visit. Subjects must be instructed to bring their unused investigational product and empty/used investigational product packaging to every visit. Drug accountability must be assessed at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (eg, bottles) or at the individual count level for opened containers/packaging. The pharmacist/nominated person will record details on the drug accountability form.

Visit to visit compliance of investigational product dosing will be assessed by site personnel. Site personnel must review the returned investigational product to assess compliance at every visit prior to dispensing additional investigational product. Any discrepancies should be reconciled

with the subject immediately. Subjects who do not return their used and unused investigational product should be reminded to bring all used and unused investigational product at their next visit.

Subjects who have taken 70-130% of the investigational product will be assessed as being compliant with the study protocol. Compliance will be assessed at each treatment visit.

7. STUDY PROCEDURES

7.1 Study Schedule

The detailed study procedures/assessments to be performed throughout the study are outlined in the Schedule of Assessments (see Table 1-1) and must be referred to in conjunction with the instructions provided in this section.

Prior to performing any study-related procedures (including those related to screening), the investigator or his/her designee must obtain written informed consent from the subject (as per local requirements). There must be documentation of consent (as per local requirements) indicating that the subject is aware of the investigational nature of the study and the required procedures and restrictions, prior to performing any study-related procedures.

7.1.1 Screening Period (Weeks -6 to 0)

The screening period starts when subjects sign informed consent. The screening period will comprise 3-6 weeks, during which all procedures listed for the screening visit (Visit -1) in Table 1-1 shall be completed. The screening period will allow for the determination of eligibility of each subject's inclusion into the study. A subject should not be instructed to discontinue use of any medication or treatment to participate in this study until informed consent has been obtained. Subjects should not stop permitted medications or treatments that are effective and well tolerated to participate in this study (see Section 5.2.1).

Screening assessments may take place across several days to allow an appropriate time frame in which to complete all procedures and confirm study eligibility.

After the screening period, subjects who meet eligibility criteria at the end of the screening visit (Visit -1) will enter the 4-week single-blind, placebo lead-in period. The placebo lead-in period should not commence until all screening assessments required to confirm initial eligibility have been completed. If the subject does not meet eligibility criteria following completion of screening assessments, the investigator or designee will document the subject as a screen failure in the IWRS.

A screen failure is a subject who has given informed consent and failed to meet the inclusion criteria and/or met at least 1 of the exclusion criteria and has not been randomized or administered randomized investigational product. Screen failures can occur at the screening, placebo lead-in, or baseline visits. Subjects cannot be rescreened once it is confirmed they do not meet inclusion/exclusion criteria unless the screen failure was due to temporary condition or incomplete information at the time of consent (Visit -1) that would make rescreening at a later date appropriate (eg, a concomitant medication that can be discontinued prior to rescreening, review of subject medical records provides new information with respect to the date of a prior esophageal dilation or diet change, or subject has a minor illness such as an upper respiratory or urinary tract infection). All reasons for rescreening (ie, reasons unrelated to inclusion/exclusion criteria) must be discussed and approved prospectively with the medical monitor.

7.1.1.1 Screening Visit (Visit -1)

The screening visit (Visit -1) assessments and procedures, beginning with informed consent, will be performed as outlined in Table 1-1.

The following procedures should be performed first:

- Obtain subject consent (or assent as applicable for subjects <18 years).
- Review eligibility criteria.
- Review medical history.
- Record vital signs (including blood pressure [systolic and diastolic], heart rate, respirations, and temperature), height, and weight. Perform stadiometry in subjects aged 11-17 years, inclusive.
- Review current use of concomitant medications, including medications taken and procedures completed within 3 months prior to the biopsy required for entrance to this study. Note: Subjects who are on a PPI must remain on the same dose of the PPI throughout the study, and if they are not taking a PPI, they must remain off of a PPI for the remainder of the study.
- Clinical chemistry, hematology, and urinalysis laboratory tests will be performed on all subjects; all subjects must fast overnight prior to collection.

The following order is recommended for the remaining procedures that will be performed at this visit or within the 6-week screening period:

- Dispense the DSQ electronic patient-reported outcome (ePRO) device for nightly completion and train the subject on its use. In order to qualify for study entry, subjects must have experienced dysphagia (response of "yes" to question 2 on DSQ) on a minimum of 4 days and completed the DSQ on ≥70% of days in any 2 consecutive weeks of the screening period.
- Perform a physical examination on all subjects. Adolescents (subjects ≤17 years) will also undergo Tanner Staging Assessment.
- **Serum** pregnancy test will be performed on all female subjects.
- Perform EGD and biopsy; both must be performed within the 6 weeks prior to the Placebo Lead-in Visit either at the investigative site or by a referring physician. Biopsy specimens must be available to be sent to the central pathology lab at least 2 weeks prior to the Placebo Lead-in Visit to allow sufficient time for processing and central review and determination of eligibility.

7.1.2 Placebo Lead-in Period (Weeks 0 to 4)

The placebo lead-in period will comprise 4 weeks, during which all procedures listed for the placebo visit (Visit 0) in Table 1-1 shall be completed.

During the 4-week single-blind placebo lead-in, all eligible subjects will self-administer 10 mL of placebo twice daily (qAM, pc, and hs).

At the end of the placebo lead-in period, eligible subjects (those with at least 4 reported dysphagia days and completion of DSQ on ≥70% of days in the 2 weeks prior to baseline [Visit 1]) will be randomized and enter the 12-week double-blind treatment period (baseline visit). Subjects must be administrated placebo during the placebo lead-in period for 4 weeks (±3 days) prior to Visit 1 (baseline) to be eligible for randomization into the 12-week double-blind treatment period.

7.1.2.1 Placebo Lead-in Visit (Visit 0)

The placebo lead-in visit (Visit 0) assessments and procedures will be performed as outlined in Table 1-1.

The following procedures should be performed first:

- Reassess eligibility according to the inclusion/exclusion criteria and medical history.
- Record vital signs (including blood pressure [systolic and diastolic], heart rate, respirations, and temperature) and weight.
- Perform AE assessments.
- Review concomitant medications and procedures.
- Clinical chemistry, hematology, and urinalysis laboratory tests; all subjects must fast overnight prior to collection.

The following order is recommended for the remaining procedures that will be performed at this visit:

- Confirm DSQ dysphagia episodes and compliance by completing screening eligibility report on DSQ device; re-dispense DSQ device to subject with instruction to continue completion of the DSQ nightly.
- Perform a physical examination and assess any changes since screening.
- **Urine** pregnancy test for female subjects.
- Perform dual-energy X-ray absorptiometry (DXA) scan for bone mineral density (BMD) and body composition in subjects aged 11-17 years, inclusive; the DXA scan may be performed any time during the placebo lead-in period, after the subject has met all screening criteria and prior to blinded-treatment randomization. Baseline and post-treatment DXA scans should be performed using the same machine and software.
- Dispense placebo study medication and review administration instructions. Subjects will self-administer the first dose of placebo in the clinic after eating breakfast. Site personnel will record the date and time of the first placebo dose in the source documents. Beginning on the evening of Visit 0, the subject will take their second dose at home and continue with the twice daily (qAM, pc, and hs) dosing regimen.

7.1.3 Double-blind Treatment Period (Visits 1-4): Weeks 4, 8, 12, and 16 (or Early Termination)

The double-blind treatment period will comprise 12 weeks, during which all assessments and procedures listed for Visits 1-4 in Table 1-1 shall be completed.

During this period, a ±3-day visit window will be permitted, unless otherwise specified. Visit windows are calculated based upon the date of the placebo lead-in visit (Visit 0).

Subjects who continue to meet all eligibility criteria will be randomized 2:1 to receive either OBS twice daily (qAM, pc, and hs) or placebo twice daily (qAM, pc, and hs). The investigator or assigned site staff will access the IWRS to randomize the subject and dispense the investigational product. Subjects who fail to meet eligibility criteria at the baseline visit (Visit 1) will be documented as screen failures in the IWRS.

