CLINICAL STUDY PROTOCOL

NCT Number: NCT03245840

Study Title: A Phase 3, Multicenter, Open-label Continuation Study with Budesonide Oral Suspension (BOS) for Adolescent and Adult Subjects with Eosinophilic Esophagitis (EoE)

Study Number: SHP621-303

Protocol Version and Date:

Amendment 3: 21 Jun 2021

TAKEDA DEVELOPMENT CENTER AMERICAS, INC.

PROTOCOL: SHP621-303

TITLE:	A Phase 3, Multicenter, Open-label Continuation Study with Budesonide Oral Suspension (BOS) for Adolescent and Adult Subjects with Eosinophilic Esophagitis (EoE)
DRUG:	SHP621, TAK-721, budesonide oral suspension (BOS)
IND:	103,173
EUDRACT NO.:	Non-EUDRACT
SPONSOR:	Takeda Development Center Americas, Inc. (TDC Americas, "Takeda") 95 Hayden Avenue, Lexington, MA 02421 USA +1-617-349-0200
PROTOCOL HISTORY:	Original Protocol: 12 Dec 2016 Protocol Amendment 1: 27 Jun 2017 Protocol Amendment 2: 10 Aug 2020 Protocol Amendment 3: 21 Jun 2021

PROTOCOL SIGNATURE PAGE

Sponsor's (Takeda) Approval

Signature: [redacted]	**Date:** 22-Jun-2021 | 02:11:45 JST
[redacted], MD	

Acknowledgement
I have read this protocol for Takeda Study SHP621-303.

Title: A Phase 3, Multicenter, Open-label Continuation Study with Budesonide Oral Suspension (BOS) for Adolescent and Adult Subjects 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 SHP621-303 protocol has been amended to update the sponsor name and address from Shire ViroPharma (Shire) to Takeda Development Center Americas Inc. (Takeda).

The corresponding sections affected by this change are listed below.

See Appendix 1 for protocol history, including all amendments.

Protocol Amendments	
Summary of Change(s) Since Last Version of Approved Protocol	
Amendment Number 3 **21 Jun 2021**	**Global Amendment**
Description of Change	**Section(s) Affected by Change**
Changed from: Shire ViroPharma Inc. (Shire, now called Shire ViroPharma LLC) 300 Shire Way, Lexington, MA 02421 USA **To:** Takeda Development Center Americas, Inc. (TDC Americas, "Takeda") 95 Hayden Avenue, Lexington, MA 02421 USA **Rationale: To update sponsor name and address.**	Headers; Cover Page; Protocol Signature Page; Emergency Contact Information Page; Product Quality Complaints; Section 1.2, Product Background and Clinical Information; Section 6.2, Administration of Investigational Product; Section 6.4, Drug Accountability; Section 10.5 Study Results/Publication Policy
Update of "Shire medical monitor" to "medical monitor' **Rationale: For consistent language throughout the protocol.**	Section 7.2.1.3, Physical Examination; Section 7.2.1.5, Clinical Laboratory Evaluations; Section 8.1.6, Pregnancy; Section 8.2.2, Reporting Procedures
Update of "Shire GDS" and "Shire Global Pharmacovigilance and Risk management Department" to "Takeda Global Patient Safety Evaluation Department" **Rationale: To reflect updated department name per sponsor name update.**	Emergency Contact Information Page; Section 8.1.6, Pregnancy; Section 8.2.2, Reporting Procedures; Section 8.2.4, Serious Adverse Event Collection Time Frame

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the Clinical Study Serious Adverse Event and Non-serious Adverse Events (AEs) Required by the Protocol Form within 24 hours to the Takeda Global Patient Safety Evaluation Department (GlobalPharmacovigilance@shire.com). A copy of this form must also be sent to the medical monitor by fax or e-mail using the details below.

[redacted], MD, [redacted]

Email: [redacted]

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

[redacted], MD, [redacted]

Office phone: [redacted]

Mobile: [redacted]

Email: [redacted]

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

[redacted], MD, [redacted]

Office phone: [redacted]

Mobile: [redacted]

Email: [redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Takeda within 24 hours. This includes any instances wherein the quality or performance of a Takeda 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	PQC@shire.com
European Union and Rest of World	PQCROW@shire.com

Telephone numbers (provided for reference if needed):

Takeda, Lexington, MA (USA)
1-888-300-6414 or 1-800-828-2088

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LIST OF ABBREVIATIONS

ACTH	adrenocorticotropic hormone
AE	adverse event
β-hCG	beta-human chorionic gonadotropin
BMD	bone mineral density
BOS	budesonide oral suspension
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
EoE-QoL-A	Adult Eosinophilic Esophagitis Quality of Life
EQ-5D-3L	EuroQol-5 Dimensions 3-level
EQ-5D	EuroQol
EQ-5D-Y	EuroQol-5 Dimensions Youth
[redacted]	[redacted]
ET	early termination
EU	European Union
FDA	Food and Drug Administration
GDS	Global Drug Safety
GCP	Good Clinical Practice
GPSE	Global Patient Safety Evaluation
GSL	Global Safety Lead
HIPAA	Health Insurance Portability and Accountability Act
HPF	high-powered field
HRQoL	health-related quality of life
hs	at bedtime
ICH	International Conference on Harmonisation

IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web-based response system
Med ID	medication identification
MedDRA	Medical Dictionary for Regulatory Activities
pc	after meals
PedsQL-EoE	Pediatric Quality of Life Inventory – EoE
PGI-S	Patient Global Impression of Severity
PPI	proton pump inhibitor
qAM	every morning
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	statistical analysis system
TA	therapeutic area
TEAE	treatment-emergent adverse event
UK	United Kingdom
US	United States

STUDY SYNOPSIS

Protocol number: SHP621-303	**Drug:** SHP621, budesonide oral suspension (BOS)
Title of the study: A Phase 3, Multicenter, Open-Label Continuation Study with Budesonide Oral Suspension (BOS) for Adolescent and Adult Subjects with Eosinophilic Esophagitis (EoE)	
Number of subjects (total): Approximately 100 subjects who have completed the SHP621-302 study will be enrolled in this continuation study.	
Investigator(s): Multicenter study	
Site(s) and Region(s): Approximately 60 sites in North America	
Study period (planned): September 2017 – October 2023	**Clinical phase:** 3

Objectives

Primary:

- To evaluate the long-term safety and tolerability of budesonide oral suspension (BOS) treatment

Exploratory:

[redacted]

Rationale:

Currently there is no approved medication for the treatment of eosinophilic esophagitis (EoE). This study is being conducted in order to provide continued access to BOS to subjects who complete both the SHP621-301 induction and SHP621-302 extension studies and are considered by the investigator to potentially benefit from continued BOS investigational treatment until commercial product is available. As there are limited data available on the potential benefits and risks of maintenance treatment of EoE with topical corticosteroids, investigators should exercise discretion in determining the duration of BOS treatment in this study and the need for and frequency of dose regimen changes or dose interruption.

Investigational product, dose, and mode of administration:

Budesonide oral suspension will be administered in 10 mL at a concentration of 0.2 mg/mL (2 mg dose), twice-daily (in the morning [qAM] after meals [breakfast, pc] and at bedtime [hs]). The 0.2 mg/mL concentration of BOS and dosing regimens were selected for use in Phase 3 studies based on the results of Study MPI 101-06, a Phase 2 study in 93 subjects with EoE and symptoms of dysphagia. For the current study, the investigational product will be supplied in amber glass, multidose bottles with child-resistant caps and refrigerated throughout the study (in the clinic and subject's home). Each bottle will contain approximately 210 mL of suspension with a budesonide concentration of 0.2 mg/mL.

The daily dose and potential total treatment duration of the current formulation of BOS with long-term continuation treatment in this study (ie, beyond the maximal 1 year total treatment duration in the SHP621-301 and SHP621-302 studies combined) may expose subjects to 21-dehydrobudesonide (21-DHB), a known breakdown product of budesonide, at a level that has an unknown risk of mutagenicity. 21-DHB is an in vitro mutagen that has been found to be negative for mutagenicity in in vivo animal studies. The relevance of this finding to humans is unknown; however, a risk of causing DNA damage or carcinogenicity cannot be excluded with long durations of treatment.

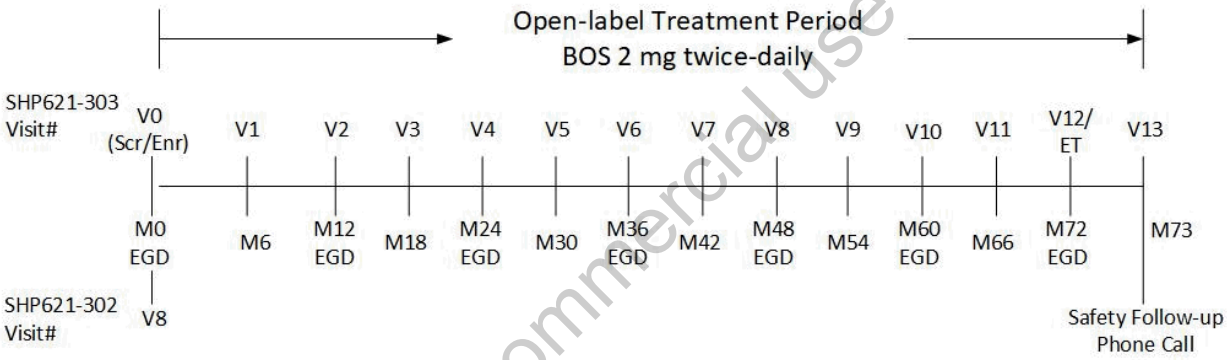
As described in the SHP621 investigator's brochure, investigators should make an individualized risk/benefit decision with respect to long-term BOS investigational treatment at the time of informed consent and when monitoring and adjusting BOS treatment in this study. The protocol allows for individualized treatment with BOS, including a dose regimen change from 2 mg twice-daily to 2 mg once-daily (qAM, pc) or treatment interruption (with resumption of treatment and/or increase in the BOS dose regimen to 2 mg twice-daily permitted at a later date while on study).

