

CLINICAL STUDY PROTOCOL

NCT Number: NCT02736409

Study Title: A Phase 3, Multicenter, Double-blind Extension Study to Evaluate Maintenance of Efficacy of Oral Budesonide Suspension (OBS) and Long-term Treatment Effect of OBS in Adolescent and Adult Subjects (11 to 55 Years of Age, Inclusive) with Eosinophilic Esophagitis (EoE)

Study Number: SHP621-302

Protocol Version and Date:

Original Protocol: 05 December 2015

Amendment 1: 22 June 2016

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PROTOCOL: SHP621-302

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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: 05 Dec 2015

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Sponsor's (Shire) Approval

Signature:

[Redacted Signature]
[Redacted Title]
MD

Date:

[Redacted Date]

Acknowledgement

I have read this protocol for Shire Study SHP621-302.

Title: A Phase 3, Multicenter, Double-blind Extension Study to Evaluate Maintenance of Efficacy of Oral Budesonide Suspension (OBS) and Long-term Treatment Effect of OBS in Adolescent and Adult Subjects (11 to 55 Years of Age, Inclusive) with Eosinophilic Esophagitis (EoE)

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Signature: _____

Date: _____

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ABBREVIATIONS

ACTH	adrenocorticotrophic hormone
AE	adverse event
β-hCG	beta-human chorionic gonadotropin
BMD	bone mineral density
CFR	Code of Federal Regulations
CI	confidence interval
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
EMA	European Medicines Agency
EoE	eosinophilic esophagitis
[REDACTED]	[REDACTED]
ePRO	electronic patient-reported outcome
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
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
[REDACTED]	[REDACTED]
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
OBS	oral budesonide suspension
pc	after meals
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
PP	per-protocol
PPI	proton pump inhibitor
qAM	every morning
SAE	serious adverse event
SAP	statistical analysis plan
SAS [®]	statistical analysis system
TEAE	treatment-emergent adverse event
UK	United Kingdom
US	United States

STUDY SYNOPSIS

Protocol number: SHP621-302	Drug: SHP621, oral budesonide suspension (OBS)
Title of the study: A Phase 3, Multicenter, Double-blind Extension Study to Evaluate Maintenance of Efficacy of Oral Budesonide Suspension (OBS) and Long-term Treatment Effect of OBS in Adolescent and Adult Subjects (11 to 55 Years of Age, Inclusive) with Eosinophilic Esophagitis (EoE)	
Number of subjects (total and for each treatment arm): Approximately 200 subjects (88%) who are randomized in the SHP621-301 study are estimated to complete the SHP621-301 study and enroll in this treatment extension study based on enrollment observed in the Phase 2 study (MPI 101-06).	
Investigator(s): Multicenter study	
Site(s) and Region(s): Approximately 60 sites in North America	
Study period (planned): April 2016 – April 2019	Clinical phase: 3
Objectives Primary: <ul style="list-style-type: none">To evaluate the maintenance of efficacy over 36 weeks, as measured by the peak eosinophilic count and the Dysphagia Symptom Questionnaire (DSQ) score, through a randomized withdrawal design for subjects who responded to 12 weeks of OBS treatment (2 mg twice daily) with a peak count of ≤ 6 eosinophils (eos)/high-powered field (HPF) across all available esophageal levels at the final treatment visit and a $\geq 30\%$ reduction in DSQ score from baseline during the SHP621-301 induction study Key Secondary: <ul style="list-style-type: none">To evaluate the long-term treatment response over an extended period of 36 weeks for subjects who were randomized to OBS treatment but did not respond after 12 weeks in the SHP621-301 induction study (subject did not have a peak count of ≤ 6 eos/HPF across all available esophageal levels at the final treatment visit and/or a $\geq 30\%$ reduction in DSQ score from baseline) Secondary: <ul style="list-style-type: none">To evaluate the response to OBS treatment over 36 weeks for subjects who received placebo in the SHP621-301 induction studyTo evaluate the effect of reinitiating OBS treatment for subjects who relapse after being randomized to placebo in the randomized withdrawal period (treatment-withdrawal-treatment reinitiation)To assess endoscopically identified esophageal features as measured by the EoE Endoscopic Reference Score (EREFS)To evaluate other response criteria based on histology and DSQTo evaluate the long-term safety and tolerability of OBS treatment Exploratory: <ul style="list-style-type: none">	

<ul style="list-style-type: none">• [REDACTED]
<p>Rationale:</p> <p>Currently there is no approved medication for the treatment of EoE. This Phase 3 study is being conducted to determine response to withdrawal of OBS, maintenance of response, extended therapy response, and response to intermittent therapy by evaluating both eosinophil counts and DSQ in adolescent and adults treated or withdrawn from OBS in this treatment extension study.</p>
<p>Investigational product, dose, and mode of administration:</p> <p>The assessments from the SHP621-301 final treatment evaluation visit (Visit 4) will be used as the screening assessments (Visit 0) of this treatment extension study. At the SHP621-301 final treatment evaluation visit, subjects will be dispensed blinded investigational product (based on treatment assignment in SHP621-301) that will last for up to 4 weeks prior to enrolling into this treatment extension study. A 4-week screening period is required to allow for blinded treatment response information (reduction in DSQ from baseline and eosinophilic count as determined by a central reader) collected during the SHP621-301 final treatment evaluation visit to be entered into the interactive web-based response system (IWRS) by the unblinded data team who is independent from the blinded study team and not involved with the day-to-day conduct of the study. Once information is available, subjects will return for the randomization visit (Visit 1) to receive investigational product as follows:</p> <ul style="list-style-type: none">• Subjects who were assigned to OBS treatment and who fully responded in the SHP621-301 study (≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ at the final treatment evaluation visit) will enter a randomized withdrawal period to receive either OBS 2 mg twice daily or placebo at a 1:1 ratio• Subjects who were assigned to OBS treatment and did not respond or partially responded to OBS treatment in the SHP621-301 study will receive OBS 2 mg twice daily• Subjects who were assigned to placebo in the SHP621-301 study will receive OBS 2 mg twice daily <p>Subjects, site staff, and study team members will remain blinded to treatment assignment and individual subject histology and individual subject DSQ data from the SHP621-301 study (post randomization) and this extension study until database lock occurs for this extension study.</p> <p>During the 36-week double-blind treatment extension study, subjects will receive oral administration of 10 mL of 0.2 mg/mL (2 mg) investigational product twice daily (every morning [qAM] after meals [breakfast, pc] and at bedtime [hs]; 4 mg total/day), with no ingestion of food or liquids permitted for 30 minutes after investigational product administration. Dosing regimens are consistent with the regimens used in the Phase 2 MPI 101-06 study and Phase 3 SHP621-301 study:</p> <ul style="list-style-type: none">• Placebo twice daily group: placebo qAM (pc) and hs• OBS twice daily group: OBS 10 mL of 0.2 mg/mL (2 mg) qAM (pc) and hs (4 mg OBS total/day) <p>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).</p> <p>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 (Total Daily Dose of OBS).</p>

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

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

At Week 12, all subjects will undergo an upper esophagogastrroduodenoscopy (EGD) with biopsy to evaluate eosinophil counts. Upon receipt of blinded EGD and DSQ data, subjects on placebo in the randomized withdrawal period who have relapsed will have their treatment assignment changed to OBS 2 mg twice daily. The criteria for relapse is having an eosinophilic count of ≥ 15 eos/HPF from at least 2 of 3 levels of the esophagus, as determined by central reader and having at least 4 days of dysphagia in the 2-week period prior to the scheduled visit, as determined by the DSQ. At least 8 daily diary entries must be completed over 14 consecutive days in order to determine the criterion for DSQ relapse. If fewer than 8 diary entries are reported within the 2-week period, then the 2-week period will be shifted backwards from the scheduled visit to include the most recent 2-week period with at least 8 diary entries over 14 consecutive days; however, the 2-week period will not be shifted by more than 2 weeks (ie, no more than 2-week period plus additional 2-week additional expansion). The criteria for relapse align with the related inclusion criteria for participation in the SHP621-301 study. The treatment assignment change will be performed in a blinded manner in IWRS by the independent unblinded data team. If both criteria for relapse are not met, the subject will remain assigned to placebo.

If at any time, the subject reports increased or worsening dysphagia symptoms to the investigator, the investigator may choose to perform an unscheduled EGD. If an unscheduled EGD is performed prior to Week 12, an EGD does not have to be repeated at Week 12. The independent, unblinded data team will review the blinded EGD and DSQ data to confirm the subject is on placebo in the randomized withdrawal period, determine if the subject meets relapse criteria, and change the subject's treatment assignment to OBS 2 mg twice daily if relapse is confirmed.

If the Week 12 or an unscheduled EGD reveals an eosinophil count of ≥ 15 from at least 2 of 3 levels of the esophagus yet relapse is not confirmed due to the criterion for dysphagia symptoms not being met, the subject will remain assigned to placebo. If the criterion for dysphagia symptoms is met at a subsequent visit and both criteria for relapse are then confirmed, the subject's treatment assignment will be changed to OBS 2 mg twice daily at the next scheduled visit.

Methodology:

This is a Phase 3, double-blind, multicenter 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 who completed the SHP621-301 induction study.

This study will comprise 3 periods: 4-week screening period, 36-week double-blind treatment period, and a 4-week safety follow-up (Study Design Flow Chart). All subjects who have completed the SHP621-301 induction study will be eligible to enroll in this extension study. Approximately 200 subjects (88%) who were randomized in the SHP621-301 study are estimated to complete the SHP621-301 study and will be enrolled in this treatment extension study based on enrollment observed in the Phase 2 study (MPI 101-06). Randomization into the randomized withdrawal period will be stratified by treatment assignment and treatment response in the SHP621-301 study. Subjects who are full responders (defined as ≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ at the final treatment evaluation visit [Visit 4]) in the SHP621-301 induction study will be eligible to enter the randomized withdrawal period to receive either OBS 2 mg twice daily or

placebo at a 1:1 ratio. The randomization of subjects who are full responders will also be stratified by age (adults and adolescents) to ensure approximately equal number of subjects within each age group are assigned to the treatment groups.

Subjects who sign informed consent (or assent as applicable for subjects <18 years) will be screened (Visit 0); assessments from the SHP621-301 final treatment evaluation visit (Visit 4) will be used as the Visit 0 screening assessments of the treatment extension study. Subjects who meet eligibility criteria at the screening visit (Visit 0) will enter the 36-week double-blind period. Eligible subjects will receive investigational product based on treatment assignment in SHP621-301 for up to 4 weeks prior to enrollment in the treatment extension study. This 4-week screening period is required to allow for blinded treatment response information (reduction in DSQ from baseline and eosinophilic count as determined by a central reader) collected during the SHP621-301 final treatment evaluation visit to be entered into IWRS by the unblinded data team who is independent from the blinded study team and not involved with the day-to-day conduct of the study. Once information is available, subjects will return for the randomization visit (Visit 1) to receive investigational product.

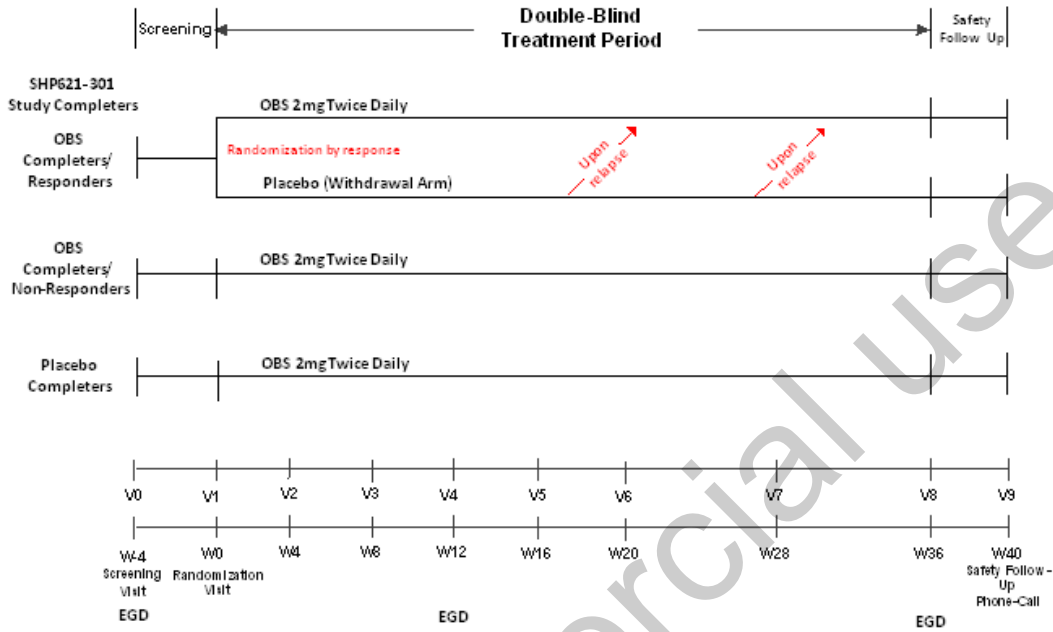
During the 36-week treatment extension study, subjects who were assigned to, and fully responded to OBS treatment in the SHP621-301 study (≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ at the final treatment evaluation visit) will enter a randomized withdrawal period to receive either OBS 2 mg twice daily or placebo at a 1:1 ratio. Subjects who were assigned to OBS treatment in the SHP621-301 study and did not respond or partially responded, will receive OBS 2 mg twice daily. Subjects who were assigned to placebo in the SHP621-301 study will receive OBS 2 mg twice daily. At Week 12, all subjects will undergo an upper esophagogastroduodenoscopy (EGD) with biopsy to evaluate eosinophil counts. Upon receipt of blinded EGD and DSQ data, subjects on placebo in the randomized withdrawal period who have relapsed (>15 eos/HPF from at least 2 levels of the esophagus and specimens and 4 days of dysphagia over 2 weeks) will have their treatment assignment changed to OBS 2 mg twice daily at the next scheduled visit. The treatment assignment change will be performed in a blinded manner in IWRS by the independent unblinded data team. If both criteria for relapse are not met, the subject will remain assigned to placebo.

Subjects who report increased or worsening dysphagia symptoms to the investigator prior to the Week 12 EGD may have an unscheduled EGD to confirm whether relapse has occurred. If an unscheduled EGD is performed prior to Week 12, an EGD does not have to be repeated at Week 12. The independent, unblinded data team will review the EGD and DSQ data to confirm the subject is on placebo in the randomized withdrawal phase, determine if the subject meets relapse criteria, and change the subject's treatment assignment to OBS 2 mg twice daily at the next scheduled visit if relapse is confirmed.

Subjects will have efficacy and safety assessments at each visit during the 36-week period. Subjects who fail to meet all eligibility criteria at Visits 0 or 1 will be considered screen failures. Subjects cannot be rescreened once they have been designated as a screen failure. Subjects who discontinue will not be replaced.

Subjects will be required to visit the site up to 8 times over up to a 36-week period. All subjects will have a Follow-up phone call 4-weeks post last dose of investigational product.

Study Design Flow Chart



Abbreviations: EGD=esophagogastroduodenoscopy; 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 completed SHP621-301 induction study.
2. 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.
3. Subject is male or female aged 11-55 years, inclusive, at time of consent for SHP621-301 study.
4. 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 0). There should be no changes to these regimens during study participation.
5. 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 and for 30 days following the last dose of investigational product.
6. Subject is willing and has an understanding and ability to fully comply with study procedures including DSQ compliance (completed the DSQ on $\geq 70\%$ of days in any 2 consecutive weeks of the screening period) 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 changes in medications that could affect the study or diet in the weeks since the final treatment evaluation visit (Visit 4) of the SHP621-301 study.
2. Subject using immunomodulatory therapy since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or anticipated use of immunomodulatory therapy during the treatment period (except for any ongoing regimen of allergy shots); 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 scheduled EGDs.
3. Subject using swallowed topical corticosteroid for EoE or systemic corticosteroid for any condition since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or anticipated 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 medical monitor prospectively but cannot occur within the 4 weeks of the scheduled EGDs.
4. Subject on inhaled or intranasal steroids and not on a stable dose between the baseline visit (Visit 1) of the SHP621-301 study and the screening EGD of this study.
5. Subject has initiated, discontinued, or changed dosage regimen of proton pump inhibitors (PPIs), H2 antagonists, antacids, antihistamines, or leukotriene inhibitors for any condition (such as gastroesophageal reflux disease, asthma or allergic rhinitis) since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or anticipated changes in the use of such medications during the treatment period.
6. Subject using Cytochrome P450 3A4 inhibitors (eg, ketoconazole, grapefruit juice) since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or anticipated use of such medications during the treatment period.
7. Subject has an appearance on screening 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 >9mm).

8. Subject is on a pure liquid diet or the six-food elimination diet.
9. Subject has presence of esophageal varices at the EGD at the final treatment evaluation visit (Visit 4) of the SHP621-301 study.
10. 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.
11. Subject has other diseases causing or associated with esophageal eosinophilia, including hypereosinophilic syndrome, collagen vascular disease, vasculitis, achalasia, or parasitic infection.
12. Subject has oropharyngeal or esophageal candidiasis that failed to respond to previous treatment. Diagnosis with oropharyngeal or esophageal candidiasis at or since the final treatment evaluation visit (Visit 4) of the SHP621-301 study is not an exclusion as long as the subject received treatment for candidiasis and is expected to respond to treatment.
13. Subject has acute or chronic infection or immunodeficiency condition, including tuberculosis, fungal, bacterial, viral/parasite infection, ocular herpes simplex, or chicken pox/measles.
14. Subject has upper gastrointestinal bleeding identified in the EGD at the final treatment evaluation visit (Visit 4) of the SHP621-301 study or since the final treatment evaluation visit (Visit 4) of the SHP621-301 study.
15. Subject has evidence of active infection with *Helicobacter pylori*.
16. Subject has evidence of unstable asthma since the final treatment evaluation visit (Visit 4) of the SHP621-301 study.
17. Subject is female and pregnant or nursing.
18. Subject has a history of intolerance, hypersensitivity, or idiosyncratic reaction to budesonide (or any other corticosteroids), or to any other ingredients of the study medication.
19. Subject has a history or high risk of noncompliance with treatment or regular clinic visits.
20. Subject is on sucralfate or anticipates using sucralfate during the treatment period.

Maximum duration of subject involvement in the study:

- Planned duration of screening period: up to 4 weeks
- Planned duration of treatment period: 36 weeks
- Planned duration of safety follow-up period: 4 weeks

Endpoints and statistical analysis:

Subject Populations

- The **safety set** will include all subjects who are randomized and receive at least 1 dose of 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 investigational product and had 1 post baseline efficacy assessment (biopsy and/or DSQ score).
- The **per-protocol (PP) set** will include all subjects in the FAS excluding subjects with major protocol deviations. 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.

Primary Efficacy Endpoint

The primary efficacy endpoint for each subject is relapse during the double-blind randomized

withdrawal period. Relapse, a binary response (either with a relapse or not), is defined as having an eosinophil count of ≥ 15 eos/HPF from at least 2 of 3 levels of the esophagus, as determined by a central reader, and having at least 4 days of dysphagia in the 2-week period prior to the scheduled study visit, as determined by the DSQ.

Key Secondary Efficacy Endpoint

The key secondary endpoint is the long-term treatment response, a binary response, over an extended period of 36 weeks in adolescent and adult subjects who were randomized to OBS treatment but did not respond after 12 weeks in the SHP621-301 induction study (subject did not have peak count of ≤ 6 eos/HPF across all available esophageal levels at the final treatment visit and/or $\geq 30\%$ reduction in DSQ score from baseline) and met the following criteria:

- Histologic response, defined as a peak eosinophil count of ≤ 6 eos/HPF across all available esophageal levels at the final treatment period evaluation (Visit 8)
- Dysphagia symptom response, defined as $\geq 30\%$ reduction in the DSQ combined score (questions 2+3) from baseline of the SHP621-301 study and from baseline of this extension study to the final treatment period evaluation (Visit 8)

Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be analyzed in all subjects:

- Histologic response, defined as a peak eosinophil count of ≤ 6 eos/HPF across all available esophageal levels at each assessment visit
- Dysphagia symptom response, defined as $\geq 30\%$ reduction in the DSQ combined score (questions 2+3) at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Change in the DSQ score and change in the peak eosinophil count at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Change in total endoscopy score, as measured by the EREFS classification, at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Peak eosinophil count < 15 eos/HPF across all available esophagus levels at each assessment visit
- Peak eosinophil count ≤ 1 eos/HPF across all available esophagus levels at each assessment visit
- Change in the peak eosinophil count at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study for each available esophageal level (proximal, mid-, and distal)
- Change in the histopathologic epithelial features combined total score (grade and stage) at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Dysphagia symptom response (binary response), defined as a $\geq 50\%$ reduction in the DSQ combined score (questions 2+3), at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension
- Change in the DSQ combined score (questions 2+3) at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Cumulative distribution function curves for the change and the percent change in the DSQ score at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Overall binary response I, defined as a reduction in the DSQ score of $\geq 30\%$ and a peak eosinophil count of ≤ 6 eos/HPF across all esophageal levels at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Overall binary response II, defined as a reduction in the DSQ score of $\geq 50\%$ and a peak eosinophil count of ≤ 6 eos/HPF across all esophageal levels at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study

- Change in the DSQ + pain score (question 2+3+4) at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Change in the DSQ pain score (question 4) at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study

For subjects who relapse on placebo during the randomized withdrawal period and who reinitiate treatment with OBS 2 mg twice daily (intermittent therapy), separate descriptive analyses for histological data and DSQ endpoints will be conducted at each assessment visit. Changes will be summarized over time from baseline of the SHP621-301 study and from the time of relapse. The same criteria for response will be applied to these subjects (≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ from the SHP621-301 baseline score).

Exploratory Efficacy Endpoints

- [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 adrenocorticotrophic 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.

- [REDACTED]
- [REDACTED]
- [REDACTED]

Statistical Methodology for Primary Efficacy Endpoint

The primary efficacy endpoint will be analyzed as the proportion of subjects with relapse during the end of the double-blind randomized withdrawal period for the FAS, using a chi-square test comparing OBS 2 mg twice daily against placebo. The primary test of treatment effect will be two-sided, and conducted at the significance level of 0.05. The proportion of subjects with relapse for each treatment group and the corresponding 95% confidence interval (CI) will be estimated. In addition, the difference in the proportion of subjects with relapse between the 2 treatment groups and its 95% CI will be estimated.

Subjects who withdraw without providing efficacy data at the early termination (ET) visit will be classified as being a relapser in the primary efficacy analysis. The null hypothesis states that there is no difference in relapse proportions between OBS 2 mg twice daily and placebo, with the two-sided alternative of a nonzero difference between groups. Relapse proportions at each adjacent double-blind visit interval will also be assessed by applying the chi-square test to the observed data at each double-blind visit.

Statistical Methodology for Key Secondary and Other Secondary Efficacy Endpoints

To evaluate the long-term treatment response over an extended period of 36 weeks for subjects who were randomized to OBS treatment but did not respond after 12 weeks in the SHP621-301 induction study (subject did not have peak count of ≤ 6 eos/HPF across all available esophageal levels at the final treatment visit and/or $\geq 30\%$ reduction in DSQ score from baseline of SHP621-301), the proportion of

subjects who responded based on the histological data and the DSQ data at the final treatment period evaluation (Visit 8) and the corresponding 95% confidence interval (CI) will be estimated and summarized.

Summary statistics of the DSQ score (questions 2+3) and the peak eosinophil count and the change from baseline of the SHP621-301 study and from baseline of this extension study at the final treatment period evaluation (Visit 8) will be summarized by each assessment visit.

To evaluate the response to OBS treatment over 36 weeks for subjects who were on placebo in the SHP621-301 induction study, the proportion of subjects who responded based on the histological data and the DSQ data at the final treatment period evaluation (Visit 8) and the corresponding 95% CI will be summarized. Summary statistics of the DSQ score (questions 2+3) and the peak eosinophil count and the change from baseline of the SHP621-301 study and from baseline of this extension study at the final treatment period evaluation (Visit 8) will be summarized by each assessment visit.

To evaluate the effect of reinitiating OBS treatment for subjects who relapse after being randomized to placebo in the randomized withdrawal period (intermittent therapy), the proportion of subjects who responded based on the histological data and the DSQ data at the final treatment period evaluation (Visit 8) and the corresponding 95% CI will be summarized.

Summary statistics will be provided for all the secondary endpoints.

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 (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.

Sample Size Justification

Approximately 200 subjects (88%) who are randomized in the SHP621-301 study are estimated to complete the SHP621-301 study and enroll in this treatment extension study based on enrollment observed in the Phase 2 study (MPI 101-06).

The primary efficacy measure of the study will be the proportion of subjects who relapse during the double-blind randomized withdrawal period. Relapse, a binary response (either with relapse or not), is defined as having an eosinophil count of ≥ 15 eos/HPF from at least 2 of 3 levels of the esophagus (determined by a central reader) and having at least 4 days of dysphagia in a 2-week period prior to the scheduled visit (determined by the DSQ). To be considered as a subject with relapse, both criteria must be met.

Based on observation in the Phase 2 study (MPI 101-06), approximately 26% of subjects, or approximately 40 subjects, who were assigned to OBS treatment in the SHP621-301 study are anticipated to respond fully after 12 weeks in the SHP621-301 study.

For this study, to detect a 50 percentage point difference between relapse proportions of 20% and 70% in the OBS and placebo groups, respectively, at 80% power and a significance level of 0.05 (two-sided) using a Chi-Square test with equal allocation to treatment groups, it is necessary to assess the primary efficacy measure for approximately 38 subjects (19 subjects in each of the OBS and placebo groups).

STUDY SCHEDULE(S)

Table 1-1: Schedule of Assessments

Procedures	Screening ^a	Double-Blind Treatment Period								Safety Follow-Up Contact ^o
	Visit 0	Randomization/ Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 or ET ⁿ	Visit 9
Week	-4	0	4	8	12	16	20	28	36	40
Window	≤4 weeks	--	±3 days	±3 days	±3 days	±3 days	±3 days	±6 days	±6 days	±3 days
Informed consent/assent	X									
Medical history review	X	X								
Inclusion/exclusion criteria review	X	X								
Vital signs ^b ; height ^c , and weight assessment	X	X	X	X	X	X	X	X	X	
EGD with endoscopy score (EREFS) and biopsy ^d	X				X				X	
Issue/Retrieve DSQ handset	X								X	
DSQ completion	Once daily completion									
DSQ compliance assessment	X	X	X	X	X	X	X	X	X	
██████████	█				█				█	
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Table 1-1: Schedule of Assessments

[illegible]

Table 1-1: Schedule of Assessments

Procedures	Screening ^a	Double-Blind Treatment Period								Safety Follow-Up Contact ^o
	Visit 0	Randomization/ Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 or ET ⁿ	Visit 9
Week	-4	0	4	8	12	16	20	28	36	40
Window	≤4 weeks	--	±3 days	±3 days	±3 days	±3 days	±3 days	±6 days	±6 days	±3 days
Study medication compliance assessment	X	X	X	X	X	X	X	X	X	
Concomitant medications and procedures recorded	X	X	X	X	X	X	X	X	X	X
Review of adverse events ^m	X	X	X	X	X	X	X	X	X	X

Abbreviations: ACTH=adrenocorticotrophic hormone; DSQ=Dysphagia Symptom Questionnaire; DXA=dual-energy X-ray absorptiometry; EGD=esophagogastroduodenoscopy;

EREFS=EoE Endoscopic Reference Score; hs=at bedtime; IWRS=interactive web-based response system;

^a The assessments from the SHP621-301 final treatment evaluation visit (Visit 4) will be used as the screening assessments (Visit 0) of this treatment extension study.

^b 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.

^c Height to be collected at screening (Visit 0) and Visit 8 only. Stadiometers will be used to measure height for subjects aged 11-17 years, inclusive.

^d Endoscopy must include esophageal biopsies; gastric and duodenal biopsies may be done at the discretion of the investigator. Endoscopies at Visit 4 and Visit 8 should occur at or within 7 days of the scheduled visit. Unscheduled endoscopies may be performed at the discretion of the investigator.

^f Tanner staging assessments will be performed for all subjects ≥11 years of age until investigator confirms subject is post puberty.

Table 1-1: Schedule of Assessments

Procedures	Screening ^a	Double-Blind Treatment Period								Safety Follow-Up Contact ^o
	Visit 0	Randomization/ Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 or ET ⁿ	Visit 9
Week	-4	0	4	8	12	16	20	28	36	40
Window	≤4 weeks	--	±3 days	±3 days	±3 days	±3 days	±3 days	±6 days	±6 days	±3 days

^g 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.

^h Urinalysis parameters will include glucose, protein, specific gravity, pH, nitrite, bilirubin, ketones, hemoglobin, urobilinogen, and leukocyte esterase.

ⁱ The serum pregnancy test will be performed for all female subjects at screening (Visit 0) and Visit 8. Urine pregnancy tests will be performed at all other visits.

^j Dual-energy X-ray absorptiometry scans should be performed using the same machine and software as used in the SHP621-301 study. Dual-energy X-ray absorptiometry scan at Visit 8 should occur at or within 7 days of the scheduled visit.

^k Randomization will occur via IWRS at Visit 1 once the subject's eligibility is confirmed.

^l Study medication is supplied at the SHP621-301 final treatment visit based on treatment assignment in SHP621-301.

^m Adverse event 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).

ⁿ If subject discontinues study prematurely during the treatment period, the evaluations listed for Visit 8 are to be performed as completely as possible.

^o A safety follow-up contact by phone will be performed 4 weeks following the last dose of study medication for all subjects (including subjects who fail screening, who discontinue early, or who complete the study).

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 an approved treatment that induces and maintains remission for patients with EoE (Furuta and Katzka, 2015).

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 nonviscous 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 2 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 eos/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 eos/HPF) and remission (eosinophil count ≤ 1 eos/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 coprimary efficacy endpoints of histologic response and change from baseline in dysphagia symptoms. Following 12 weeks of twice daily treatment (once 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).

This Phase 3 extension study follows the SHP621-301 induction study, a Phase 3 randomized, double-blind, multicenter, 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. Study SHP621-301 is designed to provide safety and efficacy data demonstrating histologic response (as measured by eosinophilic count ≤ 6 eos/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. This extension study will evaluate maintenance of treatment and treatment withdrawal in subjects who complete the induction study.

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 Phase 3 study is being conducted to determine response to withdrawal of OBS, maintenance of response, extended therapy response, and response to intermittent therapy by evaluating both eosinophil counts and DSQ in adolescent and adults treated or withdrawn from OBS in this treatment extension study.

2.2 Study Objectives

2.2.1 Primary Objective

The primary objective of the study is:

- To evaluate the maintenance of efficacy over 36 weeks, as measured by the peak eosinophilic count and the Dysphagia Symptom Questionnaire (DSQ) score, through a randomized withdrawal design for subjects who responded to 12 weeks of OBS treatment (2 mg twice daily) with a peak count of ≤ 6 eosinophils (eos)/high-powered field (HPF) across all available esophageal levels at the final treatment visit and a $\geq 30\%$ reduction in DSQ score from baseline during the SHP621-301 induction study

2.2.2 Secondary Objectives

The key secondary objective of this study is:

- To evaluate the long-term treatment response over an extended period of 36 weeks for subjects who were randomized to OBS treatment but did not respond after 12 weeks in the SHP621-301 induction study (subject did not have a peak count of ≤ 6 eos/HPF across all available esophageal levels at the final treatment visit and/or a $\geq 30\%$ reduction in DSQ score from baseline)

Additional secondary objectives of the study are:

- To evaluate the response to OBS treatment over 36 weeks for subjects who received placebo in the SHP621-301 induction study
- To evaluate the effect of reinitiating OBS treatment for subjects who relapse after being randomized to placebo in the randomized withdrawal period (treatment-withdrawal-treatment reinitiation)
- To assess endoscopically identified esophageal features as measured by the EoE Endoscopic Reference Score (EREFS)
- To evaluate other responding criteria based on histology and DSQ
- To evaluate the long-term safety and tolerability of OBS treatment

2.2.3 Exploratory Objectives

The exploratory objectives of this study are:

- [REDACTED]
- [REDACTED]

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3. STUDY DESIGN

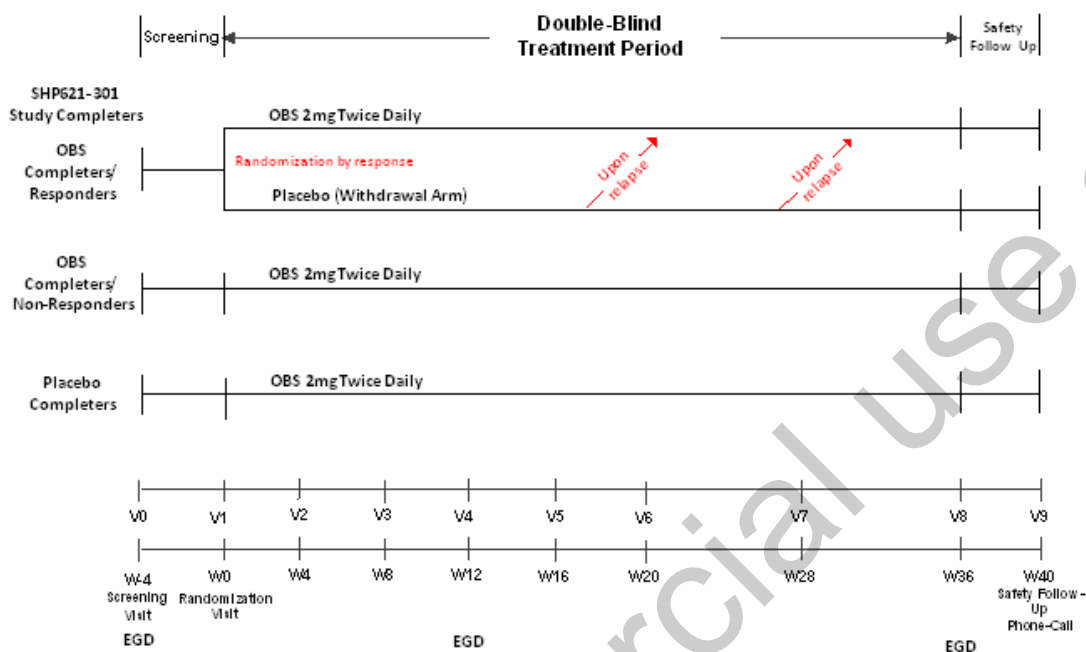
3.1 Study Design and Flow Chart

This is a Phase 3, multicenter, double-blind study to evaluate the efficacy, safety and tolerability of OBS treatment administered twice daily (qAM, pc, and hs) for 36 weeks. The study will be conducted in adolescents and adults, aged 11-55 years, inclusive, with EoE and dysphagia who completed the SHP621-301 induction study.