Subjects who complete the 12-week double-blind treatment period will have the opportunity to enroll in the treatment extension study. These subjects will continue on the blinded assigned treatment for 2-4 weeks as part of the screening prior to enrolling into the treatment extension study. Subjects who do not enroll in the treatment extension study or who discontinue prematurely at any time during the SHP621-301 (Induction) study will receive a follow-up phone call 4-weeks post last dose of investigational product.

7.1.3.1 Baseline Visit (Visit 1): Week 4

Subjects will return to the site for the baseline visit (Visit 1) to confirm eligibility. The baseline visit (Visit 1) assessments and procedures will be performed as outlined in Table 1-1.

The following procedures should be performed first:

- Reassess eligibility according to the inclusion/exclusion criteria and medical history.
- Record vital signs (including blood pressure [systolic and diastolic], heart rate, respirations, and temperature) and weight.
- Perform AE assessments, including specific assessments for signs of glucocorticoid excess. Any AE that occurs during this visit will be recorded in the CRF and considered a treatment emergent adverse event (TEAE).
- Review concomitant medications and procedures.
- Clinical chemistry, hematology, and urinalysis laboratory tests; all subjects must fast overnight prior to collection.
- Morning cortisol (performed between 6:00 and 9:00 AM). Subjects should be instructed not to take the morning dose of investigational product until after the morning cortisol test has been performed.
- Administer adrenocorticotropic hormone (ACTH) stimulation testing; the type of synthetic and route of administration will be per local lab discretion. Additional cortisol samples will

be drawn at 30 and 60 minutes following stimulation testing.

The following order is recommended for the remaining procedures that will be performed at this visit:

- Review study medication dosing compliance.
- Confirm DSQ dysphagia episodes and compliance by completing baseline eligibility report on DSQ device; re-dispense DSQ device to subject with instruction to continue completion of the DSQ nightly.
- Administer health-related quality of life (HRQoL) assessments including the EuroQol (EQ-5D), Pediatric Quality of Life Inventory – EoE (PedsQL-EoE), and Adult Eosinophilic Esophagitis Quality of Life (EoE-QoL-A) as age-appropriate.
- Administer PGI-S of disease assessment.
- Perform a physical examination and assess any changes since screening.
- Re-administer **urine** pregnancy test for female subjects.
- Dispense investigational product (OBS or placebo) according to IWRS randomization and review administration instructions. Subjects will self-administer the first dose of investigational product in the clinic during this visit after breakfast. Site personnel will record the date and time of the first randomized dose in the source documents. Beginning on the evening of Visit 1, the subject will take their first dose at home and continue with the twice daily (morning and evening) dosing regimen. For subjects who are minors (<18 years), a parent/guardian will be responsible for ensuring subject takes their investigational product appropriately.

Following all blood draws, subjects can eat breakfast and take their morning dose of investigational product.

7.1.3.2 Visits 2 and 3 (Weeks 8 and 12)

Subjects will return to the site for Visit 2 (Week 8) and Visit 3 (Week 12). Assessments at these visits will be performed as outlined in Table 1-1.

The following procedures should be performed first:

- Record vital signs (including blood pressure [systolic and diastolic], heart rate, respirations, and temperature) and weight.
- Perform AE assessments, including specific assessments for signs of glucocorticoid excess. Any AE that occurs during this visit will be recorded in the CRF and considered a TEAE.
- Review concomitant medications and procedures.
- Clinical chemistry, hematology, and urinalysis laboratory tests; all subjects must fast overnight prior to collection.
- Morning cortisol (performed between 6:00 and 9:00 AM). Subjects should be instructed not

to take the morning dose of study medication until after the morning cortisol test has been performed.

- Collect blood samples for pharmacokinetic analysis for adult subjects. Samples may be obtained one time on any day between 7 days after Visit 1 (Week 5) and through Visit 4 (Week 16). PK samples should be drawn, ideally, at pre-dose, 0.5 and 1 hours post-dose and at additional time points, if feasible (2, 3, 4, 6, 8, and 12 hours post-dose). Subjects will be instructed to take their morning dose at a set time to establish the schedule for post-dose sample collection.

The following order is recommended for the remaining procedures that will be performed at this visit:

- Review DSQ compliance and complete visit confirmation on the DSQ device; re-dispense DSQ device to subject with instruction to continue completion of the DSQ nightly.
- Administer PGI-S assessment.
- Perform a physical examination and assess any changes since screening.
- Re-administer **urine** pregnancy test for female subjects.
- Dispense investigational product (OBS or placebo) and review investigational product dosing compliance.

Following all blood draws, subjects can eat breakfast and take their morning dose of investigational product.

7.1.3.3 Visit 4 (Week 16)

Subjects will return to the site for Visit 4 (Week 16). Assessments at this visit will be performed as outlined in Table 1-1.

The following order is recommended for the procedures that will be performed at this visit:

- Record vital signs (including blood pressure [systolic and diastolic], heart rate, respirations, and temperature), height, and weight. Perform stadiometry in subjects aged 11-17 years, inclusive.
- Perform AE assessments, including specific assessments for signs of glucocorticoid excess. Any AE that occurs during this visit will be recorded in the CRF and considered a TEAE.
- Review concomitant medications and procedures.
- Clinical chemistry, hematology, and urinalysis laboratory tests; all subjects must fast overnight prior to collection.
- Morning cortisol (performed between 6:00 and 9:00 AM). Subjects should be instructed not to take the morning dose of investigational product until after the morning cortisol test has been performed.
- Administer ACTH stimulation testing; the type of synthetic and route of administration will

be per local lab discretion. Additional cortisol samples will be drawn at 30 and 60 minutes following stimulation testing.

- Collect blood samples for pharmacokinetic analysis for adult subjects. Samples may be obtained one time on any day between 7 days after Visit 1 (Week 5) and through Visit 4 (Week 16). PK samples should be drawn, ideally, at pre-dose, 0.5 and 1 hours post-dose and at additional time points, if feasible (2, 3, 4, 6, 8, and 12 hours post-dose).
- Retrieve DSQ handset, review DSQ compliance, and complete visit confirmation on DSQ device.
- Administer HRQoL assessments including the EQ-5D, PedsQL-EoE, and EoE-QoL-A as age-appropriate.
- Administer PGI-S assessment.
- Perform a physical examination and assess any changes since screening. Adolescents (subjects ≤17 years) will also undergo Tanner Staging Assessment.
- Re-administer **serum** pregnancy test for female subjects.
- Perform DXA scan for BMD and body composition in subjects aged 11-17 years, inclusive. DXA scan should be completed at or within (±) 7 days of this visit. Baseline and post-treatment DXA scans should be performed using the same machine and software.
- Perform EGD and biopsy. EGD should be completed at or within (±) 7 days of the scheduled visit. If an esophageal dilatation is performed at Visit 4 (treatment failure), subjects will not be eligible to participate in the treatment extension study.
- For eligible subjects continuing into the treatment extension study, obtain informed consent for the treatment extension study, dispense investigational product (OBS or placebo) according to IWRS randomization and review investigational product dosing compliance.

Following all safety blood draws, subjects can eat breakfast and take their morning dose of investigational product if they are continuing in the treatment extension study or staying in clinic for PK sampling (to be performed as described in Section 7.1.3.2 above).

7.1.4 Follow-up Period

The follow-up period for this protocol is 4 weeks from the last dose of investigational product. Subjects who do not enroll in the treatment extension study or who discontinue prematurely at any time during the study will receive a follow-up 4 phone call at Visit 5 (Week 20) to query for SAEs, AEs, and concomitant treatments (Section 7.1.4.1).