Methodology:

This is a Phase 3, multicenter, open-label study to evaluate the safety and tolerability of twice-daily administration of BOS (qAM, pc, and hs) in adolescent and adults with EoE.

Approximately 100 subjects who have completed the SHP621-302 study will be enrolled in this continuation study. Subjects who complete the SHP621-302 extension study are eligible to participate once they sign informed consent (or assent as applicable for subjects <18 years). Eligible subjects will be enrolled into the open-label treatment period and evaluated for safety every 6 months following the final treatment evaluation visit (Visit 8) in the SHP621-302 study until commercial product is available. Esophagogastroduodenoscopy with biopsies will be performed in all subjects annually (Month 12, Month 24, etc.).

Study Design Flow Chart



Abbreviations: BOS=budesonide oral suspension; EGD=esophagogastroduodenoscopy; Enr=Enrollment; ET=early termination; M=month; Scr=Screening; V=visit.

Subjects will be evaluated for eligibility for participation in this continuation study at the screening visit (Visit 0) which will also coincide with the final treatment evaluation visit (Visit 8) of SHP621-302. Subjects who consent and meet eligibility criteria at Visit 0 will enter the open-label treatment period in SHP621-303. Subjects may be enrolled and treated prior to receipt of results from SHP621-302 Visit 8 assessments, per investigator discretion; however, if they are subsequently determined to no longer meet eligibility criteria, they must be discontinued. Dose interruptions starting at the time of completion of the SHP621-302 study, due to administrative or other reasons, will be permitted; however, dosing should be reinitiated within 3 months of completion of treatment in SHP621-302 unless discussed prospectively with the medical monitor.

Subjects who withdraw from the study will receive a follow-up telephone call 4 weeks post last dose of BOS to query for serious adverse events (SAEs), adverse events (AEs), and concomitant treatments. If a subject discontinues from the study prematurely or transitions to commercial product upon availability, the assessments for Visit 12 are to be performed as completely as possible. Subjects who discontinue (ie, positive result on serum pregnancy test) will not be replaced.

BOS treatment may adjusted by a dose regimen change from 2 mg twice-daily to 2 mg once-daily (qAM, pc) or by treatment interruption (with resumption of treatment and/or increase in the BOS dose regimen to 2 mg twice-daily permitted at a later date while on study). Interruptions of up to 6 months are allowed. In their discretion with respect to individual subject investigational treatment adjustment, investigators should consider the subject's response to previous and current treatment, risk of relapse, and the overall risk/benefit profile of long-term treatment with BOS greater than 1 year.

Continued participation in the study (ie, complete study assessments as scheduled) is required to resume BOS. Subjects who are discontinued from the study may not reinitiate BOS treatment.

Inclusion and exclusion criteria:

Inclusion Criteria:

The subject will not be considered eligible for the study without meeting all the following criteria:

1. Subject completed SHP621-302 extension study and is considered by the investigator to potentially benefit from continued BOS investigational treatment.
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. Females of childbearing potential must agree to continue acceptable birth control measures (eg, abstinence, surgically sterile male partner, stable oral contraceptives, or double-barrier methods) throughout study participation.
4. Subject is willing and has an understanding and ability to fully comply with study procedures and restrictions defined in this protocol.

Exclusion Criteria:

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

1. Subject has changes in medications or diet during the SHP621-302 study that could affect participation in this continuation study.
2. Subject anticipates using swallowed topical corticosteroid for EoE or systemic corticosteroid for any condition during the treatment period; any temporary use (≤7 days) or initiation of new steroid treatment during the study should be documented and discussed with the medical monitor prospectively but should be avoided within 4 weeks of the scheduled esophagogastroduodenoscopy (EGDs).
3. Subject anticipates use of Cytochrome P450 3A4 inhibitors (eg, ketoconazole, grapefruit juice) during the continuation study.
4. Subject has an appearance at the EGD at the final treatment evaluation visit of SHP621-302 (Visit 8) 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).
5. Subject has presence of esophageal varices at the EGD at the final treatment evaluation visit (Visit 8) of the SHP621-302 study.
6. 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.
7. Subject has other diseases causing or associated with esophageal eosinophilia, including hypereosinophilic syndrome, collagen vascular disease, vasculitis, achalasia, or parasitic infection.
8. 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 8) of the SHP621-302 study is not an exclusion as long as the subject is expected to respond to treatment.
9. 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.
10. Subject has upper gastrointestinal bleeding identified at the EGD at the final treatment evaluation visit (Visit 8) of the SHP621-302 study.
11. Subject has evidence of active infection with *Helicobacter pylori*.
12. Subject has evidence of unstable asthma.
13. Subject is female and pregnant or nursing.
14. 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.
15. Subject has a history or high risk of noncompliance with treatment or regular clinic visits.

Maximum duration of subject involvement in the study:

Open-label treatment period for up to 6 years or until commercial product is available.

Endpoints and statistical analysis:

Subject Populations

- The full analysis set (FAS) set will include all subjects who are enrolled in the study and receive at least one dose of BOS.
- The safety set will include all subjects who receive at least 1 dose of BOS.

The primary population for safety will be the safety population [redacted]. An additional per-protocol population analysis may also be performed as secondary sensitivity analysis. Applicable analysis populations will be defined in the statistical analysis plan (SAP).

Primary Efficacy Endpoint

Not applicable.

Secondary Efficacy Endpoints

Not applicable.

Exploratory [redacted] Endpoints

[redacted]

Safety Endpoints

Safety endpoints include adverse events (AEs), physical examinations, stadiometry, vital signs (temperature, systolic and diastolic blood pressure, pulse, and respiratory rate), weight and height assessments, dual-energy X-ray absorptiometry (DXA) scans for bone mineral density (BMD) (for adolescents aged 11-17 years, inclusive), clinical laboratory tests (hematology, chemistry, urinalysis; urine pregnancy test, if appropriate), and adrenocorticotropic hormone (ACTH) stimulation tests. To account for the effects of puberty in adolescent subjects (11-17 years, inclusive), BMD z- scores will be adjusted for height z-scores.

Health Economics and Outcomes Research Endpoints

- Change in Adult Eosinophilic Esophagitis Quality of Life (EoE-QoL-A) score at all visits from baseline (last assessment prior to first dose of BOS)
- Change in EuroQol (EQ-5D; EuroQol-5 Dimensions 3-level [EQ-5D-3L] or EuroQol-5 Dimensions Youth [EQ-5D-Y], according to subject's age) score at all visits from baseline (last assessment prior to first dose of BOS)
- Change in Pediatric Quality of Life Inventory (subjects 11-17 years of age, inclusive) – EoE (PedsQL-EoE) score at all visits from baseline (last assessment prior to first dose of BOS)
- Change in Patient Global Impression of Severity (PGI-S) score at all visits from baseline (last assessment prior to first dose of BOS)

Statistical Methodology for Primary Efficacy Endpoint

Not applicable.

Statistical Methodology for Key Secondary and Other Secondary Efficacy Endpoints

Not applicable.

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 (for adolescents aged 11 17 years, inclusive), clinical laboratory results (hematology, chemistry, urinalysis; urine pregnancy test, if appropriate), and ACTH stimulation will be descriptively summarized at baseline and at each post-baseline visit.

The number and percent of subjects with treatment-emergent adverse events (TEAEs) will be presented. Treatment-emergent adverse events are defined as AEs that start or deteriorate on or after the time the informed consent is signed and through the Safety Follow-up Contact, or 31 days after the last dose of for subjects who do not have a Safety Follow-up Contact. However, for any subjects who die during the study (ie, the date of death is between the date of first dose of BOS and the date of study discontinuation entered by the site, inclusive), all AEs (including those resulting in death) that occur during the study will be considered as TEAEs irrespective of the last dose and will be included in the TEAE summaries.

Statistical Methodology for Exploratory and Health Economics and Outcomes Research Endpoints

No formal testing will be conducted for efficacy or Health Economics and Outcomes Research endpoints. All endpoints will be summarized using summary statistics at each visit. Continuous endpoints will be summarized using mean, standard deviation, median, minimum and maximum values. Categorical endpoints will be summarized using count and percentage. Ninety five percent confidence interval (CI) will be provided wherever appropriate. Listings for subject-level data will be presented.

Sample Size Justification

Approximately 100 subjects who complete the SHP621-302 extension study are anticipated to enroll into this open-label continuation study.