Approximately 200 subjects (88%) who were randomized in the SHP621-301 study are estimated to complete the SHP621-301 study and will be enrolled in this treatment extension study based on enrollment observed in the Phase 2 study (MPI 101-06). Randomization into the randomized withdrawal period will be stratified by treatment assignment and treatment response in the SHP621-301 study. Subjects who are full responders (defined as ≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ at the final treatment evaluation visit [Visit 4]) in the SHP621-301 induction study will be eligible to enter the randomized withdrawal period to receive either OBS 2 mg twice daily or placebo at a 1:1 ratio. The randomization of subjects who are full responders will also be stratified by age (adults and adolescents) to ensure approximately equal number of subjects within each age group are assigned to the treatment groups.

This study will consist of 3 periods: 4-week screening period, 36-week double-blind treatment period, and 4-week safety follow-up ([Figure 3-1](#)).

Figure 3-1: Study Design Flow Chart



Abbreviations: EGD=esophagogastroduodenoscopy; OBS=oral budesonide suspension

Subjects will be required to visit the site up to 8 times over up to a 36-week period. Following completion of the screening visit, subjects will be evaluated for eligibility and safety at Week 0 (Visit 1). Subjects who are eligible and randomized will have efficacy and safety assessments at Weeks 4, 8, 12, 16, 20, 28, and 36 (Visits 2-8) and additional safety assessments at follow-up at Week 40 (Visit 9). Subjects who fail to meet all eligibility criteria at Visits 0 or 1 will be considered screen failures. These subjects will receive a follow-up safety phone call 4 weeks after the last dose of investigational product. Subjects cannot be rescreened once they have been designated as a screen failure. 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 0]) and will be ≤4 weeks in duration. During the screening period, assessments from the SHP621-301 final treatment evaluation visit (Visit 4) will be used as the Visit 0 screening assessments of the treatment extension study. At the screening visit (Visit 0), 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. Eligible subjects will receive investigational product based on treatment assignment in SHP621-301 for up to 4 weeks prior to enrollment in the treatment extension study. This 4-week screening period is required to allow for blinded treatment

response information (reduction in DSQ from baseline and eosinophilic count as determined by a central reader) collected during the SHP621-301 final treatment evaluation visit to be entered into the interactive web-based response system (IWRS) by the unblinded data team who is independent from the blinded study team and not involved with the day-to-day conduct of the study. Once response information is available, subjects will return for the randomization visit (Visit 1) to receive investigational product. Subjects who continue to meet eligibility criteria after the screening visit (Visit 0) will enter the 36-week double-blind treatment period.

Subjects who were assigned to OBS treatment and who fully responded in the SHP621-301 study (≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ at the final treatment evaluation visit) will enter a randomized withdrawal period to receive either OBS 2 mg twice daily or placebo at a 1:1 ratio. These subjects will also be stratified by age (adults and adolescents). Subjects who were assigned to OBS treatment and did not respond or partially responded in the SHP621-301 study will receive OBS 2 mg twice daily. Subjects who were assigned to placebo in the SHP621-301 study will receive OBS 2 mg twice daily. Subjects, site staff, and study team members will remain blinded to treatment assignment and individual subject histology, and individual subject DSQ data from the SHP621-301 (post randomization) and this extension study until the database locks occurs for this extension study.

At Week 12, all subjects will undergo an upper esophagogastroduodenoscopy (EGD) with biopsy to evaluate eosinophil counts. Upon receipt of blinded EGD and DSQ data, subjects on placebo in the randomized withdrawal period who have relapsed will have their treatment assignment changed to OBS 2 mg twice daily at the next scheduled visit. The criteria for relapse is having an eosinophilic count of ≥ 15 eos/HPF from at least 2 of 3 levels of the esophagus, as determined by central reader and having at least 4 days of dysphagia in the 2-week period prior to the scheduled visit, as determined by the DSQ. The criteria for relapse align with the related inclusion criteria for participation in the SHP621-301 study. The treatment assignment change will be performed in a blinded manner in IWRS by the independent unblinded data team. If both criteria for relapse are not met, the subject will remain assigned to placebo. The upper EGD with esophageal biopsies will be repeated at the Week 36 visit (Visit 8) or at early termination (ET), to evaluate eosinophil counts. If an unscheduled EGD is performed between Week 12 and Week 36, the Week 36 EGD should still be performed.

All subjects will have a follow-up phone call 4-weeks post last dose of investigational product to query for SAEs, AEs, and concomitant treatments.

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 as EoE persists, it becomes more fibrostenotic in older patients and would not be 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.

The design of this study combines randomized withdrawal and long-term extension elements in a manner that selects appropriate patients for placebo withdrawal and maintains double-blinding of subjects in all treatment groups. Only subjects who are full responders to OBS 2 mg twice daily in the SHP621-301 induction study (≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ at the final treatment evaluation visit of SHP621-301), will be eligible for randomized withdrawal. The randomized withdrawal period is required to assess maintenance of efficacy in these subjects. The continuation of OBS 2 mg twice daily treatment for subjects in SHP621-301 who did not respond or partially responded to treatment, will evaluate whether these subjects might respond to OBS 2 mg twice daily if their treatment is extended for an additional 36 weeks. This aspect of the study is supported by the possibility that the response of EoE to topical corticosteroids may require more than 12 weeks of induction treatment.

As described, the protocol also provides multiple mechanisms for switch from placebo and potential study discontinuation of relapsing and nonresponding subjects in order to evaluate the effect of reinitiating OBS treatment in these subjects. For subjects who relapse on placebo during the randomized withdrawal and who reinitiate treatment with OBS 2 mg twice daily (intermittent therapy), separate descriptive analyses for histological data and DSQ endpoints will be conducted at each assessment visit, as described in Section 9.8.2. For all subjects, an esophageal stricture requiring dilation would be considered a treatment failure and result in withdrawal of the subject from the study. Subject withdrawal criteria are provided in Section 4.5.1.

3.2 Duration and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 44 weeks, including the 4-week screening period. Including potential treatment in SHP621-301 and the screening period of this study, the maximum total duration of OBS 2 mg twice daily may be approximately 52 weeks.

The study will be completed in approximately 36 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 8 (Week 36), inclusive of the final treatment evaluation EGD. All subjects will have a follow-up phone call 4-weeks post last dose of investigational product.

3.3 Sites and Regions

Approximately 60 sites in North America, the same sites participating in the SHP621-301 study, will participate in this extension study.

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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 completed SHP621-301 induction study.
2. 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.
3. Subject is male or female aged 11-55 years, inclusive, at time of consent for the SHP621-301 study.
4. 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 0). There should be no change to these regimens during study participation.
5. 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 and for 30 days following the last dose of investigational product.
6. Subject is willing and has an understanding and ability to fully comply with study procedures (completed the DSQ on $\geq 70\%$ of days in any 2 consecutive weeks of the screening period) 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 changes in medications that could affect the study or diet in the weeks since the final treatment evaluation visit (Visit 4) of the SHP621-301 study.
2. Subject using immunomodulatory therapy since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or anticipated use of immunomodulatory therapy during the treatment period (except for any ongoing regimen of allergy shots); 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 scheduled EGDs.

3. Subject using swallowed topical corticosteroid for EoE or systemic corticosteroid for any condition since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or anticipated 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 medical monitor prospectively but cannot occur within the 4 weeks of the scheduled EGDs.
4. Subject on inhaled or intranasal steroids and not on a stable dose between the baseline visit (Visit 1) of the SHP621-301 study and the screening EGD of this study.
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) since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or anticipated changes in the use of such medications during the treatment period.
6. Subject using Cytochrome P450 3A4 inhibitors (eg, ketoconazole, grapefruit juice) since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or anticipated use of such medications during the treatment period.
7. Subject has an appearance on screening 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 six-food elimination diet.
9. Subject has presence of esophageal varices at the EGD at the final treatment evaluation visit (Visit 4) of the SHP621-301 study.
10. 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.
11. Subject has other diseases causing or associated with esophageal eosinophilia, including hypereosinophilic syndrome, collagen vascular disease, vasculitis, achalasia, or parasitic infection.
12. Subject has oropharyngeal or esophageal candidiasis that failed to respond to previous treatment. Diagnosis with oropharyngeal or esophageal candidiasis at or since the final treatment evaluation visit (Visit 4) of the SHP621-301 study is not an exclusion as long as the subject is expected to respond to candidiasis treatment.
13. Subject has acute or chronic infection or immunodeficiency condition, including tuberculosis, fungal, bacterial, viral/parasite infection, ocular herpes simplex, or chicken pox/measles.
14. Subject has upper gastrointestinal bleeding identified in the EGD at the final treatment evaluation visit (Visit 4) of the SHP621-301 study or since the final treatment evaluation visit (Visit 4) of the SHP621-301 study.
15. Subject has evidence of active infection with *Helicobacter pylori*.

16. Subject has evidence of unstable asthma since the final treatment evaluation visit (Visit 4) of the SHP621-301 study.
17. Subject is female and pregnant or nursing.
18. Subject has a history of intolerance, hypersensitivity, or idiosyncratic reaction to budesonide (or any other corticosteroids), or to any other ingredients of the study medication.
19. Subject has a history or high risk of noncompliance with treatment or regular clinic visits.
20. Subject is on sucralfate or anticipates using sucralfate during the treatment period.

4.3 Restrictions

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

- No changes in medications or diet since the final treatment evaluation visit (Visit 4) of the SHP621-301 study.
- Temporary use (≤ 7 days) or initiation of new steroid treatment is permitted but cannot occur within the 4 weeks of the scheduled EGDs.
- 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 enrollment to resume (or discontinue) intranasal corticosteroids based on the subject's usual treatment regimen for allergy season. (In these subjects, intranasal corticosteroids must not be changed between the baseline visit [Visit 1] of the SHP621-301 study and the screening EGD of this study). Topical corticosteroid dosing changes should be avoided within 4 weeks prior to EGD. Subjects who require a change in inhaled corticosteroid treatment for an asthma exacerbation should be discussed with the medical monitor.
- No change in use of PPIs, H₂ antagonists, antacids, antihistamines, or leukotriene inhibitors for any condition (such as gastroesophageal reflux disease, asthma or allergic rhinitis).
- No use of cytochrome P450 3A4 (CYP450 3A4) inhibitors (eg, ketoconazole, grapefruit juice, see details in Section 5.2.2).
- No use of sucralfate during the study as this may interfere with the adherence of OBS.

4.4 Reproductive Potential

4.4.1 Female Contraception

All females must have a negative pregnancy test at the screening visit (Visit 0), randomization visit (Visit 1), and Visits 2-8. A serum pregnancy test will be performed at the screening visit

(Visit 0) and final treatment evaluation (Visit 8). 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 1 of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy, or bilateral salpingectomy) and at least 6 weeks post sterilization, or
- Females of childbearing potential must 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
 - 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 0), 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 1 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 8 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 (Schedule of Assessments, [Table 1-1](#)). 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 relapse and result in withdrawal of the subject from the study. Subjects with oropharyngeal or esophageal candidiasis that has failed to respond to treatment by the Week 12 EGD or upper GI bleeding at the Week 12 EGD will be withdrawn 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
- Study 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 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 (TA) Head. The PVRM TA 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 nonstudy treatment (including but not limited to herbal treatments, vitamins, behavioral treatment, and nonpharmacological treatment, such as psychotherapy, as appropriate) received at the screening visit (Visit 0) 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 at the screening visit (Visit 0). 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 in SHP621-302 (Visit 1) 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 scheduled EGDs) 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 (exception for seasonal allergic rhinitis, see Section 4.3)
2. PPIs
3. H2 antagonists
4. Antacids
5. Antihistamines
6. Leukotriene inhibitors
7. 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 since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or use within the 4 weeks of scheduled EGDs. Any temporary use (≤ 7 days) or initiation of new corticosteroid treatment during the study should be documented and discussed with the medical monitor prospectively. (Seasonal nasal corticosteroid use for seasonal allergic rhinitis is permitted; changes within 4 weeks of scheduled EGD should be avoided).
2. Swallowed topical corticosteroid for EoE or systemic corticosteroid for any condition since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or use within the 4 weeks of scheduled EGDs. Any temporary use (≤ 7 days) or initiation of new steroid treatment during the study should be documented and discussed with the medical monitor prospectively.
3. Initiation or change in dosing frequency to PPIs, H₂ antagonists, antacids, antihistamines, or leukotriene inhibitors for any condition (such as gastroesophageal reflux disease, asthma, or allergic rhinitis) since the final treatment evaluation visit (Visit 4) of the SHP621-301 study, or anticipated use of such medications during the treatment period.
4. CYP450 3A4 inhibitors (eg, ketoconazole, grapefruit juice) since the final treatment evaluation visit (Visit 4) of the SHP621-301 study, or anticipated changes in the 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.
5. Sucralfate at screening or anticipated to be used 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 8 ounce amber glass, multidose bottles. 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 8 ounce amber glass, multidose bottles with child-resistant caps and refrigerated throughout the study (in the clinic and subject's home). Each bottle contains OBS 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 suspension will also be supplied in 8 ounce amber glass multidose bottles with child-resistant caps. Placebo consists of all components of the investigational product 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 for each subject will be administered in the clinic. The subject will continue with the evening dosing regimen at home.

Oral budesonide suspension and placebo will be supplied in amber glass bottles and must be shaken well prior to administration. OBS and placebo should be refrigerated at 2-8°C (36-46°F) 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.

During the 4-week screening period, blinded treatment response information (reduction in DSQ from baseline and eosinophilic count as determined by a central reader) collected during the SHP621-301 final treatment evaluation visit will be entered into the IWRS by an independent, unblinded data team. Details on the unblinded data team will be provided in a separate charter. Once information is available, subjects will return for the randomization visit (Visit 1) to be assigned to investigational product (OBS 2 mg twice daily or placebo). While only SHP621-301 OBS 2 mg twice daily responders will be randomized to continued OBS 2 mg twice daily or placebo, all subjects will be assigned to investigational product via IWRS to maintain double-blinding of subjects, investigators, the blinded monitoring team and the sponsor (ie, sham randomization).

At the randomization visit (Visit 1), the investigator or designee will 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 4-week screening period and a double-blind treatment period. The actual treatment given to individual subjects during the double-blind treatment period will be determined by the blinded treatment response information entered at the SHP621-301 final treatment evaluation visit.

Subjects will be randomized via a computer-generated randomization schedule at the randomization visit (Visit 1) following a 4-week screening period and confirmation of study eligibility. Subjects who fully responded to OBS treatment in the SHP621-301 study (≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ at the final treatment evaluation visit) will enter a randomized withdrawal period to receive either OBS 2 mg twice daily or placebo at a 1:1 ratio. Subjects who did not respond or partially responded to OBS treatment in the SHP621-301 study will receive OBS 2 mg twice daily.

Subjects who were assigned to placebo in the SHP621-301 study will receive OBS 2 mg twice daily. Subjects, site staff, and study team members will remain blinded to treatment assignment and individual subject histology and individual subject DSQ data from the SHP621-301 study (post randomization) and until database lock occurs for this extension study.

Randomization of subjects in the randomized withdrawal period will also be stratified by age (adults and adolescents) to ensure approximately equal number of subjects within each age group are assigned to the treatment groups.

Subject numbers are assigned to all subjects as they consent to take part in the study. The subject number consists of the 3 digit study identifier, the 4 digit site identifier, and the 4 digit subject identifier. For the SHP621-302 study, the 3 digit site and 4 digit subject numbers will be the same as the SHP621-301 study.

The randomization number represents a unique number corresponding to investigational product allocated to the subject once eligibility has been determined at the randomization visit.

Individual subject treatment is automatically assigned by the IWRS.

6.2.3 Dosing

During the 4-week screening period, all subjects will receive 10 mL of blinded investigational product twice daily based on treatment assignment in SHP621-301. During the 36-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.

At Week 12, all subjects will undergo an upper esophagogastrroduodenoscopy (EGD) with biopsy to evaluate eosinophil counts. Upon receipt of blinded EGD and DSQ data, subjects on placebo in the randomized withdrawal period who have relapsed will have their treatment assignment changed to OBS 2 mg twice daily. The criteria for relapse is having an eosinophil count of ≥ 15 eos/HPF from at least 2 of 3 levels of the esophagus, as determined by a central reader, and having at least 4 days of dysphagia in the 2-week period prior to the scheduled visit, as determined by the DSQ. At least 8 daily diary entries must be completed over 14 consecutive days in order to determine the criterion for relapse. If fewer than 8 diary entries are reported within the 2-week period, the DSQ window can be expanded as described in Section 7.2.1.2. The criteria for relapse align with the related inclusion criteria for participation in the SHP621-301 study. The treatment assignment change will be performed in a blinded manner in IWRS by the independent, unblinded data team. If both criteria for relapse are not met, the subject will remain assigned to placebo.

If at any time the subject reports increased or worsening dysphagia symptoms to the investigator, the investigator may choose to perform an unscheduled EGD. If an unscheduled

EGD is performed prior to Week 12, an EGD does not have to be repeated at Week 12. The independent, unblinded data team will review the blinded EGD and DSQ data to confirm the subject is on placebo in the randomized withdrawal period, determine if the subject meets relapse criteria, and change the subject's treatment assignment to OBS 2 mg twice daily if relapse is confirmed.

If the Week 12 or an unscheduled EGD reveals an eosinophil count of ≥ 15 from at least 2 of 3 levels of the esophagus yet relapse is not confirmed due to the criterion for dysphagia symptoms not being met, the subject will remain assigned to placebo. If the criterion for dysphagia symptoms is met at a subsequent visit and both criteria for relapse are then confirmed, the subject's treatment assignment will be changed to OBS 2 mg twice daily at the next scheduled visit.

Investigational product doses that are required to be administered at the clinic include the first dose of randomized investigational product (OBS or placebo) administered at the randomization visit (Visit 1) and all morning doses of investigational product administered at Visits 2-8. 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.

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 study 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. Bottles of OBS 0.2 mg/mL or placebo 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 Storages

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 refrigerated at 2-8°C (36-46°F), 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. Please refer to the Pharmacy Manual for additional details.

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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 ([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 -4 to 0)

The screening period starts when subjects sign informed consent. The screening period will comprise up to 4 weeks, during which all procedures listed for the screening visit (Visit 0) 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 (Section [5.2.1](#)).

Assessments from the SHP621-301 final treatment evaluation visit (Visit 4) will be used as the screening assessments (Visit 0) of this treatment extension study. Screening assessments may take place across several days to allow an appropriate time frame in which to complete all procedures and confirm study eligibility. At the SHP621-301 final treatment evaluation visit, subjects will be dispensed blinded investigational product (based on treatment assignment in SHP621-301) that will last for up to 4 weeks prior to enrolling into this treatment extension study. The 4-week screening period is required to allow for blinded treatment response information (reduction in DSQ from baseline and eosinophilic count as determined by a central reader) collected during the SHP621-301 final treatment evaluation visit to be entered into the IWRS by the independent, unblinded data team.

After the screening period, subjects who meet eligibility criteria at the end of the screening visit (Visit 0) will enter the 36-week double-blind treatment period. This 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 or

randomized visits. Subjects cannot be rescreened once they have been designated as a screen failure.

7.1.1.1 Screening Visit (Visit 0) / Visit 4 of SHP621-301 Study

The screening visit (Visit 0) assessments and procedures, beginning with informed consent, will be performed as outlined in [Table 1-1](#).

The following procedures will be performed at the screening visit:

- Obtain subject consent (or assent as applicable for subjects <18 years).
- Review eligibility criteria.
- Review medical history.
- 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 current use of concomitant medications and procedures. 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.
- Dispense the DSQ electronic patient-reported outcome (ePRO) device for nightly completion and train the subject on its use.

The following procedures will be performed at the final treatment evaluation visit (Visit 4) of SHP621-301 and will be used as the screening assessments for this extension study:

- Review investigational product dosing compliance.
- 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. Vital signs will be assessed after the subject has been in a supine position for at least 5 minutes immediately prior to the assessment.
- Clinical chemistry, hematology, and urinalysis laboratory tests will be performed on all subjects; 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 adrenocorticotrophic 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.

- [REDACTED]

- [REDACTED]
- Perform a physical examination on all subjects. Adolescents (subjects ≥ 11 years until the investigator confirms subject is post puberty) will also undergo Tanner Staging Assessment.
- **Serum** pregnancy test will be performed on all female subjects.
- Perform EGD and biopsy either at the investigative site or by a referring physician. Esophagogastroduodenoscopy should be completed at or within 7 days of the scheduled visit. Biopsy specimens must be available to be sent to the central pathology lab at least 2 weeks prior to Visit 1 to allow sufficient time for processing and central review and determination of eligibility.
- Perform dual-energy X-ray absorptiometry (DXA) scan for bone mineral density (BMD) and body composition measurements in subjects aged 11-17 years, inclusive. Baseline and post treatment DXA scans should be performed using the same machine and software.
- Dispense blinded investigational product (OBS or placebo; based on treatment assignment in SHP621-301) and review administration instructions. The subject will 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.

7.1.2 Double-blind Treatment Period (Visits 1-8): Weeks 0, 4, 8, 12, 16, 20, 28 and 36 (or Early Termination)

The double-blind treatment period will comprise 36 weeks, during which all assessments and procedures listed for Visits 1-8 in [Table 1-1](#) shall be completed.

During this period, a ± 3 -day visit window will be permitted between Visits 1-6 (Weeks 0-20) and a ± 6 -day visit window will be permitted between Visits 7-8 (Weeks 28-36), unless otherwise specified. Visit windows are calculated based upon the date of the randomization visit (Visit 1).

Once information for blinded treatment response is available, subjects will return for the randomization visit (Visit 1) to receive investigational product. Subjects who continue to meet all eligibility criteria and complete the 4-week screening period will have the opportunity to enroll in the treatment extension study. Subjects will receive either OBS twice daily (qAM, pc, and hs) or placebo twice daily (qAM, pc, and hs).

Subjects who fully responded to OBS treatment in the SHP621-301 study (≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ at the final treatment evaluation visit) will enter a randomized withdrawal period to receive either OBS 2 mg twice daily or placebo at a 1:1 ratio. Subjects who did not respond or partially responded to OBS treatment in the SHP621-301 study will receive OBS 2 mg twice daily. Subjects who were assigned to placebo in the SHP621-301 study will receive OBS 2 mg twice daily. 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 randomization visit (Visit 1) will be documented as screen failures in the IWRS and discontinue study drug.

A safety follow-up contact by phone will be performed 4 weeks following the last dose of study medication for all subjects (including subjects who fail screening, who discontinue early, or who complete the study).

7.1.2.1 Randomization Visit (Visit 1): Week 0

Subjects will return to the site for the randomization visit (Visit 1) to confirm eligibility. The randomization 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. Vital signs will be assessed after the subject has been in a supine position for at least 5 minutes immediately prior to the assessment.
- 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.

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

- Review investigational product dosing compliance.
- Review DSQ compliance; provide subject with instruction to continue completion of the DSQ nightly.



- Perform a physical examination and assess any changes since screening.
- 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 **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.

7.1.2.2 Visits 2 and 3 (Weeks 4 and 8)

Subjects will return to the site for Visit 2 (Week 4) and Visit 3 (Week 8). 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. Vital signs will be assessed after the subject has been in a supine position for at least 5 minutes immediately prior to the assessment.
- 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.

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

- Review DSQ dysphagia episodes and compliance; provide subject with instruction to continue completion of the DSQ nightly.
- [REDACTED]
- Perform a physical examination and assess any changes since screening.
- Readminister **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.

7.1.2.3 Visit 4 (Week 12)

Subjects will return to the site for Visit 4 (Week 12). 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), and weight. Vital signs will be assessed after the subject has been in a supine position for at least 5 minutes immediately prior to the assessment.
- 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.
- Review DSQ dysphagia episodes and compliance; provide subject with instruction to continue completion of the DSQ nightly.

■ [REDACTED]

■ [REDACTED]

- Perform a physical examination and assess any changes since screening.
- Readminister **urine** pregnancy test for female subjects.
- Dispense investigational product (OBS or placebo) and review investigational product dosing compliance.
- Perform EGD and biopsy; EGD should be completed at or within 7 days of the scheduled visit. In addition, an earlier EGD may also occur if the subject exhibits signs of relapse (Section [6.2.3](#)).

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

7.1.2.4 Visits 5, 6, and 7 (Weeks 16, 20, and 28)

Subjects will return to the site for Visits 5, 6, and 7 (Weeks 16, 20, and 28). 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. Vital signs will be assessed after the subject has been in a supine position for at least 5 minutes immediately prior to the assessment.
- 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.

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

- Review DSQ dysphagia episodes and compliance; provide subject with instruction to continue completion of the DSQ nightly.

■ [REDACTED]

- Perform a physical examination and assess any changes since screening.
- Readminister **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.

7.1.2.5 Visit 8 (Week 36) or Early Termination

Subjects will return to the site for Visit 8 (Week 36). Assessments at this visit will be performed as outlined in [Table 1-1](#). If a subject discontinues prematurely, the assessments for Visit 8 are to be performed as completely as possible.

The following procedures should be performed first:

- 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. Vital signs will be assessed after the subject has been in a supine position for at least 5 minutes immediately prior to the assessment.
- 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 current use of concomitant medications and procedures.
- Clinical chemistry, hematology, and urinalysis laboratory tests will be performed on all subjects; all subjects must fast overnight prior to collection. Any subject with an abnormal urinary or serum glucose level will be followed closely until resolution (Section 7.2.2.5).
- 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 adrenocorticotrophic 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. Any subject with an abnormal ACTH stimulation test will be followed closely until resolution (Section 7.2.2.5).

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

- Retrieve DSQ handset and review DSQ compliance.

■ [REDACTED]

■ [REDACTED]

- Perform a physical examination on all subjects. Adolescents (subjects ≥ 11 years until the investigator confirms subject is post puberty) will also undergo Tanner Staging Assessment.
- **Serum** pregnancy test will be performed on all female subjects.
- Perform DXA scan for BMD and body composition measurements in subjects aged 11-17 years, inclusive. Dual-energy X-ray absorptiometry scans should be performed at this visit or within 7 days of the scheduled visit using the same machine and software as used in the SHP621-301 study.
- Perform EGD and biopsy; EGD should be completed at or within 7 days of the scheduled visit. An earlier EGD may occur if the subject exhibits signs of relapse (Section 6.2.3); however, the Week 36 EGD must be completed.
- Review investigational product dosing compliance.

7.1.3 Follow-up Period

The follow-up period for this protocol is 4 weeks from the last dose of investigational product. Subjects will receive a follow-up phone call at Visit 9 (Week 40) to query for SAEs, AEs, and concomitant treatments (Section 7.1.3.1).

7.1.3.1 Safety Follow-up Contact (Visit 9): Week 40

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.

7.2 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 any of the questions as this can 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](#).

The screening EGD with biopsies will be performed by a physician at the investigative site at the final treatment evaluation visit in the SHP621-301 study. Biopsy specimens must be taken and provided to the central pathology lab by at least 2 weeks prior to the planned Visit 1 to allow sufficient time for processing and central review and determination of eligibility. The independent unblinded data team will receive data from the central reader and will use it to confirm whether the subject meets the eligibility criteria for this study. Subjects, site staff, and study team members will remain blinded to eosinophil counts and histopathologic findings by the central reader throughout the duration of the study.

At the Week 12 visit (Visit 4), and Week 36 visit (Visit 8) or at early termination (ET), an EGD with esophageal biopsies is required for all subjects. If at any time, the subject reports increased or worsening dysphagia symptoms to the investigator, the investigator may choose

to perform an unscheduled EGD. If an unscheduled EGD is performed prior to Week 12, an EGD does not have to be repeated at Week 12. If an unscheduled EGD is performed between Week 12 and Week 36, the Week 36 EGD should still be performed. 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), midesophagus (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. Eosinophil counts and, histopathologic features will be evaluated by the central reader 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. At the investigator's discretion, biopsies will be taken from the stomach and duodenum 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 1 vial; biopsies from the duodenum should be submitted in a separate vial to the central pathology laboratory for processing of tissue into slides.

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 during the screening period and during the 36-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. 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.

To meet relapse criteria, the subject must have at least 4 days of dysphagia as determined by the DSQ in the 2-week period prior to the scheduled visit in addition to meeting the eosinophil histology criterion (≥ 15 eos/HPF from at least 2 of 3 levels of the esophagus). At

least 8 daily diary entries must be completed over 14 consecutive days in order to determine the criterion for relapse. If fewer than 8 diary entries are reported within the 2-week period, then the 2-week period will be shifted backwards from the scheduled visit to include the most recent 2-week period with at least 8 diary entries over 14 consecutive days; however, the 2-week period will not be shifted by more than 2 weeks (ie, no more than 2-week period plus additional 2-week additional expansion).

Calculations will be performed on daily ePRO entries during a 2-week interval prior to each study visit during the treatment period. The DSQ score for the coprimary 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:

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

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.

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

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

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

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 new clinically or medically relevant information which arose after the recording of the medical history in the antecedent study. New medical history will be collected at the screening visit (Visit 0) of this study. Medical history will be classified as EoE or non-EoE by the investigator. Adverse events recorded during the SHP621-301 study may be added as medical history at the investigator's discretion.

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 0) will be documented in the subject's source documents and on the medical history CRF. Changes after the screening visit (Visit 0) 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 0) will also include Tanner Staging Assessments for subjects <18 years of age.

Height will be collected at the screening visit (Visit 0) and Visit 8 for all subjects. Stadiometers will be used to measure height 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 each 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.) Any AE that is ongoing from the SHP621-301 study must be recorded on the CRF for this study.

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 in 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
- bilirubin
- ketones
- hemoglobin

- pH
- nitrite
- urobilinogen
- leukocyte esterase

Other tests

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

Adrenocorticotrophic hormone 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. Administration of ACTH stimulation testing and sample collection should follow the same procedures used in the SHP621-301 study.

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 0) and the final treatment evaluation visit (Visit 8) or ET visit. A urine pregnancy test is performed on all female subjects at all other visits 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 measurements will be performed in subjects aged 11-17 years, inclusive, as outlined in [Table 1-1](#).

The sites for DXA measurement will be the lumbar spine (L1-L4 preferred) and total body less head ([Bachrach, 2011](#); [Gordon et al., 2008](#); [International Society for Clinical Densitometry, 2013](#)). Dual-energy X-ray absorptiometry body composition measurements will also be collected. 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

[illegible]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

7.2.4 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)
Safety	Biochemistry and β -hCG ^a	6	9	54
	ACTH	2	4	8
	Cortisol	2	9	18
	Hematology	2	9	18
Total mL		-	-	98

Abbreviations: ACTH=adrenocorticotrophic hormone; β -hCG=beta-human chorionic gonadotropin^a β -hCG testing is for females only.

During this study, it is expected that approximately 98 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 98 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 7.1.3. This includes events occurring during the screening period 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 dechallenge. 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 reexposure 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 period, 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 7.1.3.

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 nonmedical 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 prespecified 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 parents/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 (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 7.1.3 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, unless another investigational product action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product action of "withdrawn" should not be selected solely as a result of the subject's death.

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 9.3 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.

The SAP 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

No interim analysis is planned.

9.6 Sample Size Calculation and Power Considerations

Approximately 200 subjects (88%) who are randomized in the SHP621-301 study are estimated to complete the SHP621-301 study and enroll in this treatment extension study based on enrollment observed in the Phase 2 study (MPI 101-06).

The primary efficacy measure of the study will be the proportion of subjects who relapse during the double-blind randomized withdrawal period, defined as having an eosinophil count of ≥ 15 eos/HPF from at least 2 of 3 levels of the esophagus (as determined by a central reader) and at least 4 days of dysphagia in the 2-week period prior to the scheduled visit (as determined by the DSQ). To be considered as a subject with relapse, both criteria must be met. To determine whether a subject meets the criterion for dysphagia, at least 8 daily diary entries must be completed over 14 consecutive days, as described in Section 7.2.1.2.

Based on observation in the Phase 2 study (MPI 101-06), approximately 26% of subjects, or approximately 40 subjects, who were assigned to OBS treatment in the SHP621-301 study are anticipated to respond fully after 12 weeks in the SHP621-301 study. For this study, to detect a 50 percentage point difference between relapse proportions of 20% and 70% in the OBS and placebo groups, respectively, at 80% power and a significance level of 0.05 (two-sided) using a Chi-Square test with equal allocation to treatment groups, it is necessary to assess the primary efficacy measure for approximately 38 subjects (19 subjects in each of the OBS and placebo groups).