7.1.4.1 Safety Follow-up Contact (Visit 5): Week 20

Assessments at this time, as outlined in Table 1-1, will include the following:

- Review concomitant medications and procedures.
- Perform AE assessments, including specific assessments for signs of glucocorticoid excess. Any AE that occurs during this visit will be recorded in the CRF and considered a TEAE; all

AEs and SAEs that are not resolved at the time of this contact will be followed to closure.

7.1.5 Additional Care of Subjects after the Study

No after care is planned for this study for those subjects who do not enroll in the treatment extension study.

7.2 Study Evaluations and Procedures

The full title and details about who completes the scales used in this study is included in Appendix 1.

All assessments listed below will be performed by the subject and/or a qualified/trained site staff as indicated in the assessment description. For subject-completed assessments, trained site staff should not assist the subject in completing assessments in such a manner that it would influence their responses. Site staff should review the completed assessment to ensure completeness.

If an answer is marked in error, the subject may correct it by drawing a single line through the error and initialing and dating the change; however, corrections can only be made to scales by the subject during a study visit and changes must not be made to subject-completed scales after the visit has been completed. Assessments are to be performed according to the schedule shown in Table 1-1.

7.2.1 Efficacy

7.2.1.1 Esophagogastroduodenoscopy with Esophageal Biopsy and Histopathologic Evaluation

The EGD with endoscopy score and biopsy will be performed during the study as outlined in Table 1-1.

An EGD with esophageal, gastric and duodenal biopsies will be required for study participation; the peak eosinophil count per HPF from each esophageal level will be used as a primary measure of efficacy. The qualifying/baseline EGD with biopsies must be performed by a physician at the investigative site within the 6 weeks prior to placebo lead-in visit (Visit 1). Biopsy specimens must be available to be sent to the central pathology lab by at least 2 weeks prior to the placebo lead-in visit to allow sufficient time for processing and central review and determination of eligibility.

Multiple specimens (at least 2 biopsies from each of 3 levels, 6 specimens total) will be obtained from the proximal (3 cm below the cricopharyngeus muscle), mid-esophagus (midpoint between the cricopharyngeus muscle and the gastroesophageal junction), and distal (3 cm above the gastroesophageal junction). Biopsy tissue will be placed in 3 separate vials (1 vial for each of the levels) and sent to the central pathology laboratory for processing of tissue into slides. A central pathologist will determine histologic eligibility for study entry. Peak eosinophil counts of ≥15/HPF in specimens from 2 or more levels of the esophagus will be a requirement for study entry, as determined by a central pathologist. Eosinophil counts, histopathologic features, and

gross endoscopic findings will be evaluated and scored for each EGD. Eight histopathologic epithelial features (basal layer hyperplasia, eosinophil density, eosinophil micro-abscesses, eosinophil surface layering, dilated intercellular spaces, surface epithelial alteration, dyskeratotic epithelial cells, lamina propria fibrosis) will be scored on a 4-point scale (0=normal, 3=worst) for both the severity of the abnormality (ie, grade) and the amount of tissue affected by the abnormality (ie, stage).

Endoscopic findings with separate evaluations of the proximal and distal esophagus will be recorded with respect to 5 categories by the endoscopist: 1) exudates or plaques (grade 0–2); 2) fixed esophageal rings (grade 0–3); 3) edema (grade 0–2); 4) furrows (grade 0–2); and 5) strictures (grade 0–1). An endoscopy score for each category will be calculated and summed for each anatomic location (proximal and distal). The maximum endoscopy score is 10 points for each location, and a Total Endoscopy Score is the sum of the scores for the proximal and distal locations.

In addition, the general appearance of the stomach and duodenum will be assessed by the endoscopist. Biopsies will be taken from the stomach and duodenum for the screening EGD as follows: gastric body (greater curvature): 2 specimens, gastric antrum: 2 specimens, and duodenum (third part or distal): 2 specimens. Biopsies from the stomach should be submitted in one vial; biopsies from the duodenum should be submitted in a separate vial to the central pathology laboratory for processing of tissue into slides. If the pre-treatment biopsy identifies eosinophilia in the stomach and/or duodenum, the subject will be excluded from the study.

At the Week 16 visit (Visit 4) or at early termination (ET), and EGD with esophageal biopsies (at least 2 biopsies from each of 3 levels [proximal, mid-, and distal]) is required. Endoscopic findings will be recorded by the endoscopist. Biopsies will be sent to the central laboratory for processing. A central pathologist will evaluate the slides. Gastric and duodenal biopsies may be repeated at the discretion of the investigator, but are not required.

7.2.1.2 Dysphagia Symptom Questionnaire

Subjects' dysphagia symptoms will be evaluated using a DSQ ePRO device (Appendix 3).

The questionnaire will be completed by subjects daily for a minimum of 3 weeks during the screening period, during the 4-week placebo lead-in period, and during the 12-week treatment period. Each evening before bedtime, subjects will be asked to indicate if they experienced dysphagia symptoms (eg, food passing slowly or food sticking) during that day. Subject must have experienced dysphagia (response of "yes" to question 2 on DSQ) on a minimum of 4 days total and completed the DSQ on ≥70% of days in any 2 consecutive weeks of the screening period and in the 2 weeks prior to the baseline visit (Visit 1). Subjects must fill out the DSQ at least 4 or more days during a given week in order to be compliant.

Visit to visit compliance of DSQ completion will also be assessed by site personnel. Protocol deviations will be documented for subjects who fail to complete the DSQ for 4 or more days in a given week.

Calculations will be performed on daily ePRO entries during a 2-week interval prior to each study visit during the treatment periods. The DSQ score for the co-primary endpoint and secondary endpoints will be calculated by summing the scores of responses to questions 2 and 3 only. Questions 1 and 4 will be excluded from the DSQ score:

- DSQ score= $\frac{\text{(Sum of points from questions 2+3 in the daily DSQ)}\times 14}{\text{Number of diaries reported with non-missing data}}$

The DSQ + pain score for the secondary endpoints will be calculated by summing the scores of responses to questions 2, 3, and 4. Question 1 will be excluded from the DSQ + pain score.

- DSQ + pain score= $\frac{\text{(Sum of points from questions 2+3+4 in the daily DSQ)}\times 14}{\text{Number of diaries reported with non-missing data}}$

The DSQ pain score for the secondary endpoint will be calculated by summing the scores of responses to Question 4 only.

- DSQ pain score=$\frac{\text{(Sum of points from question 4 in the daily DSQ)}\times 14}{\text{Number of diaries reported with non-missing data}}$

7.2.2 Safety

The name and address of each third-party vendor (eg, clinical laboratory) used in this study will be maintained in the investigator's and sponsor's files.

7.2.2.1 Medical and Medication History

Medical History

The investigator must record all clinically or medically relevant information regardless of how much time has elapsed since the date of any diagnosis. Medical history will be classified as EoE or non-EoE by the investigator. The EoE medical history must include any prior history of esophageal strictures and esophageal dilations.

Medication History

Refer to Section 5.1 for full details on collection of prior treatment.

Prior treatment information, including any prior treatments for EoE (eg, dietary, medication, or other), must be recorded on the appropriate CRF page.

7.2.2.2 Physical Examination (Including Height and Weight)

Abnormalities identified at the screening visit (Visit -1) will be documented in the subject's source documents and on the medical history CRF. Changes after the screening visit (Visit -1) will be captured as AEs on the AE CRF page, as deemed by the investigator.

Physical examination assessments at each visit should also include specific assessments for signs of glucocorticoid excess (eg, moon faces, acne, hirsutism, mood swings, insomnia, and depression). Physical examination at the screening visit (Visit -1) will also include Tanner Staging Assessments for subjects <18 years of age until investigator confirms subject is post-puberty.