STUDY SCHEDULE(S)

Table 1-1 Schedule of Assessments

Procedures	Open-label Treatment Phase													Safety Follow-Up Phone Contact[r]
	Visit 0[a]	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12 ET[q]	Visit 13
Months	**0**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**66**	**72**	**73**
Window		**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±3 days**
Informed consent/assent	X													
Medical history review	X													
Inclusion/exclusion criteria review	X													
Vital signs[b]; height[c], and weight[d] assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	
EGD with [redacted] and biopsy[e]	X		X		X		X		X		X		X	
EQ-5D[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	
PedsQL-EoE (subjects 11 to 17 years of age)[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	
EoE-QoL-A (subjects ≥18 years of age)	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 1-1 Schedule of Assessments

Procedures	Open-label Treatment Phase													Safety Follow-Up Phone Contact[r]
	Visit 0[a]	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12 ET[q]	Visit 13
Months	**0**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**66**	**72**	**73**
Window		**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±3 days**
PGI-S	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Tanner staging assessment[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical laboratory assessment[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy test[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Morning cortisol (target 6:00-9:00 am)	X		X		X		X		X		X		X	
ACTH stimulation testing[m]	X		X		X		X		X		X		X	
DXA Scan (subjects 11 to 17 years of age)[n]	X		X		X		X		X		X		X	
BOS supplied[o]	X	X	X	X	X	X	X	X	X	X		X		
BOS administration[p]	Twice-daily administration													
BOS compliance assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 1-1 Schedule of Assessments

Procedures	Open-label Treatment Phase													Safety Follow-Up Phone Contact[r]
	Visit 0[a]	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12 ET[q]**	**Visit 13**
Months	**0**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**66**	**72**	**73**
Window		**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±3 days**
Review of concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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

[a] The assessments from the final treatment evaluation visit (Visit 8) in SHP621-302 will be used to determine eligibility for participation in this continuation study. Subjects may be enrolled and treated prior to receipt of results from SHP621-302 Visit 8 assessments, per investigator discretion; however, if they are subsequently determined to no longer meet eligibility criteria, they must be discontinued. Subjects, site staff, and study team members involved with the conduct of the study will remain blinded to treatment assignment and individual subject histology data from the SHP621-301 and SHP621-302 studies until database lock occurs for SHP621-302.

[b] Vital signs will be assessed after the subject has been resting (and in a supine position for Visit 0 only) 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 measurements for adolescents (11-17 years, inclusive) should be measured in triplicate using stadiometers at every visit. Height measurement for adults is required at Visits 2, 4, 6, 8, 10, and 12 only.

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

Table 1-1 Schedule of Assessments

Procedures	Open-label Treatment Phase													Safety Follow-Up Phone Contact[r]
	Visit 0[a]	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12 ET[q]	Visit 13
Months	0	6	12	18	24	30	36	42	48	54	60	66	72	73
Window		±4 weeks	±4 weeks	±4 weeks	±4 weeks	±4 weeks	±4 weeks	±4 weeks	±4 weeks	±4 weeks	±4 weeks	±4 weeks	±4 weeks	±3 days

[e] Endoscopy must include esophageal biopsies; gastric and duodenal biopsies may be done at the discretion of the investigator. Unscheduled endoscopies may be performed at the discretion of the investigator to assess relapse, to determine whether or not BOS treatment should be interrupted or restarted, or to adjust BOS dose (Section 7.2.1). Endoscopy does not have to be completed at scheduled visit if unscheduled endoscopy was performed within 3 months of the scheduled visit (ie, 3 months before or after Visit 2, 4, 6, 8, or 10). If an unscheduled endoscopy is performed within 3 months of Visit 12 or ET, the Visit 12 (or ET) endoscopy does not need to be completed if discussed prospectively with the medical monitor and determined to be unnecessary.

[f] Subjects 11-17 years of age, inclusive, at the time of consent into the SHP621-301 study, will complete the EQ-5D-Y throughout study participation; subjects ≥18 years of age (at the time of consent into the SHP621-301 study) will complete the EQ-5D-3L.

[g] Subjects 11-17 years of age, inclusive, at the time of consent into the SHP621-301 study will complete the PedsQL-EoE throughout study participation.

[h] Physical examination must include specific assessments for signs of glucocorticoid excess (eg, moon facies, acne, hirsutism, mood swings, insomnia, and depression).

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

[j] 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.

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

[l] Serum pregnancy tests will be performed for all female subjects at Visit 8 of SHP621-302. All females with a positive pregnancy test will be discontinued from the study. Urine pregnancy tests will be performed at subsequent scheduled visits starting with Visit 1 for all female subjects during the conduct of SHP621-303.

[m] Unscheduled ACTH stimulation tests may be performed at the investigator's discretion.

[n] Dual-energy X-ray absorptiometry scans should be performed using the same machine and software as used in the SHP621-301 and SHP621-302 studies.

Table 1-1 Schedule of Assessments

Procedures	Open-label Treatment Phase													Safety Follow-Up Phone Contact[r]
	Visit 0[a]	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12 ET[q]	Visit 13
Months	0	6	12	18	24	30	36	42	48	54	60	66	72	73
Window		±4 weeks	±4 weeks	±4 weeks	±4 weeks	±4 weeks	±4 weeks	±4 weeks	±4 weeks	±4 weeks	±4 weeks	±4 weeks	±4 weeks	±3 days

[o] Investigational product may be supplied at unscheduled visits given the long duration in between scheduled visits and to assess subjects for treatment interruption or reinitiation (see Section 6.2.3).

[p] Subjects will receive oral administration of 10 mL of BOS twice-daily (qAM, pc, and hs), with no ingestion of food or liquids permitted for 30 minutes after investigational product administration. At the investigator's discretion, administration may be stopped (allowable up to 6 months) and/or stopped and reinitiated (see Section 3.1 and Section 6.2.3). Dose interruptions (up to 3 months) due to administrative or other reasons will also be allowed at the time of completion of the SHP621-302 study. In such instances, unscheduled safety and efficacy assessments may be required prior to dispensing study drug considering the time off of investigational treatment and the study schedule.

[q] If subject discontinues study prematurely or transitions to commercial product upon availability, the evaluations listed for Visit 12 should be performed as soon as possible.

[r] For subjects who withdraw from the treatment period, a safety follow-up contact by telephone will be performed 4 weeks following the last dose of BOS.

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 signs and 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(eos)/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., 2014; 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 Food and Drug Administration (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

Budesonide oral suspension (BOS) 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. Takeda is developing BOS 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 United States (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 (Food and Drug Administration 2011).

The efficacy of BOS for the treatment of EoE has been demonstrated in 2 Phase 2 studies in the BOS clinical development program. Studies MPI 101-01 and MPI 101-06 evaluated the efficacy of BOS 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 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 mg to2.0 mg daily) and high-dose (2.8 mg to 4.0 mg daily) BOS groups compared to placebo following 12 weeks of treatment.

In Study MPI 101-06, a significant treatment effect for BOS 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]), BOS-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 open-label continuation study follows the SHP621-301 induction study and SHP621-302 extension study. Study SHP621-301 is a Phase 3 randomized, double-blind, multicenter, study to evaluate the efficacy, safety, and tolerability of twice-daily administration of BOS (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 BOS in adolescent and adult subjects with EoE. The SHP621-302 extension study is designed to evaluate maintenance of treatment and treatment withdrawal in subjects who complete the induction study.

As there are no currently approved medications for the treatment of EoE, the objective of this study is to provide continued access to BOS until commercial product is available. To date, there are limited data on the efficacy and safety on long-term swallowed corticosteroid therapy (Alexander, 2014). In light of evidence that long-term corticosteroid treatment may reduce esophageal inflammation (Straumann et al., 2011) and that untreated EoE may result in esophageal fibrosis and stricture (Furuta and Katzka, 2015), EoE treatment guidelines recommend an individualized approach to potential long-term maintenance swallowed corticosteroid treatment (Liacouras et al., 2011; Dellon et al., 2013). Subjects who are considered by the investigator to potentially benefit from continued BOS investigational treatment after completing SHP621-301 and SHP621-302 will be eligible to participate in this study. The proposed dose of BOS for this study is the same that is currently employed in Studies SHP621-301 and SHP621-302, 2 mg BOS twice-daily. To allow for continuation treatment to be individualized, this protocol allows for the BOS dosing regimen to be changed from 2 mg twice-daily to 2 mg once-daily (qAM, pc) or for BOS to be stopped (allowable up to 6 months) and reinitiated at the investigator's discretion (Section 6.2.3). To ensure that safety monitoring is complete, subjects must continue to remain in the protocol to be eligible to reinitiate BOS after treatment interruption.

The daily dose and potential total treatment duration of the current formulation of BOS with long-term continuation treatment in this study (ie, beyond the maximal 1 year total treatment duration in the SHP621-301 and SHP621-302 studies combined) may expose subjects to 21-dehydrobudesonide (21-DHB), a known breakdown product of budesonide, at a level that has an unknown risk of mutagenicity. 21-DHB is an in vitro mutagen that has been found to be negative for mutagenicity in in vivo animal studies. The relevance of this finding to humans is unknown; however, a risk of causing DNA damage or carcinogenicity cannot be excluded with long durations of treatment. As described in the SHP621 investigator's brochure, investigators should make an individualized risk/benefit decision with respect to long-term BOS investigational treatment at the time of informed consent and when monitoring and adjusting BOS treatment in this study. The protocol allows for individualized treatment with BOS, including a dose regimen change from 2 mg twice-daily to 2 mg once-daily (qAM, pc) or treatment interruption (with resumption of treatment and/or increase in the BOS dose regimen to 2 mg twice-daily permitted at a later date while on 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. Budesonide oral suspension is under clinical development for the treatment of EoE through 2 ongoing Phase 3 studies: SHP62-301, a randomized, double-blind induction study, and SHP621-302, a double-blind extension study. Because EoE is considered a seriously debilitating disease and there is an unmet medical need, this open-label continuation study is proposed to provide continued access to BOS for subjects who complete both the SHP621-301 and SHP621-302 studies and are considered by the investigator to potentially benefit from continued BOS investigational treatment until commercial product is available.