9.7 Study Population

The **safety set** will include all subjects who are randomized and receive at least 1 dose of 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 investigational product and had 1 post baseline efficacy assessment (biopsy and/or DSQ score).

The **per-protocol (PP)** set will include all subjects in the FAS excluding subjects with major protocol deviations. 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.

9.8 Efficacy Analyses

9.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint for each subject is relapse during the double-blind randomized withdrawal period. Relapse, a binary response (either with a relapse or not), is defined as having an eosinophil count of ≥ 15 eos/HPF from at least 2 of 3 levels of the esophagus, as determined by a central reader, and having at least 4 days of dysphagia in the 2-week period prior to the scheduled visit, as determined by the DSQ. To determine whether a subject meets the criterion for dysphagia, at least 8 daily diary entries must be completed over 14 consecutive days, as described in Section 7.2.1.2.

The primary efficacy endpoint will be analyzed as the proportion of subjects with relapse during the double-blind randomized withdrawal period for the FAS, using a Chi-Square test comparing OBS 2 mg twice daily against placebo. The primary test of treatment effect will be two-sided, and conducted at the significance level of 0.05. The proportion of subjects with relapse for each treatment group and the corresponding 95% confidence interval (CI) will be estimated. In addition, the difference in the proportion of subjects with relapse between the 2 treatment groups and its 95% CI will be estimated.

Subjects who withdraw without providing efficacy data at the ET visit will be classified as being relapsers in the primary efficacy analysis. The null hypothesis states that there is no difference in relapse proportions between OBS 2 mg twice daily and placebo, with the two-sided alternative of a nonzero difference between groups. Relapse proportions at each adjacent double-blind visit interval will also be assessed by applying the chi-square test to the observed data at each double-blind visit.

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

Similar analyses used for the ITT population will be repeated using the FAS and the PP datasets. Sensitivity analyses will be performed using the ITT population by classifying subjects who withdraw without providing efficacy data at the ET visit as non-relapsers. In addition, the subjects who were prematurely withdrawn from the study without the primary efficacy endpoint will be imputed randomly according to the distribution of relapsers with available data; and the similar statistical test will be performed using the imputed data.

9.8.2 Secondary Efficacy Endpoints

9.8.2.1 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is the long-term treatment response, a binary response over an extended period of 36 weeks in adolescent and adult subjects who were randomized to OBS treatment but did not respond after 12 weeks in the SHP621-301 induction study (subject did not have peak count of ≤ 6 eos/HPF across all available esophageal levels at the final treatment visit and/or $\geq 30\%$ reduction in DSQ score from baseline) and met the following criteria:

- Histologic response, defined as a peak eosinophil count of ≤ 6 eos/HPF across all available esophageal levels at the final treatment period evaluation (Visit 8)
- Dysphagia symptom response, defined as $\geq 30\%$ reduction in the DSQ combined score (questions 2+3) from baseline of the SHP621-301 study and from baseline of this extension study to the final treatment period evaluation (Visit 8)

The key secondary efficacy endpoint will be analyzed as the proportion of subjects who responded based on the histological data and the DSQ data at the final treatment period evaluation (Visit 8). The proportion of subjects with long-term treatment response and the corresponding 95% confidence interval (CI) will be estimated and summarized.

The following secondary efficacy endpoints will be analyzed in all subjects:

- Histologic response, defined as a peak eosinophil count of ≤ 6 eos/HPF across all available esophageal levels at each assessment visit
- Dysphagia symptom response, defined as $\geq 30\%$ reduction in the DSQ combined score (questions 2+3) at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Change in the DSQ score and change in the peak eosinophilic count at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Change in total endoscopy score, as measured by the EREFS classification, at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Peak eosinophil count < 15 eos/HPF across all available esophagus levels at each assessment visit
- Peak eosinophil count ≤ 1 eos/HPF across all available esophagus levels at each assessment visit
- Change in the peak eosinophil count at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study at each assessment visit for each available esophageal level (proximal, mid-, and distal)
- Change in the histopathologic epithelial features combined total score (grade and stage) at

each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study

- Dysphagia symptom response (binary response), defined as a $\geq 50\%$ reduction in the DSQ combined score (questions 2+3), at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Change in the DSQ combined score (questions 2+3) at each assessment from baseline of the SHP621-301 study and from baseline of this extension study
- Cumulative distribution function curves for the change and the percent change in the DSQ score at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Overall binary response I, defined as a reduction in the DSQ score of $\geq 30\%$ and a peak eosinophil count of ≤ 6 eos/HPF across all esophageal levels at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Overall binary response II, defined as a reduction in the DSQ score of $\geq 50\%$ and a peak eosinophil count of ≤ 6 eos/HPF across all esophageal levels at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Change in the DSQ + pain score (question 2+3+4) at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Change in the DSQ pain score (question 4) at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study

Summary statistics of the DSQ score (questions 2+3) and the peak eosinophil count and the change from baseline of the SHP621-301 study and from baseline of this extension study at the final treatment period evaluation (Visit 8) will be summarized by each assessment visit.

To evaluate the response to OBS treatment over 36 weeks for subjects who were on placebo in the SHP621-301 induction study, the proportion of subjects who responded based on the histological data and the DSQ data at the final treatment period evaluation (Visit 8) and the corresponding 95% CI will be summarized. Summary statistics of the DSQ score (questions 2+3) and the peak eosinophil count and the change from baseline of the SHP621-301 study and from baseline of this extension study at the final treatment period evaluation (Visit 8) will be summarized by each assessment visit.

For subjects who relapse on placebo during the randomized withdrawal and who reinstate treatment with OBS 2 mg twice daily (intermittent therapy), separate descriptive analyses for histological data and DSQ endpoints will be conducted at each assessment visit. Changes will be summarized over time from baseline of the SHP621-301 study and from the time of relapse. The same criteria for response will be applied to these subjects (≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ from SHP621-301 baseline score).

Summary statistics will be provided for all other secondary endpoints.

9.8.3 Exploratory Efficacy Endpoints

The exploratory endpoints that will be explored are 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 randomization visit (Visit 1), or at the screening visit (Visit 0) 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 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, preferred term, 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 ([Bone Mineral Density in Childhood Study, 2015](#)). Safety parameters will be descriptively summarized by treatment group at baseline and for each post baseline visit.

[REDACTED]

[REDACTED]

[REDACTED]

█ [REDACTED]

█ [REDACTED]

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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 nonpediatric 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 subinvestigators 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.

The data from the central pathologist will be recorded directly onto paper CRF.

All other data will have separate source documentation; no data will be recorded directly onto the CRF. The following data collected for assessments and procedures performed at the SHP621-301 final treatment evaluation visit (Visit 4) will not be recollected in the SHP621-302 database as follows (Section 7.1.1.1):

- Vital signs, height, and weight assessment
- EGD with endoscopy score (EREFS) and biopsy
- DSQ compliance assessment

■ [REDACTED]
■ [REDACTED]

■ [REDACTED]
■ [REDACTED]

- Physical examination
- Tanner Staging Assessment
- Clinical laboratory tests
- Urinalysis
- Pregnancy test
- Morning cortisol
- ACTH Stimulation Testing
- DXA Scan (subjects 11 to 17 years of age)

All other 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 parents/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 noncommercial 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.

11. REFERENCES

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[REDACTED]

[REDACTED]

[REDACTED]

For non-commercial use only

12. APPENDIX

For non-commercial use only

Appendix 1 Scales and Assessments

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

Full Title of Scale/Assessment	Completed By
DSQ	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
Tanner Staging Assessment	Site
EREFS	Site

Abbreviations: DSQ=Dysphagia Symptom Questionnaire; [REDACTED]

[REDACTED] EREFS=EoE Endoscopic Reference Score; [REDACTED]
[REDACTED]

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

Daily Diary	Daily Diary	Daily Diary
This daily diary includes questions about your eosinophilic esophagitis (EoE). We are interested in any trouble you had today swallowing foods such as meat, rice, fruit, bread, etc.	Please complete this questionnaire after you have had your last meal of the day.	Read each question on the following screens and answer by selecting the box that best describes your experience. There are no right or wrong answers to any of the questions.

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



PROTOCOL: SHP621-302

TITLE: A Phase 3, Multicenter, Double-blind Extension Study to Evaluate Maintenance of Efficacy of Oral Budesonide Suspension (OBS) and Long-term Treatment Effect of OBS in Adolescent and Adult Subjects (11 to 55 Years of Age, Inclusive) with Eosinophilic Esophagitis (EoE)

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: 05 Dec 2015
Protocol Amendment 1: 22 Jun 2016

This document contains confidential and proprietary information of Shire and is disclosed pursuant to confidentiality and nondisclosure obligations. This information should be used solely for the purposes for which it was provided and should not be copied, shared with, or disclosed to any third party without the express written consent of Shire.

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [Redacted] [Redacted], MD [Redacted]	Date: [Redacted]
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Acknowledgement

I have read this protocol for Shire Study SHP621-302.

Title: A Phase 3, Multicenter, Double-blind Extension Study to Evaluate Maintenance of Efficacy of Oral Budesonide Suspension (OBS) and Long-term Treatment Effect of OBS in Adolescent and Adult Subjects (11 to 55 Years of Age, Inclusive) with Eosinophilic Esophagitis (EoE)

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 SHP621-302 protocol is amended to address the following items:

- Clarification of relapse criterion based on days of dysphagia reported on the Dysphagia Symptom Questionnaire prior to study visits with consideration of the potential for missing diary entries
- Additional safety monitoring added for subjects with clinical evidence of adverse HPA effects
- Clarification of withdrawal criteria to ensure that only subjects with severe signs and symptoms of EoE are withdrawn from the study
- Methods for primary efficacy analysis updated from chi-square test to Fisher's Exact test

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 22 June 2016	Global Amendment
Description of Change		Section(s) Affected by Change
Changed from: <div style="background-color: black; width: 150px; height: 1.2em; margin: 5px 0;"></div> To: <div style="background-color: black; width: 150px; height: 1.2em; margin: 5px 0;"></div>		Emergency Contact Information Page
A 4-week screening period is required to allow for blinded treatment response information (reduction in DSQ from baseline and eosinophilic count as determined by a central reader) collected during the SHP621-301 final treatment evaluation visit to be entered into the interactive web-based response system (IWRS) by Only the unblinded data team who is independent from the blinded study team and not involved with the day-to-day conduct of the study will have restricted access to blinded treatment response information. <p>Rationale: This text has been clarified to emphasize that access to blinded treatment response information will be restricted to the unblinded data team. Blinded treatment response data will not be accessed by the study team; therefore, the double-blind will be maintained.</p>		Synopsis: Investigational product, dose, and mode of administration; Synopsis: Methodology; Section 3.1: Study Design and Flow Chart
At least 8 daily diary entries must be completed over 14 consecutive days in order to determine the criterion for DSQ relapse. Considering the potential for missing diary entries, the determination of relapse based on days of dysphagia reported on the DSQ will occur as follows: <ul style="list-style-type: none"> • If at least 4 days of dysphagia are reported on the DSQ in order 		Synopsis: Investigational product, dose, and mode of administration; Section 6.2.3: Dosing; Section 7.2.1.2: Dysphagia

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<p>the 2-week period prior to the visit, the subject would meet the criterion for dysphagia symptom relapse. If fewer</p> <ul style="list-style-type: none"> If less than 4 days of dysphagia are reported and at least 8 diary entries are recorded within the 2-week period, the subject would not meet criterion for dysphagia symptom relapse. If less than 4 days of dysphagia are reported in the DSQ and less fewer than 8 diary entries are reported recorded within the 2-week period, then the 2-week period will be shifted backwards from the scheduled visit, 1 day at a time, to include the most recent 2-week period with at least 8 diary entries confirm if the most recent 2-week period with at least 8 diary entries subject meets the criteria for dysphagia symptom relapse over 14 consecutive days; however, the 2-week period will not be shifted further if at least 8 diary entries are recorded in the 14-day period and will not be shifted by more than 2 weeks in total (ie, no more than 2-week period plus additional 2-week additional expansion). <p>The criteria for relapse align with the related inclusion criteria for participation in the SHP621-301 study. If both histology and dysphagia symptom relapse criteria are met, then the treatment assignment change will be performed in a blinded manner in IWRS at the subsequent study visit by the independent unblinded data team.</p> <p>Rationale: Additional text is provided to clarify the evaluation of dysphagia symptoms for determination of relapse based on days of dysphagia reported on the DSQ prior to study visits with the potential for missing diary entries.</p>		Symptom Questionnaire
<p>The independent, unblinded data team will review the blinded EGD and DSQ data to confirm the If a subject is on placebo in the randomized withdrawal period, determine if the subject meets relapse criteria, and change for relapse, the subject's treatment assignment will be changed in a blinded manner from placebo to OBS 2 mg twice daily if relapse is confirmed at the subsequent study visit.</p>		<p>Synopsis: Investigational product, dose, and mode of administration</p> <p>Synopsis: Methodology; Section 6.2.3: Dosing</p>
<p>6. Subject is willing and has an understanding and ability to fully comply with study procedures including DSQ compliance (completed the DSQ on ≥70% of days in any 2 consecutive weeks of the screening period) and restrictions defined in this protocol.</p>		<p>Synopsis: Inclusion Criteria; Section 4.1: Inclusion Criteria</p>
<p>5. Subject has initiated, discontinued, or changed dosage regimen of proton pump inhibitors (PPIs), H2 antagonists, antacids, antihistamines, or leukotriene inhibitors for any condition (such as gastroesophageal reflux disease, asthma or allergic rhinitis) since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or anticipated changes in the use of such medications during the treatment period.</p>		<p>Synopsis: Exclusion Criteria; Section 4.2: Exclusion Criteria</p>
<p>12. Subject has oropharyngeal or esophageal candidiasis that failed to respond to previous treatment. Diagnosis with oropharyngeal or esophageal candidiasis at or since the final treatment evaluation visit (Visit 4) of the SHP621-301 study is not an exclusion as long as the subject received is treatment for candidiasis and is expected to respond to treatment.</p>		<p>Synopsis: Exclusion Criteria; Section 4.2: Exclusion Criteria</p>

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13. Subject has a potentially serious acute or chronic infection or immunodeficiency condition, including tuberculosis, fungal, bacterial, viral/parasite infection, ocular herpes simplex, or chicken pox/measles.		Synopsis : Exclusion Criteria; Section 4.2 : Exclusion Criteria
The primary efficacy endpoint will be analyzed as the proportion of subjects with relapse during the end of the double-blind randomized withdrawal period for the FAS, using Fisher's Exact a chi-square test comparing OBS 2 mg twice daily against placebo. Relapse proportions at each adjacent double-blind visit interval will also be assessed by applying the Fisher's Exact chi-square test to the observed data at each double-blind visit. Rationale : The primary efficacy analysis method has been changed from the Chi-square test to Fisher's exact test. Considering the expected number of subjects in the randomized withdrawal portion of the study, and the very small number of subjects who are expected to relapse in the OBS group, the Fisher's exact test is considered a more appropriate method.		Synopsis : Statistical Methodology for Primary Efficacy Endpoint Section 9.8.1 : Primary Efficacy Endpoint
For this study, to detect a 50 percentage point difference between relapse proportions of 20% and 70% in the OBS and placebo groups, respectively, at more than 80% power and a significance level of 0.05 (2-sided) using the Fisher's Exact a Chi-Square test with equal allocation to treatment groups, it is necessary to assess the primary efficacy measure for approximately 38 subjects (19 subjects in each of the OBS and placebo groups)		Synopsis : Sample Size Justification; Section 9.6 : Sample Size Calculation and Power Considerations
c Height to be collected at screening (Visit 0) and Visit 8 only. Stadiometers will be used to measure height for all subjects aged 11-17 years, inclusive. c Height to be collected at Visit 4 for adolescents only (11-17 years, inclusive). Height measurements for adolescents should be measured in triplicate using stadiometers.		Table 1-1 , Footnote c; Section 7.1.2.3 : Visit 4 (Week 12)
d Weight measurements for adolescents (11-17 years, inclusive) should be measured in duplicate.		Table 1-1 , Footnote d
The treatment assignment change will be performed in a blinded manner in IWRS at the subsequent study visit by the independent unblinded data team.		Section 3.1 : Study Design and Flow Chart
<ul style="list-style-type: none"> No change in use of PPIs, H2 antagonists, antacids, antihistamines, or leukotriene inhibitors for any condition (such as gastroesophageal reflux disease, asthma or allergic rhinitis). 		Section 4.3 : Restrictions
<ul style="list-style-type: none"> Acceptable methods of contraception are: <ul style="list-style-type: none"> Surgically sterile male partner 		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, weight loss due to severe dysphagia, and/or upper GI bleed worsening signs and symptoms of EoE (eg, weight loss or increased dysphagia) , would be considered a relapse and result in withdrawal of the subject from the study.		Section 4.5.1 : Subject Withdrawal Criteria

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Rationale: The terms “worsening signs and symptoms of EoE” have been more clearly defined as “severe signs and symptoms of EoE” to prevent subjects with only minor to moderate symptoms being withdrawn from the study.		
Antihistamines Rationale: Antihistamines were removed from the list of permitted medications that require consultation with the medical monitor prior to initiating changes in the dosing regimen. Antihistamine use, including any changes to the dosing regimen, is permitted during the course of the study.		Section 5.2.1: Permitted Treatment
3. Initiation or change in dosing frequency to PPIs, H2 antagonists, antacids, antihistamines , or leukotriene inhibitors for any condition...		Section 5.2.2: Prohibited Treatment
During the 4-week screening period, blinded treatment response information (reduction in DSQ from baseline and eosinophilic count as determined by a central reader) collected during the SHP621-301 final treatment evaluation visit will be entered into the IWRS by an independent, unblinded data team in a blinded manner in a blinded manner. Details on the unblinded data team will be provided in a separate charter. Once information is available in IWRS, subjects will return...		Section 6.2.1: Interactive Response Technology for Investigational Product Management
Sites will enter confirm eligibility criteria information prior to randomization		
The 4-week screening period is required to allow for blinded treatment response information (reduction in DSQ from baseline and eosinophilic count as determined by a central reader) collected during the SHP621-301 final treatment evaluation visit to be entered into the IWRS by the independent, unblinded, data team.		Section 7.1.1: Screening Period (Weeks -4 to 0)
<ul style="list-style-type: none"> Record vital signs (including blood pressure [systolic and diastolic], heart rate, respirations, and temperature), height (measured in triplicate for adolescents 11-17 years, inclusive), and weight (measured in duplicate for adolescents 11-17 years, inclusive). Perform stadiometry in adolescent subjects. aged 11-17 years, inclusive. 		Section 7.1.1.1: Screening Visit (Visit 0)/Visit 4 of SHP621-301 Study; Section 7.1.2.3: Visit 4 (Week 12); Section 7.1.2.5: Visit 8 (Week 36) or Early Termination
<ul style="list-style-type: none"> Record vital signs (including blood pressure [systolic and diastolic], heart rate, respirations, and temperature) and weight (measured in duplicate for adolescents 11-17 years, inclusive). 		Section 7.1.2.1: Randomization Visit (Visit 1)/Week 0; Section 7.1.2.2: Visits 2 and 3 (Weeks 4 and 8); Section 7.1.2.4: Visits 5, 6, and 7 (Weeks 16, 20, and 28)
Any subject with clinical evidence of reduced height velocity and/or delayed Tanner staging will be followed closely until resolution (Section 7.2.2.2).		Section 7.1.2.5: Visit 8 (Week 36) or Early Termination
The independent unblinded data team will receive data from the central reader and will use it to confirm whether the subject meets the eligibility criteria for this study.		Section 7.2.1.1: Esophagogastroduodenoscopy with Esophageal Biopsy and

Protocol Amendments		
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Amendment Number 1	Amendment Date 22 June 2016	Global Amendment
Description of Change		Section(s) Affected by Change
Height will be collected at the screening visit (Visit 0) and Visit 8 for all subjects, and at Visit 4 for adolescents (11-17 years, inclusive) only.		Histopathologic Evaluation
Height will be measured in triplicate in adolescents (11-17 years, inclusive) and recorded in the CRF.		
Weight will be measured in duplicate in adolescents (11-17 years, inclusive) and recorded in the CRF.		
All subjects with clinical evidence of reduced height velocity and/or delayed Tanner Staging, as determined by the investigator, must be followed closely until resolution (ie, resumption of normal for age height velocity, or the resumption of Tanner Stage development). Subjects who discontinue from the treatment period at any time and have clinical evidence of reduced height velocity and/or delayed Tanner Stage development at the early termination visit will be monitored beyond the end of the study until resolution is established.		
Rationale: This text was added to ensure that any subjects demonstrating laboratory or clinical findings suggestive of adverse HPA effect will be appropriately monitored 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 ACTH testing approximately 6 weeks post last dose of investigational product to ensure that ACTH levels have normalized and followed to resolution of the abnormality.		Section 7.2.2.5: Clinical Laboratory Evaluations
To determine whether a subject meets the criterion for dysphagia, refer to at least 8 daily diary entries must be completed over 14 consecutive days, as described in Section 7.2.1.2.		Section 9.6: Sample Size Calculation and Power Considerations Section 9.8.1: Primary Efficacy Endpoint

See [Appendix 1](#) for protocol history, including all amendments.

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the Shire Clinical Study Serious Adverse Event and Non-serious Adverse Events (AEs) Required by the Protocol Form 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 this form must also be sent to the contract research organization (CRO)/Shire Medical Monitor by fax or e-mail using the details below.

██████████, MD

Email: ██████████

Fax: ██████████

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

██████████, MD

Phone: ██████████

Mobile: ██████████

Email: ██████████

Fax: ██████████

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

██████████, MD

Mobile: ██████████

Email: ██████████

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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LIST OF ABBREVIATIONS

ACTH	adrenocorticotrophic hormone
AE	adverse event
β -hCG	beta-human chorionic gonadotropin
BMD	bone mineral density
CFR	Code of Federal Regulations
CI	confidence interval
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
EMA	European Medicines Agency
EoE	eosinophilic esophagitis
[REDACTED]	[REDACTED]
ePRO	electronic patient-reported outcome
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
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
[REDACTED]	[REDACTED]
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
OBS	oral budesonide suspension
pc	after meals
PP	per-protocol
PPI	proton pump inhibitor
qAM	every morning
SAE	serious adverse event
SAP	statistical analysis plan
SAS [®]	statistical analysis system
TEAE	treatment-emergent adverse event
UK	United Kingdom
US	United States

STUDY SYNOPSIS

Protocol number: SHP621-302	Drug: SHP621, oral budesonide suspension (OBS)
Title of the study: A Phase 3, Multicenter, Double-blind Extension Study to Evaluate Maintenance of Efficacy of Oral Budesonide Suspension (OBS) and Long-term Treatment Effect of OBS in Adolescent and Adult Subjects (11 to 55 Years of Age, Inclusive) with Eosinophilic Esophagitis (EoE)	
Number of subjects (total and for each treatment arm): Approximately 200 subjects (88%) who are randomized in the SHP621-301 study are estimated to complete the SHP621-301 study and enroll in this treatment extension study based on enrollment observed in the Phase 2 study (MPI 101-06).	
Investigator(s): Multicenter study	
Site(s) and Region(s): Approximately 60 sites in North America	
Study period (planned): April 2016–April 2019	Clinical phase: 3
Objectives Primary: <ul style="list-style-type: none">To evaluate the maintenance of efficacy over 36 weeks, as measured by the peak eosinophilic count and the Dysphagia Symptom Questionnaire (DSQ) score, through a randomized withdrawal design for subjects who responded to 12 weeks of OBS treatment (2 mg twice daily) with a peak count of ≤ 6 eosinophils (eos)/high-powered field (HPF) across all available esophageal levels at the final treatment visit and a $\geq 30\%$ reduction in DSQ score from baseline during the SHP621-301 induction study Key Secondary: <ul style="list-style-type: none">To evaluate the long-term treatment response over an extended period of 36 weeks for subjects who were randomized to OBS treatment but did not respond after 12 weeks in the SHP621-301 induction study (subject did not have a peak count of ≤ 6 eos/HPF across all available esophageal levels at the final treatment visit and/or a $\geq 30\%$ reduction in DSQ score from baseline) Secondary: <ul style="list-style-type: none">To evaluate the response to OBS treatment over 36 weeks for subjects who received placebo in the SHP621-301 induction studyTo evaluate the effect of reinitiating OBS treatment for subjects who relapse after being randomized to placebo in the randomized withdrawal period (treatment-withdrawal-treatment reinitiation)To assess endoscopically identified esophageal features as measured by the EoE Endoscopic Reference Score (EREFS)To evaluate other response criteria based on histology and DSQTo evaluate the long-term safety and tolerability of OBS treatment Exploratory: <ul style="list-style-type: none">[REDACTED][REDACTED]	

Rationale:

Currently there is no approved medication for the treatment of EoE. This Phase 3 study is being conducted to determine response to withdrawal of OBS, maintenance of response, extended therapy response, and response to intermittent therapy by evaluating both eosinophil counts and DSQ in adolescent and adults treated or withdrawn from OBS in this treatment extension study.

Investigational product, dose, and mode of administration:

The assessments from the SHP621-301 final treatment evaluation visit (Visit 4) will be used as the screening assessments (Visit 0) of this treatment extension study. At the SHP621-301 final treatment evaluation visit, subjects will be dispensed blinded investigational product (based on treatment assignment in SHP621-301) that will last for up to 4 weeks prior to enrolling into this treatment extension study. A 4-week screening period is required to allow for blinded treatment response information (reduction in DSQ from baseline and eosinophilic count as determined by a central reader) collected during the SHP621-301 final treatment evaluation visit to be entered into the interactive web-based response system (IWRS). Only the unblinded data team who is independent from the blinded study team and not involved with the day-to-day conduct of the study will have restricted access to blinded treatment response information. Once information is available in IWRS, subjects will return for the randomization visit (Visit 1) to receive investigational product as follows:

- Subjects who were assigned to OBS treatment and who fully responded in the SHP621-301 study (≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ at the final treatment evaluation visit) will enter a randomized withdrawal period to receive either OBS 2 mg twice daily or placebo at a 1:1 ratio
- Subjects who were assigned to OBS treatment and did not respond or partially responded to OBS treatment in the SHP621-301 study will receive OBS 2 mg twice daily
- Subjects who were assigned to placebo in the SHP621-301 study will receive OBS 2 mg twice daily

Subjects, site staff, and study team members will remain blinded to treatment assignment and individual subject histology and individual subject DSQ data from the SHP621-301 study (post randomization) and this extension study until database lock occurs for this extension study.

During the 36-week double-blind treatment extension study, subjects will receive oral administration of 10 mL of 0.2 mg/mL (2 mg) investigational product twice daily (every morning [qAM] after meals [breakfast, pc] and at bedtime [hs]; 4 mg total/day), with no ingestion of food or liquids permitted for 30 minutes after investigational product administration. Dosing regimens are consistent with the regimens used in the Phase 2 MPI 101-06 study and Phase 3 SHP621-301 study:

- Placebo twice-daily group: placebo qAM (pc) and hs
- OBS twice-daily group: OBS 10 mL of 0.2 mg/mL (2 mg) qAM (pc) and hs (4 mg OBS total/day)

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).

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.

Total Daily Dose of OBS

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

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

At Week 12, all subjects will undergo an upper esophagogastrroduodenoscopy (EGD) with biopsy to evaluate eosinophil counts. Upon receipt of blinded EGD and DSQ data, subjects on placebo in the randomized withdrawal period who have relapsed will have their treatment assignment changed to OBS 2 mg twice daily. The criteria for relapse is having an eosinophilic count of ≥ 15 eos/HPF from at least 2 of 3 levels of the esophagus, as determined by central reader and having at least 4 days of dysphagia in the 2-week period prior to the scheduled visit, as determined by the DSQ. Considering the potential for missing diary entries, the determination of relapse based on days of dysphagia reported on the DSQ will occur as follows:

- If at least 4 days of dysphagia are reported on the DSQ in the 2-week period prior to the visit, the subject would meet the criterion for dysphagia symptom relapse.
- If less than 4 days of dysphagia are reported and at least 8 diary entries are recorded within the 2-week period, the subject would not meet criterion for dysphagia symptom relapse.
- If less than 4 days of dysphagia are reported in the DSQ and less than 8 diary entries are recorded within the 2-week period, then the 2-week period will be shifted backwards from the scheduled visit, 1 day at a time, to confirm if the subject meets the criteria for dysphagia symptom relapse over 14 consecutive days; however, the 2-week period will not be shifted further if at least 8 diary entries are recorded in the 14-day period and will not be shifted by more than 2 weeks in total (ie, no more than 2-week period plus additional 2-week additional expansion).

The criteria for relapse align with the related inclusion criteria for participation in the SHP621-301 study. If both histology and dysphagia symptom relapse criteria are met, the treatment assignment change will be performed in a blinded manner in IWRS at the subsequent study visit. If both criteria for relapse are not met, the subject will remain assigned to placebo.

If at any time, the subject reports increased or worsening dysphagia symptoms to the investigator, the investigator may choose to perform an unscheduled EGD. If an unscheduled EGD is performed prior to Week 12, an EGD does not have to be repeated at Week 12. If a subject on placebo meets the criteria for relapse, the subject's treatment assignment will be changed in a blinded manner from placebo to OBS 2 mg twice daily at the subsequent study visit.

If the Week 12 or an unscheduled EGD reveals an eosinophil count of ≥ 15 from at least 2 of 3 levels of the esophagus yet relapse is not confirmed due to the criterion for dysphagia symptoms not being met, the subject will remain assigned to placebo. If the criterion for dysphagia symptoms is met at a subsequent visit and both criteria for relapse are then confirmed, the subject's treatment assignment will be changed to OBS 2 mg twice daily at the next scheduled visit.

Methodology:

This is a Phase 3, double-blind, multicenter 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 who completed the SHP621-301 induction study.

This study will comprise 3 periods: 4-week screening period, 36-week double-blind treatment period, and a 4-week safety follow-up (Study Design Flow Chart). All subjects who have completed the SHP621-301 induction study will be eligible to enroll in this extension study. Approximately 200 subjects (88%) who were randomized in the SHP621-301 study are estimated to complete the SHP621-301 study and will be enrolled in this treatment extension study based on enrollment observed in the Phase 2 study (MPI 101-06). Randomization into the randomized withdrawal period will be stratified by treatment assignment and treatment response in the SHP621-301 study. Subjects who are full responders (defined as ≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ at the final treatment evaluation visit [Visit 4]) in the SHP621-301 induction study will be eligible to enter the randomized withdrawal period to receive either OBS 2 mg twice daily or placebo at a 1:1 ratio. The randomization of subjects who are full responders will also be stratified by age (adults and adolescents) to ensure approximately equal number of subjects within each age group are assigned to the treatment groups.

Subjects who sign informed consent (or assent as applicable for subjects < 18 years) will be screened (Visit 0); assessments from the SHP621-301 final treatment evaluation visit (Visit 4) will be used as the Visit 0 screening assessments of the treatment extension study. Subjects who meet eligibility criteria at the screening visit (Visit 0) will enter the 36-week double-blind period. Eligible subjects will receive investigational product based on treatment assignment in SHP621-301 for up to 4 weeks prior to enrollment in the treatment extension study. This 4-week screening period is required to allow for blinded treatment response information (reduction in DSQ from baseline and eosinophilic count as determined by a central reader) collected during the SHP621-301 final treatment evaluation visit to be entered into IWRS. Only the unblinded data team who is independent from the blinded study

Subjects will be required to visit the site up to 8 times over up to a 36-week period. All subjects will have a follow-up phone call 4-weeks post last dose of investigational product.

SHP621-301 Study Timeline

The study timeline is divided into three main phases:

- Screening:** From W-4 to W0.
- Double-Blind Treatment Period:** From W0 to W8.
- Safety Follow-Up:** From W8 to W40.

The treatment period is divided into two arms:

- OBS 2mg Twice Daily:** This arm includes the following groups:
 - SHP621-301 Study Completers:** This group includes the **OBS 2mg Twice Daily** group.
 - OBS Completers/ Responders:** This group includes the **OBS 2mg Twice Daily** group.
 - OBS Completers/ Non-Responders:** This group includes the **OBS 2mg Twice Daily** group.
 - Placebo Completers:** This group includes the **OBS 2mg Twice Daily** group.
- Placebo (Withdrawal Arm):** This arm includes the following groups:
 - SHP621-301 Study Completers:** This group includes the **Placebo (Withdrawal Arm)** group.
 - OBS Completers/ Responders:** This group includes the **Placebo (Withdrawal Arm)** group.
 - OBS Completers/ Non-Responders:** This group includes the **Placebo (Withdrawal Arm)** group.
 - Placebo Completers:** This group includes the **Placebo (Withdrawal Arm)** group.

The timeline includes visits V0 through V9 and corresponding weeks W-4 through W40. A 'Upon relapse' arrow points from the Placebo arm to the OBS arm at W20.