Height will be collected at the screening visit (Visit -1) and Visit 4 for all subjects. Stadiometers will be used to measure height at Visit -1 and Visit 4 for subjects aged 11-17 years, inclusive. Statural height will be measured by trained site staff using a stabilized stadiometer. The same stadiometer should be used for the baseline and post-treatment measurements. Standard measuring procedures should be followed (eg, removal of socks, shoes, and hats). The stadiometer must be calibrated at least once daily, and as feasible, within 4 hours of measurement. All measurements should be recorded to the nearest 10^{th} of a centimeter (1 mm); measurements for adolescent subjects (11-17 years of age, inclusive), should be measured in triplicate. Please refer to the study manual for additional details.

Weight measurements for adolescent subjects (11-17 years, inclusive) should be measured in duplicate.

7.2.2.3 Adverse Event Collection

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?"). AEs are collected from the time informed consent is signed. (Please refer to Section 8, Adverse and Serious Adverse Events Assessment.)

AE assessments at each visit should also include specific assessments for signs of glucocorticoid excess (eg, moon facies, acne, hirsutism, mood swings, insomnia, and depression).

7.2.2.4 Vital Signs

Vital signs will be conducted after the subject has been supine for at least 5 minutes immediately prior to the assessment and will include blood pressure (systolic and diastolic), heart rate, respirations, and temperature. Blood pressure should be determined by cuff (using the same method, the same arm, and in the same position throughout the study). Any clinically significant deviations from baseline (Visit 1) vital signs that are deemed clinically significant in the opinion of the investigator are to be recorded as an AE.

7.2.2.5 Clinical Laboratory Evaluations

All clinical laboratory assays will be performed according to the laboratory's normal procedures. All subjects must fast overnight prior to collection of clinical laboratory tests.

Reference ranges are to be supplied by the laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

The following clinical laboratory assessments will be performed:

Biochemistry

- alkaline phosphatase
- aspartate aminotransferase
- alanine aminotransferase
- total bilirubin
- total protein
- albumin
- glucose
- blood urea nitrogen
- creatinine
- sodium
- potassium
- chloride
- calcium
- carbon dioxide

Hematology

- hemoglobin
- hematocrit
- mean corpuscular hemoglobin
- mean corpuscular hemoglobin concentration
- mean corpuscular volume
- erythrocyte count
- leukocyte count
- neutrophils
- lymphocytes
- monocytes
- eosinophils
- basophils
- platelet count

Urinalysis

- glucose
- protein
- specific gravity
- pH
- nitrite
- bilirubin
- ketones
- hemoglobin
- urobilinogen
- leukocyte esterase

Other tests

- serum pregnancy
- urine pregnancy
- morning cortisol (6:00-9:00 AM collection)
- ACTH stimulation testing

ACTH stimulation testing will be performed by measuring the levels of cortisol in the blood following the injection of a synthetic form of ACTH. The type of synthetic and route of administration will be per local lab discretion. Blood samples will be collected just prior to and approximately 30 and 60 minutes following the injection.

In the event of clinically significant abnormal laboratory test results, follow-up laboratory tests may be conducted. All subjects with an abnormal ACTH stimulation test or urinary or serum glucose level must be followed closely until resolution. For subjects who discontinue from the treatment period at any time and have an abnormal ACTH stimulation test at the ET visit, subjects will be scheduled for repeat testing approximately 6 weeks post last dose of investigational product to ensure that ACTH levels have normalized. Any clinically significant abnormalities noted in the laboratory tests will be discussed with the medical monitor.

7.2.2.6 Pregnancy Test

A serum β-hCG pregnancy test is performed on all female subjects at the screening visit (Visit -1) and the final treatment evaluation visit (Visit 4) or ET visit. A urine pregnancy test is performed on all female subjects at the placebo lead-in visit (Visit 0), baseline visit (Visit 1), Visit 2, and Visit 3 or if pregnancy is suspected.

7.2.2.7 Dual-energy X-ray Absorptiometry for Bone Mineral Density

Dual-energy X-ray absorptiometry (also referred to as DEXA) scans for determination of BMD and body composition will be performed in subjects aged 11-17 years, inclusive, as outlined in Table 1-1.

The sites for DXA measurement will be the lumber spine (L1-L4 preferred) and total body less head (Bachrach and Sills, 2011; Gordon et al., 2008; ISCD, 2014). The same DXA machine and software should be used for the baseline and post-treatment scans. The DXA manufacturer, model, and software version should be recorded in the CRF.

7.2.3 Other Assessments

7.2.3.1 Health-related Quality-of-life Assessment

EuroQol-5 Dimensions 3-level Questionnaire

The EuroQol-5 Dimensions 3-level (EQ-5D-3L; for subjects ≥18 years) and the EuroQol-5 Dimensions Youth (EQ-5D-Y; for subjects 11-17 years of age, inclusive) will be performed during the study as outlined in Table 1-1.

The EQ-5D-3L is a standardized measure of health status for use in adult populations that was developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQol, 1990). The EQ-5D-3L provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of healthcare as well as in population health surveys. It consists of a 5-item descriptive system that measures 5 dimensions of health, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is represented by a single item with 3 levels of responses. The EQ-5D-3L will be completed by the subject. The EQ-5D-3L should take the subject a few minutes to complete.

The EQ-5D-Y is a self-report version of the EQ-5D that was developed by the EuroQol Group for use in younger populations (Wille et al., 2010). The EQ-5D-Y provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of healthcare as well as in population health surveys. It consists of a 5-item descriptive system that measures 5 dimensions of health, including mobility, looking after myself, doing usual activities, having pain or discomfort, and feeling worried, sad, or unhappy. Each dimension is represented by a single item with 3 levels of responses. The EQ-5D-Y will be completed by the subject and should take a few minutes to complete.

Pediatric Quality of Life – EoE Questionnaire

The PedsQL-EoE questionnaire will be completed by subjects 11-17 years of age, inclusive, and their parent or legal guardian, as outlined in Table 1-1.

The PedsQL-EoE is a modular, disease-specific instrument designed to measure HRQoL in children and adolescents (2-18 years of age) with EoE (Franciosi et al., 2013; PROQOLID, 2015). The PedsQL-EoE module consists of 35 items for children and teenagers encompassing the following 7 scales: 1) Symptoms I (6 items; chest/throat/stomach pain and nausea/vomiting), 2) Symptoms II (4 items; trouble swallowing), 3) Treatment (5 items; treatment barriers), 4) Worry (6 items; worries about treatment and disease), 5) Communication (5 items; communication with others about EoE), 6) Food and Eating (4 items; food and eating allergies and limitations), and 7) Food Feelings (3 items; emotions associated with food allergies). The PedsQL-EoE should take the subject and parent approximately 10 minutes to complete.

Adult Eosinophilic Esophagitis Quality of Life Questionnaire

The EoE-QoL-A will be performed in subjects ≥18 years of age as outlined in Table 1-1.

The EoE-QoL-A is a disease-specific measure of HRQoL in adult patients (≥18 years of age) with EoE (Taft et al., 2011). The EoE-QoL-A consists of a 30-item test with 5 subscales: eating/diet impact, social impact, emotional impact, disease anxiety, and choking anxiety. The EoE-QoL-A will be completed by the subject and should take the subject approximately 15 minutes to complete.

7.2.3.2 Severity of Disease Assessments

Patient Global Impression of Severity

The PGI-S will be performed in all subjects as outlined in Table 1-1.

The PGI-S is a global index (Appendix 4) that can be used to rate the severity of a specific condition - in this case, dysphagia in EoE. Subjects will be asked to rate the severity of their dysphagia over the last 7 days using a 5-point scale.

7.2.4 Clinical Pharmacology Assessments

Blood samples will be collected from adult subjects (≥18 years of age) as outlined in Table 1-1 to measure plasma concentrations of budesonide. Subjects who do not participate in pharmacokinetic sampling will not be discontinued from the study, and lack of participation will not be a considered protocol deviation.