2.2 Study Objectives

2.2.1 Primary Objective

The primary objective of the study is to evaluate the long-term safety and tolerability of BOS treatment.

2.2.2 Secondary Objectives

Not applicable.

2.2.3 Exploratory Objectives

The exploratory objectives of this study are:

- [redacted]
- [redacted]

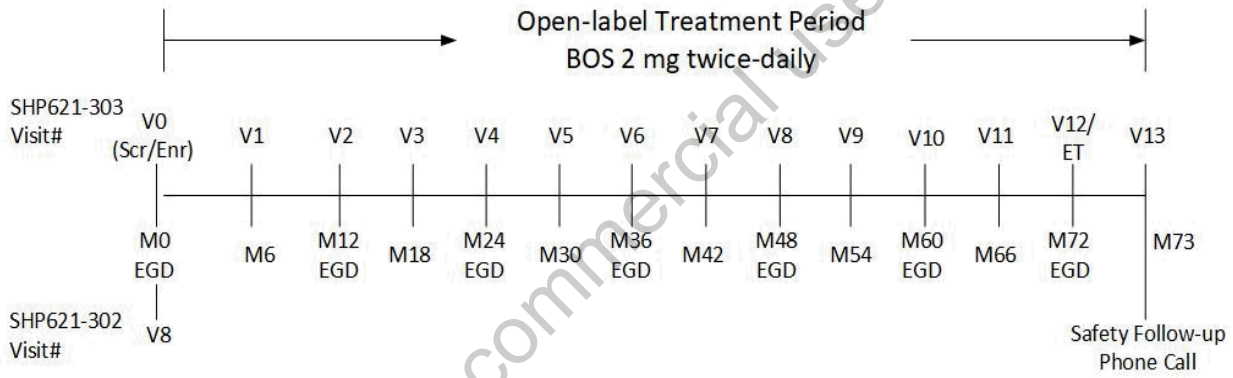
3. STUDY DESIGN

3.1 Study Design and Flow Chart

This is a Phase 3, multicenter, open-label study to evaluate the safety and tolerability of twice-daily administration of BOS (qAM, pc, and hs) in adolescent and adults with EoE.

Approximately 100 subjects who have completed the SHP621-302 study will be enrolled in this continuation study. Subjects who complete the SHP621-302 extension study are eligible to participate once they sign informed consent (or assent as applicable for subjects <18 years). Eligible subjects will be enrolled into the open-label treatment period and evaluated for safety every 6 months following the final treatment evaluation visit (Visit 8) in the SHP621-302 study until commercial product is available. Esophagogastroduodenoscopy with biopsies will be performed in all subjects annually (Month 12, Month 24, etc.) (Figure 3-1).

Figure 3-1 Study Design Flow Chart



BOS=budesonide oral suspension; EGD=esophagogastroduodenoscopy; Enr=enrollment; ET=early termination; M=month; Scr=screening; V=visit

Subjects will be evaluated for eligibility for participation in this continuation study at the screening visit (Visit 0) which will also coincide with the final treatment evaluation visit (Visit 8) of SHP621-302. Subjects who consent and meet eligibility criteria at Visit 0 will enter the open-label treatment period in SHP621-303. Subjects may be enrolled and treated prior to receipt of results from SHP621-302 Visit 8 assessments, per investigator discretion; however, if they are subsequently determined to no longer meet eligibility criteria, they must be discontinued. Dose interruptions starting at the time of completion of the SHP621-302 study, due to administrative or other reasons, will be permitted; however, dosing should be reinitiated within 3 months of completion of treatment in SHP621-302 unless discussed prospectively with the medical monitor.

As there are limited data on the potential benefits and risks of maintenance treatment of EoE with topical corticosteroids, investigators should exercise discretion in determining the duration of BOS treatment in this study and the need for and frequency of dose regimen changes or dose interruption as described in Section 1.2.

BOS treatment may be adjusted by a dose regimen change from 2 mg twice-daily to 2 mg once-daily (qAM, pc) or by treatment interruption (with resumption of treatment and/or increase in the BOS dose regimen to 2 mg twice-daily permitted at a later date while on study). Interruptions of up to 6 months are allowed (see Section 6.2.3). In their discretion with respect to individual subject investigational treatment adjustment, investigators should consider the subject's response to previous and current treatment, risk of relapse, and the overall risk/benefit profile of long-term treatment with BOS greater than 1 year (see Section 1.2).

Continued participation in the study (ie, completion of scheduled study assessments) is required to resume BOS treatment. Subjects who are discontinued from the study may not reinitiate BOS treatment.

Subjects, site staff, and study team members involved with the conduct of the study will remain blinded to treatment assignment and individual subject histology data from the SHP621-301 and SHP621-302 studies until database lock occurs for SHP621-302.

Subjects who withdraw from the study will receive a follow-up telephone call 4 weeks post last dose of BOS to query for serious adverse events (SAEs), adverse events (AEs), and concomitant treatments. If a subject discontinues from the study prematurely or transitions to commercial product upon availability, the assessments for Visit 12 are to be performed as completely as possible. Subjects who discontinue (ie, positive result on serum pregnancy test) will not be replaced.

3.2 Duration and Study Completion Definition

No fixed duration of subject participation is specified. Subjects may participate in the study for up to 6 years or until commercial product is available.

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.

3.3 Sites and Regions

Approximately 60 sites in North America, the same sites participating in the SHP621-301 and SHP621-302 studies, will participate in this open-label continuation 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 the following criteria:

1. Subject completed the SHP621-302 extension study and is considered by the investigator to potentially benefit from continued BOS investigational treatment.
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. Females of childbearing potential must agree to continue acceptable birth control measures (eg, abstinence, surgically sterile male partner, stable oral contraceptives, or double-barrier methods) throughout study participation.
4. Subject is willing and has an understanding and ability to fully comply with study procedures and restrictions defined in this protocol.

4.2 Exclusion Criteria

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

1. Subject has changes in medications or diet during the SHP621-302 study that could affect participation in this continuation study.
2. Subject anticipates using swallowed topical corticosteroid for EoE or systemic corticosteroid for any condition during the treatment period; any temporary use (≤7 days) or initiation of new steroid treatment during the study should be documented and discussed with the medical monitor prospectively but should be avoided within 4 weeks of the scheduled esophagogastroduodenoscopy (EGDs).
3. Subject anticipates use of Cytochrome P450 3A4 inhibitors (eg, ketoconazole, grapefruit juice) during the continuation study.
4. Subject has an appearance at the EGD at the final treatment evaluation visit of SHP621-302 (Visit 8) 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).
5. Subject has presence of esophageal varices at the EGD at the final treatment evaluation visit (Visit 8) of the SHP621-302 study.
6. 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.

7. Subject has other diseases causing or associated with esophageal eosinophilia, including hypereosinophilic syndrome, collagen vascular disease, vasculitis, achalasia, or parasitic infection.
8. 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 8) of the SHP621-302 study is not an exclusion as long as the subject is expected to respond to treatment.
9. 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.
10. Subject has upper gastrointestinal bleeding identified at the EGD at the final treatment evaluation visit (Visit 8) of the SHP621-302 study.
11. Subject has evidence of active infection with *Helicobacter pylori*.
12. Subject has evidence of unstable asthma.
13. Subject is female and pregnant or nursing.
14. 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.
15. Subject has a history or high risk of noncompliance with treatment or regular clinic visits.

4.3 Restrictions

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

- Temporary use (≤7 days) or initiation of new steroid treatment is permitted but should be avoided within the 4 weeks of the scheduled EGDs.
- No use of cytochrome P450 3A4 (CYP450 3A4) inhibitors (eg, ketoconazole, grapefruit juice, see details in Section 5.2.2).

4.4 Reproductive Potential

4.4.1 Female Contraception

Serum pregnancy tests will be performed for all female subjects at Visit 8 of SHP621-302. All females with a positive pregnancy test will be discontinued from the study (Section 4.5.2).

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 BOS.
  - Acceptable methods of contraception are:
    - Abstinence
    - Surgically sterile male partner
    - 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 BOS with the medical monitor when possible.

If BOS is discontinued and results in subject discontinuation from the study, regardless of the reason, the evaluations listed for Visit 12/Early Termination are to be performed as completely as possible. If the investigator adjusts BOS treatment at their discretion by interrupting treatment (allowable for up to 6 months prior to restarting treatment, see Section 3.1), the subject may continue in the study (ie, complete study assessments as scheduled). If the investigator adjusts BOS treatment at their discretion by decreasing the frequency of BOS dose from 2 mg twice-daily to 2 mg once-daily, the duration of dose regimen change does not impact continued study participation. Subjects with BOS treatment interruptions greater than 6 months should be discontinued after completing the Visit 12/Early Termination evaluations. Once subjects are discontinued from the study, they may not be re-enrolled.