Abbreviations: EGD=esophagogastroduodenoscopy; 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 completed SHP621-301 induction study.
2. 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.
3. Subject is male or female aged 11-55 years, inclusive, at time of consent for SHP621-301 study.
4. 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 0). There should be no changes to these regimens during study participation.
5. 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 and for 30 days following the last dose of investigational product.
6. Subject is willing and has an understanding and ability to fully comply with study procedures including DSQ compliance 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 changes in medications that could affect the study or diet in the weeks since the final treatment evaluation visit (Visit 4) of the SHP621-301 study.
2. Subject using immunomodulatory therapy since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or anticipated use of immunomodulatory therapy during the treatment period (except for any ongoing regimen of allergy shots); 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 scheduled EGDs.
3. Subject using swallowed topical corticosteroid for EoE or systemic corticosteroid for any condition since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or anticipated 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 medical monitor prospectively but cannot occur within the 4 weeks of the scheduled EGDs.
4. Subject on inhaled or intranasal steroids and not on a stable dose between the baseline visit (Visit 1) of the SHP621-301 study and the screening EGD of this study.
5. Subject has initiated, discontinued, or changed dosage regimen of proton pump inhibitors (PPIs), H₂ antagonists, antacids, or leukotriene inhibitors for any condition (such as gastroesophageal reflux disease, asthma or allergic rhinitis) since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or anticipated changes in the use of such medications during the treatment period.
6. Subject using Cytochrome P450 3A4 inhibitors (eg, ketoconazole, grapefruit juice) since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or anticipated use of such medications during the treatment period.
7. Subject has an appearance on screening 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 six-food elimination diet.
9. Subject has presence of esophageal varices at the EGD at the final treatment evaluation visit (Visit 4) of the SHP621-301 study.
10. 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.

11. Subject has other diseases causing or associated with esophageal eosinophilia, including hypereosinophilic syndrome, collagen vascular disease, vasculitis, achalasia, or parasitic infection.
12. Subject has oropharyngeal or esophageal candidiasis that failed to respond to previous treatment. Diagnosis with oropharyngeal or esophageal candidiasis at or since the final treatment evaluation visit (Visit 4) of the SHP621-301 study is not an exclusion as long as the subject is expected to respond to treatment.
13. Subject has a potentially serious acute or chronic infection or immunodeficiency condition, including tuberculosis, fungal, bacterial, viral/parasite infection, ocular herpes simplex, or chicken pox/measles.
14. Subject has upper gastrointestinal bleeding identified in the EGD at the final treatment evaluation visit (Visit 4) of the SHP621-301 study or since the final treatment evaluation visit (Visit 4) of the SHP621-301 study.
15. Subject has evidence of active infection with *Helicobacter pylori*.
16. Subject has evidence of unstable asthma since the final treatment evaluation visit (Visit 4) of the SHP621-301 study.
17. Subject is female and pregnant or nursing.
18. Subject has a history of intolerance, hypersensitivity, or idiosyncratic reaction to budesonide (or any other corticosteroids), or to any other ingredients of the study medication.
19. Subject has a history or high risk of noncompliance with treatment or regular clinic visits.
20. Subject is on sucralfate or anticipates using sucralfate during the treatment period.

Maximum duration of subject involvement in the study:

- Planned duration of screening period: up to 4 weeks
- Planned duration of treatment period: 36 weeks
- Planned duration of safety follow-up period: 4 weeks

Endpoints and statistical analysis:

Subject Populations

- The **safety set** will include all subjects who are randomized and receive at least 1 dose of 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 investigational product and had 1 post baseline efficacy assessment (biopsy and/or DSQ score).
- The **per-protocol (PP) set** will include all subjects in the FAS excluding subjects with major protocol deviations. 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.

Primary Efficacy Endpoint

The primary efficacy endpoint for each subject is relapse during the double-blind randomized withdrawal period. Relapse, a binary response (either with a relapse or not), is defined as having an eosinophil count of ≥ 15 eos/HPF from at least 2 of 3 levels of the esophagus, as determined by a central reader, and having at least 4 days of dysphagia in the 2-week period prior to the scheduled study visit, as determined by the DSQ.

Key Secondary Efficacy Endpoint

The key secondary endpoint is the long-term treatment response, a binary response, over an extended period of 36 weeks in adolescent and adult subjects who were randomized to OBS treatment but did not respond after 12 weeks in the SHP621-301 induction study (subject did not have peak count of ≤ 6 eos/HPF across all available esophageal levels at the final treatment visit and/or $\geq 30\%$ reduction in DSQ score from baseline) and met the following criteria:

- Histologic response, defined as a peak eosinophil count of ≤ 6 eos/HPF across all available esophageal levels at

the final treatment period evaluation (Visit 8)

- Dysphagia symptom response, defined as $\geq 30\%$ reduction in the DSQ combined score (questions 2+3) from baseline of the SHP621-301 study and from baseline of this extension study to the final treatment period evaluation (Visit 8)

Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be analyzed in all subjects:

- Histologic response, defined as a peak eosinophil count of ≤ 6 eos/HPF across all available esophageal levels at each assessment visit
- Dysphagia symptom response, defined as $\geq 30\%$ reduction in the DSQ combined score (questions 2+3) at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Change in the DSQ score and change in the peak eosinophilic count at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Change in total endoscopy score, as measured by the EREFS classification, at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Peak eosinophil count < 15 eos/HPF across all available esophagus levels at each assessment visit
- Peak eosinophil count ≤ 1 eos/HPF across all available esophagus levels at each assessment visit
- Change in the peak eosinophil count at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study for each available esophageal level (proximal, mid-, and distal)
- Change in the histopathologic epithelial features combined total score (grade and stage) at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Dysphagia symptom response (binary response), defined as a $\geq 50\%$ reduction in the DSQ combined score (questions 2+3), at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension
- Change in the DSQ combined score (questions 2+3) at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Cumulative distribution function curves for the change and the percent change in the DSQ score at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Overall binary response I, defined as a reduction in the DSQ score of $\geq 30\%$ and a peak eosinophil count of ≤ 6 eos/HPF across all esophageal levels at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Overall binary response II, defined as a reduction in the DSQ score of $\geq 50\%$ and a peak eosinophil count of ≤ 6 eos/HPF across all esophageal levels at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Change in the DSQ + pain score (question 2+3+4) at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Change in the DSQ pain score (question 4) at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study

For subjects who relapse on placebo during the randomized withdrawal period and who reinitiate treatment with OBS 2 mg twice daily (intermittent therapy), separate descriptive analyses for histological data and DSQ endpoints will be conducted at each assessment visit. Changes will be summarized over time from baseline of the SHP621-301 study and from the time of relapse. The same criteria for response will be applied to these subjects (≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ from the SHP621-301 baseline score).

Exploratory Efficacy Endpoints

- [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 adrenocorticotrophic 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.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Statistical Methodology for Primary Efficacy Endpoint

The primary efficacy endpoint will be analyzed as the proportion of subjects with relapse during the end of the double-blind randomized withdrawal period for the FAS, using Fisher's Exact test comparing OBS 2 mg twice daily against placebo. The primary test of treatment effect will be 2-sided, and conducted at the significance level of 0.05. The proportion of subjects with relapse for each treatment group and the corresponding 95% confidence interval (CI) will be estimated. In addition, the difference in the proportion of subjects with relapse between the 2 treatment groups and its 95% CI will be estimated.

Subjects who withdraw without providing efficacy data at the early termination (ET) visit will be classified as being a relapser in the primary efficacy analysis. The null hypothesis states that there is no difference in relapse proportions between OBS 2 mg twice daily and placebo, with the 2-sided alternative of a nonzero difference between groups. Relapse proportions at each adjacent double-blind visit interval will also be assessed by applying the Fisher's Exact test to the observed data at each double-blind visit.

Statistical Methodology for Key Secondary and Other Secondary Efficacy Endpoints

To evaluate the long-term treatment response over an extended period of 36 weeks for subjects who were randomized to OBS treatment but did not respond after 12 weeks in the SHP621-301 induction study (subject did not have peak count of ≤ 6 eos/HPF across all available esophageal levels at the final treatment visit and/or $\geq 30\%$ reduction in DSQ score from baseline of SHP621-301), the proportion of subjects who responded based on the histological data and the DSQ data at the final treatment period evaluation (Visit 8) and the corresponding 95% confidence interval (CI) will be estimated and summarized.

Summary statistics of the DSQ score (questions 2+3) and the peak eosinophil count and the change from baseline of the SHP621-301 study and from baseline of this extension study at the final treatment period evaluation (Visit 8) will be summarized by each assessment visit.

To evaluate the response to OBS treatment over 36 weeks for subjects who were on placebo in the SHP621-301 induction study, the proportion of subjects who responded based on the histological data and the DSQ data at the final treatment period evaluation (Visit 8) and the corresponding 95% CI will be summarized. Summary statistics of the DSQ score (questions 2+3) and the peak eosinophil count and the change from baseline of the SHP621-301 study and from baseline of this extension study at the final treatment period evaluation (Visit 8) will be summarized by each assessment visit.

To evaluate the effect of reinitiating OBS treatment for subjects who relapse after being randomized to placebo in the randomized withdrawal period (intermittent therapy), the proportion of subjects who responded based on the histological data and the DSQ data at the final treatment period evaluation (Visit 8) and the corresponding 95% CI will be summarized.

Summary statistics will be provided for all the secondary endpoints.

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 (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.

Sample Size Justification

Approximately 200 subjects (88%) who are randomized in the SHP621-301 study are estimated to complete the SHP621-301 study and enroll in this treatment extension study based on enrollment observed in the Phase 2 study (MPI 101-06).

The primary efficacy measure of the study will be the proportion of subjects who relapse during the double-blind randomized withdrawal period. Relapse, a binary response (either with relapse or not), is defined as having an eosinophil count of ≥ 15 eos/HPF from at least 2 of 3 levels of the esophagus (determined by a central reader) and having at least 4 days of dysphagia in a 2-week period prior to the scheduled visit (determined by the DSQ). To be considered as a subject with relapse, both criteria must be met.

Based on observation in the Phase 2 study (MPI 101-06), approximately 26% of subjects, or approximately 40 subjects, who were assigned to OBS treatment in the SHP621-301 study are anticipated to respond fully after 12 weeks in the SHP621-301 study.

For this study, to detect a 50 percentage point difference between relapse proportions of 20% and 70% in the OBS and placebo groups, respectively, at more than 80% power and a significance level of 0.05 (2-sided) using the Fisher's Exact test with equal allocation to treatment groups, it is necessary to assess the primary efficacy measure for approximately 38 subjects (19 subjects in each of the OBS and placebo groups).

STUDY SCHEDULE(S)

Table 1-1: Schedule of Assessments

Procedures	Screening ^a	Double-blind Treatment Period								Safety Follow-up Contact ^p
	Visit 0	Randomization/ Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 or ET ^o	Visit 9
Week	-4	0	4	8	12	16	20	28	36	40
Window	≤4 weeks	--	±3 days	±3 days	±3 days	±3 days	±3 days	±6 days	±6 days	±3 days
Informed consent/assent	X									
Medical history review	X	X								
Inclusion/exclusion criteria review	X	X								
Vital signs ^b , height ^c , and weight assessment ^d	X	X	X	X	X	X	X	X	X	
EGD with endoscopy score (EREFS) and biopsy ^e	X				X				X	
Issue/Retrieve DSQ handset	X								X	
DSQ completion	Once-daily completion									
DSQ compliance assessment	X	X	X	X	X	X	X	X	X	
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Table 1-1: Schedule of Assessments

Procedures	Screening ^a	Double-blind Treatment Period								Safety Follow-up Contact ^p
	Visit 0	Randomization/ Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 or ET ^o	Visit 9
Week	-4	0	4	8	12	16	20	28	36	40
Window	≤4 weeks	--	±3 days	±3 days	±3 days	±3 days	±3 days	±6 days	±6 days	±3 days
Concomitant medications and procedures recorded	X	X	X	X	X	X	X	X	X	X
Review of adverse events ⁿ	X	X	X	X	X	X	X	X	X	X

Abbreviations: ACTH=adrenocorticotrophic hormone; DSQ=Dysphagia Symptom Questionnaire; DXA=dual-energy X-ray absorptiometry;

EGD=esophagogastroduodenoscopy;

EREFS=EoE Endoscopic Reference Score; hs=at bedtime; IWRS=interactive web-based response system;

^a The assessments from the SHP621-301 final treatment evaluation visit (Visit 4) will be used as the screening assessments (Visit 0) of this treatment extension study.

^b 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.

^c Height to be collected at screening (Visit 0) and Visit 8 for all subjects. Height to be collected at Visit 4 for adolescents only (11-17 years, inclusive). Height measurements for adolescents should be measured in triplicate using stadiometers.

^d Weight measurements for adolescents (11-17 years, inclusive) should be measured in duplicate.

^e Endoscopy must include esophageal biopsies; gastric and duodenal biopsies may be done at the discretion of the investigator. Endoscopies at Visit 4 and Visit 8 should occur at or within 7 days of the scheduled visit. Unscheduled endoscopies may be performed at the discretion of the investigator.

^g Tanner staging assessments will be performed for all subjects ≥11 years of age 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,

Table 1-1: Schedule of Assessments

Procedures	Screening ^a	Double-blind Treatment Period								Safety Follow-up Contact ^p
	Visit 0	Randomization/ Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 or ET ^o	Visit 9
Week	-4	0	4	8	12	16	20	28	36	40
Window	≤4 weeks	--	±3 days	±3 days	±3 days	±3 days	±3 days	±6 days	±6 days	±3 days

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.

- 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 screening (Visit 0) and Visit 8. Urine pregnancy tests will be performed at all other visits.
- ^k Dual-energy X-ray absorptiometry scans should be performed using the same machine and software as used in the SHP621-301 study. Dual-energy X-ray absorptiometry scan at Visit 8 should occur at or within 7 days of the scheduled visit.
- ^l Randomization will occur via IWRS at Visit 1 once the subject's eligibility is confirmed.
- ^m Study medication is supplied at the SHP621-301 final treatment visit based on treatment assignment in SHP621-301.
- ⁿ Adverse event 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 during the treatment period, the evaluations listed for Visit 8 are to be performed as completely as possible.
- ^p A safety follow-up contact by phone will be performed 4 weeks following the last dose of study medication for all subjects (including subjects who fail screening, who discontinue early, or who complete the study).

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 an approved treatment that induces and maintains remission for patients with EoE (Furuta and Katzka 2015).

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 nonviscous 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 2 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 eos/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 eos/HPF) and remission (eosinophil count ≤ 1 eos/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 coprimary efficacy endpoints of histologic response and change from baseline in dysphagia symptoms. Following 12 weeks of twice daily treatment (once 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).

This Phase 3 extension study follows the SHP621-301 induction study, a Phase 3 randomized, double-blind, multicenter, 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. Study SHP621-301 is designed to provide safety and efficacy data demonstrating histologic response (as measured by eosinophilic count ≤ 6 eos/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. This extension study will evaluate maintenance of treatment and treatment withdrawal in subjects who complete the induction study.

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 Phase 3 study is being conducted to determine response to withdrawal of OBS, maintenance of response, extended therapy response, and response to intermittent therapy by evaluating both eosinophil counts and DSQ in adolescent and adults treated or withdrawn from OBS in this treatment extension study.

2.2 Study Objectives

2.2.1 Primary Objective

The primary objective of the study is:

- To evaluate the maintenance of efficacy over 36 weeks, as measured by the peak eosinophilic count and the Dysphagia Symptom Questionnaire (DSQ) score, through a randomized withdrawal design for subjects who responded to 12 weeks of OBS treatment (2 mg twice daily) with a peak count of ≤ 6 eosinophils (eos)/high-powered field (HPF) across all available esophageal levels at the final treatment visit and a $\geq 30\%$ reduction in DSQ score from baseline during the SHP621-301 induction study

2.2.2 Secondary Objectives

The key secondary objective of this study is:

- To evaluate the long-term treatment response over an extended period of 36 weeks for subjects who were randomized to OBS treatment but did not respond after 12 weeks in the SHP621-301 induction study (subject did not have a peak count of ≤ 6 eos/HPF across all available esophageal levels at the final treatment visit and/or a $\geq 30\%$ reduction in DSQ score from baseline)

Additional secondary objectives of the study are:

- To evaluate the response to OBS treatment over 36 weeks for subjects who received placebo in the SHP621-301 induction study
- To evaluate the effect of reinitiating OBS treatment for subjects who relapse after being randomized to placebo in the randomized withdrawal period (treatment-withdrawal-treatment reinitiation)
- To assess endoscopically identified esophageal features as measured by the EoE Endoscopic Reference Score (EREFS)
- To evaluate other responding criteria based on histology and DSQ
- To evaluate the long-term safety and tolerability of OBS treatment

2.2.3 Exploratory Objectives

The exploratory objectives of this study are:

- [REDACTED]

- [REDACTED]

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3. STUDY DESIGN

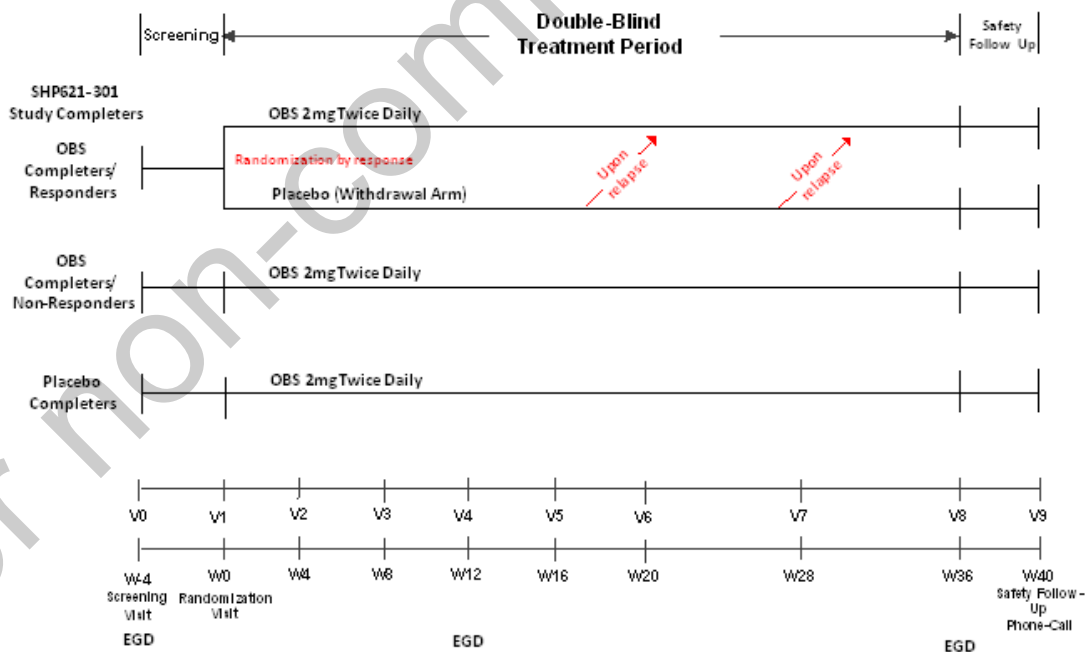
3.1 Study Design and Flow Chart

This is a Phase 3, multicenter, double-blind study to evaluate the efficacy, safety and tolerability of OBS treatment administered twice daily (qAM, pc, and hs) for 36 weeks. The study will be conducted in adolescents and adults, aged 11-55 years, inclusive, with EoE and dysphagia who completed the SHP621-301 induction study.

Approximately 200 subjects (88%) who were randomized in the SHP621-301 study are estimated to complete the SHP621-301 study and will be enrolled in this treatment extension study based on enrollment observed in the Phase 2 study (MPI 101-06). Randomization into the randomized withdrawal period will be stratified by treatment assignment and treatment response in the SHP621-301 study. Subjects who are full responders (defined as ≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ at the final treatment evaluation visit [Visit 4]) in the SHP621-301 induction study will be eligible to enter the randomized withdrawal period to receive either OBS 2 mg twice daily or placebo at a 1:1 ratio. The randomization of subjects who are full responders will also be stratified by age (adults and adolescents) to ensure approximately equal number of subjects within each age group are assigned to the treatment groups.

This study will consist of 3 periods: 4-week screening period, 36-week double-blind treatment period, and 4-week safety follow-up (Figure 3-1).

Figure 3-1: Study Design Flow Chart



Abbreviations: EGD=esophagogastroduodenoscopy; OBS=oral budesonide suspension

Subjects will be required to visit the site up to 8 times over up to a 36-week period. Following completion of the screening visit, subjects will be evaluated for eligibility and safety at Week 0 (Visit 1). Subjects who are eligible and randomized will have efficacy and safety assessments at Weeks 4, 8, 12, 16, 20, 28, and 36 (Visits 2-8) and additional safety assessments at follow-up at Week 40 (Visit 9). Subjects who fail to meet all eligibility criteria at Visits 0 or 1 will be considered screen failures. These subjects will receive a follow-up safety phone call 4 weeks after the last dose of investigational product. Subjects cannot be rescreened once they have been designated as a screen failure. 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 0]) and will be ≤ 4 weeks in duration. During the screening period, assessments from the SHP621-301 final treatment evaluation visit (Visit 4) will be used as the Visit 0 screening assessments of the treatment extension study. At the screening visit (Visit 0), 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. Eligible subjects will receive investigational product based on treatment assignment in SHP621-301 for up to 4 weeks prior to enrollment in the treatment extension study. This 4-week screening period is required to allow for blinded treatment response information (reduction in DSQ from baseline and eosinophilic count as determined by a central reader) collected during the SHP621-301 final treatment evaluation visit to be entered into the interactive web-based response system (IWRS). Only the unblinded data team who is independent from the blinded study team and not involved with the day-to-day conduct of the study will have restricted access to blinded treatment response information. Once response information is available, subjects will return for the randomization visit (Visit 1) to receive investigational product. Subjects who continue to meet eligibility criteria after the screening visit (Visit 0) will enter the 36-week double-blind treatment period.

Subjects who were assigned to OBS treatment and who fully responded in the SHP621-301 study (≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ at the final treatment evaluation visit) will enter a randomized withdrawal period to receive either OBS 2 mg twice daily or placebo at a 1:1 ratio. These subjects will also be stratified by age (adults and adolescents). Subjects who were assigned to OBS treatment and did not respond or partially responded in the SHP621-301 study will receive OBS 2 mg twice daily. Subjects who were assigned to placebo in the SHP621-301 study will receive OBS 2 mg twice daily. Subjects, site staff, and study team members will remain blinded to treatment assignment and individual subject histology, and individual subject DSQ data from the SHP621-301 (post randomization) and this extension study until the database locks occurs for this extension study.

At Week 12, all subjects will undergo an upper esophagogastrroduodenoscopy (EGD) with biopsy to evaluate eosinophil counts. Upon receipt of blinded EGD and DSQ data, subjects on placebo in the randomized withdrawal period who have relapsed will have their treatment assignment changed to OBS 2 mg twice daily at the next scheduled visit. The criteria for relapse is having an eosinophilic count of ≥ 15 eos/HPF from at least 2 of 3 levels of the esophagus, as determined by central reader and having at least 4 days of dysphagia in the 2-week period prior to the scheduled visit, as determined by the DSQ. The criteria for relapse align with the related inclusion criteria for participation in the SHP621-301 study. The treatment assignment change will be performed in a blinded manner in IWRS at the subsequent study visit. If both criteria for

relapse are not met, the subject will remain assigned to placebo. The upper EGD with esophageal biopsies will be repeated at the Week 36 visit (Visit 8) or at early termination (ET), to evaluate eosinophil counts. If an unscheduled EGD is performed between Week 12 and Week 36, the Week 36 EGD should still be performed.

All subjects will have a follow-up phone call 4-weeks post last dose of investigational product to query for SAEs, AEs, and concomitant treatments.

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 as EoE persists, it becomes more fibrostenotic in older patients and would not be 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.

The design of this study combines randomized withdrawal and long-term extension elements in a manner that selects appropriate patients for placebo withdrawal and maintains double-blinding of subjects in all treatment groups. Only subjects who are full responders to OBS 2 mg twice daily in the SHP621-301 induction study (≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ at the final treatment evaluation visit of SHP621-301), will be eligible for randomized withdrawal. The randomized withdrawal period is required to assess maintenance of efficacy in these subjects. The continuation of OBS 2 mg twice daily treatment for subjects in SHP621-301 who did not respond or partially responded to treatment, will evaluate whether these subjects might respond to OBS 2 mg twice daily if their treatment is extended for an additional 36 weeks. This aspect of the study is supported by the possibility that the response of EoE to topical corticosteroids may require more than 12 weeks of induction treatment.

As described, the protocol also provides multiple mechanisms for switch from placebo and potential study discontinuation of relapsing and nonresponding subjects in order to evaluate the effect of reinitiating OBS treatment in these subjects. For subjects who relapse on placebo during the randomized withdrawal and who reinitiate treatment with OBS 2 mg twice daily (intermittent therapy), separate descriptive analyses for histological data and DSQ endpoints will be conducted at each assessment visit, as described in Section 9.8.2. For all subjects, an esophageal stricture requiring dilation would be considered a treatment failure and result in withdrawal of the subject from the study. Subject withdrawal criteria are provided in Section 4.5.1.

3.2 Duration and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 44 weeks, including the 4-week screening period. Including potential treatment in SHP621-301 and the screening period of this study, the maximum total duration of OBS 2 mg twice daily may be approximately 52 weeks.

The study will be completed in approximately 36 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 8 (Week 36), inclusive of the final treatment evaluation EGD. All subjects will have a follow-up phone call 4-weeks post last dose of investigational product.

3.3 Sites and Regions

Approximately 60 sites in North America, the same sites participating in the SHP621-301 study, will participate in this extension study.

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 completed SHP621-301 induction study.
2. 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.
3. Subject is male or female aged 11-55 years, inclusive, at time of consent for the SHP621-301 study.
4. 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 0). There should be no change to these regimens during study participation.
5. 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 and for 30 days following the last dose of investigational product.
6. Subject is willing and has an understanding and ability to fully comply with study procedures including DSQ compliance 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 changes in medications that could affect the study or diet in the weeks since the final treatment evaluation visit (Visit 4) of the SHP621-301 study.
2. Subject using immunomodulatory therapy since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or anticipated use of immunomodulatory therapy during the treatment period (except for any ongoing regimen of allergy shots); 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 scheduled EGDs.
3. Subject using swallowed topical corticosteroid for EoE or systemic corticosteroid for any condition since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or anticipated 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 medical monitor prospectively but cannot occur within the 4 weeks of the scheduled EGDs.

4. Subject on inhaled or intranasal steroids and not on a stable dose between the baseline visit (Visit 1) of the SHP621-301 study and the screening EGD of this study.
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) since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or anticipated changes in the use of such medications during the treatment period.
6. Subject using Cytochrome P450 3A4 inhibitors (eg, ketoconazole, grapefruit juice) since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or anticipated use of such medications during the treatment period.
7. Subject has an appearance on screening 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 >9mm).
8. Subject is on a pure liquid diet or the six-food elimination diet.
9. Subject has presence of esophageal varices at the EGD at the final treatment evaluation visit (Visit 4) of the SHP621-301 study.
10. 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.
11. Subject has other diseases causing or associated with esophageal eosinophilia, including hypereosinophilic syndrome, collagen vascular disease, vasculitis, achalasia, or parasitic infection.
12. Subject has oropharyngeal or esophageal candidiasis that failed to respond to previous treatment. Diagnosis with oropharyngeal or esophageal candidiasis at or since the final treatment evaluation visit (Visit 4) of the SHP621-301 study is not an exclusion as long as the subject is expected to respond to treatment.
13. Subject has a potentially serious acute or chronic infection or immunodeficiency condition, including tuberculosis, fungal, bacterial, viral/parasite infection, ocular herpes simplex, or chicken pox/measles.
14. Subject has upper gastrointestinal bleeding identified in the EGD at the final treatment evaluation visit (Visit 4) of the SHP621-301 study or since the final treatment evaluation visit (Visit 4) of the SHP621-301 study.
15. Subject has evidence of active infection with *Helicobacter pylori*.
16. Subject has evidence of unstable asthma since the final treatment evaluation visit (Visit 4) of the SHP621-301 study.
17. Subject is female and pregnant or nursing.
18. Subject has a history of intolerance, hypersensitivity, or idiosyncratic reaction to budesonide (or any other corticosteroids), or to any other ingredients of the study medication.
19. Subject has a history or high risk of noncompliance with treatment or regular clinic visits.
20. Subject is on sucralfate or anticipates using sucralfate during the treatment period.

4.3 Restrictions

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

- No changes in medications or diet since the final treatment evaluation visit (Visit 4) of the SHP621-301 study.
- Temporary use (≤ 7 days) or initiation of new steroid treatment is permitted but cannot occur within the 4 weeks of the scheduled EGDs.
- 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 enrollment to resume (or discontinue) intranasal corticosteroids based on the subject's usual treatment regimen for allergy season. (In these subjects, intranasal corticosteroids must not be changed between the baseline visit [Visit 1] of the SHP621-301 study and the screening EGD of this study). Topical corticosteroid dosing changes should be avoided within 4 weeks prior to EGD. Subjects who require a change in inhaled corticosteroid treatment for an asthma exacerbation should be discussed with the medical monitor.
- No change in use of PPIs, H2 antagonists, antacids, or leukotriene inhibitors for any condition (such as gastroesophageal reflux disease, asthma or allergic rhinitis).
- No use of cytochrome P450 3A4 (CYP450 3A4) inhibitors (eg, ketoconazole, grapefruit juice; see details in Section 5.2.2).
- No use of sucralfate during the study as this may interfere with the adherence of OBS.

4.4 Reproductive Potential

4.4.1 Female Contraception

All females must have a negative pregnancy test at the screening visit (Visit 0), randomization visit (Visit 1), and Visits 2-8. A serum pregnancy test will be performed at the screening visit (Visit 0) and final treatment evaluation (Visit 8). 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 1 of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy, or bilateral salpingectomy) and at least 6 weeks post sterilization, or
- Females of childbearing potential must 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 0), 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 1 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 8 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 (Schedule of Assessments, [Table 1-1](#)). 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 relapse and result in withdrawal of the subject from the study. Subjects with oropharyngeal or esophageal candidiasis that has failed to respond to treatment by the Week 12 EGD or upper GI bleeding at the Week 12 EGD will be withdrawn 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
- Study 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 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 (TA) Head. The PVRM TA 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 nonstudy treatment (including but not limited to herbal treatments, vitamins, behavioral treatment, and nonpharmacological treatment, such as psychotherapy, as appropriate) received at the screening visit (Visit 0) 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 at the screening visit (Visit 0). 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 in SHP621-302 (Visit 1) 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 scheduled EGDs) 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 (exception for seasonal allergic rhinitis; see Section 4.3)
2. PPIs
3. H2 antagonists
4. Antacids
5. Leukotriene inhibitors
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 since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or use within the 4 weeks of scheduled EGDs. Any temporary use (≤ 7 days) or initiation of new corticosteroid treatment during the study should be documented and discussed with the medical monitor prospectively. (Seasonal nasal corticosteroid use for seasonal allergic rhinitis is permitted; changes within 4 weeks of scheduled EGD should be avoided).
2. Swallowed topical corticosteroid for EoE or systemic corticosteroid for any condition since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or use within the 4 weeks of scheduled EGDs. Any temporary use (≤ 7 days) or initiation of new steroid treatment during the study should be documented and discussed with the medical monitor prospectively.
3. Initiation or change in dosing frequency to PPIs, H2 antagonists, antacids, or leukotriene inhibitors for any condition (such as gastroesophageal reflux disease, asthma, or allergic rhinitis) since the final treatment evaluation visit (Visit 4) of the SHP621-301 study, or anticipated use of such medications during the treatment period.
4. CYP450 3A4 inhibitors (eg, ketoconazole, grapefruit juice) since the final treatment evaluation visit (Visit 4) of the SHP621-301 study, or anticipated changes in the 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.
5. Sucralfate at screening or anticipated to be used 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 8 ounce amber glass, multidose bottles. 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 8 ounce amber glass, multidose bottles with child-resistant caps and refrigerated throughout the study (in the clinic and subject's home). Each bottle contains OBS 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 suspension will also be supplied in 8 ounce amber glass multidose bottles with child-resistant caps. Placebo consists of all components of the investigational product 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 for each subject will be administered in the clinic. The subject will continue with the evening dosing regimen at home.

Oral budesonide suspension and placebo will be supplied in amber glass bottles and must be shaken well prior to administration. OBS and placebo should be refrigerated at 2-8°C (36-46°F) 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.

During the 4-week screening period, blinded treatment response information (reduction in DSQ from baseline and eosinophilic count as determined by a central reader) collected during the SHP621-301 final treatment evaluation visit will be entered into the IWRS in a blinded manner. Once information is available in IWRS, subjects will return for the randomization visit (Visit 1) to be assigned to investigational product (OBS 2 mg twice daily or placebo). While only SHP621-301 OBS 2 mg twice daily responders will be randomized to continued OBS 2 mg twice daily or placebo, all subjects will be assigned to investigational product via IWRS to maintain double-blinding of subjects, investigators, the blinded monitoring team and the sponsor (ie, sham randomization).

At the randomization visit (Visit 1), the investigator or designee will access the IWRS to either document a screen failure or, if the subject has met all entry criteria, to randomize the subject. Sites will confirm 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 4-week screening period and a double-blind treatment period. The actual treatment given to individual subjects during the double-blind treatment period will be determined by the blinded treatment response information entered at the SHP621-301 final treatment evaluation visit.

Subjects will be randomized via a computer-generated randomization schedule at the randomization visit (Visit 1) following a 4-week screening period and confirmation of study eligibility. Subjects who fully responded to OBS treatment in the SHP621-301 study (≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ at the final treatment evaluation visit) will enter a randomized withdrawal period to receive either OBS 2 mg twice daily or placebo at a 1:1 ratio. Subjects who did not respond or partially responded to OBS treatment in the SHP621-301 study will receive OBS 2 mg twice daily. Subjects who were assigned to placebo in the SHP621-301 study will receive OBS 2 mg twice daily. Subjects, site staff, and study team members will remain blinded to treatment assignment and individual subject histology and individual subject DSQ data from the SHP621-301 study (post randomization) and until database lock occurs for this extension study.