Actual pharmacokinetic blood sample collection times vs time of dosing will be monitored. The sponsor's expectation is that the investigator will ensure that every effort will be made to collect all pharmacokinetic blood samples at the precise protocol scheduled time. Pharmacokinetic blood collection must not deviate from the nominal collection time set forth in the protocol by more than ± 5 minutes for samples drawn within 4 hours post-dose or by more than ± 15 minutes for samples drawn after 4 hours post-dose. Samples drawn outside these parameters will be considered a protocol deviation.

Blood samples (4 mL) for pharmacokinetic analysis will be drawn by direct venipuncture into K2EDTA tubes, capped and mixed by inversion (×3), and chilled immediately on crushed ice. The actual blood collection time will be recorded in the subject's source documents and on the appropriate CRF page (24-hour format). After applying a tourniquet, venous blood will be drawn with a disposable needle. If a catheter is used, the first milliliter of blood on each sampling occasion will be discarded. Saline can be used to keep catheters patent.

Within 15 minutes following each sample collection, the blood tubes will be centrifuged at approximately 1500 g (15 minutes, 4°C). The separated plasma will be decanted into appropriately labeled primary and backup polypropylene tubes via a plastic pipette. All samples will be stored nominally at -20°C, and the freezer temperature will be controlled, monitored, and recorded during the storage period until the samples are shipped to the designated bioanalytical laboratory for analysis.

For additional information detailing sample handling, storage, and shipment, see Appendix 5.

7.2.5 Volume of Blood to Be Drawn from Each Subject

Table 7-1: Approximate Volume of Blood to Be Drawn from Each Subject

Assessment		Sample Volume (mL)	Number of Samples	Approximate Total Volume (mL)
Pharmacokinetic samples[a]		5	9	45
Safety	Biochemistry and β-hCG[b]	6	6	36
	ACTH	2	4	8
	Cortisol	2	4	8
	Hematology	2	6	12
Total mL				109

ACTH=adrenocorticotropic hormone; β-hCG=beta-human chorionic gonadotropin

[a] If a catheter is used, the first mL is to be discarded; then take 4 mL into appropriate tube for pharmacokinetic sample. A total of 5 mL of blood drawn has been used in determination of sample volume.

[b] β-hCG testing is for females only.

During this study, it is expected that approximately 109 mL of blood will be drawn from all subjects, regardless of sex.

Note: The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment; however, the total volume drawn over the course of the study should be approximately 109 mL. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments may be combined.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An **AE** is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 7.1.4. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the CRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE CRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pretreatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate CRF).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related." Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related" based on the definitions in Table 8-1. The causality assessment must be documented in the source document.

Table 8-1: Adverse Event Relatedness

Term	Relationship Definition
Not Related	Unrelated to study drug.
Possibly Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of study drug, but which could also be explained by concurrent disease or other drugs or chemicals.
Probably Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of study drug, unlikely to be attributable to concurrent disease or other drugs and chemicals and which follows a clinically reasonable response on de-challenge. The association of the clinical event or laboratory abnormality must also have some biologic plausibility, at least on theoretical grounds.
Definitely Related	The event follows a reasonable temporal sequence from administration of the study drug, follows a known or suspected response pattern to the study drug, is confirmed by improvement upon stopping the study drug (dechallenge), and reappears upon repeated exposure (rechallenge). Note that this is not to be construed as requiring re-exposure of the patient to study drug; however, the determination of definitely related can only be used when recurrence of event is observed.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the CRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved With Sequelae
- Recovering/Resolving
- Unknown

8.1.4 Symptoms of the Disease under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE.

8.1.5 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory or vital sign assessment can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory or vital sign values which were not present at the pretreatment value observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory or vital sign parameter is clinically significant and therefore represents an AE.

8.1.6 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 7.1.4.

Any report of pregnancy for any female study participant must be reported within 24 hours to the Shire Global GDS Department using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO/Shire medical monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days postpartum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β-HCG test or ultrasound result will determine the pregnancy onset date.

8.1.7 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- **Overdose** – Intentional or unintentional intake of a dose of an investigational product exceeding a pre-specified total daily dose of 4 mg of the product.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of the unassigned treatment is/are always reportable as a medication error.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

All investigational product provided to pediatric subjects should be supervised by the parent/legally authorized representative/caregiver.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is the investigator brochure, which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global GDS Department and the CRO medical monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.7) unless they result in an SAE.

The investigator must complete, sign, and date the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested) and fax or e-mail the form to the Shire Global GDS Department. A copy of the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol (and any applicable follow-up reports) must also be sent to the CRO medical monitor using the details specified in the emergency contact information section of the protocol.

8.2.3 Serious Adverse Event Definition

A **SAE** is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for preexisting conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of

such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.4 and must be reported to the Shire GDS Department and the medical monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire GDS Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, leading up to the onset date of the SAE, or following the resolution date of the SAE must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject's death (ie, the SAE was noted as the primary cause of death) must have "fatal" checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered as not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product).

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The sponsor and the clinical CRO are responsible for notifying the relevant regulatory authorities/US central Institutional Review Boards (IRBs) of related, unexpected SAEs.

In addition, the sponsor and the clinical CRO are responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP621 program.

The investigator is responsible for notifying the local IRB, local ethics committee (EC), or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the CRF. A study monitor will visit each site in accordance with the monitoring plan and review the CRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is randomized, it is expected that site personnel will complete the CRF entry within approximately 3 business days of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the CRO's data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Data Handling Considerations

Data that may potentially unblind the treatment assignment (ie, investigational product serum concentrations, treatment allocation, and investigational product preparation/accountability data) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, prior to unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

9.4 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent. All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC, USA) version 9.1 or higher.

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

In addition to a final SAP for the final analysis, a separate interim SAP for the interim analysis will be finalized prior to unblinding and performing the analysis. The SAP for the final analysis will be finalized prior to final database lock and performing analysis (ie, unblinding) to preserve the integrity of the statistical analysis and study conclusions.

9.5 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

A planned interim analysis for each of the co-primary endpoints will take place after 50% of all randomized subjects have either completed the study or prematurely withdrawn from the study, whichever comes first. The purpose of the unblinded interim analysis is to reassess the appropriateness of assumptions used for each of co-primary efficacy endpoints when the study was designed. The reassessment of the sample size will utilize the conditional power approach under certain conditions that do not inflate the type I error (Mehta and Pocock, 2011). The planned interim analysis will be conducted by an external independent statistical (EIS) group; the individuals involved in the day-to-day conduct of the trial will not be involved in the interim analysis or have access to the results of the interim analysis. The Sponsor will only be notified by the EIS group if any recommendation of increasing the sample size is needed from the conditional power; this will be detailed in the prespecified interim SAP including a potential maximum sample size to be increased if deemed necessary.

A very minimal fraction of alpha (0.0001) will be spent at the interim analysis as the trial will not stop due to the interim results. The final analysis will use 4.99% for each of the co-primary endpoints in order to preserve an overall type I error at 5% level.

9.6 Sample Size Calculation and Power Considerations

Based on at least a 30-percentage-point reduction in DSQ score, there is an expected difference between treatment response proportions of 69% and 45% in the OBS 2 mg twice daily (qAM, pc, and hs) and placebo groups, respectively. The original protocol noted that a total of 228 subjects (152 subjects randomized to OBS and 76 subjects randomized to placebo) are required to achieve 90% power at the significance level of 0.0499 (2-sided) using a 2-group chi-square test with unequal allocation 2:1 to treatment groups (OBS 2 mg twice daily and placebo). With the specified number of subjects per treatment group, the study will be powered at 99% assuming histological response proportions of 40% and 3% in the OBS 2 mg twice daily and placebo groups, respectively. The overall study power for the co-primary endpoints was estimated to be at least 85%. Therefore, approximately 228 (approximately 152:76 OBS and placebo subjects, respectively) were to be randomized in the study to allow for a loss of approximately 5% of subjects due to dropouts or invalid data. Expected response and dropout rates are based on observation from the Phase 2 study (MPI 101-06).