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 and date of stopping BOS must be recorded in the case report form (CRF) and source documents.

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 high grade esophageal stricture (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], weight loss due to severe dysphagia, and/or upper GI bleed would result in withdrawal of the subject from the study. Subjects with oropharyngeal or esophageal candidiasis that has failed to respond to treatment, per investigator discretion, should have BOS treatment interrupted or 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 investigational product
- 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
- 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 BOS.

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 investigational product
- Two SAEs of similar type (defined as same or similar Medical Dictionary for Regulatory Activities [MedDRA] higher level group code), and considered related to the investigational product

The urgent review will be performed by a sponsor safety review group, which will include the study Global Safety Lead (GSL), Global Patient Safety Evaluation (GPSE) and the GDS therapeutic area (TA) Head. Following the sponsor's review of safety data, one of the following actions will be taken with respect to study status:

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

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

5. PRIOR AND CONCOMITANT TREATMENT

All non-study treatment (including but not limited to herbal treatments, vitamins, behavioral treatment, and nonpharmacological treatment, such as psychotherapy, as appropriate) received 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 prior to providing consent for SHP621-303. 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 BOS in SHP621-303 (Visit 0) 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 investigator must contact the medical monitor either retrospectively or prospectively to discuss any changes to concomitant steroid regimens that may impact the outcome of the study. Maintenance immunotherapy (allergy shots of sublingual immunotherapy for allergies), influenzae, 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. Swallowed topical corticosteroid for EoE (other than investigational product). Systemic corticosteroid for any condition since the final treatment evaluation visit (Visit 8) of the SHP621-302 study or use within the 4 weeks of scheduled EGDs should be avoided. Any temporary use (≤7 days) or initiation of new steroid treatment during the study should be documented and discussed with the medical monitor prospectively.
2. CYP450 3A4 inhibitors (eg, ketoconazole, grapefruit juice, some herbal products) since the final treatment evaluation visit (Visit 8) of the SHP621-302 study, or anticipated use of such medications during the treatment period. For an expanded list of CYP3A inhibitors, investigators should refer to the 2012 FDA Draft Guidance on Drug Interactions and use their clinical judgment with respect to specific medications.

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The test product is BOS (budesonide oral 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.

6.1.1 Blinding the Treatment Assignment

Not applicable for this open-label study.

6.2 Administration of Investigational Product

All BOS and supplies (eg, dosing spoons) will be provided by Takeda or its designee. At each visit, subjects will be supplied with enough BOS to last until the subsequent visit. If home storage is a factor, subjects may need to return to the clinic for an unscheduled visit(s) to obtain additional supply of BOS. The first dose of BOS for each subject will be administered in the clinic. The subject will continue with the evening dosing regimen at home.

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

Subjects will be instructed not to eat or drink for 30 minutes after taking BOS. 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 BOS Management

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

At Visit 0, the investigator or designee will access the IWRS to assign open-label treatment to a subject. Sites will confirm eligibility criteria information prior to treatment assignment. 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 an open-label continuous treatment period during which all subjects will receive BOS.

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 3 digit site identifier, and the 4 digit subject identifier. For the SHP621-303 study, the 3 digit site and 4 digit subject numbers will be the same as the SHP621-301 and SHP621-302 studies.

6.2.3 Dosing

All subjects will receive 10 mL of BOS at a concentration of 0.2 mg/mL (2 mg dose). Budesonide oral suspension will be administered twice-daily (in the morning [qAM] after meals [breakfast, pc] and at bedtime [hs]), with no ingestion of food or liquids permitted for 30 minutes after investigational product administration.

Budesonide oral suspension doses that are required to be administered at the clinic include the first dose of BOS administered at Visit 0 and all morning doses of BOS administered at scheduled bi-annual visits. Subjects will be required to eat breakfast at the clinic prior to self-administering these doses. Subjects can self-administer all other doses of BOS at home.

At the investigator's discretion, changes to the dosage regimen are allowable. BOS treatment may be changed from twice-daily administration (2 mg twice-daily) to once-daily administration (qAM, pc). In addition, BOS treatment may be interrupted by stopping and planning to reinitiate investigational product treatment up to 6 months later (see Section 3.1). In these instances, investigational product treatment will be stopped while the subject remains in the study and continues to have other protocol assessments. Investigational product must be resumed within 6 months and multiple treatment interruptions are permitted throughout study participation (ie, 3 months on and 3 months off treatment). BOS dose regimen changes and dose interruptions must be recorded by the subject and study site. Continued participation in the study is required to resume BOS.

Dose interruptions starting at the time of completion of the SHP621-302 study, due to administrative or other reasons, will also be permitted; however, dosing should be reinitiated within 3 months of completion of treatment in SHP621-302 unless discussed prospectively with the medical monitor (eg, in instances when SHP621-302 investigational treatment was completed more than 3 months prior to the investigator’s site initiation in this study). In such instances, the visit schedule in this study will be based off the final treatment evaluation visit (Visit 8) in SHP621-302, regardless of dose interruption at the time of completion of SHP621-302 or timing of consent to participate in this study.

Unscheduled safety and efficacy assessments may be required and should be discussed prospectively with the medical monitor prior to dispensing study drug considering the time off of investigational treatment and the study schedule (see Table 1-1).

6.2.4 Unblinding the Treatment Assignment

Not applicable for this open-label study.

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

Budesonide oral suspension is packaged in the following labeled containers:

The sponsor will supply the following medication to the study sites: BOS 0.2 mg/mL in an 8-ounce amber glass bottle for multiple uses. Bottles of BOS 0.2 mg/mL will be packaged in an appropriately labeled carton.

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

6.3.3 Storage

The investigator has overall responsibility for ensuring that BOS 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.

Budesonide oral suspension must be refrigerated at 2-8ºC (36-46ºF), protected from light.

Budesonide oral suspension is 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. 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 Takeda-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.

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 contract research organization [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 product delivered with those used and returned. All investigational product 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.

Compliance will be assessed at each treatment visit. Please refer to the Pharmacy Manual for additional details. If BOS is discontinued at the investigator's discretion (for potential resumption later), the investigational product interruption period will not be counted in compliance determination.

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.

In acknowledgement of hospital, local, state, or national government restrictions or other site related factors caused by unavoidable circumstances (eg, COVID-19 pandemic) which may prevent investigators from conducting the study according to the Schedule of Assessments at the clinical study site, investigators should consider the subject's overall risk/benefit profile including overall response to previous and current treatment for EoE in deciding whether to continue subjects in the study. For delayed on-site visits, investigators should consider whether health status and study assessments (eg, review of adverse events, concomitant medications and procedures, IP compliance, and PGI-S) can be accurately and comprehensively collected via telephone or whether the subject (or caregivers) can complete the health-related QoL assessments at home during the scheduled window. Investigators should reach out to the medical monitor for any questions or concerns.

7.1.1 Screening/Enrollment/Visit 0 (Month 0)

Screening will begin once subjects sign informed consent. The screening visit 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 SHP621-302 final treatment evaluation visit (Visit 8) will be used as the screening assessments (Visit 0) for this open-label continuation study. Subjects may be enrolled and treated prior to receipt of results from SHP621-302 Visit 8 assessments, per investigator discretion; however, if they are subsequently determined to no longer meet eligibility criteria, they must be discontinued. At the SHP621-302 final treatment evaluation visit (ie, final assessment is completed in SHP621-302), subjects who meet eligibility criteria at Visit 0 will be dispensed BOS and enter the open-label treatment period. Dose interruptions starting at the time of completion of the SHP621-302 study, due to administrative or other reasons, will be permitted; however, dosing should be reinitiated within 3 months of completion of treatment in SHP621-302 unless discussed prospectively with the medical monitor (eg, in instances when SHP621-302 investigational treatment was completed more than 3 months prior to the investigator's site initiation in this study).

In such instances, unscheduled safety and efficacy assessments may be required prior to dispensing study drug considering the time off of investigational treatment and the study schedule (Table 1-1).

Serum pregnancy tests will be performed as part of Visit 8 of SHP621-302. Subjects who test positive for pregnancy, via the serum pregnancy test will be discontinued from the SHP621-303 study.

7.1.1.1 Screening/Enrollment Visit (Visit 0)/Visit 8 of SHP621-302 Study

The screening/enrollment 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.
- Review current use of concomitant medications and procedures
- Dispense BOS and review administration instructions. Subjects will self-administer the first dose of BOS in the clinic during this visit after breakfast. Site personnel will record the date and time of the first dose in the source documents. Beginning on the evening of Visit 0, the subject will take their first dose at home and continue with the twice-daily (morning and evening) dosing regimen. The subject will continue with the twice-daily (morning and evening) dosing regimen unless otherwise instructed by the investigator (Section 6.2.3). For subjects who are minors (<18 years), a parent/guardian will be responsible for ensuring subject takes BOS appropriately.

The following procedures will be performed at the final treatment evaluation visit (Visit 8) of SHP621-302 and will be used as the screening assessments for this open-label continuation study. Subjects may be enrolled and treated prior to receipt of results from SHP621-302 Visit 8 assessments, per investigator discretion; however, if they are subsequently determined to no longer meet eligibility criteria, they must be discontinued.