Randomization of subjects in the randomized withdrawal period will also be stratified by age (adults and adolescents) to ensure approximately equal number of subjects within each age group are assigned to the treatment groups.

Subject numbers are assigned to all subjects as they consent to take part in the study. The subject number consists of the 3 digit study identifier, the 4 digit site identifier, and the 4 digit subject identifier. For the SHP621-302 study, the 3 digit site and 4 digit subject numbers will be the same as the SHP621-301 study.

The randomization number represents a unique number corresponding to investigational product allocated to the subject once eligibility has been determined at the randomization visit.

Individual subject treatment is automatically assigned by the IWRS.

6.2.3 Dosing

During the 4-week screening period, all subjects will receive 10 mL of blinded investigational product twice daily based on treatment assignment in SHP621-301. During the 36-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.

At Week 12, all subjects will undergo an upper esophagogastroduodenoscopy (EGD) with biopsy to evaluate eosinophil counts. Upon receipt of blinded EGD and DSQ data, subjects on placebo in the randomized withdrawal period who have relapsed will have their treatment assignment changed to OBS 2 mg twice daily. The criteria for relapse is having an eosinophil count of ≥ 15 eos/HPF from at least 2 of 3 levels of the esophagus, as determined by a central reader, and having at least 4 days of dysphagia in the 2-week period prior to the scheduled visit, as determined by the DSQ. Considering the potential for missing diary entries, the determination of relapse based on days of dysphagia reported on the DSQ will occur as follows:

- If at least 4 days of dysphagia are reported on the DSQ in the 2-week period prior to the visit, the subject would meet the criterion for dysphagia symptom relapse.
- If less than 4 days of dysphagia are reported and at least 8 diary entries are recorded within the 2-week period, the subject would not meet criterion for dysphagia symptom relapse.
- If less than 4 days of dysphagia are reported in the DSQ and fewer than 8 diary entries are recorded within the 2-week period, the DSQ window can be expanded as described in Section 7.2.1.2.

The criteria for relapse align with the related inclusion criteria for participation in the SHP621-301 study. If both histology and dysphagia symptom relapse criteria are met, then the treatment assignment change will be performed in a blinded manner in IWRS at the subsequent study visit. If both criteria for relapse are not met, the subject will remain assigned to placebo.

If at any time the subject reports increased or worsening dysphagia symptoms to the investigator, the investigator may choose to perform an unscheduled EGD. If an unscheduled EGD is performed prior to Week 12, an EGD does not have to be repeated at Week 12. If a subject on placebo meets the criteria for relapse, the subject's treatment assignment will be changed in a blinded manner from placebo to OBS 2 mg twice daily at the subsequent study visit.

If the Week 12 or an unscheduled EGD reveals an eosinophil count of ≥ 15 from at least 2 of 3 levels of the esophagus yet relapse is not confirmed due to the criterion for dysphagia symptoms not being met, the subject will remain assigned to placebo. If the criterion for dysphagia symptoms is met at a subsequent visit and both criteria for relapse are then confirmed, the subject's treatment assignment will be changed to OBS 2 mg twice daily at the next scheduled visit.

Investigational product doses that are required to be administered at the clinic include the first dose of randomized investigational product (OBS or placebo) administered at the randomization visit (Visit 1) and all morning doses of investigational product administered at Visits 2-8. 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.

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 study 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. Bottles of OBS 0.2 mg/mL or placebo 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 Storages

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 refrigerated at 2-8°C (36-46°F), 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. Please refer to the Pharmacy Manual for additional details.

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 ([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 -4 to 0)

The screening period starts when subjects sign informed consent. The screening period will comprise up to 4 weeks, during which all procedures listed for the screening visit (Visit 0) 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 (Section [5.2.1](#)).

Assessments from the SHP621-301 final treatment evaluation visit (Visit 4) will be used as the screening assessments (Visit 0) of this treatment extension study. Screening assessments may take place across several days to allow an appropriate time frame in which to complete all procedures and confirm study eligibility. At the SHP621-301 final treatment evaluation visit, subjects will be dispensed blinded investigational product (based on treatment assignment in SHP621-301) that will last for up to 4 weeks prior to enrolling into this treatment extension study. The 4-week screening period is required to allow for blinded treatment response information (reduction in DSQ from baseline and eosinophilic count as determined by a central reader) collected during the SHP621-301 final treatment evaluation visit to be entered into the IWRS.

After the screening period, subjects who meet eligibility criteria at the end of the screening visit (Visit 0) will enter the 36-week double-blind treatment period. This 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 or randomized visits. Subjects cannot be rescreened once they have been designated as a screen failure.

7.1.1.1 Screening Visit (Visit 0)/Visit 4 of SHP621-301 Study

The screening visit (Visit 0) assessments and procedures, beginning with informed consent, will be performed as outlined in [Table 1-1](#).

The following procedures will be performed at the screening visit:

- Obtain subject consent (or assent as applicable for subjects <18 years).
- Review eligibility criteria.
- Review medical history.
- 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 current use of concomitant medications and procedures. 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.
- Dispense the DSQ electronic patient-reported outcome (ePRO) device for nightly completion and train the subject on its use.

The following procedures will be performed at the final treatment evaluation visit (Visit 4) of SHP621-301 and will be used as the screening assessments for this extension study:

- Review investigational product dosing compliance.
- Record vital signs (including blood pressure [systolic and diastolic], heart rate, respirations, and temperature), height (measured in triplicate for adolescents 11-17 years, inclusive), and weight (measured in duplicate for adolescents 11-17 years, inclusive). Perform stadiometry in adolescent subjects. Vital signs will be assessed after the subject has been in a supine position for at least 5 minutes immediately prior to the assessment.
- Clinical chemistry, hematology, and urinalysis laboratory tests will be performed on all subjects; 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 adrenocorticotrophic 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.

[REDACTED]

[REDACTED]

- Perform a physical examination on all subjects. Adolescents (subjects ≥ 11 years until the investigator confirms subject is post puberty) will also undergo Tanner Staging Assessment.

- **Serum** pregnancy test will be performed on all female subjects.
- Perform EGD and biopsy either at the investigative site or by a referring physician. Esophagogastroduodenoscopy should be completed at or within 7 days of the scheduled visit. Biopsy specimens must be available to be sent to the central pathology lab at least 2 weeks prior to Visit 1 to allow sufficient time for processing and central review and determination of eligibility.
- Perform dual-energy X-ray absorptiometry (DXA) scan for bone mineral density (BMD) and body composition measurements in subjects aged 11-17 years, inclusive. Baseline and post treatment DXA scans should be performed using the same machine and software.
- Dispense blinded investigational product (OBS or placebo; based on treatment assignment in SHP621-301) and review administration instructions. The subject will 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.

7.1.2 Double-blind Treatment Period (Visits 1-8): Weeks 0, 4, 8, 12, 16, 20, 28, and 36 (or Early Termination)

The double-blind treatment period will comprise 36 weeks, during which all assessments and procedures listed for Visits 1-8 in [Table 1-1](#) shall be completed.

During this period, a ± 3 -day visit window will be permitted between Visits 1-6 (Weeks 0-20) and a ± 6 -day visit window will be permitted between Visits 7-8 (Weeks 28-36), unless otherwise specified. Visit windows are calculated based upon the date of the randomization visit (Visit 1).

Once information for blinded treatment response is available, subjects will return for the randomization visit (Visit 1) to receive investigational product. Subjects who continue to meet all eligibility criteria and complete the 4-week screening period will have the opportunity to enroll in the treatment extension study. Subjects will receive either OBS twice daily (qAM, pc, and hs) or placebo twice daily (qAM, pc, and hs).

Subjects who fully responded to OBS treatment in the SHP621-301 study (≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ at the final treatment evaluation visit) will enter a randomized withdrawal period to receive either OBS 2 mg twice daily or placebo at a 1:1 ratio. Subjects who did not respond or partially responded to OBS treatment in the SHP621-301 study will receive OBS 2 mg twice daily. Subjects who were assigned to placebo in the SHP621-301 study will receive OBS 2 mg twice daily. 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 randomization visit (Visit 1) will be documented as screen failures in the IWRS and discontinue study drug.

A safety follow-up contact by phone will be performed 4 weeks following the last dose of study medication for all subjects (including subjects who fail screening, who discontinue early, or who complete the study).


7.1.2.1 Randomization Visit (Visit 1): Week 0

Subjects will return to the site for the randomization visit (Visit 1) to confirm eligibility. The randomization 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 (measured in duplicate in adolescents, 11-17 years, inclusive). Vital signs will be assessed after the subject has been in a supine position for at least 5 minutes immediately prior to the assessment.
- 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.

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

- Review investigational product dosing compliance.
- Review DSQ compliance; provide subject with instruction to continue completion of the DSQ nightly.
- 
- Perform a physical examination and assess any changes since screening.
- 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 **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.


7.1.2.2 Visits 2 and 3 (Weeks 4 and 8)

Subjects will return to the site for Visit 2 (Week 4) and Visit 3 (Week 8). 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 (measured in duplicate for adolescents, 11-17 years, inclusive). Vital signs will be assessed after the subject has been in a supine position for at least 5 minutes immediately prior to the assessment.
- 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.

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

- Review DSQ dysphagia episodes and compliance; provide subject with instruction to continue completion of the DSQ nightly.
- 
- Perform a physical examination and assess any changes since screening.
- Readminister **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.

7.1.2.3 Visit 4 (Week 12)

Subjects will return to the site for Visit 4 (Week 12). 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 (measured in triplicate for adolescents 11-17 years, inclusive), and weight (measured in duplicate for adolescents 11-17 years, inclusive). Perform stadiometry in adolescent subjects. Vital signs will be assessed after the subject has been in a supine

position for at least 5 minutes immediately prior to the assessment.

- 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.
- Review DSQ dysphagia episodes and compliance; provide subject with instruction to continue completion of the DSQ nightly.

█ [REDACTED]

█ [REDACTED]

- Perform a physical examination and assess any changes since screening.
- Readminister **urine** pregnancy test for female subjects.
- Dispense investigational product (OBS or placebo) and review investigational product dosing compliance.
- Perform EGD and biopsy; EGD should be completed at or within 7 days of the scheduled visit. In addition, an earlier EGD may also occur if the subject exhibits signs of relapse (Section 6.2.3).

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

7.1.2.4 Visits 5, 6, and 7 (Weeks 16, 20, and 28)

Subjects will return to the site for Visits 5, 6, and 7 (Weeks 16, 20, and 28). 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 (measured in duplicate for adolescents 11-17 years, inclusive). Vital signs will be assessed after the subject has been in a supine position for at least 5 minutes immediately prior to the assessment.
- 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.

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

- Review DSQ dysphagia episodes and compliance; provide subject with instruction to continue completion of the DSQ nightly.

■ [REDACTED]

- Perform a physical examination and assess any changes since screening.
- Readminister **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.

7.1.2.5 Visit 8 (Week 36) or Early Termination

Subjects will return to the site for Visit 8 (Week 36). Assessments at this visit will be performed as outlined in [Table 1-1](#). If a subject discontinues prematurely, the assessments for Visit 8 are to be performed as completely as possible.

The following procedures should be performed first:

- Record vital signs (including blood pressure [systolic and diastolic], heart rate, respirations, and temperature), height (measured in triplicate for adolescents 11-17 years, inclusive), and weight (measured in duplicate for adolescents 11-17 years, inclusive). Perform stadiometry in adolescent subjects. Vital signs will be assessed after the subject has been in a supine position for at least 5 minutes immediately prior to the assessment.
- 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 current use of concomitant medications and procedures.
- Clinical chemistry, hematology, and urinalysis laboratory tests will be performed on all subjects; all subjects must fast overnight prior to collection. Any subject with an abnormal urinary or serum glucose level will be followed closely until resolution (Section [7.2.2.5](#)).
- 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 adrenocorticotrophic 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. Any subject with an abnormal ACTH stimulation test will be followed closely until resolution (Section [7.2.2.5](#)).

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

- Retrieve DSQ handset and review DSQ compliance.

■

[REDACTED]

■

[REDACTED]

- Perform a physical examination on all subjects. Adolescents (subjects ≥ 11 years until the investigator confirms subject is post puberty) will also undergo Tanner Staging Assessment. Any subject with clinical evidence of reduced height velocity and/or delayed Tanner staging will be followed closely until resolution (Section 7.2.2.2).
- **Serum** pregnancy test will be performed on all female subjects.
- Perform DXA scan for BMD and body composition measurements in subjects aged 11-17 years, inclusive. Dual-energy X-ray absorptiometry scans should be performed at this visit or within 7 days of the scheduled visit using the same machine and software as used in the SHP621-301 study.
- Perform EGD and biopsy; EGD should be completed at or within 7 days of the scheduled visit. An earlier EGD may occur if the subject exhibits signs of relapse (Section 6.2.3); however, the Week 36 EGD must be completed.
- Review investigational product dosing compliance.

7.1.3 Follow-up Period

The follow-up period for this protocol is 4 weeks from the last dose of investigational product. Subjects will receive a follow-up phone call at Visit 9 (Week 40) to query for SAEs, AEs, and concomitant treatments (Section 7.1.3.1).

7.1.3.1 Safety Follow-up Contact (Visit 9): Week 40

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.

7.2 Study Evaluations and Procedures

The full title and details about who completes the scales used in this study is included in Appendix 2.

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 any of the questions as this can 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](#).

The screening EGD with biopsies will be performed by a physician at the investigative site at the final treatment evaluation visit in the SHP621-301 study. Biopsy specimens must be taken and provided to the central pathology lab by at least 2 weeks prior to the planned Visit 1 to allow sufficient time for processing and central review and determination of eligibility. Subjects, site staff, and study team members will remain blinded to eosinophil counts and histopathologic findings by the central reader throughout the duration of the study.

At the Week 12 visit (Visit 4), and Week 36 visit (Visit 8) or at early termination (ET), an EGD with esophageal biopsies is required for all subjects. If at any time, the subject reports increased or worsening dysphagia symptoms to the investigator, the investigator may choose to perform an unscheduled EGD. If an unscheduled EGD is performed prior to Week 12, an EGD does not have to be repeated at Week 12. If an unscheduled EGD is performed between Week 12 and Week 36, the Week 36 EGD should still be performed. 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), midesophagus (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. Eosinophil counts and, histopathologic features will be evaluated by the central reader 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. At the investigator's discretion, biopsies will be taken from the stomach and duodenum 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 1 vial; biopsies from the duodenum should be submitted in a separate vial to the central pathology laboratory for processing of tissue into slides.

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 during the screening period and during the 36-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. 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.

To meet relapse criteria, the subject must have at least 4 days of dysphagia as determined by the DSQ in the 2-week period prior to the scheduled visit in addition to meeting the eosinophil histology criterion (≥ 15 eos/HPF from at least 2 of 3 levels of the esophagus). Considering the potential for missing diary entries, the determination of relapse based on days of dysphagia reported on the DSQ will occur as follows:

- If at least 4 days of dysphagia are reported on the DSQ in the 2-week period prior to the visit, the subject would meet the criterion for dysphagia symptom relapse.
- If less than 4 days of dysphagia are reported and at least 8 diary entries are recorded within the 2-week period, the subject would not meet criterion for dysphagia symptom relapse.
- If less than 4 days of dysphagia are reported and less than 8 diary entries are recorded within the 2-week period, then the 2-week period will be shifted backwards from the scheduled visit, 1 day at a time, to confirm if the subject meets the criteria for dysphagia symptom relapse over 14 consecutive days; however, the 2-week period will not be shifted further if at least 8 diary entries are recorded in the 14-day period and will not be shifted by more than 2 weeks (ie, no more than 2-week period plus additional 2-week additional expansion).

Calculations will be performed on daily ePRO entries during a 2-week interval prior to each study visit during the treatment period. The DSQ score for the coprimary 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:

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

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.

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

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

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

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 new clinically or medically relevant information which arose after the recording of the medical history in the antecedent study. New medical history will be collected at the screening visit (Visit 0) of this study. Medical history will be classified as EoE or non-EoE by the investigator. Adverse events recorded during the SHP621-301 study may be added as medical history at the investigator's discretion.

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 0) will be documented in the subject's source documents and on the medical history CRF. Changes after the screening visit (Visit 0) 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 0) will also include Tanner Staging Assessments for subjects <18 years of age.

Height will be collected at the screening visit (Visit 0) and Visit 8 for all subjects and at Visit 4 for adolescents (11-17 years, inclusive) only. Stadiometers will be used to measure height for subjects aged 11-17 years, inclusive. Statural height will be measured by trained site staff using a stabilized stadiometer. Height will be measured in triplicate in adolescents (11-17 years, inclusive) and recorded in the CRF. 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 each measurement. All measurements should be recorded to the nearest 10th of a centimeter (1 mm). Please refer to the study manual for additional details.

Weight will be measured in duplicate in adolescents (11-17 years, inclusive) and recorded in the CRF.

All subjects with clinical evidence of reduced height velocity and/or delayed Tanner Staging, as determined by the investigator, must be followed closely until resolution (ie, resumption of normal for age height velocity, or the resumption of Tanner Stage development). Subjects who discontinue from the treatment period at any time and have clinical evidence of reduced height velocity and/or delayed Tanner Stage development at the early termination visit will be monitored beyond the end of the study until resolution is established.

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) Any AE that is ongoing from the SHP621-301 study must be recorded on the CRF for this study.

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 in 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

Adrenocorticotrophic hormone 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. Administration of ACTH

stimulation testing and sample collection should follow the same procedures used in the SHP621-301 study.

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. Subjects who discontinue from the treatment period at any time and have an abnormal ACTH stimulation test at the early termination visit will be scheduled for repeat ACTH testing approximately 6 weeks post last dose of investigational product and followed to resolution of the abnormality. 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 0) and the final treatment evaluation visit (Visit 8) or ET visit. A urine pregnancy test is performed on all female subjects at all other visits 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 measurements will be performed in subjects aged 11-17 years, inclusive, as outlined in [Table 1-1](#).

The sites for DXA measurement will be the lumbar spine (L1-L4 preferred) and total body less head (Bachrach 2011; Gordon et al. 2008; International Society for Clinical Densitometry 2013). Dual-energy X-ray absorptiometry body composition measurements will also be collected. 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

[REDACTED]
 [REDACTED]
 [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

7.2.4 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)
Safety	Biochemistry and β -hCG ^a	6	9	54
	ACTH	2	4	8
	Cortisol	2	9	18
	Hematology	2	9	18
Total mL		-	-	98

Abbreviations: ACTH=adrenocorticotrophic hormone; β -hCG=beta-human chorionic gonadotropin^a β -hCG testing is for females only.

During this study, it is expected that approximately 98 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 98 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 7.1.3. This includes events occurring during the screening period 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 dechallenge. 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 reexposure 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 period, 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 7.1.3.

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 nonmedical 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 prespecified 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 parents/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 (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 7.1.3 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, unless another investigational product action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as “dose not changed” or “not applicable” (if the subject never received investigational product). The investigational product action of “withdrawn” should not be selected solely as a result of the subject’s death.

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 9.3 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.

The SAP 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

No interim analysis is planned.

9.6 Sample Size Calculation and Power Considerations

Approximately 200 subjects (88%) who are randomized in the SHP621-301 study are estimated to complete the SHP621-301 study and enroll in this treatment extension study based on enrollment observed in the Phase 2 study (MPI 101-06).

The primary efficacy measure of the study will be the proportion of subjects who relapse during the double-blind randomized withdrawal period, defined as having an eosinophil count of ≥ 15 eos/HPF from at least 2 of 3 levels of the esophagus (as determined by a central reader) and at least 4 days of dysphagia in the 2-week period prior to the scheduled visit (as determined by the DSQ). To be considered as a subject with relapse, both criteria must be met. To determine whether a subject meets the criterion for dysphagia, refer to Section 7.2.1.2.

Based on observation in the Phase 2 study (MPI 101-06), approximately 26% of subjects, or approximately 40 subjects, who were assigned to OBS treatment in the SHP621-301 study are anticipated to respond fully after 12 weeks in the SHP621-301 study. For this study, to detect a 50 percentage point difference between relapse proportions of 20% and 70% in the OBS and placebo groups, respectively, at more than 80% power and a significance level of 0.05 (2-sided) using the Fisher's Exact test with equal allocation to treatment groups, it is necessary to assess the primary efficacy measure for approximately 38 subjects (19 subjects in each of the OBS and placebo groups).

9.7 Study Population

The **safety set** will include all subjects who are randomized and receive at least 1 dose of 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 investigational product and had 1 post baseline efficacy assessment (biopsy and/or DSQ score).

The **per-protocol (PP)** set will include all subjects in the FAS excluding subjects with major protocol deviations. 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.

9.8 Efficacy Analyses

9.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint for each subject is relapse during the double-blind randomized withdrawal period. Relapse, a binary response (either with a relapse or not), is defined as having an eosinophil count of ≥ 15 eos/HPF from at least 2 of 3 levels of the esophagus, as determined

by a central reader, and having at least 4 days of dysphagia in the 2-week period prior to the scheduled visit, as determined by the DSQ (refer to Section 7.2.1.2).

The primary efficacy endpoint will be analyzed as the proportion of subjects with relapse during the double-blind randomized withdrawal period for the FAS, using a Fisher's Exact test comparing OBS 2 mg twice daily against placebo. The primary test of treatment effect will be 2-sided, and conducted at the significance level of 0.05. The proportion of subjects with relapse for each treatment group and the corresponding 95% confidence interval (CI) will be estimated. In addition, the difference in the proportion of subjects with relapse between the 2 treatment groups and its 95% CI will be estimated.

Subjects who withdraw without providing efficacy data at the ET visit will be classified as being relapsers in the primary efficacy analysis. The null hypothesis states that there is no difference in relapse proportions between OBS 2 mg twice daily and placebo, with the 2-sided alternative of a nonzero difference between groups. Relapse proportions at each adjacent double-blind visit interval will also be assessed by applying the Fisher's Exact test to the observed data at each double-blind visit.

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

Similar analyses used for the ITT population will be repeated using the FAS and the PP datasets. Sensitivity analyses will be performed using the ITT population by classifying subjects who withdraw without providing efficacy data at the ET visit as non-relapsers. In addition, the subjects who were prematurely withdrawn from the study without the primary efficacy endpoint will be imputed randomly according to the distribution of relapsers with available data; and the similar statistical test will be performed using the imputed data.

9.8.2 Secondary Efficacy Endpoints

9.8.2.1 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is the long-term treatment response, a binary response over an extended period of 36 weeks in adolescent and adult subjects who were randomized to OBS treatment but did not respond after 12 weeks in the SHP621-301 induction study (subject did not have peak count of ≤ 6 eos/HPF across all available esophageal levels at the final treatment visit and/or $\geq 30\%$ reduction in DSQ score from baseline) and met the following criteria:

- Histologic response, defined as a peak eosinophil count of ≤ 6 eos/HPF across all available esophageal levels at the final treatment period evaluation (Visit 8)
- Dysphagia symptom response, defined as $\geq 30\%$ reduction in the DSQ combined score (questions 2+3) from baseline of the SHP621-301 study and from baseline of this extension study to the final treatment period evaluation (Visit 8)

The key secondary efficacy endpoint will be analyzed as the proportion of subjects who responded based on the histological data and the DSQ data at the final treatment period evaluation (Visit 8). The proportion of subjects with long-term treatment response and the corresponding 95% confidence interval (CI) will be estimated and summarized.

The following secondary efficacy endpoints will be analyzed in all subjects:

- Histologic response, defined as a peak eosinophil count of ≤ 6 eos/HPF across all available esophageal levels at each assessment visit
- Dysphagia symptom response, defined as $\geq 30\%$ reduction in the DSQ combined score (questions 2+3) at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Change in the DSQ score and change in the peak eosinophilic count at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Change in total endoscopy score, as measured by the EREFS classification, at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Peak eosinophil count < 15 eos/HPF across all available esophagus levels at each assessment visit
- Peak eosinophil count ≤ 1 eos/HPF across all available esophagus levels at each assessment visit
- Change in the peak eosinophil count at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study at each assessment visit for each available esophageal level (proximal, mid-, and distal)
- Change in the histopathologic epithelial features combined total score (grade and stage) at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Dysphagia symptom response (binary response), defined as a $\geq 50\%$ reduction in the DSQ combined score (questions 2+3), at each assessments visit from baseline of the SHP621-301 study and from baseline of this extension study
- Change in the DSQ combined score (questions 2+3) at each assessment from baseline of the SHP621-301 study and from baseline of this extension study
- Cumulative distribution function curves for the change and the percent change in the DSQ score at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Overall binary response I, defined as a reduction in the DSQ score of $\geq 30\%$ and a peak eosinophil count of ≤ 6 eos/HPF across all esophageal levels at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Overall binary response II, defined as a reduction in the DSQ score of $\geq 50\%$ and a peak eosinophil count of ≤ 6 eos/HPF across all esophageal levels at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Change in the DSQ + pain score (question 2+3+4) at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Change in the DSQ pain score (question 4) at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study

Summary statistics of the DSQ score (questions 2+3) and the peak eosinophil count and the change from baseline of the SHP621-301 study and from baseline of this extension study at the final treatment period evaluation (Visit 8) will be summarized by each assessment visit.

To evaluate the response to OBS treatment over 36 weeks for subjects who were on placebo in the SHP621-301 induction study, the proportion of subjects who responded based on the histological data and the DSQ data at the final treatment period evaluation (Visit 8) and the corresponding 95% CI will be summarized. Summary statistics of the DSQ score (questions 2+3) and the peak eosinophil count and the change from baseline of the SHP621-301 study and from baseline of this extension study at the final treatment period evaluation (Visit 8) will be summarized by each assessment visit.

For subjects who relapse on placebo during the randomized withdrawal and who reinitiate treatment with OBS 2 mg twice daily (intermittent therapy), separate descriptive analyses for histological data and DSQ endpoints will be conducted at each assessment visit. Changes will be summarized over time from baseline of the SHP621-301 study and from the time of relapse. The same criteria for response will be applied to these subjects (≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ from SHP621-301 baseline score).

Summary statistics will be provided for all other secondary endpoints.

9.8.3 Exploratory Efficacy Endpoints

The exploratory endpoints that will be explored are 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 randomization visit (Visit 1), or at the screening visit (Visit 0) 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 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, preferred term, 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 ([Bone Mineral Density in Childhood Study 2015](#)). Safety parameters will be descriptively summarized by treatment group at baseline and for each post baseline visit.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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 nonpediatric 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 subinvestigators 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.

The data from the central pathologist will be recorded directly onto paper CRF.

All other data will have separate source documentation; no data will be recorded directly onto the CRF. The following data collected for assessments and procedures performed at the SHP621-301 final treatment evaluation visit (Visit 4) will not be recollected in the SHP621-302 database as follows (Section 7.1.1.1):

- Vital signs, height, and weight assessment
- EGD with endoscopy score (EREFS) and biopsy
- DSQ compliance assessment

5

103

103

1

- Physical examination
- Tanner Staging Assessment
- Clinical laboratory tests
- Urinalysis
- Pregnancy test
- Morning cortisol
- ACTH Stimulation Testing

- DXA Scan (subjects 11 to 17 years of age)

All other 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 parents/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 noncommercial 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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[REDACTED]

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12. APPENDIX

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Appendix 1 Protocol History

Document	Date	Global/Country/Site Specific
Protocol Amendment 1	22 Jun 2016	Global
Original Protocol	05 Dec 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
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
Tanner Staging Assessment	Site
EREFS	Site

Abbreviations: DSQ=Dysphagia Symptom Questionnaire; [REDACTED]
[REDACTED] EREFS=EoE Endoscopic Reference Score; [REDACTED]
[REDACTED]

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

Daily Diary	Daily Diary	Daily Diary
This daily diary includes questions about your eosinophilic esophagitis (EoE). We are interested in any trouble you had today swallowing foods such as meat, rice, fruit, bread, etc.	Please complete this questionnaire after you have had your last meal of the day.	Read each question on the following screens and answer by selecting the box that best describes your experience. There are no right or wrong answers to any of the questions.

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

[REDACTED] [REDACTED]

The diagram illustrates a simple neural network structure. It consists of three layers: an input layer with one node, a hidden layer with five nodes, and an output layer with one node. The input node is connected to all five hidden nodes, and the hidden nodes are connected to the output node.

The diagram shows a cross-section of a structure. A horizontal line is drawn across the top. Below this line, on the left, is a vertical dashed line. On the right, there is a series of horizontal bars of varying lengths, stacked vertically, resembling a staircase or a series of steps. A large, light gray watermark is oriented diagonally across the entire image, reading "For non-commercial use only".



PROTOCOL: SHP621-302

TITLE: A Phase 3, Multicenter, Double-blind Extension Study to Evaluate Maintenance of Efficacy of Oral Budesonide Suspension (OBS) and Long-term Treatment Effect of OBS in Adolescent and Adult Subjects (11 to 55 Years of Age, Inclusive) with Eosinophilic Esophagitis (EoE)

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: 05 Dec 2015
Protocol Amendment 1: 22 Jun 2016
Protocol Amendment 2: 19 Dec 2016

This document contains confidential and proprietary information of Shire and is disclosed pursuant to confidentiality and nondisclosure obligations. This information should be used solely for the purposes for which it was provided and should not be copied, shared with, or disclosed to any third party without the express written consent of Shire.

19 Dec 2016

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [REDACTED]

MD

Date: [REDACTED]

Acknowledgement

I have read this protocol for Shire Study SHP621-302.

Title: A Phase 3, Multicenter, Double-blind Extension Study to Evaluate Maintenance of Efficacy of Oral Budesonide Suspension (OBS) and Long-term Treatment Effect of OBS in Adolescent and Adult Subjects (11 to 55 Years of Age, Inclusive) with Eosinophilic Esophagitis (EoE)

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 SHP621-302 protocol is amended to address the following items:

- Update the dysphagia relapse criterion as it pertains to missing diary data. This change to this criterion will result in subjects being considered a relapse for treatment assignment change from placebo if they meet the dysphagia symptom criterion by missing diary data **and** meet the eosinophil histology criterion.
- Clarify the primary efficacy analyses, including providing for sensitivity analysis in which patients with missing diary data be treated as **not** being relapsed.

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 2	Amendment Date 19 Dec 2016	Global Amendment
Description of Change		Section(s) Affected by Change
<ul style="list-style-type: none"> If less than 4 days of dysphagia are reported in the DSQ and less than 8 diary entries are recorded within the 2 week period, then the 2-week period will be shifted backwards from the scheduled visit, 1 day at a time, to confirm if the subject meets the criteria for dysphagia symptom relapse over 14 consecutive days; however, the 2-week period will not be shifted further if at least 8 diary entries are recorded in the 14 day period and will not be shifted by more than 2 weeks in total (ie, no more than 2-week period plus additional 2-week additional expansion). the subject would be designated as meeting the criterion for dysphagia symptom relapse due to missing diary data. <p>Rationale: To update the dysphagia symptom relapse criterion to result in subjects being considered a relapse for treatment assignment change from placebo if they meet the dysphagia symptom criterion by missing diary data and meet the eosinophil histology criterion</p>		<p>Synopsis: Investigational product, dose, and mode of administration; Section 6.2.3: Dosing; Section 7.2.1.2: Dysphagia Symptom Questionnaire</p>
<p>4. Subject on inhaled or intranasal steroids and not on a stable dose between in the baseline visit (Visit 1) of the SHP621-301 study and 4 weeks before the screening EGD of this study</p>		<p>Synopsis: Exclusion Criteria; Section 4.2: Exclusion Criteria</p>
<p>Sensitivity analyses will be performed using the ITT population by classifying subjects who met the histology relapse criterion and met the dysphagia symptom relapse criterion due to missing diary data as non-relapsers.</p> <p>Rationale: To provide for sensitivity analysis in which patients with missing</p>		<p>Synopsis: Statistical Methodology for Primary Efficacy Endpoint Section 9.8.1: Primary Efficacy Endpoint</p>

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 2	Amendment Date 19 Dec 2016	Global Amendment
Description of Change		Section(s) Affected by Change
diary data are treated as not being relapsed.		
<p>The following sensitivity and supportive analyses will be performed for the primary endpoint to evaluate the robustness of the results from the primary analysis methods.</p> <p>Similar analyses used for the ITT population will be repeated using the FAS and the PP datasets. Sensitivity analyses will be performed using the ITT population by classifying subjects who withdraw without providing efficacy data at the ET visit as non-relapsers.</p> <p>In addition, the subjects who were prematurely withdrawn from the study without the primary efficacy endpoint will be imputed randomly according to the distribution of relapsers with available data; and the similar statistical test will be performed using the imputed data.</p> <p>Rationale: Added text to the synopsis describing sensitivity analyses for the primary endpoint to be consistent with text in Section 9.8.1.</p>		<p>Synopsis: Statistical Methodology for Primary Efficacy Endpoint Section 9.8.1: Primary Efficacy Endpoint</p>
<ul style="list-style-type: none"> 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 enrollment to resume (or discontinue) intranasal corticosteroids based on the subject's usual treatment regimen for allergy season. (In these subjects, intranasal corticosteroids must not be changed between the baseline visit [Visit 1] of the SHP621-301 study and the screening EGD of this study). All topical corticosteroid dosing changes, including those for seasonal allergic rhinitis, should be avoided within 4 weeks prior to EGD. Subjects who require a change in inhaled corticosteroid treatment for an asthma exacerbation should be discussed with the medical monitor. 		Section 4.3 : Restrictions
Relapse, a binary response (either with a relapse or not), is defined as having an eosinophil count of ≥ 15 eos/HPF from at least 2 of 3 levels of the esophagus, as determined by a central reader, and having at least 4 days of dysphagia in the 2-week period prior to the scheduled visit, as determined by the DSQ (refer to Section 7.2.1.2 for additional detail, including missing diary data handling).		Section 9.8.1 : Primary Efficacy Endpoint

See [Appendix 1](#) for protocol history, including all amendments.