In this protocol amendment, in order to ensure that a sufficient number of subjects will complete this study and enroll in the treatment extension study, up to approximately 420 subjects will be enrolled in the placebo lead-in period to allow for approximately 306 subjects to be randomized into the double blind period of this study (approximately 204:102 OBS and placebo subjects, respectively). With a total of 306 randomized subjects in this study, using the same assumptions

for the co-primary endpoints and the dropout rate, the overall study power for the co-primary endpoints is estimated to be at least 95%.

9.7 Study Population

The **safety set** will include all subjects who receive at least 1 dose of any double-blind investigational product.

The **intent-to-treat (ITT)** set will include all randomized subjects. Subjects will be analyzed according to their assigned treatment, regardless of the treatment actually received.

The **full analysis set (FAS)** will include all randomized subjects who received at least 1 dose of a double-blind investigational product and have both an evaluable post-baseline biopsy in the treatment period (ie, peak eosinophil count is reported for at least 2 esophageal levels) and a post-baseline DSQ score.

The **per-protocol (PP)** set will include all subjects in the FAS excluding subjects with protocol violations. The PP set will be identified prior to unblinding the treatment assignments by a team consisting of, at a minimum, a physician and a statistician from Shire.

The **pharmacokinetic set** will include all subjects in the safety set for whom the primary pharmacokinetic data are considered sufficient and interpretable.

9.8 Efficacy Analyses

The primary, key secondary and secondary efficacy analyses will be performed on the ITT set and presented by treatment group.

Data collected at the baseline visit (Visit 1) will be used as the baseline for all efficacy analyses.

9.8.1 Primary Efficacy Endpoints

The co-primary efficacy endpoints are the following:

- Histologic response, defined as a peak eosinophil count of ≤6/HPF across all available esophageal levels at the final treatment period evaluation (Visit 4)
- Dysphagia symptom response, defined as ≥30% reduction in the DSQ combined score (questions 2+3) from baseline to the final treatment period evaluation (Visit 4)

The co-primary efficacy endpoints will be analyzed based on the ITT set. Each of the co-primary efficacy endpoints is a binary response (ie, responders vs non-responders); the endpoint will be analyzed using the Cochran-Mantel-Haenszel (CMH) test adjusting for age group (either <18 years or ≥18 years) and diet restriction for EoE or other health-related conditions (no diet restriction or any diet restriction). The adjusted odds ratio of being a responder on each of the co-primary endpoints for the OBS 2 mg twice daily group vs placebo group and associated 95%

confidence interval (CI) will be provided. Subjects who withdraw without providing efficacy data at the final treatment period evaluation (Visit 4, Week 16) will be classified as non-responders in the primary efficacy analysis.

Additionally, the proportion of responders based on each of the co-primary endpoints for each treatment group will be summarized, and their respective 95% CI will be reported. The difference in the proportion of responders between the 2 treatment groups and the corresponding 95% CI will also be summarized.

The following sensitivity and supportive analyses will be performed for the co-primary to evaluate the robustness of the results from the primary analysis methods:

- Each of the co-primary efficacy endpoints will be analyzed using a logistic regression with the effects of treatment group, age group (either <18 years or ≥18 years) and diet restriction for EoE or other health-related conditions (no diet restriction or any diet restriction). The odds ratio of being a responder on each of the co-primary endpoints for the OBS 2 mg twice daily group vs placebo group and associated 95% CI will be estimated from the final model. Subjects who withdraw without providing efficacy data at the final treatment period evaluation (Visit 4, Week 16) will be classified as non-responders in the primary efficacy analysis.

- Analyses will be repeated using the FAS and the PP set.

- Analyses will be repeated by considering subjects who withdraw without providing efficacy data at the final treatment period evaluation (Visit 4) and will be classified as responders.

9.8.1.1 Missing Data Imputation

Method 1: Distribution-based Imputation

The subjects with missing co-primary efficacy endpoints will be assigned randomly according to the distribution of responders with available data for each of the co-primary endpoints (ie, those with non-missing data) across the 2 treatment groups by strata (see Table 9-1).

Table 9-1: Percentage of Responders for All Available Data (ie, Non-missing Data) by Strata

Strata	No	Yes
<18 years	X0%	X1%
≥18 years	Y0%	Y1%

For instance, if there are N subjects with missing data in strata 1 (age <18 years), then X0%*N subjects will be randomly assigned as non-responders and X1%*N subjects will be randomly assigned as responders.

Conversely, if there are M subjects with missing data in strata 2 (age ≥18 years), the Y0%*M subjects will be randomly assigned as non-responders and Y1%*M subjects will be randomly assigned as responders.

Method 2: Multiple Imputations

Multiple imputation (MI) methods will utilize the SAS procedures PROC MI and PROC MIANALYZE. The MI procedure will involve fitting a logistic regression model with the binary outcome (responders vs non-responders) as the dependent variable and the age group and the treatment group as the independent variables. The MI procedure will generate 10 version datasets with binary outcome imputed from the subjects with complete data. Once the missing values are imputed and each dataset is created, the results will be appropriately pooled across the multiply imputed estimated regression coefficients and their standard errors using PROC MIANALYZE.

Other sensitivity analyses will be explored, and details will be provided in the SAP.

9.8.2 Secondary Efficacy Endpoints

9.8.2.1 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is defined as the change in DSQ combined score (questions 2+3) from baseline to the final treatment period evaluation (Visit 4). The change from baseline DSQ score at the final treatment period evaluation (Visit 4) will be analyzed using an analysis of covariance (ANCOVA) model with treatment group and age group as factors and the baseline DSQ score as a continuous covariate.

The additional secondary efficacy endpoints are the following:

- Change in total endoscopy score, as measured by the EREFS classification, from baseline to the final treatment period evaluation (Visit 4)
- Peak eosinophil count <15/HPF across all available esophagus levels at the final treatment period evaluation (Visit 4)
- Peak eosinophil count ≤1/HPF across all available esophagus levels at the final treatment period evaluation (Visit 4)
- Change from baseline in the peak eosinophil count to the final treatment period evaluation (Visit 4) for each available esophageal level (proximal, mid-, and distal)
- Change from baseline in the histopathologic epithelial features combined total score (grade and stage) to the final treatment period evaluation (Visit 4)
- Dysphagia symptom response (binary response), defined as a ≥50% reduction in the DSQ combined score (questions 2+3), from baseline to the final treatment period evaluation (Visit 4)
- Change from baseline in the DSQ combined score (questions 2+3) over time including post baseline visits

- Cumulative distribution function curves for the change and the percent change in the DSQ score from baseline to the final treatment period evaluation (Visit 4)
- Overall binary response I, defined as a reduction in the DSQ score of ≥30% from baseline to the final treatment period evaluation (Visit 4) and a peak eosinophil count of ≤6/HPF across all esophageal levels at the final treatment period evaluation (Visit 4)
- Overall binary response II, defined as a reduction in the DSQ score of ≥50% from baseline to the final treatment period evaluation (Visit 4) and a peak eosinophil count of ≤6/HPF across all esophageal levels at the final treatment period evaluation (Visit 4)
- Change in the DSQ + pain score (questions 2+3+4) from baseline to the final treatment period evaluation (Visit 4)
- Change in the DSQ pain score (question 4) from baseline to the final treatment period evaluation (Visit 4)

The binary response endpoints will be analyzed using the same logistic model as the co-primary efficacy endpoints.

Continuous endpoints will be analyzed as a change from baseline using an ANCOVA model that includes treatment group and age group as factors and baseline score as a covariate.