- Review BOS 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 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.
- 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 AM and 9:00 AM). Subjects should be instructed not to take the morning dose of BOS until after the morning cortisol test has been performed.
- Administer adrenocorticotropic hormone (ACTH, 250 mcg) stimulation testing; the type of synthetic and route of administration will be per investigator discretion. Additional cortisol samples will be drawn at 30- and 60-minutes following stimulation testing.
- Administer health-related quality-of-life (HRQoL) assessments including the EuroQol (EQ-5D), Pediatric Quality of Life Inventory – EoE (PedsQL-EoE), and Adult Eosinophilic Esophagitis Quality of Life (EoE-QoL-A) as age-appropriate.
- Administer Patient Global Impression of Severity (PGI-S) of disease assessment
- 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 as described in Section 7.2.1.3.
- Serum pregnancy test will be performed on all female subjects; subjects who test positive for pregnancy will be discontinued from the study (Section 4.5.2).
- Perform EGD and biopsy either at the investigative site or by a referring physician. Refer to guidance provided in the SHP621-302 protocol for sending specimens for central review.
- Perform dual-energy X-ray absorptiometry (DXA) scan for bone mineral density (BMD) in subjects aged 11-17 years, inclusive. Baseline and post treatment DXA scans should be performed using the same machine and software, when feasible.

7.1.2 Open-label Treatment Period (Visits 1-12)

There is no fixed duration to the open-label treatment period; subjects will continue to receive treatment (with potential treatment interruption at the investigator's discretion) until commercial product is available.

During this period, a ±4-week visit window will be permitted between scheduled visits. Visit windows are calculated based upon the date of Visit 0.

Subjects will continue to receive BOS twice-daily (qAM, pc, and hs) throughout the open-label treatment period. At the investigator's discretion, the dose regimen may be changed from twice-daily to once-daily (qAM, pc) or may be stopped (allowable up to 6 months) and/or stopped and reinitiated (Section 6.2.3). Subjects may continue in the study (ie, complete study assessments as scheduled); however, they will not receive investigational product until the investigator restarts BOS. Subjects who are discontinued from the study may not reinitiate BOS treatment.

7.1.2.1 Visits 1, 3, 5, 7, 9, 11 (Months 6, 18, 30, 42, 54, 66)

Assessments and procedures listed for all visits that occur during the open-label treatment period will be completed as listed 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), height (measured in triplicate for adolescents 11 years to 17 years, inclusive), and weight (measured in duplicate for adolescents 11 years to 17 years, inclusive). Perform stadiometry in subjects aged 11 years to 17 years, inclusive. Vital signs will be assessed after the subject has been resting 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 7.2.1.5).

The following order is recommended for the remaining procedures that will be performed at these visits:

- Administer HRQoL assessments including the EQ-5D, PedsQL-EoE, and EoE-QoL-A as age-appropriate.
- Administer PGI-S of disease assessment.
- 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 as described in Section 7.2.1.3.
- Urine pregnancy test will be performed on all female subjects.
- Review BOS dosing compliance.
- Dispense BOS and review administration instructions. Subjects whose doses have been stopped or interrupted (allowable up to 6 months), per investigator's discretion, will not receive BOS until dose has been reinitiated at the investigator's discretion (Section 6.2.3).

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

7.1.2.2 Visits 2, 4, 6, 8, 10 (Months 12, 24, 36, 48, 60)

Assessments and procedures listed for all visits that occur during the open-label treatment period will be completed as listed 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), height (measured in triplicate for adolescents 11 years to 17 years, inclusive), and weight (measured in duplicate for adolescents 11 years to 17 years, inclusive). Perform stadiometry in subjects aged 11 years to 17 years, inclusive. Vital signs will be assessed after the subject has been resting 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 7.2.1.5).
- Morning cortisol (performed between 6:00 AM and 9:00 AM). Subjects should be instructed not to take the morning dose of BOS until after the morning cortisol test has been performed.
- Administer adrenocorticotropic hormone (ACTH, 250 mcg) stimulation testing; the type of synthetic and route of administration will be per investigator 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 7.2.1.5). (Unscheduled ACTH stimulation tests may be performed at the investigator's discretion between scheduled visits).

The following order is recommended for the remaining procedures that will be performed at these visits:

- Administer HRQoL assessments including the EQ-5D, PedsQL-EoE, and EoE-QoL-A as age-appropriate.
- Administer PGI-S of disease assessment.
- 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 as described in Section 7.2.1.3.
- Urine pregnancy test will be performed on all female subjects.
- Perform DXA scan for BMD in subjects aged 11 years to 17 years, inclusive. Dual-energy X-ray absorptiometry scans should be performed at this visit or within 28 days of the scheduled visit using the same machine and software, when feasible.
- Perform EGD and biopsy; EGD should be completed at or within 28 days of the scheduled visit. An earlier EGD may occur at the investigator's discretion if the subject exhibits signs of relapse, or increased, worsening or persistent dysphagia symptoms (Section 4.5.1).
- Review BOS dosing compliance.
- Dispense BOS and review administration instructions. Subjects whose doses have been stopped or interrupted (allowable up to 6 months), per investigator's discretion, will not receive BOS until dose has been reinitiated at the investigator's discretion (Section 6.2.3).

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

7.1.2.3 Visit 12 (Month 72) or Early Termination

Assessments at this visit will be performed as outlined in Table 1-1. If a subject discontinues the trial prematurely or if the trial is terminated (eg, at commercial availability of BOS), the assessments for Visit 12 are to be performed as completely as possible. Subjects whose BOS treatment is interrupted at the investigator's discretion will continue in the study for potential resumption of BOS treatment; these subjects will not undergo Early Termination assessments when investigational product is interrupted.

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 years to 17 years, inclusive), and weight (measured in duplicate for adolescents 11 years to 17 years, inclusive). Perform stadiometry in subjects aged 11 years to 17 years, inclusive. Vital signs will be assessed after the subject has been resting 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 7.2.1.5).
- Morning cortisol (performed between 6:00 AM and 9:00 AM). Subjects should be instructed not to take the morning dose of BOS until after the morning cortisol test has been performed.
- Administer adrenocorticotropic hormone (ACTH, 250 mcg) stimulation testing; the type of synthetic and route of administration will be per investigator 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 7.2.1.5). (Unscheduled ACTH stimulation tests may be performed at the investigator's discretion between scheduled visits).

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

- Administer HRQoL assessments including the EQ-5D, PedsQL-EoE, and EoE-QoL-A as age-appropriate.
- Administer PGI-S of disease assessment.
- 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 as described in Section 7.2.1.3.
- Urine pregnancy test will be performed on all female subjects.

- Perform DXA scan for BMD and in subjects aged 11-17 years, inclusive. Dual-energy X-ray absorptiometry scans should be performed at this visit or within 28 days of the scheduled visit using the same machine and software when feasible.
- Perform EGD and biopsy; EGD should be completed at or within 28 days of the scheduled visit. An earlier EGD may occur at the investigator's discretion if the subject exhibits signs of relapse, or increased, worsening or persistent dysphagia symptoms (Section 4.5.1).
- Review BOS dosing compliance.

7.1.3 Safety Follow-up Telephone Contact/Visit 13:

The follow-up period for this protocol is 4 weeks from the last dose of investigational product treatment. Subjects who withdraw from study treatment will receive a follow-up telephone call at Visit 13 to query for SAEs, AEs, and concomitant treatments.

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 (Section 8.1).

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 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.

7.2.1.1 Esophagogastroduodenoscopy with Esophageal Biopsy and Histopathologic Evaluation

The EGD with [redacted] and biopsy will be performed during the study as outlined in Table 1-1.

All EGDs with biopsies will be performed by a physician at the investigative site. For all EGDs after screening (after the SHP621-302 Visit 8 EGD), the local endoscopist will submit biopsy specimens to a clinical pathology laboratory for histopathology including assessment of eosinophil counts and histopathologic features of EoE per local procedures.

An EGD with esophageal biopsies is required for all subjects prior to enrolling in the study and then every year thereafter until the subject either completes or withdraws from the study. If at any time, the subject exhibits signs of relapse, or increased, worsening or persistent dysphagia symptoms, the investigator may choose to perform an unscheduled EGD. Investigators may perform an unscheduled EGD to evaluate subjects in their determination to interrupt or restart treatment, or to change the BOS dose (see Section 3.1). An unscheduled EGD may replace a scheduled interim EGD if it occurs within 3 months of the latter (ie, 3 months before or after Visit 2, 4, 6, 8, or 10). If an unscheduled EGD is performed within 3 months of Visit 12 (or ET), the Visit 12 (or ET) does not need to be completed if discussed prospectively with the medical monitor and determined to be unnecessary.

[redacted]

In addition, the general appearance of the stomach and duodenum will be assessed by the endoscopist. At the investigator's discretion, biopsies may be taken from the stomach and duodenum per local procedures.

7.2.1.2 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 SHP621-302 final treatment evaluation visit (Visit 8). Medical history will be classified as EoE or non-EoE by the investigator. Adverse events recorded during the SHP621-302 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.

7.2.1.3 Physical Examination (Including Height and Weight)

Abnormalities identified at the SHP621-302 final treatment evaluation visit (Visit 8) will be documented in the subject's source documents and on the medical history CRF. Changes after this visit 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 will also include Tanner Staging Assessments for subjects <18 years of age unless the investigator confirms subject is post puberty.