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the Shire Clinical Study Serious Adverse Event and Non-serious Adverse Events (AEs) Required by the Protocol Form 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 this form must also be sent to the contract research organization (CRO)/Shire Medical Monitor by fax or e-mail using the details below.

[REDACTED], MD

Email: [REDACTED]

Fax: [REDACTED]

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

[REDACTED], MD

Phone: [REDACTED]

Mobile: [REDACTED]

Email: [REDACTED]

Fax: [REDACTED]

For protocol- or safety-related issues outside of normal business hours, 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	
European Union and Rest of World	

Telephone numbers (provided for reference if needed):

Shire, Lexington, MA (USA)

or

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LIST OF ABBREVIATIONS

ACTH	adrenocorticotrophic hormone
AE	adverse event
β-hCG	beta-human chorionic gonadotropin
BMD	bone mineral density
CFR	Code of Federal Regulations
CI	confidence interval
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	esophagogastrroduodenoscopy
EMA	European Medicines Agency
EoE	eosinophilic esophagitis
ePRO	electronic patient-reported outcome
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
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
OBS	oral budesonide suspension
pc	after meals
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
PP	per-protocol
PPI	proton pump inhibitor
qAM	every morning
SAE	serious adverse event
SAP	statistical analysis plan
SAS [®]	statistical analysis system
TEAE	treatment-emergent adverse event
UK	United Kingdom
US	United States

STUDY SYNOPSIS

Protocol number: SHP621-302	Drug: SHP621, oral budesonide suspension (OBS)
Title of the study: A Phase 3, Multicenter, Double-blind Extension Study to Evaluate Maintenance of Efficacy of Oral Budesonide Suspension (OBS) and Long-term Treatment Effect of OBS in Adolescent and Adult Subjects (11 to 55 Years of Age, Inclusive) with Eosinophilic Esophagitis (EoE)	
Number of subjects (total and for each treatment arm): Approximately 200 subjects (88%) who are randomized in the SHP621-301 study are estimated to complete the SHP621-301 study and enroll in this treatment extension study based on enrollment observed in the Phase 2 study (MPI 101-06).	
Investigator(s): Multicenter study	
Site(s) and Region(s): Approximately 60 sites in North America	
Study period (planned): April 2016–April 2019	Clinical phase: 3
Objectives Primary: <ul style="list-style-type: none">To evaluate the maintenance of efficacy over 36 weeks, as measured by the peak eosinophilic count and the Dysphagia Symptom Questionnaire (DSQ) score, through a randomized withdrawal design for subjects who responded to 12 weeks of OBS treatment (2 mg twice daily) with a peak count of ≤ 6 eosinophils (eos)/high-powered field (HPF) across all available esophageal levels at the final treatment visit and a $\geq 30\%$ reduction in DSQ score from baseline during the SHP621-301 induction study Key Secondary: <ul style="list-style-type: none">To evaluate the long-term treatment response over an extended period of 36 weeks for subjects who were randomized to OBS treatment but did not respond after 12 weeks in the SHP621-301 induction study (subject did not have a peak count of ≤ 6 eos/HPF across all available esophageal levels at the final treatment visit and/or a $\geq 30\%$ reduction in DSQ score from baseline) Secondary: <ul style="list-style-type: none">To evaluate the response to OBS treatment over 36 weeks for subjects who received placebo in the SHP621-301 induction studyTo evaluate the effect of reinitiating OBS treatment for subjects who relapse after being randomized to placebo in the randomized withdrawal period (treatment-withdrawal-treatment reinitiation)To assess endoscopically identified esophageal features as measured by the EoE Endoscopic Reference Score (EREFS)To evaluate other response criteria based on histology and DSQTo evaluate the long-term safety and tolerability of OBS treatment Exploratory: <ul style="list-style-type: none">[REDACTED][REDACTED]	

Rationale:

Currently there is no approved medication for the treatment of EoE. This Phase 3 study is being conducted to determine response to withdrawal of OBS, maintenance of response, extended therapy response, and response to intermittent therapy by evaluating both eosinophil counts and DSQ in adolescent and adults treated or withdrawn from OBS in this treatment extension study.

Investigational product, dose, and mode of administration:

The assessments from the SHP621-301 final treatment evaluation visit (Visit 4) will be used as the screening assessments (Visit 0) of this treatment extension study. At the SHP621-301 final treatment evaluation visit, subjects will be dispensed blinded investigational product (based on treatment assignment in SHP621-301) that will last for up to 4 weeks prior to enrolling into this treatment extension study. A 4-week screening period is required to allow for blinded treatment response information (reduction in DSQ from baseline and eosinophilic count as determined by a central reader) collected during the SHP621-301 final treatment evaluation visit to be entered into the interactive web-based response system (IWRS). Only the unblinded data team who is independent from the blinded study team and not involved with the day-to-day conduct of the study will have restricted access to blinded treatment response information. Once information is available in IWRS, subjects will return for the randomization visit (Visit 1) to receive investigational product as follows:

- Subjects who were assigned to OBS treatment and who fully responded in the SHP621-301 study (≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ at the final treatment evaluation visit) will enter a randomized withdrawal period to receive either OBS 2 mg twice daily or placebo at a 1:1 ratio
- Subjects who were assigned to OBS treatment and did not respond or partially responded to OBS treatment in the SHP621-301 study will receive OBS 2 mg twice daily
- Subjects who were assigned to placebo in the SHP621-301 study will receive OBS 2 mg twice daily

Subjects, site staff, and study team members will remain blinded to treatment assignment and individual subject histology and individual subject DSQ data from the SHP621-301 study (post randomization) and this extension study until database lock occurs for this extension study.

During the 36-week double-blind treatment extension study, subjects will receive oral administration of 10 mL of 0.2 mg/mL (2 mg) investigational product twice daily (every morning [qAM] after meals [breakfast, pc] and at bedtime [hs]; 4 mg total/day), with no ingestion of food or liquids permitted for 30 minutes after investigational product administration. Dosing regimens are consistent with the regimens used in the Phase 2 MPI 101-06 study and Phase 3 SHP621-301 study:

- Placebo twice-daily group: placebo qAM (pc) and hs
- OBS twice-daily group: OBS 10 mL of 0.2 mg/mL (2 mg) qAM (pc) and hs (4 mg OBS total/day)

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).

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.

Total Daily Dose of OBS

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

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

At Week 12, all subjects will undergo an upper esophagogastroduodenoscopy (EGD) with biopsy to evaluate eosinophil counts. Upon receipt of blinded EGD and DSQ data, subjects on placebo in the randomized withdrawal period who have relapsed will have their treatment assignment changed to OBS 2 mg twice daily. The criteria for relapse is having an eosinophilic count of ≥ 15 eos/HPF from at least 2 of 3 levels of the esophagus, as determined by central reader and having at least 4 days of dysphagia in the 2-week period prior to the scheduled visit, as determined by the DSQ. Considering the potential for missing diary entries, the determination of relapse based on days of dysphagia reported on the DSQ will occur as follows:

- If at least 4 days of dysphagia are reported on the DSQ in the 2-week period prior to the visit, the subject would meet the criterion for dysphagia symptom relapse.
- If less than 4 days of dysphagia are reported and at least 8 diary entries are recorded within the 2-week period, the subject would not meet the criterion for dysphagia symptom relapse.
- If less than 4 days of dysphagia are reported in the DSQ and less than 8 diary entries are recorded within the 2-week period, the subject would be designated as meeting the criterion for dysphagia symptom relapse due to missing diary data.

The criteria for relapse align with the related inclusion criteria for participation in the SHP621-301 study. If both histology and dysphagia symptom relapse criteria are met, the treatment assignment change will be performed in a blinded manner in IWRS at the subsequent study visit. If both criteria for relapse are not met, the subject will remain assigned to placebo.

If at any time, the subject reports increased or worsening dysphagia symptoms to the investigator, the investigator may choose to perform an unscheduled EGD. If an unscheduled EGD is performed prior to Week 12, an EGD does not have to be repeated at Week 12. If a subject on placebo meets the criteria for relapse, the subject's treatment assignment will be changed in a blinded manner from placebo to OBS 2 mg twice daily at the subsequent study visit.

If the Week 12 or an unscheduled EGD reveals an eosinophil count of ≥ 15 from at least 2 of 3 levels of the esophagus yet relapse is not confirmed due to the criterion for dysphagia symptoms not being met, the subject will remain assigned to placebo. If the criterion for dysphagia symptoms is met at a subsequent visit and both criteria for relapse are then confirmed, the subject's treatment assignment will be changed to OBS 2 mg twice daily at the next scheduled visit.

Methodology:

This is a Phase 3, double-blind, multicenter 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 who completed the SHP621-301 induction study.

This study will comprise 3 periods: 4-week screening period, 36-week double-blind treatment period, and a 4-week safety follow-up (Study Design Flow Chart). All subjects who have completed the SHP621-301 induction study will be eligible to enroll in this extension study. Approximately 200 subjects (88%) who were randomized in the SHP621-301 study are estimated to complete the SHP621-301 study and will be enrolled in this treatment extension study based on enrollment observed in the Phase 2 study (MPI 101-06). Randomization into the randomized withdrawal period will be stratified by treatment assignment and treatment response in the SHP621-301 study. Subjects who are full responders (defined as ≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ at the final treatment evaluation visit [Visit 4]) in the SHP621-301 induction study will be eligible to enter the randomized withdrawal period to receive either OBS 2 mg twice daily or placebo at a 1:1 ratio. The randomization of subjects who are full responders will also be stratified by age (adults and adolescents) to ensure approximately equal number of subjects within each age group are assigned to the treatment groups.

Subjects who sign informed consent (or assent as applicable for subjects < 18 years) will be screened (Visit 0); assessments from the SHP621-301 final treatment evaluation visit (Visit 4) will be used as the Visit 0 screening assessments of the treatment extension study. Subjects who meet eligibility criteria at the screening visit (Visit 0) will enter the 36-week double-blind period. Eligible subjects will receive investigational product based on treatment assignment in SHP621-301 for up to 4 weeks prior to enrollment in the treatment extension study. This 4-week screening period is required to allow for blinded treatment response information (reduction in DSQ from baseline and eosinophilic count as determined by a central reader) collected during the SHP621-301 final treatment evaluation visit to be entered into IWRS. Only the unblinded data team who is independent from the blinded study

team and not involved with the day-to-day conduct of the study will have restricted access to blinded treatment response information. Once information is available in IWRS, subjects will return for the randomization visit (Visit 1) to receive investigational product.

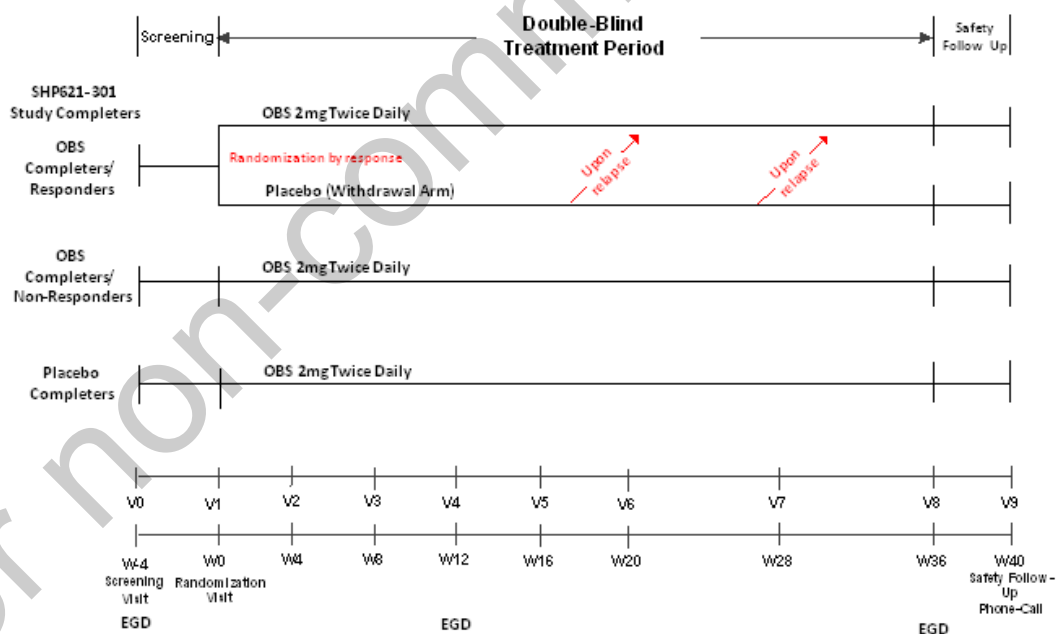
During the 36-week treatment extension study, subjects who were assigned to, and fully responded to OBS treatment in the SHP621-301 study (≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ at the final treatment evaluation visit) will enter a randomized withdrawal period to receive either OBS 2 mg twice daily or placebo at a 1:1 ratio. Subjects who were assigned to OBS treatment in the SHP621-301 study and did not respond or partially responded, will receive OBS 2 mg twice daily. Subjects who were assigned to placebo in the SHP621-301 study will receive OBS 2 mg twice daily. At Week 12, all subjects will undergo an upper esophagogastroduodenoscopy (EGD) with biopsy to evaluate eosinophil counts. Upon receipt of blinded EGD and DSQ data, subjects on placebo in the randomized withdrawal period who have relapsed (>15 eos/HPF from at least 2 levels of the esophagus and specimens and 4 days of dysphagia over 2 weeks) will have their treatment assignment changed to OBS 2 mg twice daily at the next scheduled visit. The treatment assignment change will be performed in a blinded manner in IWRS at the subsequent study visit. If both criteria for relapse are not met, the subject will remain assigned to placebo.

Subjects who report increased or worsening dysphagia symptoms to the investigator prior to the Week 12 EGD may have an unscheduled EGD to confirm whether relapse has occurred. If an unscheduled EGD is performed prior to Week 12, an EGD does not have to be repeated at Week 12. If a subject on placebo meets the criteria for relapse, the subject's treatment assignment will be changed in a blinded manner from placebo to OBS 2 mg twice daily at the subsequent study visit.

Subjects will have efficacy and safety assessments at each visit during the 36-week period. Subjects who fail to meet all eligibility criteria at Visits 0 or 1 will be considered screen failures. Subjects cannot be rescreened once they have been designated as a screen failure. Subjects who discontinue will not be replaced.

Subjects will be required to visit the site up to 8 times over up to a 36-week period. All subjects will have a follow-up phone call 4-weeks post last dose of investigational product.

Study Design Flow Chart



Abbreviations: EGD=esophagogastroduodenoscopy; 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 completed SHP621-301 induction study.
2. 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.
3. Subject is male or female aged 11-55 years, inclusive, at time of consent for SHP621-301 study.
4. 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 0). There should be no changes to these regimens during study participation.
5. 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 and for 30 days following the last dose of investigational product.
6. Subject is willing and has an understanding and ability to fully comply with study procedures including DSQ compliance 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 changes in medications that could affect the study or diet in the weeks since the final treatment evaluation visit (Visit 4) of the SHP621-301 study.
2. Subject using immunomodulatory therapy since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or anticipated use of immunomodulatory therapy during the treatment period (except for any ongoing regimen of allergy shots); 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 scheduled EGDs.
3. Subject using swallowed topical corticosteroid for EoE or systemic corticosteroid for any condition since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or anticipated 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 medical monitor prospectively but cannot occur within the 4 weeks of the scheduled EGDs.
4. Subject on inhaled or intranasal steroids and not on a stable dose in the 4 weeks before the screening EGD of this study.
5. Subject has initiated, discontinued, or changed dosage regimen of proton pump inhibitors (PPIs), H₂ antagonists, antacids, or leukotriene inhibitors for any condition (such as gastroesophageal reflux disease, asthma or allergic rhinitis) since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or anticipated changes in the use of such medications during the treatment period.
6. Subject using Cytochrome P450 3A4 inhibitors (eg, ketoconazole, grapefruit juice) since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or anticipated use of such medications during the treatment period.
7. Subject has an appearance on screening 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 six-food elimination diet.
9. Subject has presence of esophageal varices at the EGD at the final treatment evaluation visit (Visit 4) of the SHP621-301 study.
10. 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.

11. Subject has other diseases causing or associated with esophageal eosinophilia, including hypereosinophilic syndrome, collagen vascular disease, vasculitis, achalasia, or parasitic infection.
12. Subject has oropharyngeal or esophageal candidiasis that failed to respond to previous treatment. Diagnosis with oropharyngeal or esophageal candidiasis at or since the final treatment evaluation visit (Visit 4) of the SHP621-301 study is not an exclusion as long as the subject is expected to respond to treatment.
13. Subject has a potentially serious acute or chronic infection or immunodeficiency condition, including tuberculosis, fungal, bacterial, viral/parasite infection, ocular herpes simplex, or chicken pox/measles.
14. Subject has upper gastrointestinal bleeding identified in the EGD at the final treatment evaluation visit (Visit 4) of the SHP621-301 study or since the final treatment evaluation visit (Visit 4) of the SHP621-301 study.
15. Subject has evidence of active infection with *Helicobacter pylori*.
16. Subject has evidence of unstable asthma since the final treatment evaluation visit (Visit 4) of the SHP621-301 study.
17. Subject is female and pregnant or nursing.
18. Subject has a history of intolerance, hypersensitivity, or idiosyncratic reaction to budesonide (or any other corticosteroids), or to any other ingredients of the study medication.
19. Subject has a history or high risk of noncompliance with treatment or regular clinic visits.
20. Subject is on sucralfate or anticipates using sucralfate during the treatment period.

Maximum duration of subject involvement in the study:

- Planned duration of screening period: up to 4 weeks
- Planned duration of treatment period: 36 weeks
- Planned duration of safety follow-up period: 4 weeks

Endpoints and statistical analysis:

Subject Populations

- The **safety set** will include all subjects who are randomized and receive at least 1 dose of 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 investigational product and had 1 post baseline efficacy assessment (biopsy and/or DSQ score).
- The **per-protocol (PP) set** will include all subjects in the FAS excluding subjects with major protocol deviations. 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.

Primary Efficacy Endpoint

The primary efficacy endpoint for each subject is relapse during the double-blind randomized withdrawal period. Relapse, a binary response (either with a relapse or not), is defined as having an eosinophil count of ≥ 15 eos/HPF from at least 2 of 3 levels of the esophagus, as determined by a central reader, and having at least 4 days of dysphagia in the 2-week period prior to the scheduled study visit, as determined by the DSQ.

Key Secondary Efficacy Endpoint

The key secondary endpoint is the long-term treatment response, a binary response, over an extended period of 36 weeks in adolescent and adult subjects who were randomized to OBS treatment but did not respond after 12 weeks in the SHP621-301 induction study (subject did not have peak count of ≤ 6 eos/HPF across all available esophageal levels at the final treatment visit and/or $\geq 30\%$ reduction in DSQ score from baseline) and met the following criteria:

- Histologic response, defined as a peak eosinophil count of ≤ 6 eos/HPF across all available esophageal levels at

the final treatment period evaluation (Visit 8)

- Dysphagia symptom response, defined as $\geq 30\%$ reduction in the DSQ combined score (questions 2+3) from baseline of the SHP621-301 study and from baseline of this extension study to the final treatment period evaluation (Visit 8)

Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be analyzed in all subjects:

- Histologic response, defined as a peak eosinophil count of ≤ 6 eos/HPF across all available esophageal levels at each assessment visit
- Dysphagia symptom response, defined as $\geq 30\%$ reduction in the DSQ combined score (questions 2+3) at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Change in the DSQ score and change in the peak eosinophilic count at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Change in total endoscopy score, as measured by the EREFS classification, at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Peak eosinophil count < 15 eos/HPF across all available esophagus levels at each assessment visit
- Peak eosinophil count ≤ 1 eos/HPF across all available esophagus levels at each assessment visit
- Change in the peak eosinophil count at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study for each available esophageal level (proximal, mid-, and distal)
- Change in the histopathologic epithelial features combined total score (grade and stage) at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Dysphagia symptom response (binary response), defined as a $\geq 50\%$ reduction in the DSQ combined score (questions 2+3), at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension
- Change in the DSQ combined score (questions 2+3) at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Cumulative distribution function curves for the change and the percent change in the DSQ score at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Overall binary response I, defined as a reduction in the DSQ score of $\geq 30\%$ and a peak eosinophil count of ≤ 6 eos/HPF across all esophageal levels at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Overall binary response II, defined as a reduction in the DSQ score of $\geq 50\%$ and a peak eosinophil count of ≤ 6 eos/HPF across all esophageal levels at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Change in the DSQ + pain score (question 2+3+4) at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Change in the DSQ pain score (question 4) at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study

For subjects who relapse on placebo during the randomized withdrawal period and who reinitiate treatment with OBS 2 mg twice daily (intermittent therapy), separate descriptive analyses for histological data and DSQ endpoints will be conducted at each assessment visit. Changes will be summarized over time from baseline of the SHP621-301 study and from the time of relapse. The same criteria for response will be applied to these subjects (≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ from the SHP621-301 baseline score).

Exploratory Efficacy Endpoints

- [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 adrenocorticotrophic 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.

Statistical Methodology for Primary Efficacy Endpoint

The primary efficacy endpoint will be analyzed as the proportion of subjects with relapse during the end of the double-blind randomized withdrawal period for the FAS, using Fisher's Exact test comparing OBS 2 mg twice daily against placebo. The primary test of treatment effect will be 2-sided, and conducted at the significance level of 0.05. The proportion of subjects with relapse for each treatment group and the corresponding 95% confidence interval (CI) will be estimated. In addition, the difference in the proportion of subjects with relapse between the 2 treatment groups and its 95% CI will be estimated.

Subjects who withdraw without providing efficacy data at the early termination (ET) visit will be classified as being a relapser in the primary efficacy analysis. The null hypothesis states that there is no difference in relapse proportions between OBS 2 mg twice daily and placebo, with the 2-sided alternative of a nonzero difference between groups. Relapse proportions at each adjacent double-blind visit interval will also be assessed by applying the Fisher's Exact test to the observed data at each double-blind visit.

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

Similar analyses used for the ITT population will be repeated using the FAS and the PP datasets. Sensitivity analyses will be performed using the ITT population by classifying subjects who withdraw without providing efficacy data at the ET visit as non-relapsers. Sensitivity analyses will be performed using the ITT population by classifying subjects who met the histology relapse criterion and met the dysphagia symptom relapse criterion due to missing diary data as non-relapsers. In addition, the subjects who were prematurely withdrawn from the study without the primary efficacy endpoint will be imputed randomly according to the distribution of relapsers with available data; and the similar statistical test will be performed using the imputed data.

Statistical Methodology for Key Secondary and Other Secondary Efficacy Endpoints

To evaluate the long-term treatment response over an extended period of 36 weeks for subjects who were randomized to OBS treatment but did not respond after 12 weeks in the SHP621-301 induction study (subject did not have peak count of ≤ 6 eos/HPF across all available esophageal levels at the final treatment visit and/or $\geq 30\%$ reduction in DSQ score from baseline of SHP621-301), the proportion of subjects who responded based on the histological data and the DSQ data at the final treatment period evaluation (Visit 8) and the corresponding 95% confidence interval (CI) will be estimated and summarized.

Summary statistics of the DSQ score (questions 2+3) and the peak eosinophil count and the change from baseline of the SHP621-301 study and from baseline of this extension study at the final treatment period evaluation (Visit 8) will be summarized by each assessment visit.

To evaluate the response to OBS treatment over 36 weeks for subjects who were on placebo in the SHP621-301 induction study, the proportion of subjects who responded based on the histological data and the DSQ data at the final treatment period evaluation (Visit 8) and the corresponding 95% CI will be summarized. Summary statistics of the DSQ score (questions 2+3) and the peak eosinophil count and the change from baseline of the SHP621-301 study and from baseline of this extension study at the final treatment period evaluation (Visit 8) will be summarized by each assessment visit.

To evaluate the effect of reinitiating OBS treatment for subjects who relapse after being randomized to placebo in

the randomized withdrawal period (intermittent therapy), the proportion of subjects who responded based on the histological data and the DSQ data at the final treatment period evaluation (Visit 8) and the corresponding 95% CI will be summarized.

Summary statistics will be provided for all the secondary endpoints.

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 (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.

Sample Size Justification

Approximately 200 subjects (88%) who are randomized in the SHP621-301 study are estimated to complete the SHP621-301 study and enroll in this treatment extension study based on enrollment observed in the Phase 2 study (MPI 101-06).

The primary efficacy measure of the study will be the proportion of subjects who relapse during the double-blind randomized withdrawal period. Relapse, a binary response (either with relapse or not), is defined as having an eosinophil count of ≥ 15 eos/HPF from at least 2 of 3 levels of the esophagus (determined by a central reader) and having at least 4 days of dysphagia in a 2-week period prior to the scheduled visit (determined by the DSQ). To be considered as a subject with relapse, both criteria must be met.

Based on observation in the Phase 2 study (MPI 101-06), approximately 26% of subjects, or approximately 40 subjects, who were assigned to OBS treatment in the SHP621-301 study are anticipated to respond fully after 12 weeks in the SHP621-301 study.

For this study, to detect a 50 percentage point difference between relapse proportions of 20% and 70% in the OBS and placebo groups, respectively, at more than 80% power and a significance level of 0.05 (2-sided) using the Fisher's Exact test with equal allocation to treatment groups, it is necessary to assess the primary efficacy measure for approximately 38 subjects (19 subjects in each of the OBS and placebo groups).

Table 1-1 Schedule of Assessments

[illegible]

Table 1-1 Schedule of Assessments

Procedures	Screening ^a	Double-blind Treatment Period								Safety Follow-up Contact ^p
	Visit 0	Randomization/ Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 or ET ^o	Visit 9
Week	-4	0	4	8	12	16	20	28	36	40
Window	≤4 weeks	--	±3 days	±3 days	±3 days	±3 days	±3 days	±6 days	±6 days	±3 days
Tanner Staging Assessment ^e	X								X	
Clinical laboratory tests ^h	X	X	X	X	X	X	X	X	X	
Urinalysis ⁱ	X	X	X	X	X	X	X	X	X	
Pregnancy test ^j	X	X	X	X	X	X	X	X	X	
Morning cortisol (target 6:00-9:00 am)	X	X	X	X	X	X	X	X	X	
ACTH Stimulation Testing	X								X	
DXA Scan (subjects 11 to 17 years of age) ^k	X								X	
Randomization ^l		X								
Study medication supplied	X ^m	X	X	X	X	X	X	X		
Study medication administration	Twice-daily administration of study medication									
Study medication compliance assessment	X	X	X	X	X	X	X	X	X	
Concomitant medications and procedures recorded	X	X	X	X	X	X	X	X	X	X
Review of adverse events ⁿ	X	X	X	X	X	X	X	X	X	X

Abbreviations: ACTH=adrenocorticotropic hormone; DSQ=Dysphagia Symptom Questionnaire; DXA=dual-energy X-ray absorptiometry;

EGD=esophagogastroduodenoscopy;

EREFS=EoE Endoscopic Reference Score; hs=at bedtime; IWRS=interactive web-based response system;

pc=after meals;

Table 1-1 Schedule of Assessments

Procedures	Screening ^a	Double-blind Treatment Period								Safety Follow-up Contact ^p
	Visit 0	Randomization/ Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 or ET ^o	Visit 9
Week	-4	0	4	8	12	16	20	28	36	40
Window	≤4 weeks	--	±3 days	±3 days	±3 days	±3 days	±3 days	±6 days	±6 days	±3 days

^a The assessments from the SHP621-301 final treatment evaluation visit (Visit 4) will be used as the screening assessments (Visit 0) of this treatment extension study.

^b 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.

^c Height to be collected at screening (Visit 0) and Visit 8 for all subjects. Height to be collected at Visit 4 for adolescents only (11-17 years, inclusive). Height measurements for adolescents should be measured in triplicate using stadiometers.

^d Weight measurements for adolescents (11-17 years, inclusive) should be measured in duplicate.

^e Endoscopy must include esophageal biopsies; gastric and duodenal biopsies may be done at the discretion of the investigator. Endoscopies at Visit 4 and Visit 8 should occur at or within 7 days of the scheduled visit. Unscheduled endoscopies may be performed at the discretion of the investigator.

^f [REDACTED]

^g Tanner staging assessments will be performed for all subjects ≥11 years of age 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 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 screening (Visit 0) and Visit 8. Urine pregnancy tests will be performed at all other visits.

^k Dual-energy X-ray absorptiometry scans should be performed using the same machine and software as used in the SHP621-301 study. Dual-energy X-ray absorptiometry scan at Visit 8 should occur at or within 7 days of the scheduled visit.

^l Randomization will occur via IWRS at Visit 1 once the subject's eligibility is confirmed.

^m Study medication is supplied at the SHP621-301 final treatment visit based on treatment assignment in SHP621-301.

ⁿ Adverse event assessments at each visit and physical examination must include specific assessments for signs of glucocorticoid excess (eg, moon facies,

Table 1-1 Schedule of Assessments

Procedures	Screening ^a	Double-blind Treatment Period								Safety Follow-up Contact ^p
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Week	-4	0	4	8	12	16	20	28	36	40
Window	≤4 weeks	--	±3 days	±3 days	±3 days	±3 days	±3 days	±6 days	±6 days	±3 days

acne, hirsutism, mood swings, insomnia, and depression).

^o If subject discontinues study prematurely during the treatment period, the evaluations listed for Visit 8 are to be performed as completely as possible.

^p A safety follow-up contact by phone will be performed 4 weeks following the last dose of study medication for all subjects (including subjects who fail screening, who discontinue early, or who complete the study).

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 an approved treatment that induces and maintains remission for patients with EoE (Furuta and Katzka 2015).

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 nonviscous 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 2 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 eos/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

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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 eos/HPF) and remission (eosinophil count ≤ 1 eos/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 coprimary efficacy endpoints of histologic response and change from baseline in dysphagia symptoms. Following 12 weeks of twice daily treatment (once 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).

This Phase 3 extension study follows the SHP621-301 induction study, a Phase 3 randomized, double-blind, multicenter, 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. Study SHP621-301 is designed to provide safety and efficacy data demonstrating histologic response (as measured by eosinophilic count ≤ 6 eos/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. This extension study will evaluate maintenance of treatment and treatment withdrawal in subjects who complete the induction study.

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 Phase 3 study is being conducted to determine response to withdrawal of OBS, maintenance of response, extended therapy response, and response to intermittent therapy by evaluating both eosinophil counts and DSQ in adolescent and adults treated or withdrawn from OBS in this treatment extension study.

2.2 Study Objectives

2.2.1 Primary Objective

The primary objective of the study is:

- To evaluate the maintenance of efficacy over 36 weeks, as measured by the peak eosinophilic count and the Dysphagia Symptom Questionnaire (DSQ) score, through a randomized withdrawal design for subjects who responded to 12 weeks of OBS treatment (2 mg twice daily) with a peak count of ≤ 6 eosinophils (eos)/high-powered field (HPF) across all available esophageal levels at the final treatment visit and a $\geq 30\%$ reduction in DSQ score from baseline during the SHP621-301 induction study

2.2.2 Secondary Objectives

The key secondary objective of this study is:

- To evaluate the long-term treatment response over an extended period of 36 weeks for subjects who were randomized to OBS treatment but did not respond after 12 weeks in the SHP621-301 induction study (subject did not have a peak count of ≤ 6 eos/HPF across all available esophageal levels at the final treatment visit and/or a $\geq 30\%$ reduction in DSQ score from baseline)

Additional secondary objectives of the study are:

- To evaluate the response to OBS treatment over 36 weeks for subjects who received placebo in the SHP621-301 induction study
- To evaluate the effect of reinitiating OBS treatment for subjects who relapse after being randomized to placebo in the randomized withdrawal period (treatment-withdrawal-treatment reinitiation)
- To assess endoscopically identified esophageal features as measured by the EoE Endoscopic Reference Score (EREFS)
- To evaluate other responding criteria based on histology and DSQ
- To evaluate the long-term safety and tolerability of OBS treatment

2.2.3 Exploratory Objectives

The exploratory objectives of this study are:

- [REDACTED]
- [REDACTED]

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3. STUDY DESIGN

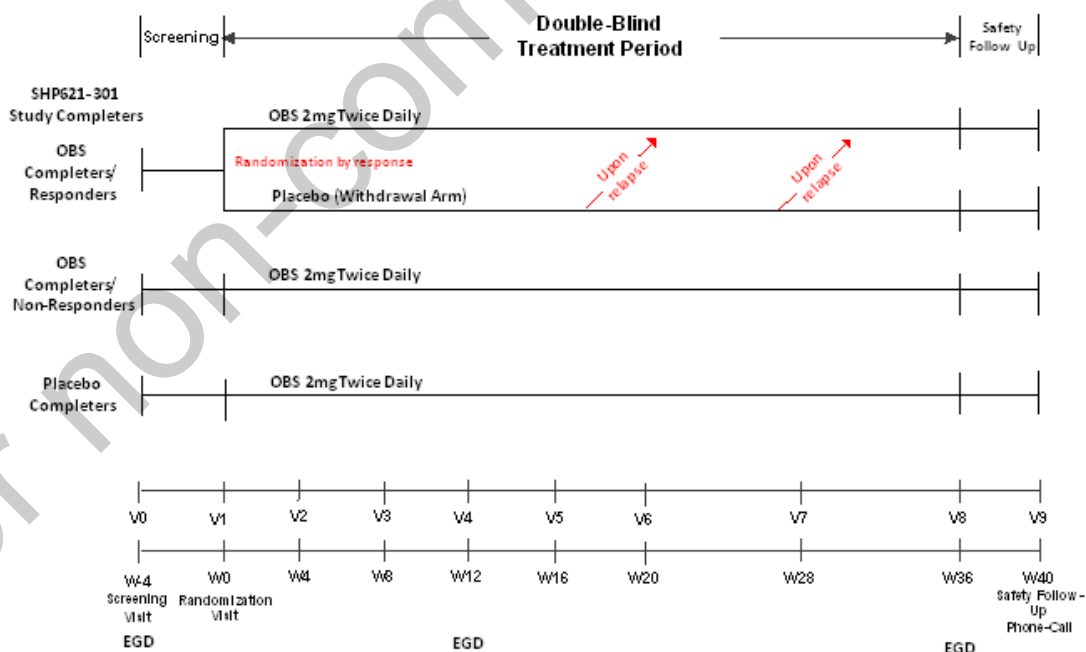
3.1 Study Design and Flow Chart

This is a Phase 3, multicenter, double-blind study to evaluate the efficacy, safety and tolerability of OBS treatment administered twice daily (qAM, pc, and hs) for 36 weeks. The study will be conducted in adolescents and adults, aged 11-55 years, inclusive, with EoE and dysphagia who completed the SHP621-301 induction study.