The analyses for all secondary efficacy endpoints (including the key secondary efficacy endpoint) will be carried out using 2-sided tests at the 5% level of significance. For each of the secondary efficacy endpoints, the treatment difference, corresponding 95% CI for the difference and treatment comparison p-value for testing the null hypothesis of zero treatment effect based on the final statistical model (ie, either logistic regression model or ANCOVA model) will be provided.

9.8.3 Exploratory Efficacy Endpoint

The exploratory endpoint that will be explored is the following:

[redacted]

9.9 Safety Analyses

Safety data will be presented for the safety set by treatment group.

The safety data collected at the baseline visit (Visit 1) or the last preceding visit if not collected at Visit 1 will be used as the baseline value for safety analyses.

TEAEs are defined as AEs that start or deteriorate on or after the first dose of investigational product (Visit 1) and no later than 3 days following the last dose of investigational product. However, for any subjects who die during the study (ie, the date of death is between the date of first dose of investigational product and the date of study discontinuation entered by the site,

inclusive), all AEs (including those resulting in death) that occur during the study will be considered as TEAEs irrespective of the last dose and will be included in the TEAE summaries.

AEs will be coded using MedDRA. The number of events, incidence, and percentage of TEAEs will be calculated overall by system organ class (SOC), preferred term (PT), and treatment group. TEAEs will be further summarized by severity and relationship to investigational product. AEs related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.

Safety parameters will include monitoring of AEs, physical examinations, stadiometry, vital signs (temperature, systolic and diastolic blood pressure, pulse, and respiratory rate), weight and height assessments, DXA scans for BMD and body composition measurements (for adolescents aged 11-17 years, inclusive), clinical laboratory tests (hematology, chemistry, urinalysis; serum pregnancy test, if appropriate), and ACTH stimulation tests. To account for the effects of puberty in adolescent subjects (11-17 years of age, inclusive), BMD z-scores will be adjusted for height z-scores using the Bone Mineral Density in Childhood Study calculator (BMDCS 2015) (http://www.bmdcspublic.com). Safety parameters will be descriptively summarized by treatment group at baseline and for each post-baseline visit.

9.10 Other Analyses

9.10.1 Health-related Quality-of-life Analyses

The health economics and outcomes research endpoints that will be explored are the following:

- EoE-QoL-A Questionnaire (Taft et al., 2011)
- EQ-5D (EQ-5D-3L or EQ-5D-Y, according to subject's age)
- PedsQL-EoE

The submodules of the EoE-QoL-A and PedsQL-EoE will be assessed in addition to the overall score with a focus on emotional and physical elements. For all HRQoL analyses, change from baseline to the final treatment period evaluation (Visit 4) will be assessed.

9.10.2 Pharmacokinetic Analyses

Pharmacokinetic parameters will be determined from the plasma concentration-time data for budesonide by non-compartmental analysis for subjects who provide sufficient numbers of intensive PK samples. For all subjects who provide PK samples (ie, limited or intensive samples) population PK analysis will be conducted. A report for the population PK analysis will be provided separately from the clinical study report (CSR).

The pharmacokinetic endpoints will include but not be limited to those listed in Table 9-2.

Table 9-2: Pharmacokinetic Parameters

Parameter	Definition
$AUC_{0\text{-}tau}$	Area under the curve for the defined interval between doses
C_{max}	Maximum concentration occurring at t_{max}
t_{max}	Time of maximum observed concentration sampled during a dosing interval

Summary statistics (number of observations, mean, standard deviation, coefficient of variation, median, maximum, minimum, and geometric mean) will be determined for all pharmacokinetic parameters by overall and by week. Plasma concentrations at each nominal sampling time will also be summarized using descriptive statistics.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and its updates, and local ethical and legal requirements.

The name and address of each third-party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and CRFs in accordance with current good clinical practice (GCP) and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied to the CRO as necessary.

10.1.3 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.4 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the community guideline on GCP. This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance.

10.1.5 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study, which has been posted to a designated public website, will be updated accordingly.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub-investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal investigator is appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any coinvestigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

Electronic CRFs are supplied by the CRO and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto CRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Case report forms must be completed by the investigator or designee as stated in the site delegation log.

All data from the investigator will have separate source documentation; no data will be recorded directly onto the CRF.

All data sent to the sponsor must be endorsed by the investigator.

The data from the central pathologist will be recorded directly onto paper CRFs.

The clinical research associate (CRA)/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include but are not limited to subject’s medical file, original clinical laboratory reports, and histology and pathology reports.

All key data must be recorded in the subject’s medical records.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The CRA/study monitor (and auditors, IRB/EC, or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays, etc.).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

Laboratory samples (blood and urine) will be stored by the clinical laboratory for as long as is required to:

- Complete the study
- Publish data related to the study
- Support any regulatory applications for the study drug

Samples could be stored for up to about 15 years.

Biopsy specimens should be stored by the local laboratory per federal and local regulations.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for

ongoing consultation, or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent (or assent as applicable for subjects <18 years of age) from all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally authorized representative, as applicable, is requested to sign and date the subject's informed consent form or a certified translation, if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

Within the source documents, site personnel should document instruction of and understanding by the parent/legally authorized representative/caregiver of the safe, responsible storage and administration of investigational product to the study subject.

The principal investigator provides the sponsor with a copy of the consent form consent (or assent as applicable for subjects <18 years of age) that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB's/EC's written favorable opinion/approval of these documents must be provided to the sponsor, prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information, and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

For sites within the EU, the applicant for an EC opinion can be the sponsor or the investigator or, for multicenter studies, the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent (or assent as applicable for subjects <18 years of age) documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the CRO has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; for sites within the EU, this can be done by the sponsor or the investigator or, for multicenter studies, the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with HIPAA of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the CRO/sponsor.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives' reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market SHP621; national or local regulatory authorities; and the IRBs/ECs which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (eg, to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to and used in other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purposes of any such transfer would include supporting regulatory submissions, conducting new data analyses to publish or present the study results, or answering questions asked by regulatory or health authorities.

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (eg, Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2-4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral, or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish, and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single-site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors current standards. Participation as an investigator does not confer any rights to authorship of publications.

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12. APPENDICES

Appendix 1 Protocol History

Document	Date	Global/Country/Site Specific
Protocol Amendment 2	26 Jan 2018	Global
Protocol Amendment 1	16 Dec 2015	Global
Original Protocol	31 Aug 2015	Global

Appendix 2 Scales and Assessments

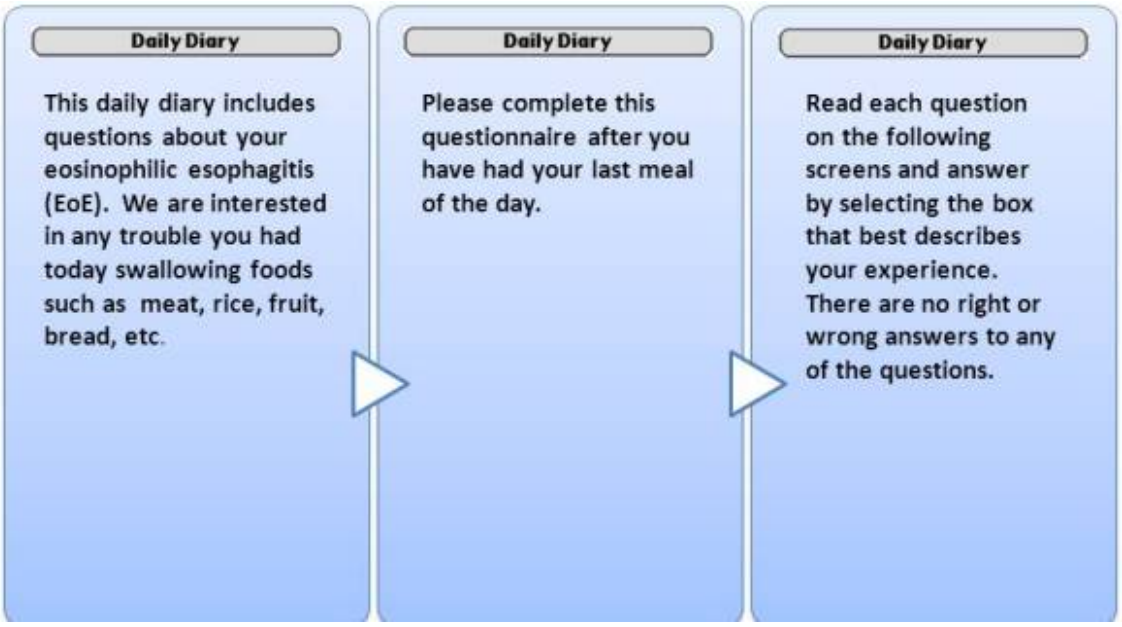
The following scales/assessments will be utilized in this study:

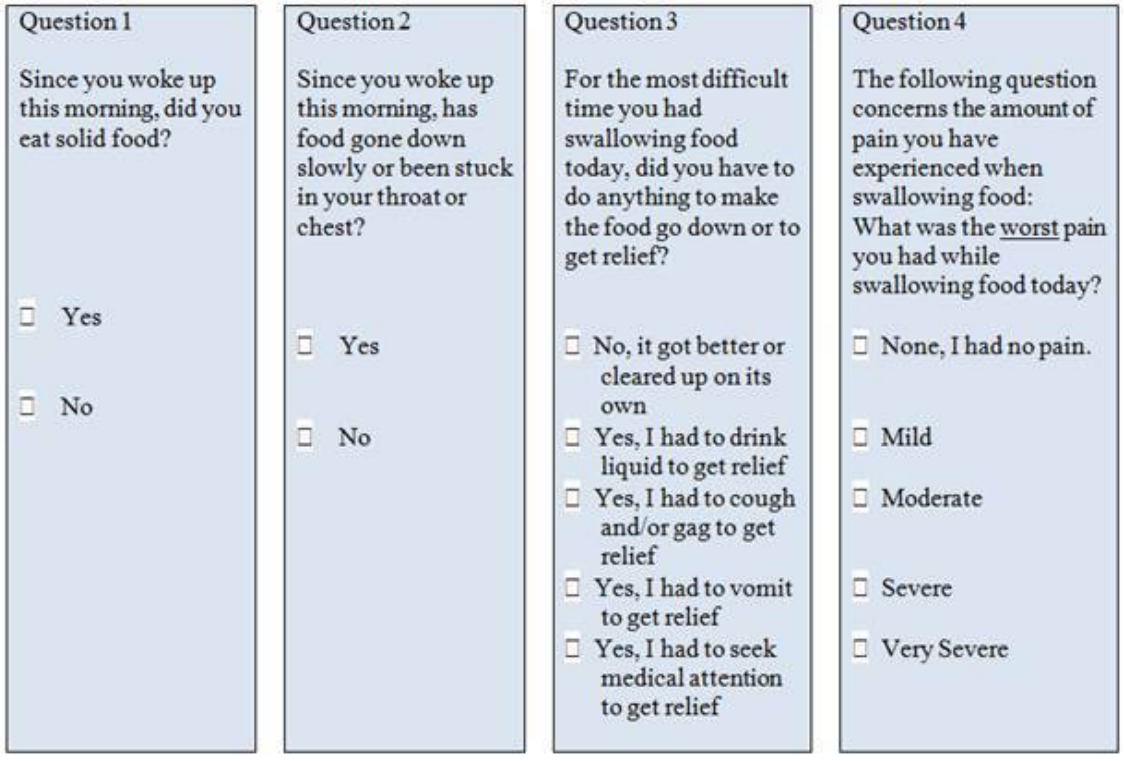
Full Title of Scale/Assessment	Completed By
DSQ	Subject
EQ-5D-3L (for subjects ≥18 years) EQ-5D-Y (for subjects 11-17 years of age, inclusive)	Subject
PedsQL-EoE (subjects 11-17 years of age, inclusive)	Subject and parent or legal guardian
EoE-QoL-A (subjects ≥18 years of age)	Subject
PGI-S	Subject
Tanner Staging Assessment (for subjects 11-17 years of age, inclusive)	Site
EREFS	Site

DSQ=Dysphagia Symptom Questionnaire; EoE-QoL-A=Adult Eosinophilic Esophagitis Quality of Life; EQ-5D=EuroQol; EREFS=EoE Endoscopic Reference Score; PedsQL-EoE=Pediatric Quality of Life Inventory – EoE; PGI-S=Patient Global Impression of Severity

A separate master file containing each scale/assessment listed above will be provided to the site. Updates to scales/assessments during the study (if applicable) will be documented in the table above, and a new master file containing the revised scale/assessment will be provided to the site.

Appendix 3 Dysphagia Symptom Questionnaire ePRO for EoE





Appendix 4 Patient Global Impression of Severity

How would you rate the overall severity of your dysphagia (difficulty swallowing) over the past 7 days?

Rating	Description
0	No dysphagia
1	Mild dysphagia
2	Moderate dysphagia
3	Severe dysphagia
4	Very severe dysphagia

Appendix 5 Biosciences Generic Clinical Protocol Insert

Blood Sample Collection

Blood samples will be collected at the times specified in Table 1-1 to measure plasma concentrations of budesonide. Potential metabolites may also be determined as appropriate.

Blood samples 4 mL for pharmacokinetic analysis will be drawn by in-dwelling catheters or direct venipuncture into K2EDTA tubes, capped and mixed by inversion (x3), and chilled immediately on crushed ice. The actual time that the sample was obtained will be recorded in the subject's source document and on the appropriate CRF page. After applying a tourniquet, venous blood will be drawn with a disposable needle. If a catheter is used, the first milliliter of blood on each sampling occasion will be discarded. Saline can be used to keep catheters patent.

Blood/Plasma Sample Handling

Samples should be kept on crushed ice until plasma is separated as soon as possible after collection within <15 minutes, unless advised otherwise by refrigerated centrifugation (4°C, 1500 rpm 15 minutes). The separated plasma will be decanted into appropriately labeled polypropylene tubes via a plastic pipette. All samples will be stored at approximately -20°C or colder and the freezer temperature will be controlled, monitored, and recorded during the storage period until they are transferred in the frozen state to a designated bioanalytical contract laboratory. Samples will remain frozen at -20°C or colder until analysis.

Plasma sample tubes for bioanalysis must be freezer-safe and identified with freezer-safe labels provided by the central laboratory. The labels will contain the following information:

- Study number
- Subject identifier (randomization number)
- Matrix identifier (plasma)
- Visit
- Nominal time

Shipment of Plasma Samples

Plasma samples should be double-bagged to contain leaks and packed with a sufficient quantity of dry ice to ensure that they remain frozen for at least 72 hours to allow for delays in shipment. All applicable shipping regulations must be followed. Shipments should be scheduled so that no samples arrive on the weekend and should be shipped Monday to Wednesday only.

Plasma samples, along with the corresponding documentation, will be shipped to:

PPD

2 Tesseneer Drive

Highland Heights, KY 41076, USA

Email: [redacted]

Phone: [redacted] **or** [redacted], [redacted]

Fax: [redacted]

Plasma samples will be stored nominally at -20°C prior to and after analysis at Quest Pharmaceutical Services (QPS) until their disposal is authorized by Shire.

Assay Methodology

Drug analysis will be performed at QPS under the guidance of the NCE group at Shire. Plasma sample analysis will be performed according to the bioanalytical study plans prepared for the study.

Plasma samples will be analyzed at QPS for budesonide using the most current validated bioanalytical method.

In addition, selected plasma samples may be used to investigate incurred sample reproducibility (full details will be described in the bioanalytical study plan). The presence of other metabolites or artifacts may be monitored or quantified as appropriate.

Raw data will be stored in the archives at QPS.