Height will be measured in triplicate at all visits for adolescents (11 years to 17 years, inclusive). Height will be measured in adults annually at Visits 2, 4, 6, 8, 10, and 12. Statural height in adolescents will be measured at each visit 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. Subjects who turn 18 over the course of the study (ie, after providing consent for the SHP621-303 study), will be considered to be adults and triplicate readings using stadiometers will not be required.

Weight will be measured in duplicate in adolescents (11 years to 17 years, inclusive) and recorded in the CRF. Subjects who turn 18 over the course of the study (ie, after providing consent for the SHP621-303 study), will be considered to be adults and duplicate measurements will no longer be required.

All subjects with clinical evidence of reduced height velocity and/or delayed Tanner Staging during the study should be followed up at investigator discretion and within 3 months with repeat follow-up as necessary until resolution. Such clinically significant findings should be discussed with the medical monitor. The investigator should determine whether it is appropriate for the subject to continue investigational product treatment (or have treatment interrupted for potential restart at a later date). Subjects who discontinue from the study or have treatment interrupted and have clinical evidence of reduced height velocity and/or delayed Tanner Stage development at a study visit (including the early termination visit) should be followed up at investigator discretion and within 3 months with repeat follow-up as necessary until resolution.

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 SHP621-302 study must be recorded on the CRF for this study.

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

7.2.1.4 Vital Signs

Vital signs will be conducted after the subject has been resting (and in a supine position for Visit 0 only) 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.

7.2.1.5 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 (Section 8.1.5). 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

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

Adrenocorticotropic hormone stimulation testing will be performed by measuring the levels of cortisol in the blood following the injection of a synthetic form of ACTH (250 mcg). The type of synthetic and route of administration will be per investigator 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 SHP621-302 study.

Clinically significant abnormal laboratory test results during the study should be followed up at investigator discretion and within 3 months. All subjects with an abnormal ACTH stimulation test or urinary or serum glucose level must be followed closely during the study until resolution. The investigator, in consultation with the medical monitor, should determine whether it is appropriate for subjects to continue study drug treatment. Subjects who discontinue from the treatment period at any time and have abnormal ACTH stimulation test or urinary or serum glucose level should also be followed up at investigator discretion and within 3 months with repeat follow-up as necessary until resolution.

7.2.1.6 Pregnancy Test

A urine pregnancy test is performed on all female subjects at all visits, except Visit 0, or if pregnancy is suspected.

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

Dual-energy X-ray absorptiometry (also referred to as DEXA) scans for determination of BMD will be performed in subjects aged 11-17 years, inclusive, as outlined in Table 1-1. Subjects who turn 18 over the course of the study (ie, after providing consent for the SHP621-303 study) will be considered to be adults and DXA scans will not be required.

The sites for DXA measurement will be the lumber spine (L1-L4 preferred) and total body less head (Bachrach and Sills, 2011; Gordon et al., 2008; International Society for Clinical Densitometry 2014). The same DXA machine and software should be used for the baseline and post treatment scans, when feasible. The DXA manufacturer, model, and software version should be recorded in the CRF.

7.2.2 Other Assessments

7.2.2.1 Health-related Quality-of-life Assessment

EuroQol-5 Dimensions 3-level Questionnaire

The EuroQol-5D Dimensions 3-level (EQ-5D-3L; for subjects ≥18 years) and the EuroQol-5 Dimensions Youth (EQ-5D-Y; for subjects 11-17 years of age, inclusive) will be performed during the study as outlined in Table 1-1. Subjects who turn 18 after over the course of the study (ie, after providing consent for the SHP621-303 study), will continue to fill out the same questionnaire for continuity of data collection.

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

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

Pediatric Quality of Life – EoE Questionnaire

The PedsQL-EoE questionnaire will be completed by subjects 11-17 years of age, inclusive, and their parent or legal guardian, as outlined in Table 1-1. Subjects who turn 18 over the course of the study will continue to fill out the same questionnaire for continuity of data collection.

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

Adult Eosinophilic Esophagitis Quality of Life Questionnaire

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

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

7.2.2.2 Severity of Disease Assessments

Patient Global Impression of Severity

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

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

7.2.3 Volume of Blood to Be Drawn from Each Subject

Table 7-1 Approximate Volume of Blood to Be Drawn from Each Subject (Visits 1-12)

Assessment		Sample Volume (mL)	Number of Samples	Approximate Total Volume (mL)
Safety	Biochemistry and β-hCG[a]	6	12	72
	ACTH	2	12	24
	Cortisol	2	6	12
	Hematology	2	12	24
Total mL		12	-	132

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

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

During this study, at scheduled Visits 1 through 12, it is expected that approximately 132 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 132 mL. When more than one 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 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 investigational product.
Possibly Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, 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 investigational product, 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 investigational product, follows a known or suspected response pattern to the investigational product, is confirmed by improvement upon stopping the investigational product (dechallenge), and reappears upon repeated exposure (rechallenge). Note that this is not to be construed as requiring re-exposure of the patient to investigational product; 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 Takeda Global Patient Safety Evaluation Department using the Investigational and Marketed Products Pregnancy Report Form. A copy of the Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the 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 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 Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol as well as the 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 Takeda Global Patient Safety Evaluation Department (GlobalPharmacovigilance@shire.com) and the 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 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 Takeda Global Patient Safety Evaluation Department. A copy of the 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 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 Takeda Global Patient Safety Evaluation 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 Takeda Global Patient Safety Evaluation 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 enrolled, 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

Eligibility for participation in this continuation study will be determined based on assessments performed at the final treatment evaluation visit (Visit 8) of SHP621-302. However, subjects, site staff, and study team members involved with the conduct of the study will remain blinded to treatment assignment and individual subject histology data from the SHP621-301 and SHP621-302 studies until database lock occurs for SHP621-302.

9.4 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent. All statistical analyses will be performed using statistical analysis system (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.

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 100 subjects who complete the SHP621-302 extension study are anticipated to enroll into this open-label continuation study.

9.7 Study Population

The safety set will include all subjects who receive at least 1 dose of BOS.

The full analysis (FAS) set will include all subjects who are enrolled in the study and receive at least 1 dose of BOS.

The primary population for safety will be the safety population [redacted]. An additional per-protocol population analysis may also be performed as secondary sensitivity analysis. Applicable analysis populations will be defined in the statistical analysis plan (SAP).

9.8 Efficacy Analyses

9.8.1 Primary Efficacy Endpoint

Not applicable.

9.8.2 Secondary Efficacy Endpoints

9.8.2.1 Key Secondary Efficacy Endpoint

Not applicable.

9.8.3 Exploratory [redacted] Endpoints

The exploratory endpoints that will be explored are the following:

- [redacted]
- [redacted]

[redacted]

9.9 Safety Analyses

All safety endpoints, including AEs, physical examinations, stadiometry, vital signs (temperature, systolic and diastolic blood pressure, pulse, and respiratory rate), weight and height assessments, DXA scans for BMD (for adolescents aged 11 years to 17 years, inclusive), clinical laboratory tests (hematology, chemistry, urinalysis; urine pregnancy test, if appropriate), and ACTH stimulation tests, will be descriptively summarized at baseline and at each post-baseline visit. To account for the effects of puberty in adolescent subjects (11 years to 17 years of age, inclusive), BMD z-scores will be adjusted for height z-scores.

The number and percent of subjects with treatment-emergent adverse events (TEAEs) will be presented. Treatment-emergent adverse events are defined as AEs that start or deteriorate on or after the time the informed consent is signed and 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. 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.

Adverse events 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. Treatment-emergent adverse events will be further summarized by severity and relationship to BOS. Adverse events related to BOS, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.

The following adverse events of special interest (AESIs) related to corticosteroid use will be categorized with preferred terms (SOC where applicable):

- Infections:
  - System Organ Classes of infections and infestations
  - Candidiasis related: esophageal candidiasis, oral candidiasis, candidiasis, oropharyngeal candidiasis, tongue fungal infection, vulvovaginal mycotic infection, anal candidiasis.
- Potential systemic effects of corticosteroid use (including adrenal function):
  - Adrenal effects: adrenal suppression, adrenal insufficiency, ACTH stimulation test abnormal, and blood cortisol decrease or increase, blood cortisol abnormal, cushingoid
  - CNS/Mood effects: insomnia, mood swings, suicidal ideation, OCD, anxiety, depression, major depression, irritability, restlessness, sleep disorder, disturbance in attention, headache, dizziness, vertigo, lethargy, paranesthesia, hypoesthesia, psychomotor hyperactivity
  - Metabolic effects: blood glucose increased, blood glucose abnormal, glucose intolerance impaired, diabetes mellitus, intraocular pressure increased, acne, weight increased, weight fluctuation, hepatic steatosis, hirsutism, dermatitis acneiform, skin striae, skin texture abnormal, obesity, menopausal symptoms, metrorrhagia

  - Cardiac effects: edema peripheral, peripheral swelling, hypertension, palpitations
  - Fractures: foot fracture, upper limb fracture, humerus fracture, rib fracture, wrist fracture
- GI effects:
  - Esophagitis pain, esophagitis, vomiting, nausea, diarrhea, abdominal pain, abdominal pain upper, constipation, abdominal distention, abdominal discomfort, hiatus hernia, dyspepsia, gastritis, gastritis erosive, chronic gastritis, dry mouth, erosive esophagitis, and gastroesophageal reflux disease, mouth ulceration, gastric ulcer, duodenal ulcer, erosive duodenitis, mouth ulceration, esophageal ulcer.