Approximately 200 subjects (88%) who were randomized in the SHP621-301 study are estimated to complete the SHP621-301 study and will be enrolled in this treatment extension study based on enrollment observed in the Phase 2 study (MPI 101-06). Randomization into the randomized withdrawal period will be stratified by treatment assignment and treatment response in the SHP621-301 study. Subjects who are full responders (defined as ≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ at the final treatment evaluation visit [Visit 4]) in the SHP621-301 induction study will be eligible to enter the randomized withdrawal period to receive either OBS 2 mg twice daily or placebo at a 1:1 ratio. The randomization of subjects who are full responders will also be stratified by age (adults and adolescents) to ensure approximately equal number of subjects within each age group are assigned to the treatment groups.

This study will consist of 3 periods: 4-week screening period, 36-week double-blind treatment period, and 4-week safety follow-up (Figure 3-1).

Figure 3-1 Study Design Flow Chart



Abbreviations: EGD=esophagogastroduodenoscopy; OBS=oral budesonide suspension

Subjects will be required to visit the site up to 8 times over up to a 36-week period. Following completion of the screening visit, subjects will be evaluated for eligibility and safety at Week 0 (Visit 1). Subjects who are eligible and randomized will have efficacy and safety assessments at Weeks 4, 8, 12, 16, 20, 28, and 36 (Visits 2-8) and additional safety assessments at follow-up at Week 40 (Visit 9). Subjects who fail to meet all eligibility criteria at Visits 0 or 1 will be considered screen failures. These subjects will receive a follow-up safety phone call 4 weeks after the last dose of investigational product. Subjects cannot be rescreened once they have been designated as a screen failure. 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 0]) and will be ≤ 4 weeks in duration. During the screening period, assessments from the SHP621-301 final treatment evaluation visit (Visit 4) will be used as the Visit 0 screening assessments of the treatment extension study. At the screening visit (Visit 0), 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. Eligible subjects will receive investigational product based on treatment assignment in SHP621-301 for up to 4 weeks prior to enrollment in the treatment extension study. This 4-week screening period is required to allow for blinded treatment response information (reduction in DSQ from baseline and eosinophilic count as determined by a central reader) collected during the SHP621-301 final treatment evaluation visit to be entered into the interactive web-based response system (IWRS). Only the unblinded data team who is independent from the blinded study team and not involved with the day-to-day conduct of the study will have restricted access to blinded treatment response information. Once response information is available, subjects will return for the randomization visit (Visit 1) to receive investigational product. Subjects who continue to meet eligibility criteria after the screening visit (Visit 0) will enter the 36-week double-blind treatment period.

Subjects who were assigned to OBS treatment and who fully responded in the SHP621-301 study (≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ at the final treatment evaluation visit) will enter a randomized withdrawal period to receive either OBS 2 mg twice daily or placebo at a 1:1 ratio. These subjects will also be stratified by age (adults and adolescents). Subjects who were assigned to OBS treatment and did not respond or partially responded in the SHP621-301 study will receive OBS 2 mg twice daily. Subjects who were assigned to placebo in the SHP621-301 study will receive OBS 2 mg twice daily. Subjects, site staff, and study team members will remain blinded to treatment assignment and individual subject histology, and individual subject DSQ data from the SHP621-301 (post randomization) and this extension study until the database locks occurs for this extension study.

At Week 12, all subjects will undergo an upper esophagogastroduodenoscopy (EGD) with biopsy to evaluate eosinophil counts. Upon receipt of blinded EGD and DSQ data, subjects on placebo in the randomized withdrawal period who have relapsed will have their treatment assignment changed to OBS 2 mg twice daily at the next scheduled visit. The criteria for relapse is having an eosinophilic count of ≥ 15 eos/HPF from at least 2 of 3 levels of the esophagus, as determined by central reader and having at least 4 days of dysphagia in the 2-week period prior to the scheduled visit, as determined by the DSQ. The criteria for relapse align with the related

inclusion criteria for participation in the SHP621-301 study. The treatment assignment change will be performed in a blinded manner in IWRS at the subsequent study visit. If both criteria for relapse are not met, the subject will remain assigned to placebo. The upper EGD with esophageal biopsies will be repeated at the Week 36 visit (Visit 8) or at early termination (ET), to evaluate eosinophil counts. If an unscheduled EGD is performed between Week 12 and Week 36, the Week 36 EGD should still be performed.

All subjects will have a follow-up phone call 4-weeks post last dose of investigational product to query for SAEs, AEs, and concomitant treatments.

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 as EoE persists, it becomes more fibrostenotic in older patients and would not be 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.

The design of this study combines randomized withdrawal and long-term extension elements in a manner that selects appropriate patients for placebo withdrawal and maintains double-blinding of subjects in all treatment groups. Only subjects who are full responders to OBS 2 mg twice daily in the SHP621-301 induction study (≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ at the final treatment evaluation visit of SHP621-301), will be eligible for randomized withdrawal. The randomized withdrawal period is required to assess maintenance of efficacy in these subjects. The continuation of OBS 2 mg twice daily treatment for subjects in SHP621-301 who did not respond or partially responded to treatment, will evaluate whether these subjects might respond to OBS 2 mg twice daily if their treatment is extended for an additional 36 weeks. This aspect of the study is supported by the possibility that the response of EoE to topical corticosteroids may require more than 12 weeks of induction treatment.

As described, the protocol also provides multiple mechanisms for switch from placebo and potential study discontinuation of relapsing and nonresponding subjects in order to evaluate the effect of reinitiating OBS treatment in these subjects. For subjects who relapse on placebo during the randomized withdrawal and who reinitiate treatment with OBS 2 mg twice daily (intermittent therapy), separate descriptive analyses for histological data and DSQ endpoints will be conducted at each assessment visit, as described in Section 9.8.2. For all subjects, an esophageal stricture requiring dilation would be considered a treatment failure and result in withdrawal of the subject from the study. Subject withdrawal criteria are provided in Section 4.5.1.

3.2 Duration and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 44 weeks, including the 4-week screening period. Including potential treatment in SHP621-301 and the

screening period of this study, the maximum total duration of OBS 2 mg twice daily may be approximately 52 weeks.

The study will be completed in approximately 36 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 8 (Week 36), inclusive of the final treatment evaluation EGD. All subjects will have a follow-up phone call 4-weeks post last dose of investigational product.

3.3 Sites and Regions

Approximately 60 sites in North America, the same sites participating in the SHP621-301 study, will participate in this extension study.

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 completed SHP621-301 induction study.
2. 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.
3. Subject is male or female aged 11-55 years, inclusive, at time of consent for the SHP621-301 study.
4. 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 0). There should be no change to these regimens during study participation.
5. 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 and for 30 days following the last dose of investigational product.
6. Subject is willing and has an understanding and ability to fully comply with study procedures including DSQ compliance 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 changes in medications that could affect the study or diet in the weeks since the final treatment evaluation visit (Visit 4) of the SHP621-301 study.
2. Subject using immunomodulatory therapy since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or anticipated use of immunomodulatory therapy during the treatment period (except for any ongoing regimen of allergy shots); 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 scheduled EGDs.
3. Subject using swallowed topical corticosteroid for EoE or systemic corticosteroid for any condition since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or anticipated 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 medical monitor prospectively but cannot occur within the 4 weeks of the scheduled EGDs.

4. Subject on inhaled or intranasal steroids and not on a stable dose in the 4 weeks before the screening EGD of this study.
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) since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or anticipated changes in the use of such medications during the treatment period.
6. Subject using Cytochrome P450 3A4 inhibitors (eg, ketoconazole, grapefruit juice) since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or anticipated use of such medications during the treatment period.
7. Subject has an appearance on screening 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 >9mm).
8. Subject is on a pure liquid diet or the six-food elimination diet.
9. Subject has presence of esophageal varices at the EGD at the final treatment evaluation visit (Visit 4) of the SHP621-301 study.
10. 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.
11. Subject has other diseases causing or associated with esophageal eosinophilia, including hypereosinophilic syndrome, collagen vascular disease, vasculitis, achalasia, or parasitic infection.
12. Subject has oropharyngeal or esophageal candidiasis that failed to respond to previous treatment. Diagnosis with oropharyngeal or esophageal candidiasis at or since the final treatment evaluation visit (Visit 4) of the SHP621-301 study is not an exclusion as long as the subject is expected to respond to treatment.
13. Subject has a potentially serious acute or chronic infection or immunodeficiency condition, including tuberculosis, fungal, bacterial, viral/parasite infection, ocular herpes simplex, or chicken pox/measles.
14. Subject has upper gastrointestinal bleeding identified in the EGD at the final treatment evaluation visit (Visit 4) of the SHP621-301 study or since the final treatment evaluation visit (Visit 4) of the SHP621-301 study.
15. Subject has evidence of active infection with *Helicobacter pylori*.
16. Subject has evidence of unstable asthma since the final treatment evaluation visit (Visit 4) of the SHP621-301 study.
17. Subject is female and pregnant or nursing.
18. Subject has a history of intolerance, hypersensitivity, or idiosyncratic reaction to budesonide (or any other corticosteroids), or to any other ingredients of the study medication.

19. Subject has a history or high risk of noncompliance with treatment or regular clinic visits.
20. Subject is on sucralfate or anticipates using sucralfate during the treatment period.

4.3 Restrictions

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

- No changes in medications or diet since the final treatment evaluation visit (Visit 4) of the SHP621-301 study.
- Temporary use (≤ 7 days) or initiation of new steroid treatment is permitted but cannot occur within the 4 weeks of the scheduled EGDs.
- 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 enrollment 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 EGD. Subjects who require a change in inhaled corticosteroid treatment for an asthma exacerbation should be discussed with the medical monitor.
- No change in use of PPIs, H2 antagonists, antacids, or leukotriene inhibitors for any condition (such as gastroesophageal reflux disease, asthma or allergic rhinitis).
- No use of cytochrome P450 3A4 (CYP450 3A4) inhibitors (eg, ketoconazole, grapefruit juice; see details in Section 5.2.2).
- No use of sucralfate during the study as this may interfere with the adherence of OBS.

4.4 Reproductive Potential

4.4.1 Female Contraception

All females must have a negative pregnancy test at the screening visit (Visit 0), randomization visit (Visit 1), and Visits 2-8. A serum pregnancy test will be performed at the screening visit (Visit 0) and final treatment evaluation (Visit 8). 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 1 of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy, or bilateral salpingectomy) and at least 6 weeks post sterilization, or
- Females of childbearing potential must 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 0), 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 1 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 8 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 (Schedule of Assessments, [Table 1-1](#)). 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 relapse and result in withdrawal of the subject from the study. Subjects with oropharyngeal or esophageal candidiasis that has failed to respond to treatment by the Week 12 EGD or upper GI bleeding at the Week 12 EGD will be withdrawn 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
- Study 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 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 (TA) Head. The PVRM TA 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 nonstudy treatment (including but not limited to herbal treatments, vitamins, behavioral treatment, and nonpharmacological treatment, such as psychotherapy, as appropriate) received at the screening visit (Visit 0) 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 at the screening visit (Visit 0). 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 in SHP621-302 (Visit 1) 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 scheduled EGDs) 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 (exception for seasonal allergic rhinitis; see Section 4.3)
2. PPIs
3. H2 antagonists
4. Antacids
5. Leukotriene inhibitors
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 since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or use within the 4 weeks of scheduled EGDs. Any temporary use (≤ 7 days) or initiation of new corticosteroid treatment during the study should be documented and discussed with the medical monitor prospectively. (Seasonal nasal corticosteroid use for seasonal allergic rhinitis is permitted; changes within 4 weeks of scheduled EGD should be avoided).
2. Swallowed topical corticosteroid for EoE or systemic corticosteroid for any condition since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or use within the 4 weeks of scheduled EGDs. Any temporary use (≤ 7 days) or initiation of new steroid treatment during the study should be documented and discussed with the medical monitor prospectively.
3. Initiation or change in dosing frequency to PPIs, H2 antagonists, antacids, or leukotriene inhibitors for any condition (such as gastroesophageal reflux disease, asthma, or allergic rhinitis) since the final treatment evaluation visit (Visit 4) of the SHP621-301 study, or anticipated use of such medications during the treatment period.
4. CYP450 3A4 inhibitors (eg, ketoconazole, grapefruit juice) since the final treatment evaluation visit (Visit 4) of the SHP621-301 study, or anticipated changes in the 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.
5. Sucralfate at screening or anticipated to be used 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 8 ounce amber glass, multidose bottles. 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 8 ounce amber glass, multidose bottles with child-resistant caps and refrigerated throughout the study (in the clinic and subject's home). Each bottle contains OBS 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 suspension will also be supplied in 8 ounce amber glass multidose bottles with child-resistant caps. Placebo consists of all components of the investigational product 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 for each subject will be administered in the clinic. The subject will continue with the evening dosing regimen at home.

Oral budesonide suspension and placebo will be supplied in amber glass bottles and must be shaken well prior to administration. OBS and placebo should be refrigerated at 2-8°C (36-46°F) 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.

During the 4-week screening period, blinded treatment response information (reduction in DSQ from baseline and eosinophilic count as determined by a central reader) collected during the SHP621-301 final treatment evaluation visit will be entered into the IWRS in a blinded manner. Once information is available in IWRS, subjects will return for the randomization visit (Visit 1) to be assigned to investigational product (OBS 2 mg twice daily or placebo). While only SHP621-301 OBS 2 mg twice daily responders will be randomized to continued OBS 2 mg twice daily or placebo, all subjects will be assigned to investigational product via IWRS to maintain double-blinding of subjects, investigators, the blinded monitoring team and the sponsor (ie, sham randomization).

At the randomization visit (Visit 1), the investigator or designee will access the IWRS to either document a screen failure or, if the subject has met all entry criteria, to randomize the subject. Sites will confirm 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 4-week screening period and a double-blind treatment period. The actual treatment given to individual subjects during the double-blind treatment period will be determined by the blinded treatment response information entered at the SHP621-301 final treatment evaluation visit.

Subjects will be randomized via a computer-generated randomization schedule at the randomization visit (Visit 1) following a 4-week screening period and confirmation of study eligibility. Subjects who fully responded to OBS treatment in the SHP621-301 study (≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ at the final treatment evaluation visit) will enter a randomized withdrawal period to receive either OBS 2 mg twice daily or placebo at a 1:1 ratio. Subjects who did not respond or partially responded to OBS treatment in the SHP621-301 study will receive OBS 2 mg twice daily. Subjects who were assigned to placebo in the SHP621-301 study will receive OBS 2 mg twice daily. Subjects, site staff, and study team members will remain blinded to treatment assignment and individual subject histology and individual subject DSQ data from the SHP621-301 study (post randomization) and until database lock occurs for this extension study.

Randomization of subjects in the randomized withdrawal period will also be stratified by age (adults and adolescents) to ensure approximately equal number of subjects within each age group are assigned to the treatment groups.

Subject numbers are assigned to all subjects as they consent to take part in the study. The subject number consists of the 3 digit study identifier, the 4 digit site identifier, and the 4 digit subject identifier. For the SHP621-302 study, the 3 digit site and 4 digit subject numbers will be the same as the SHP621-301 study.

The randomization number represents a unique number corresponding to investigational product allocated to the subject once eligibility has been determined at the randomization visit.

Individual subject treatment is automatically assigned by the IWRS.

6.2.3 Dosing

During the 4-week screening period, all subjects will receive 10 mL of blinded investigational product twice daily based on treatment assignment in SHP621-301. During the 36-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.

At Week 12, all subjects will undergo an upper esophagogastrroduodenoscopy (EGD) with biopsy to evaluate eosinophil counts. Upon receipt of blinded EGD and DSQ data, subjects on placebo in the randomized withdrawal period who have relapsed will have their treatment assignment changed to OBS 2 mg twice daily. The criteria for relapse is having an eosinophil count of ≥ 15 eos/HPF from at least 2 of 3 levels of the esophagus, as determined by a central reader, and having at least 4 days of dysphagia in the 2-week period prior to the scheduled visit, as determined by the DSQ. Considering the potential for missing diary entries, the determination of relapse based on days of dysphagia reported on the DSQ will occur as follows:

- If at least 4 days of dysphagia are reported on the DSQ in the 2-week period prior to the visit, the subject would meet the criterion for dysphagia symptom relapse.
- If less than 4 days of dysphagia are reported and at least 8 diary entries are recorded within the 2-week period, the subject would not meet the criterion for dysphagia symptom relapse.
- If less than 4 days of dysphagia are reported in the DSQ and fewer than 8 diary entries are recorded within the 2-week period, the subject would be designated as meeting the criterion for dysphagia symptom relapse due to missing diary data as described in Section 7.2.1.2.

The criteria for relapse align with the related inclusion criteria for participation in the SHP621-301 study. If both histology and dysphagia symptom relapse criteria are met, then the treatment assignment change will be performed in a blinded manner in IWRS at the subsequent study visit. If both criteria for relapse are not met, the subject will remain assigned to placebo.

If at any time the subject reports increased or worsening dysphagia symptoms to the investigator, the investigator may choose to perform an unscheduled EGD. If an unscheduled EGD is

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performed prior to Week 12, an EGD does not have to be repeated at Week 12. If a subject on placebo meets the criteria for relapse, the subject's treatment assignment will be changed in a blinded manner from placebo to OBS 2 mg twice daily at the subsequent study visit.

If the Week 12 or an unscheduled EGD reveals an eosinophil count of ≥ 15 from at least 2 of 3 levels of the esophagus yet relapse is not confirmed due to the criterion for dysphagia symptoms not being met, the subject will remain assigned to placebo. If the criterion for dysphagia symptoms is met at a subsequent visit and both criteria for relapse are then confirmed, the subject's treatment assignment will be changed to OBS 2 mg twice daily at the next scheduled visit.

Investigational product doses that are required to be administered at the clinic include the first dose of randomized investigational product (OBS or placebo) administered at the randomization visit (Visit 1) and all morning doses of investigational product administered at Visits 2-8. 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.

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 study 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. Bottles of OBS 0.2 mg/mL or placebo 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 Storages

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 refrigerated at 2-8°C (36-46°F), 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. Please refer to the Pharmacy Manual for additional details.

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 ([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 -4 to 0)

The screening period starts when subjects sign informed consent. The screening period will comprise up to 4 weeks, during which all procedures listed for the screening visit (Visit 0) 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 (Section [5.2.1](#)).

Assessments from the SHP621-301 final treatment evaluation visit (Visit 4) will be used as the screening assessments (Visit 0) of this treatment extension study. Screening assessments may take place across several days to allow an appropriate time frame in which to complete all procedures and confirm study eligibility. At the SHP621-301 final treatment evaluation visit, subjects will be dispensed blinded investigational product (based on treatment assignment in SHP621-301) that will last for up to 4 weeks prior to enrolling into this treatment extension study. The 4-week screening period is required to allow for blinded treatment response information (reduction in DSQ from baseline and eosinophilic count as determined by a central reader) collected during the SHP621-301 final treatment evaluation visit to be entered into the IWRS.

After the screening period, subjects who meet eligibility criteria at the end of the screening visit (Visit 0) will enter the 36-week double-blind treatment period. This 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 or randomized visits. Subjects cannot be rescreened once they have been designated as a screen failure.

7.1.1.1 Screening Visit (Visit 0)/Visit 4 of SHP621-301 Study

The screening visit (Visit 0) assessments and procedures, beginning with informed consent, will be performed as outlined in [Table 1-1](#).

The following procedures will be performed at the screening visit:

- Obtain subject consent (or assent as applicable for subjects <18 years).
- Review eligibility criteria.
- Review medical history.
- 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 current use of concomitant medications and procedures. 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.
- Dispense the DSQ electronic patient-reported outcome (ePRO) device for nightly completion and train the subject on its use.

The following procedures will be performed at the final treatment evaluation visit (Visit 4) of SHP621-301 and will be used as the screening assessments for this extension study:

- Review investigational product dosing compliance.
- Record vital signs (including blood pressure [systolic and diastolic], heart rate, respirations, and temperature), height (measured in triplicate for adolescents 11-17 years, inclusive), and weight (measured in duplicate for adolescents 11-17 years, inclusive). Perform stadiometry in adolescent subjects. Vital signs will be assessed after the subject has been in a supine position for at least 5 minutes immediately prior to the assessment.
- Clinical chemistry, hematology, and urinalysis laboratory tests will be performed on all subjects; 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 adrenocorticotrophic 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.

[REDACTED]

- Perform a physical examination on all subjects. Adolescents (subjects ≥ 11 years until the investigator confirms subject is post puberty) will also undergo Tanner Staging Assessment.

- **Serum** pregnancy test will be performed on all female subjects.
- Perform EGD and biopsy either at the investigative site or by a referring physician. Esophagogastroduodenoscopy should be completed at or within 7 days of the scheduled visit. Biopsy specimens must be available to be sent to the central pathology lab at least 2 weeks prior to Visit 1 to allow sufficient time for processing and central review and determination of eligibility.
- Perform dual-energy X-ray absorptiometry (DXA) scan for bone mineral density (BMD) and body composition measurements in subjects aged 11-17 years, inclusive. Baseline and post treatment DXA scans should be performed using the same machine and software.
- Dispense blinded investigational product (OBS or placebo; based on treatment assignment in SHP621-301) and review administration instructions. The subject will 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.

7.1.2 Double-blind Treatment Period (Visits 1-8): Weeks 0, 4, 8, 12, 16, 20, 28, and 36 (or Early Termination)

The double-blind treatment period will comprise 36 weeks, during which all assessments and procedures listed for Visits 1-8 in [Table 1-1](#) shall be completed.

During this period, a ± 3 -day visit window will be permitted between Visits 1-6 (Weeks 0-20) and a ± 6 -day visit window will be permitted between Visits 7-8 (Weeks 28-36), unless otherwise specified. Visit windows are calculated based upon the date of the randomization visit (Visit 1).

Once information for blinded treatment response is available, subjects will return for the randomization visit (Visit 1) to receive investigational product. Subjects who continue to meet all eligibility criteria and complete the 4-week screening period will have the opportunity to enroll in the treatment extension study. Subjects will receive either OBS twice daily (qAM, pc, and hs) or placebo twice daily (qAM, pc, and hs).

Subjects who fully responded to OBS treatment in the SHP621-301 study (≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ at the final treatment evaluation visit) will enter a randomized withdrawal period to receive either OBS 2 mg twice daily or placebo at a 1:1 ratio. Subjects who did not respond or partially responded to OBS treatment in the SHP621-301 study will receive OBS 2 mg twice daily. Subjects who were assigned to placebo in the SHP621-301 study will receive OBS 2 mg twice daily. 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 randomization visit (Visit 1) will be documented as screen failures in the IWRS and discontinue study drug.

A safety follow-up contact by phone will be performed 4 weeks following the last dose of study medication for all subjects (including subjects who fail screening, who discontinue early, or who complete the study).


7.1.2.1 Randomization Visit (Visit 1): Week 0

Subjects will return to the site for the randomization visit (Visit 1) to confirm eligibility. The randomization 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 (measured in duplicate in adolescents, 11-17 years, inclusive). Vital signs will be assessed after the subject has been in a supine position for at least 5 minutes immediately prior to the assessment.
- 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.

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

- Review investigational product dosing compliance.
- Review DSQ compliance; provide subject with instruction to continue completion of the DSQ nightly.
- 
- Perform a physical examination and assess any changes since screening.
- 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 **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.

7.1.2.2 Visits 2 and 3 (Weeks 4 and 8)

Subjects will return to the site for Visit 2 (Week 4) and Visit 3 (Week 8). 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 (measured in duplicate for adolescents, 11-17 years, inclusive). Vital signs will be assessed after the subject has been in a supine position for at least 5 minutes immediately prior to the assessment.
- 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.

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

- Review DSQ dysphagia episodes and compliance; provide subject with instruction to continue completion of the DSQ nightly.

■ [REDACTED]

- Perform a physical examination and assess any changes since screening.
- Readminister **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.

7.1.2.3 Visit 4 (Week 12)

Subjects will return to the site for Visit 4 (Week 12). 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 (measured in triplicate for adolescents 11-17 years, inclusive), and weight (measured in duplicate for adolescents 11-17 years, inclusive). Perform stadiometry in adolescent subjects. Vital signs will be assessed after the subject has been in a supine

position for at least 5 minutes immediately prior to the assessment.

- 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.
- Review DSQ dysphagia episodes and compliance; provide subject with instruction to continue completion of the DSQ nightly.

█ [REDACTED]

█ [REDACTED]

- Perform a physical examination and assess any changes since screening.
- Readminister **urine** pregnancy test for female subjects.
- Dispense investigational product (OBS or placebo) and review investigational product dosing compliance.
- Perform EGD and biopsy; EGD should be completed at or within 7 days of the scheduled visit. In addition, an earlier EGD may also occur if the subject exhibits signs of relapse (Section 6.2.3).

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

7.1.2.4 Visits 5, 6, and 7 (Weeks 16, 20, and 28)

Subjects will return to the site for Visits 5, 6, and 7 (Weeks 16, 20, and 28). 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 (measured in duplicate for adolescents 11-17 years, inclusive). Vital signs will be assessed after the subject has been in a supine position for at least 5 minutes immediately prior to the assessment.
- 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.

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

- Review DSQ dysphagia episodes and compliance; provide subject with instruction to continue completion of the DSQ nightly.

■ [REDACTED]

- Perform a physical examination and assess any changes since screening.
- Readminister **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.

7.1.2.5 Visit 8 (Week 36) or Early Termination

Subjects will return to the site for Visit 8 (Week 36). Assessments at this visit will be performed as outlined in [Table 1-1](#). If a subject discontinues prematurely, the assessments for Visit 8 are to be performed as completely as possible.

The following procedures should be performed first:

- Record vital signs (including blood pressure [systolic and diastolic], heart rate, respirations, and temperature), height (measured in triplicate for adolescents 11-17 years, inclusive), and weight (measured in duplicate for adolescents 11-17 years, inclusive). Perform stadiometry in adolescent subjects. Vital signs will be assessed after the subject has been in a supine position for at least 5 minutes immediately prior to the assessment.
- 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 current use of concomitant medications and procedures.
- Clinical chemistry, hematology, and urinalysis laboratory tests will be performed on all subjects; all subjects must fast overnight prior to collection. Any subject with an abnormal urinary or serum glucose level will be followed closely until resolution ([Section 7.2.2.5](#)).
- 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 adrenocorticotrophic 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. Any subject with an abnormal ACTH stimulation test will be followed closely until resolution (Section 7.2.2.5).

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

- Retrieve DSQ handset and review DSQ compliance.

■ [REDACTED]

■ [REDACTED]

- Perform a physical examination on all subjects. Adolescents (subjects ≥ 11 years until the investigator confirms subject is post puberty) will also undergo Tanner Staging Assessment. Any subject with clinical evidence of reduced height velocity and/or delayed Tanner staging will be followed closely until resolution (Section 7.2.2.2).
- **Serum** pregnancy test will be performed on all female subjects.
- Perform DXA scan for BMD and body composition measurements in subjects aged 11-17 years, inclusive. Dual-energy X-ray absorptiometry scans should be performed at this visit or within 7 days of the scheduled visit using the same machine and software as used in the SHP621-301 study.
- Perform EGD and biopsy; EGD should be completed at or within 7 days of the scheduled visit. An earlier EGD may occur if the subject exhibits signs of relapse (Section 6.2.3); however, the Week 36 EGD must be completed.
- Review investigational product dosing compliance.

7.1.3 Follow-up Period

The follow-up period for this protocol is 4 weeks from the last dose of investigational product. Subjects will receive a follow-up phone call at Visit 9 (Week 40) to query for SAEs, AEs, and concomitant treatments (Section 7.1.3.1).

7.1.3.1 Safety Follow-up Contact (Visit 9): Week 40

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.

7.2 Study Evaluations and Procedures

The full title and details about who completes the scales used in this study is included in Appendix 2.

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 any of the questions as this can 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](#).

The screening EGD with biopsies will be performed by a physician at the investigative site at the final treatment evaluation visit in the SHP621-301 study. Biopsy specimens must be taken and provided to the central pathology lab by at least 2 weeks prior to the planned Visit 1 to allow sufficient time for processing and central review and determination of eligibility. Subjects, site staff, and study team members will remain blinded to eosinophil counts and histopathologic findings by the central reader throughout the duration of the study.

At the Week 12 visit (Visit 4), and Week 36 visit (Visit 8) or at early termination (ET), an EGD with esophageal biopsies is required for all subjects. If at any time, the subject reports increased or worsening dysphagia symptoms to the investigator, the investigator may choose to perform an unscheduled EGD. If an unscheduled EGD is performed prior to Week 12, an EGD does not have to be repeated at Week 12. If an unscheduled EGD is performed between Week 12 and Week 36, the Week 36 EGD should still be performed. 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), midesophagus (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. Eosinophil counts and, histopathologic features will be evaluated by the central reader 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. At the investigator's discretion, biopsies will be taken from the stomach and duodenum 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 1 vial; biopsies from the duodenum should be submitted in a separate vial to the central pathology laboratory for processing of tissue into slides.

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 during the screening period and during the 36-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. 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.

To meet relapse criteria, the subject must have at least 4 days of dysphagia as determined by the DSQ in the 2-week period prior to the scheduled visit in addition to meeting the eosinophil histology criterion (≥ 15 eos/HPF from at least 2 of 3 levels of the esophagus). Considering the potential for missing diary entries, the determination of relapse based on days of dysphagia reported on the DSQ will occur as follows:

- If at least 4 days of dysphagia are reported on the DSQ in the 2-week period prior to the visit, the subject would meet the criterion for dysphagia symptom relapse.
- If less than 4 days of dysphagia are reported and at least 8 diary entries are recorded within the 2-week period, the subject would not meet the criterion for dysphagia symptom relapse.
- If less than 4 days of dysphagia are reported and less than 8 diary entries are recorded within the 2-week period, the subject would be designated as meeting the criterion for dysphagia symptom relapse due to missing diary data.

Calculations will be performed on daily ePRO entries during a 2-week interval prior to each study visit during the treatment period. The DSQ score for the coprimary 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:

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

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.

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

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

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

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 new clinically or medically relevant information which arose after the recording of the medical history in the antecedent study. New medical history will be collected at the screening visit (Visit 0) of this study. Medical history will be classified as EoE or non-EoE by the investigator. Adverse events recorded during the SHP621-301 study may be added as medical history at the investigator's discretion.

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 0) will be documented in the subject's source documents and on the medical history CRF. Changes after the screening visit (Visit 0) 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 0) will also include Tanner Staging Assessments for subjects <18 years of age.

Height will be collected at the screening visit (Visit 0) and Visit 8 for all subjects and at Visit 4 for adolescents (11-17 years, inclusive) only. Stadiometers will be used to measure height for subjects aged 11-17 years, inclusive. Statural height will be measured by trained site staff using a stabilized stadiometer. Height will be measured in triplicate in adolescents (11-17 years, inclusive) and recorded in the CRF. 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 each measurement. All measurements should be recorded to the nearest 10th of a centimeter (1 mm). Please refer to the study manual for additional details.

Weight will be measured in duplicate in adolescents (11-17 years, inclusive) and recorded in the CRF.

All subjects with clinical evidence of reduced height velocity and/or delayed Tanner Staging, as determined by the investigator, must be followed closely until resolution (ie, resumption of normal for age height velocity, or the resumption of Tanner Stage development). Subjects who discontinue from the treatment period at any time and have clinical evidence of reduced height velocity and/or delayed Tanner Stage development at the early termination visit will be monitored beyond the end of the study until resolution is established.

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) Any AE that is ongoing from the SHP621-301 study must be recorded on the CRF for this study.

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 in 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

Adrenocorticotrophic hormone 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. Administration of ACTH stimulation testing and sample collection should follow the same procedures used in the SHP621-301 study.

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. Subjects who discontinue from the treatment period at any time and have an abnormal ACTH stimulation test at the early termination visit will be scheduled for repeat ACTH testing approximately 6 weeks post last dose of investigational product and followed to resolution of the abnormality. 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 0) and the final treatment evaluation visit (Visit 8) or ET visit. A urine pregnancy test is performed on all female subjects at all other visits 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 measurements will be performed in subjects aged 11-17 years, inclusive, as outlined in [Table 1-1](#).

The sites for DXA measurement will be the lumbar spine (L1-L4 preferred) and total body less head (Bachrach 2011; Gordon et al. 2008; International Society for Clinical Densitometry 2013). Dual-energy X-ray absorptiometry body composition measurements will also be collected. 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

[illegible]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

7.2.4 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)
Safety	Biochemistry and β -hCG ^a	6	9	54
	ACTH	2	4	8
	Cortisol	2	9	18
	Hematology	2	9	18
Total mL		-	-	98

Abbreviations: ACTH=adrenocorticotrophic hormone; β -hCG=beta-human chorionic gonadotropin^a β -hCG testing is for females only.

During this study, it is expected that approximately 98 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 98 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 7.1.3. This includes events occurring during the screening period 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.

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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 dechallenge. 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 reexposure 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 period, 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 7.1.3.

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 nonmedical 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 prespecified 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 parents/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 (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 7.1.3 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, unless another investigational product action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as “dose not changed” or “not applicable” (if the subject never received investigational product). The investigational product action of “withdrawn” should not be selected solely as a result of the subject’s death.

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 9.3 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.

The SAP 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

No interim analysis is planned.

9.6 Sample Size Calculation and Power Considerations

Approximately 200 subjects (88%) who are randomized in the SHP621-301 study are estimated to complete the SHP621-301 study and enroll in this treatment extension study based on enrollment observed in the Phase 2 study (MPI 101-06).

The primary efficacy measure of the study will be the proportion of subjects who relapse during the double-blind randomized withdrawal period, defined as having an eosinophil count of ≥ 15 eos/HPF from at least 2 of 3 levels of the esophagus (as determined by a central reader) and at least 4 days of dysphagia in the 2-week period prior to the scheduled visit (as determined by the DSQ). To be considered as a subject with relapse, both criteria must be met. To determine whether a subject meets the criterion for dysphagia, refer to Section 7.2.1.2.

Based on observation in the Phase 2 study (MPI 101-06), approximately 26% of subjects, or approximately 40 subjects, who were assigned to OBS treatment in the SHP621-301 study are anticipated to respond fully after 12 weeks in the SHP621-301 study. For this study, to detect a 50 percentage point difference between relapse proportions of 20% and 70% in the OBS and placebo groups, respectively, at more than 80% power and a significance level of 0.05 (2-sided) using the Fisher's Exact test with equal allocation to treatment groups, it is necessary to assess the primary efficacy measure for approximately 38 subjects (19 subjects in each of the OBS and placebo groups).

9.7 Study Population

The **safety set** will include all subjects who are randomized and receive at least 1 dose of 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 investigational product and had 1 post baseline efficacy assessment (biopsy and/or DSQ score).

The **per-protocol (PP)** set will include all subjects in the FAS excluding subjects with major protocol deviations. 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.

9.8 Efficacy Analyses

9.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint for each subject is relapse during the double-blind randomized withdrawal period. Relapse, a binary response (either with a relapse or not), is defined as having an eosinophil count of ≥ 15 eos/HPF from at least 2 of 3 levels of the esophagus, as determined by a central reader, and having at least 4 days of dysphagia in the 2-week period prior to the scheduled visit, as determined by the DSQ (refer to Section 7.2.1.2 for additional details).

The primary efficacy endpoint will be analyzed as the proportion of subjects with relapse during the double-blind randomized withdrawal period for the FAS, using a Fisher's Exact test comparing OBS 2 mg twice daily against placebo. The primary test of treatment effect will be 2-sided, and conducted at the significance level of 0.05. The proportion of subjects with relapse for each treatment group and the corresponding 95% confidence interval (CI) will be estimated. In addition, the difference in the proportion of subjects with relapse between the 2 treatment groups and its 95% CI will be estimated.

Subjects who withdraw without providing efficacy data at the ET visit will be classified as being relapsers in the primary efficacy analysis. The null hypothesis states that there is no difference in relapse proportions between OBS 2 mg twice daily and placebo, with the 2-sided alternative of a nonzero difference between groups. Relapse proportions at each adjacent double-blind visit interval will also be assessed by applying the Fisher's Exact test to the observed data at each double-blind visit.

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

Similar analyses used for the ITT population will be repeated using the FAS and the PP datasets. Sensitivity analyses will be performed using the ITT population by classifying subjects who withdraw without providing efficacy data at the ET visit as non-relapsers. Sensitivity analyses will be performed using the ITT population by classifying subjects who met the histology relapse criterion and met the dysphagia symptom relapse criterion due to missing diary data as non-relapsers. In addition, the subjects who were prematurely withdrawn from the study without the primary efficacy endpoint will be imputed randomly according to the distribution of relapsers with available data; and the similar statistical test will be performed using the imputed data.

9.8.2 Secondary Efficacy Endpoints

9.8.2.1 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is the long-term treatment response, a binary response over an extended period of 36 weeks in adolescent and adult subjects who were randomized to OBS treatment but did not respond after 12 weeks in the SHP621-301 induction study (subject did not have peak count of ≤ 6 eos/HPF across all available esophageal levels at the final treatment visit and/or $\geq 30\%$ reduction in DSQ score from baseline) and met the following criteria:

- Histologic response, defined as a peak eosinophil count of ≤ 6 eos/HPF across all available

esophageal levels at the final treatment period evaluation (Visit 8)

- Dysphagia symptom response, defined as $\geq 30\%$ reduction in the DSQ combined score (questions 2+3) from baseline of the SHP621-301 study and from baseline of this extension study to the final treatment period evaluation (Visit 8)

The key secondary efficacy endpoint will be analyzed as the proportion of subjects who responded based on the histological data and the DSQ data at the final treatment period evaluation (Visit 8). The proportion of subjects with long-term treatment response and the corresponding 95% confidence interval (CI) will be estimated and summarized.

The following secondary efficacy endpoints will be analyzed in all subjects:

- Histologic response, defined as a peak eosinophil count of ≤ 6 eos/HPF across all available esophageal levels at each assessment visit
- Dysphagia symptom response, defined as $\geq 30\%$ reduction in the DSQ combined score (questions 2+3) at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Change in the DSQ score and change in the peak eosinophilic count at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Change in total endoscopy score, as measured by the EREFS classification, at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Peak eosinophil count < 15 eos/HPF across all available esophagus levels at each assessment visit
- Peak eosinophil count ≤ 1 eos/HPF across all available esophagus levels at each assessment visit
- Change in the peak eosinophil count at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study at each assessment visit for each available esophageal level (proximal, mid-, and distal)
- Change in the histopathologic epithelial features combined total score (grade and stage) at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Dysphagia symptom response (binary response), defined as a $\geq 50\%$ reduction in the DSQ combined score (questions 2+3), at each assessments visit from baseline of the SHP621-301 study and from baseline of this extension study
- Change in the DSQ combined score (questions 2+3) at each assessment from baseline of the SHP621-301 study and from baseline of this extension study
- Cumulative distribution function curves for the change and the percent change in the DSQ score at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Overall binary response I, defined as a reduction in the DSQ score of $\geq 30\%$ and a peak

eosinophil count of ≤ 6 eos/HPF across all esophageal levels at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study

- Overall binary response II, defined as a reduction in the DSQ score of $\geq 50\%$ and a peak eosinophil count of ≤ 6 eos/HPF across all esophageal levels at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Change in the DSQ + pain score (question 2+3+4) at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study
- Change in the DSQ pain score (question 4) at each assessment visit from baseline of the SHP621-301 study and from baseline of this extension study

Summary statistics of the DSQ score (questions 2+3) and the peak eosinophil count and the change from baseline of the SHP621-301 study and from baseline of this extension study at the final treatment period evaluation (Visit 8) will be summarized by each assessment visit.

To evaluate the response to OBS treatment over 36 weeks for subjects who were on placebo in the SHP621-301 induction study, the proportion of subjects who responded based on the histological data and the DSQ data at the final treatment period evaluation (Visit 8) and the corresponding 95% CI will be summarized. Summary statistics of the DSQ score (questions 2+3) and the peak eosinophil count and the change from baseline of the SHP621-301 study and from baseline of this extension study at the final treatment period evaluation (Visit 8) will be summarized by each assessment visit.

For subjects who relapse on placebo during the randomized withdrawal and who reinitiate treatment with OBS 2 mg twice daily (intermittent therapy), separate descriptive analyses for histological data and DSQ endpoints will be conducted at each assessment visit. Changes will be summarized over time from baseline of the SHP621-301 study and from the time of relapse. The same criteria for response will be applied to these subjects (≤ 6 eos/HPF across all available esophageal levels and at least a 30% reduction in DSQ from SHP621-301 baseline score).

Summary statistics will be provided for all other secondary endpoints.

9.8.3 Exploratory Efficacy Endpoints

The exploratory endpoints that will be explored are 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 randomization visit (Visit 1), or at the screening visit (Visit 0) if not collected at Visit 1, will be used as the baseline value for safety analyses.

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TEAEs are defined as AEs that start or deteriorate on or after 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.

AEs will be coded using MedDRA. The number of events, incidence, and percentage of TEAEs will be calculated overall by system organ class, preferred term, 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 ([Bone Mineral Density in Childhood Study 2015](#)). Safety parameters will be descriptively summarized by treatment group at baseline and for each post baseline visit.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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 nonpediatric 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 subinvestigators 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.

The data from the central pathologist will be recorded directly onto paper CRF.

All other data will have separate source documentation; no data will be recorded directly onto the CRF. The following data collected for assessments and procedures performed at the SHP621-301 final treatment evaluation visit (Visit 4) will not be recollected in the SHP621-302 database as follows (Section 7.1.1.1):

- Vital signs, height, and weight assessment
- EGD with endoscopy score (EREFS) and biopsy
- DSO compliance assessment

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- Physical examination
- Tanner Staging Assessment
- Clinical laboratory tests
- Urinalysis
- Pregnancy test
- Morning cortisol
- ACTH Stimulation Testing

- DXA Scan (subjects 11 to 17 years of age)

All other 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 parents/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 noncommercial 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.

11. REFERENCES

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12. APPENDIX

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Appendix 1 Protocol History

Document	Date	Global/Country/Site Specific
Protocol Amendment 2	19 Dec 2016	Global
Protocol Amendment 1	22 Jun 2016	Global
Original Protocol	05 Dec 2015	Global

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	Amendment Date 22 June 2016	Global Amendment
Description of Change		Section(s) Affected by Change
<p>Changed from: [REDACTED]</p> <p>To: [REDACTED]</p>		Emergency Contact Information Page
<p>A 4-week screening period is required to allow for blinded treatment response information (reduction in DSQ from baseline and eosinophilic count as determined by a central reader) collected during the SHP621-301 final treatment evaluation visit to be entered into the interactive web-based response system (IWRS) by. Only the unblinded data team who is independent from the blinded study team and not involved with the day-to-day conduct of the study will have restricted access to blinded treatment response information.</p> <p>Rationale: This text has been clarified to emphasize that access to blinded treatment response information will be restricted to the unblinded data team. Blinded treatment response data will not be accessed by the study team; therefore, the double-blind will be maintained.</p>		Synopsis: Investigational product, dose, and mode of administration; Synopsis Methodology; Section 3.1: Study Design and Flow Chart
<p>At least 8 daily diary entries must be completed over 14 consecutive days in order to determine the criterion for DSQ relapse. Considering the potential for missing diary entries, the determination of relapse based on days of dysphagia reported on the DSQ will occur as follows:</p> <ul style="list-style-type: none"> • If at least 4 days of dysphagia are reported on the DSQ in order the 2-week period prior to the visit, the subject would meet the criterion for dysphagia symptom relapse. If fewer • If less than 4 days of dysphagia are reported and at least 8 diary entries are recorded within the 2-week period, the subject would not meet criterion for dysphagia symptom relapse. • If less than 4 days of dysphagia are reported in the DSQ and less fewer than 8 diary entries are reported recorded within the 2-week period, then the 2-week period will be shifted backwards from the scheduled visit, 1 day at a time, to include the most recent 2-week period with at least 8 diary entries confirm if the most recent 2-week period with at least 8 diary entries subject meets the criteria for dysphagia symptom relapse over 14 consecutive days; however, the 2-week period will not be shifted further if at least 8 diary entries are recorded in the 14-day period and will not be shifted by more than 2 weeks in total (ie, no more than 2-week period plus additional 2-week additional expansion). <p>The criteria for relapse align with the related inclusion criteria for participation in the SHP621-301 study. If both histology and dysphagia symptom relapse criteria are met, then the treatment assignment change will be performed in a blinded manner in IWRS at the subsequent study visit by the independent unblinded data team.</p> <p>Rationale: Additional text is provided to clarify the evaluation of dysphagia</p>		Synopsis: Investigational product, dose, and mode of administration; Section 6.2.3: Dosing; Section 7.2.1.2: Dysphagia Symptom Questionnaire

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	Amendment Date 22 June 2016	Global Amendment
Description of Change		Section(s) Affected by Change
symptoms for determination of relapse based on days of dysphagia reported on the DSQ prior to study visits with the potential for missing diary entries.		
<p>The independent, unblinded data team will review the blinded EGD and DSQ data to confirm the If a subject is on placebo in the randomized withdrawal period, determine if the subject meets relapse-the criteria, and change for relapse, the subject's treatment assignment will be changed in a blinded manner from placebo to OBS 2 mg twice daily if relapse is confirmed at the subsequent study visit.</p>		<p>Synopsis: Investigational product, dose, and mode of administration</p> <p>Synopsis: Methodology; Section 6.2.3: Dosing</p>
6. Subject is willing and has an understanding and ability to fully comply with study procedures including DSQ compliance (completed the DSQ on $\geq 70\%$ of days in any 2 consecutive weeks of the screening period) and restrictions defined in this protocol.		Synopsis: Inclusion Criteria; Section 4.1: Inclusion Criteria
5. Subject has initiated, discontinued, or changed dosage regimen of proton pump inhibitors (PPIs), H2 antagonists, antacids, antihistamines , or leukotriene inhibitors for any condition (such as gastroesophageal reflux disease, asthma or allergic rhinitis) since the final treatment evaluation visit (Visit 4) of the SHP621-301 study or anticipated changes in the use of such medications during the treatment period.		Synopsis: Exclusion Criteria; Section 4.2: Exclusion Criteria
12. Subject has oropharyngeal or esophageal candidiasis that failed to respond to previous treatment. Diagnosis with oropharyngeal or esophageal candidiasis at or since the final treatment evaluation visit (Visit 4) of the SHP621-301 study is not an exclusion as long as the subject received is treatment for candidiasis and is expected to respond to treatment.		Synopsis: Exclusion Criteria; Section 4.2: Exclusion Criteria
13. Subject has a potentially serious acute or chronic infection or immunodeficiency condition, including tuberculosis, fungal, bacterial, viral/parasite infection, ocular herpes simplex, or chicken pox/measles.		Synopsis: Exclusion Criteria; Section 4.2: Exclusion Criteria
<p>The primary efficacy endpoint will be analyzed as the proportion of subjects with relapse during the end of the double-blind randomized withdrawal period for the FAS, using Fisher's Exact a chi-square test comparing OBS 2 mg twice daily against placebo.</p> <p>Relapse proportions at each adjacent double-blind visit interval will also be assessed by applying the Fisher's Exact chi-square test to the observed data at each double-blind visit.</p> <p>Rationale: The primary efficacy analysis method has been changed from the Chi-square test to Fisher's exact test. Considering the expected number of subjects in the randomized withdrawal portion of the study, and the very small number of subjects who are expected to relapse in the OBS group, the Fisher's exact test is considered a more appropriate method.</p>		<p>Synopsis: Statistical Methodology for Primary Efficacy Endpoint</p> <p>Section 9.8.1: Primary Efficacy Endpoint</p>
For this study, to detect a 50 percentage point difference between relapse proportions of 20% and 70% in the OBS and placebo groups, respectively, at more than 80% power and a significance level of 0.05 (2-sided) using the Fisher's Exact a Chi-Square test with equal allocation to treatment groups, it is necessary to assess the primary efficacy measure for approximately 38		<p>Synopsis: Sample Size Justification;</p> <p>Section 9.6: Sample Size Calculation and Power</p>

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	Amendment Date 22 June 2016	Global Amendment
Description of Change		Section(s) Affected by Change
subjects (19 subjects in each of the OBS and placebo groups)		Considerations
c Height to be collected at screening (Visit 0) and Visit 8 only. Stadiometers will be used to measure height for all subjects aged 11-17 years, inclusive. Height to be collected at Visit 4 for adolescents only (11-17 years, inclusive). Height measurements for adolescents should be measured in triplicate using stadiometers. will be used to measure height for subjects aged 11-17 years, inclusive.		Table 1-1, Footnote c; Section 7.1.2.3: Visit 4 (Week 12)
d Weight measurements for adolescents (11-17 years, inclusive) should be measured in duplicate.		Table 1-1, Footnote d
The treatment assignment change will be performed in a blinded manner in IWRS at the subsequent study visit by the independent unblinded data team.		Section 3.1: Study Design and Flow Chart
<ul style="list-style-type: none"> No change in use of PPIs, H2 antagonists, antacids, antihistamines, or leukotriene inhibitors for any condition (such as gastroesophageal reflux disease, asthma or allergic rhinitis). 		Section 4.3: Restrictions
<ul style="list-style-type: none"> Acceptable methods of contraception are: <ul style="list-style-type: none"> Surgically sterile male partner 		Section 4.4.1: Female Contraception
<p>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 worsening signs and symptoms of EoE (eg, weight loss or increased dysphagia), would be considered a relapse and result in withdrawal of the subject from the study.</p> <p>Rationale: The terms "worsening signs and symptoms of EoE" have been more clearly defined as "severe signs and symptoms of EoE" to prevent subjects with only minor to moderate symptoms being withdrawn from the study.</p>		Section 4.5.1: Subject Withdrawal Criteria
<p>Antihistamines</p> <p>Rationale: Antihistamines were removed from the list of permitted medications that require consultation with the medical monitor prior to initiating changes in the dosing regimen. Antihistamine use, including any changes to the dosing regimen, is permitted during the course of the study.</p>		Section 5.2.1: Permitted Treatment
3. Initiation or change in dosing frequency to PPIs, H2 antagonists, antacids, antihistamines , or leukotriene inhibitors for any condition...		Section 5.2.2: Prohibited Treatment
<p>During the 4-week screening period, blinded treatment response information (reduction in DSQ from baseline and eosinophilic count as determined by a central reader) collected during the SHP621-301 final treatment evaluation visit will be entered into the IWRS by an independent, unblinded data team in a blinded manner in a blinded manner. Details on the unblinded data team will be provided in a separate charter. Once information is available in IWRS, subjects will return...</p> <p>Sites will enter confirm eligibility criteria information prior to randomization</p>		Section 6.2.1: Interactive Response Technology for Investigational Product Management

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	Amendment Date 22 June 2016	Global Amendment
Description of Change		Section(s) Affected by Change
The 4-week screening period is required to allow for blinded treatment response information (reduction in DSQ from baseline and eosinophilic count as determined by a central reader) collected during the SHP621-301 final treatment evaluation visit to be entered into the IWRS by the independent, unblinded, data team.		Section 7.1.1: Screening Period (Weeks -4 to 0)
<ul style="list-style-type: none"> Record vital signs (including blood pressure [systolic and diastolic], heart rate, respirations, and temperature), height (measured in triplicate for adolescents 11-17 years, inclusive), and weight (measured in duplicate for adolescents 11-17 years, inclusive). Perform stadiometry in adolescent subjects. aged 11-17 years, inclusive. 		Section 7.1.1.1: Screening Visit (Visit 0)/Visit 4 of SHP621-301 Study; Section 7.1.2.3: Visit 4 (Week 12); Section 7.1.2.5: Visit 8 (Week 36) or Early Termination
<ul style="list-style-type: none"> Record vital signs (including blood pressure [systolic and diastolic], heart rate, respirations, and temperature) and weight (measured in duplicate for adolescents 11-17 years, inclusive). 		Section 7.1.2.1: Randomization Visit (Visit 1)/Week 0; Section 7.1.2.2: Visits 2 and 3 (Weeks 4 and 8); Section 7.1.2.4: Visits 5, 6, and 7 (Weeks 16, 20, and 28)
Any subject with clinical evidence of reduced height velocity and/or delayed Tanner staging will be followed closely until resolution (Section 7.2.2.2).		Section 7.1.2.5: Visit 8 (Week 36) or Early Termination
The independent unblinded data team will receive data from the central reader and will use it to confirm whether the subject meets the eligibility criteria for this study.		Section 7.2.1.1: Esophagogastroduodenoscopy with Esophageal Biopsy and Histopathologic Evaluation

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	Amendment Date 22 June 2016	Global Amendment
Description of Change		Section(s) Affected by Change
<p>Height will be collected at the screening visit (Visit 0) and Visit 8 for all subjects, and at Visit 4 for adolescents (11-17 years, inclusive) only.</p> <p>Height will be measured in triplicate in adolescents (11-17 years, inclusive) and recorded in the CRF.</p> <p>Weight will be measured in duplicate in adolescents (11-17 years, inclusive) and recorded in the CRF.</p> <p>All subjects with clinical evidence of reduced height velocity and/or delayed Tanner Staging, as determined by the investigator, must be followed closely until resolution (ie, resumption of normal for age height velocity, or the resumption of Tanner Stage development). Subjects who discontinue from the treatment period at any time and have clinical evidence of reduced height velocity and/or delayed Tanner Stage development at the early termination visit will be monitored beyond the end of the study until resolution is established.</p> <p>Rationale: This text was added to ensure that any subjects demonstrating laboratory or clinical findings suggestive of adverse HPA effect will be appropriately monitored until resolution.</p>		Section 7.2.2.2: Physical Examination (Including Height and Weight)
<p>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 ACTH testing approximately 6 weeks post last dose of investigational product to ensure that ACTH levels have normalized and followed to resolution of the abnormality.</p>		Section 7.2.2.5: Clinical Laboratory Evaluations
<p>To determine whether a subject meets the criterion for dysphagia, refer to at least 8 daily diary entries must be completed over 14 consecutive days, as described in Section 7.2.1.2.</p>		Section 9.6: Sample Size Calculation and Power Considerations Section 9.8.1: Primary Efficacy Endpoint

Appendix 2 Scales and Assessments

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

Full Title of Scale/Assessment	Completed By
DSQ	Subject
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
Tanner Staging Assessment	Site
EREFS	Site

Abbreviations: DSQ=Dysphagia Symptom Questionnaire; [REDACTED]
[REDACTED] EREFS=EoE Endoscopic Reference Score; [REDACTED]
[REDACTED]

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

Daily Diary

This daily diary includes questions about your eosinophilic esophagitis (EoE). We are interested in any trouble you had today swallowing foods such as meat, rice, fruit, bread, etc.

Daily Diary

Please complete this questionnaire after you have had your last meal of the day.

Daily Diary

Read each question on the following screens and answer by selecting the box that best describes your experience. There are no right or wrong answers to any of the questions.

Question 1

Since you woke up this morning, did you eat solid food?

☐ Yes

☐ No

Question 2

Since you woke up this morning, has food gone down slowly or been stuck in your throat or chest?

☐ Yes

☐ No

Question 3

For the most difficult time you had swallowing food today, did you have to do anything to make the food go down or to get relief?

☐ No, it got better or cleared up on its own

☐ Yes, I had to drink liquid to get relief

☐ Yes, I had to cough and/or gag to get relief

☐ Yes, I had to vomit to get relief

☐ Yes, I had to seek medical attention to get relief

Question 4

The following question concerns the amount of pain you have experienced when swallowing food: What was the worst pain you had while swallowing food today?

☐ None, I had no pain.

☐ Mild

☐ Moderate

☐ Severe

☐ Very Severe

The diagram shows a horizontal beam supported by a single vertical post in the center. On the left side of the beam, there is a single rectangular block. On the right side, there is a stack of five rectangular blocks, with the top block being the smallest and the bottom block being the largest, creating a stepped appearance.

MEMORANDUM

To: SHP621-302 Investigators and Study Coordinators
From: [REDACTED], MD, [REDACTED]
Date: 20 February 2019
Re: SHP621-302 Protocol Amendment 2 - Administrative Change

This memorandum provides an administrative change made to SHP621-302 Protocol Amendment 2 (dated 19 December 2016).

Rationale for changes:

- To provide clarification on recording of adverse events (AEs) in the clinical database
- To provide clarifications on statistical methods for the final analysis
- To provide the accurate text of the Dysphagia Symptom Questionnaire (DSQ)

Protocol Section	Protocol Amendment 2 Text	Clarification
7.1.1.1 Screening Visit (Visit 0)/Visit 4 of SHP621-301 Study	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.	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.
7.2.2.3 Adverse Event Collection	AEs are collected from the time informed consent is signed.	AEs are collected from the time the informed consent is signed <u>first dose of investigational product (Visit 1).</u>
8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events	All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 7.1.3. This includes events occurring during the screening period of the study, regardless of whether or not investigational product is administered.	All AEs are collected from the time the informed consent is signed <u>first dose of investigational product (Visit 1)</u> until the defined follow-up period stated in Section 7.1.3. This includes events occurring during the screening period of the study; regardless of whether or not investigational product is administered <u>if they are ongoing at the time of Visit 1. Any AE that occurs and resolves prior to Visit 1 will be recorded in the SHP621-301 clinical database.</u>
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 7.1.3.	All pregnancies are to be reported from the time the informed consent is signed <u>first dose of investigational product (Visit 1)</u> until the defined follow-up period stated in Section 7.1.3.
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 7.1.3 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.	All SAEs (regardless of relationship to study) are collected from the time the informed consent is signed <u>first dose of investigational product (Visit 1)</u> until the defined follow-up period stated in Section 7.1.3 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.

MEMORANDUM

Protocol Section	Protocol Amendment 2 Text	Clarification
8.2.5 Serious Adverse Event Onset and Resolution Dates	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.	In addition, any signs or symptoms experienced by the subject after signing the informed consent form <u>the first dose of investigational product (Visit 1)</u> , 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.
9.7 Study Population	<p>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.</p> <p>The full analysis set (FAS) will include all randomized subjects who received at least 1 dose of investigational product and had 1 post baseline efficacy assessment (biopsy and/or DSQ score).</p>	<p>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.</p> <p>The full analysis set (FAS) will include all randomized subjects who received at least 1 dose of investigational product and had 1 post baseline efficacy assessment (biopsy and/or DSQ score).</p>
9.8.1 Primary Efficacy Endpoints	Similar analyses used for the ITT population will be repeated using the FAS and the PP datasets. Sensitivity analyses will be performed using the ITT population by classifying subjects who withdraw without providing efficacy data at the ET visit as non-relapsers. Sensitivity analyses will be performed using the ITT population by classifying subjects who met the histology relapse criterion and met the dysphagia symptom relapse criterion due to missing diary data as nonrelapsers.	Similar analyses used for the ITT <u>FAS</u> population will be repeated using the FAS <u>and the PP</u> datasets. Sensitivity analyses will be performed using the ITT <u>FAS</u> population by classifying subjects who withdraw without providing efficacy data at the ET visit as non-relapsers. Sensitivity analyses will be performed using the ITT <u>FAS</u> population by classifying subjects who met the histology relapse criterion and met the dysphagia symptom relapse criterion due to missing diary data as non-relapsers.
9.9 Safety Analyses	TEAEs are defined as AEs that start or deteriorate on or after the first dose of investigational product and no later than 3 days following the last dose of investigational product.	TEAEs are defined as AEs that start or deteriorate on or after the first dose of investigational product <u>(Visit 1)</u> and no later than 3 days following <u>through the Safety Follow-up Contact, or 31 days after the last dose of investigational product for subjects who do not have a Safety Follow-up Contact.</u>
Appendix 3 Dysphagia Symptom Questionnaire ePRO for EoE	<p>Question 2</p> <p>Since you woke up this morning, has food done down slowly or been stuck in your throat or chest?</p>	<p>Question 2</p> <p>Since you woke up this morning, has food done down slowly or been stuck in your throat or chest?</p>

The above administrative changes do not impact the overall study design or study conduct. These changes will be documented in a forthcoming protocol amendment should the need arise. In the meantime, please submit this memo to your IRB notifying them of these changes, if appropriate per local requirements, and please file this memo in your study file records.

MEMORANDUM

If you have further questions, please do not hesitate to contact your PPD Clinical Research Associate, the PPD Remote Site Monitor, or Shire directly.

Sincerely,

[Redacted Signature]

[Redacted Name], MD
[Redacted Title]

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MEMORANDUM

To: SHP621-302 Investigators and Study Coordinators
From: [REDACTED], MD, [REDACTED]
Date: 9 December 2019
Re: SHP621-302 Protocol Amendment 2 - Administrative Change

This memorandum serves to provide administrative changes made to SHP621-301 Protocol Amendment 2 (dated 19 Dec 2016) that do not impact the overall study design, safety, or study conduct and in accordance with Takeda procedures.

Rationale for changes:

- To update technical aspects of the statistical testing method for the primary endpoint
- To describe the fixed sequence procedure for hierarchy testing of certain secondary endpoints
- To provide clarification on the intent of the key secondary endpoint
- To include additional exploratory endpoints

Protocol Section	Protocol Amendment 2 Text	Clarification
9.6 Sample Size Calculation and Power Considerations	For this study, to detect a 50 percentage point difference between relapse proportions of 20% and 70% in the OBS and placebo groups, respectively, at more than 80% power and a significance level of 0.05 (2-sided) using the Fisher's Exact test with equal allocation to treatment groups, it is necessary to assess the primary efficacy measure for approximately 38 subjects (19 subjects in each of the OBS and placebo groups).	<p>For this study, to detect a 50 percentage point difference between relapse proportions of 20% and 70% in the OBS and placebo groups, respectively, at more than 80% power and a significance level of 0.05 (2-sided) <u>0.025 (1-sided)</u> using the Fisher's Exact test with equal allocation to treatment groups, it is necessary to assess the primary efficacy measure for approximately 38 subjects (19 subjects in each of the OBS and placebo groups).</p> <p><u>Hierarchical testing with fixed sequence procedure will be used to control the Type I error for the multiple endpoints tested at one-sided $\alpha = 0.025$. For a test to be considered statistically significant within the testing hierarchy, it must be statistically significant at the one-sided 0.025 level, and all previous tests within the testing hierarchy must be statistically significant at the one-sided 0.025 level. The fixed sequence of testing hierarchy is as follows:</u></p> <ol style="list-style-type: none">1. <u>Relapse during the double-blind randomized withdrawal period.</u>2. <u>Histologic response [peak eosinophil count of ≤ 6/high-powered field (HPF) across all available esophageal levels] at Visit 8 (Week 36)</u>

MEMORANDUM

Protocol Section	Protocol Amendment 2 Text	Clarification
		<p>3. Dysphagia symptom response [$\geq 30\%$ reduction in the Dysphagia Symptom Questionnaire (DSQ) combined score (questions 2+3) from baseline of the SHP621-301 study] at Visit 8 (Week 36)</p> <p>4. Change in total endoscopy score from baseline of the SHP621-301 study, as measured by the EREFS classification, at Visit 8 (Week 36)</p>
9.8.1 Primary Efficacy Endpoint	The primary efficacy endpoint will be analyzed as the proportion of subjects with relapse during the double-blind randomized withdrawal period for the FAS, using a Fisher's Exact test comparing OBS 2 mg twice daily against placebo. The primary test of treatment effect will be 2-sided, and conducted at the significance level of 0.05.	The primary efficacy endpoint will be analyzed as the proportion of subjects with relapse during the double-blind randomized withdrawal period for the FAS, using a Fisher's Exact test comparing OBS 2 mg twice daily against placebo. The primary test of treatment effect will be 2-sided 1-sided , and conducted at the significance level of 0.05 0.025 .
9.8.1 Primary Efficacy Endpoint (sensitivity analyses)	In addition, the subjects who were prematurely withdrawn from the study without the primary efficacy endpoint will be imputed randomly according to the distribution of relapsers with available data; and the similar statistical test will be performed using the imputed data.	In addition, the subjects who were prematurely withdrawn from the study without the primary efficacy endpoint will be imputed randomly according to the distribution of relapsers with available data; and the similar statistical test will be performed using the imputed data. Analysis will be repeated based on FAS using different missing data handling methods to assess the impact of missing data on relapse.
9.8.2.1 Key Secondary Efficacy Endpoint	Dysphagia symptom response, defined as $\geq 30\%$ reduction in the DSQ combined score (questions 2+3) from baseline of the SHP621-301 study and from baseline of this extension study to the final treatment period evaluation (Visit 8)	Dysphagia symptom response, defined as $\geq 30\%$ reduction in the DSQ combined score (questions 2+3) from baseline of the SHP621-301 study and separately from baseline of this extension study to the final treatment period evaluation (Visit 8)
9.8.3 Exploratory Efficacy Endpoints	The exploratory endpoints that will be explored are the following:	<p>The exploratory endpoints that will be explored are the following:</p> <ul style="list-style-type: none"> Eosinophil histology relapse for subjects in the SHP621-301 BOS full responder group, defined as peak eosinophil count

MEMORANDUM

Protocol Section	Protocol Amendment 2 Text	Clarification
		<p>of ≥ 15/high-powered field (HPF) from at least 2 of 3 levels of the esophagus) during the double-blind randomized withdrawal period</p> <ul style="list-style-type: none">• [REDACTED]

As stated above, the administrative changes do not impact the overall study design, safety, or study conduct. Please file this memo in your study file records. If appropriate per local requirements, please submit this memo to your IRB notifying them of these changes.

If you have further questions, please do not hesitate to contact your PPD Clinical Research Associate, the PPD Remote Site Monitor, or Takeda directly.

Sincerely,

[REDACTED]

[REDACTED], MD
[REDACTED]