9.10 Health-related Quality-of-life Analyses

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

- Change in Adult Eosinophilic Esophagitis Quality of Life (EoE-QoL-A) score at all visits from baseline (last assessment prior to first dose of BOS)
- Change in EuroQol (EQ-5D; EuroQol-5 Dimensions 3-level [EQ-5D-3L] or EuroQol-5 Dimensions Youth [EQ-5D-Y], according to subject's age) score at all visits from baseline (last assessment prior to first dose of BOS)
- Change in Pediatric Quality of Life Inventory (subjects 11-17 years of age, inclusive) - EoE (PedsQL-EoE) score at all visits from baseline (last assessment prior to first dose of BOS)
- Change in Patient Global Impression of Severity (PGI-S) score at all visits from baseline (last assessment prior to first dose of BOS)

No formal testing will be conducted for Health Economics and Outcomes Research endpoints. All endpoints will be summarized using summary statistics at each visit. Continuous endpoints will be summarized using mean, standard deviation, median, minimum and maximum values. Categorical endpoints will be summarized using count and percentage. Ninety five percent confidence interval (CI) will be provided wherever appropriate. Listings for subject-level data will be presented.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, European Union (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 BOS 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 BOS, containers, and other study materials to the sponsor.

Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

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

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

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

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

All data will have separate source documentation; no data will be recorded directly onto the CRF. The following data collected for assessments and procedures performed at the SHP621-302 final treatment evaluation visit (Visit 8) will not be recollected in the SHP621-303 database as follows (Section 7.1.1.1):

- Vital signs, height, and weight assessment
- EGD with [redacted] and biopsy
- EQ-5D
- PedsQL-EoE (subjects 11 to 17 years of age)
- EoE-QoL-A (subjects ≥18 years of age)
- PGI-S
- Physical examination
- Tanner Staging Assessment
- Clinical laboratory tests
- Urinalysis
- Serum Pregnancy test
- Morning cortisol
- ACTH Stimulation Testing
- DXA Scan (subjects 11 to 17 years of age)

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

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

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

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

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

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

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

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

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

Laboratory samples (blood and urine) will be stored by the clinical laboratory for as long as is required to:

- Complete the study
- Publish data related to the study
- Support any regulatory applications for the study drug

Samples could be stored for up to about 15 years.

Biopsy specimens should be stored by the local laboratory per federal and local regulations.

10.2.3.3 Audit/Inspection

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

10.2.3.4 Financial Disclosure

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

Budesonide oral suspension 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 Health Insurance Portability and Accountability Act (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

Takeda 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, Takeda 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 Takeda. 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 Takeda products or projects must undergo appropriate technical and intellectual property review, with Takeda 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 Takeda, 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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Appendix 1 Protocol History

Document	Date	Global/Country/Site Specific
Protocol Amendment 3	21 Jun 2021	Global
Protocol Amendment 2	10 Aug 2020	Global
Protocol Amendment 1	27 Jun 2017	Global
Original Protocol	05 Dec 2015	Global

Protocol Amendments	
Summary of Change(s) Since Last Version of Approved Protocol	
Amendment Number 2 **10 Aug 2020**	**Global Amendment**
Description of Change	**Section(s) Affected by Change**
Changed from: [redacted], MD **To:** [redacted], MD Added email address for Shire Global Pharmacovigilance and Risk Management Department **Rationale: To provide updated emergency contact information.**	Protocol Signature Page; Emergency Contact Information Page
Updated study design flow chart and Schedule of Assessments to reflect addition of 2 new study visits **Rationale: To extend treatment period until product is commercially available.**	Synopsis: Study Period Planned, Methodology; Table 1-1 Schedule of Assessments Section 3.1: Study Design and Flow Chart; Section 7.1.2.1: Visit 1, 3, 5, 7, 9, 11 (Months 6, 18, 30, 42, 54, 66); Section 7.1.2.2: Visits 2, 4, 6, 8, 10 (Months 12, 24, 36, 48, 60); Section 7.1.2.3: Visit 12 (Month 72); Section 7.1.3:Safety Follow-up Telephone Contact/Visit 13 *Throughout document*
Replaced intent-to-treat analysis set (ITT) with full analysis set (FAS). Indicated that exploratory [redacted] analyses will be performed on the FAS, not the ITT. **Rationale: To provide clarification on statistical methods for the final analysis.**	Synopsis: Study Populations Section 9.7: Study Population
Updated text describing analyses of Health Economics and Outcomes Research and exploratory endpoints to indicate they will not be summarized by duration of exposure.	Synopsis: Methodology; Section 9.8.3: Exploratory [redacted] Endpoints Section 9.10: Health-related Quality-of-life Analyses

Protocol Amendments	
Summary of Change(s) Since Last Version of Approved Protocol	
Amendment Number 2 **10 Aug 2020**	**Global Amendment**
Description of Change	**Section(s) Affected by Change**
Rationale: To clarify that analyses will be summarized by visit, not by duration of exposure.	
Corrected text describing collection of treatment-adverse events (TEAE) to indicate that they will be collected from the time of informed consent. **Rationale: To clarify TEAE collection period.**	Synopsis: Statistical Methodology for Safety Endpoints Section 9.9: Safety Analyses
Added language to guide investigators in anticipation of potential deviations from study procedures due to unavoidable circumstances such as the COVID-19 pandemic. **Rationale: To provide direction to investigators to allow for continuation of subjects in the study despite missed study visits/missed study assessments due to unavoidable circumstances (eg, COVID-19 pandemic).**	Section 7: Study Procedures
Updated blood volumes. **Rationale: To provide clarification on approximate volume of blood to be drawn from each subject.**	Section 7.2.3: Volume of Blood to Be Drawn from Each Subject
Removed the Bone Mineral Density in Childhood Study calculator as this reference is no longer available. **Rationale: To remove an outdated reference.**	Synopsis: Statistical Methodology for Safety Endpoints Section 9.9: Safety Analyses
Added language describing how long laboratory samples (blood, urine, and biopsy samples) will be stored by the clinical laboratory. **Rationale: To clarify the retention period for laboratory sample storage.**	Section 10.2.3.2: Recording, Access, and Retention of Source Data and Study Documents

Summary of Change(s) for Protocol Amendment 1		
Amendment Number 1	**Amendment Date** **27 Jun 2017**	**Global Amendment**
Description of Change		**Section(s) Affected by Change**
As there are limited data available on the potential benefits and risks of maintenance treatment of EoE with topical corticosteroids, investigators should exercise discretion in determining the duration of BOS treatment in this study and the need for and frequency of dose regimen changes or dose interruption.		Synopsis: Rationale; Section 3.1: Study Design and Flow Chart

Summary of Change(s) for Protocol Amendment 1		
Amendment Number 1	**Amendment Date** **27 Jun 2017**	**Global Amendment**
Description of Change		**Section(s) Affected by Change**
~~At the investigator's discretion, BOS administration may be stopped (allowable up to 6 months) and/or stopped and reinitiated. Continued participation in the study is required to resume BOS.~~ **The daily dose and potential total treatment duration of the current formulation of BOS with long-term continuation treatment in this study (ie, beyond the maximal 1 year total treatment duration in the SHP621-301 and SHP621-302 studies combined) may expose subjects to 21-dehydrobudesonide (21-DHB), a known breakdown product of budesonide, at a level that has an unknown risk of mutagenicity. 21-DHB is an in vitro mutagen that has been found to be negative for mutagenicity in in vivo animal studies. The relevance of this finding to humans is unknown; however, a risk of causing DNA damage or carcinogenicity cannot be excluded with long durations of treatment. As described in the SHP621 investigator's brochure, investigators should make an individualized risk/benefit decision with respect to long-term BOS investigational treatment at the time of informed consent and when monitoring and adjusting BOS treatment in this study. The protocol allows for individualized treatment with BOS, including dose-regimen change from 2 mg twice-daily to 2 mg once-daily (qAM, pc) or treatment interruption (with resumption of treatment and/or increase in the BOS dose regimen to 2 mg twice-daily permitted at a later date while on study).**		Synopsis: Investigational product, dose, and mode of administration; Section 3.1: Product Background and Clinical Information
BOS treatment may be adjusted by a dose regimen change from 2 mg twice-daily to 2 mg once-daily (qAM, pc) or by treatment interruption (with resumption of treatment and/or increase in the BOS dose regimen to 2 mg twice-daily permitted at a later date while on study). Interruptions of up to 6 months are allowed. In their discretion with respect to individual subject investigational treatment adjustment, investigators should consider the subject's response to previous and current treatment, risk of relapse, and the overall risk/benefit profile of long-term treatment with BOS greater than 1 year. ~~At the investigator's discretion, BOS administration may be stopped during the study (allowable up to 6 months) and/or stopped and reinitiated (Section 6.2.3).~~		Synopsis: Investigational product, dose, and mode of administration; Methodology; Section 3.1: Study Design and Flow Chart
Edited footnote 'b' to indicate that vital signs may be assessed after the subject has been resting for at least 5 minutes.		Table 1-1, Footnote b
Edited footnote 'e' to clarify that unscheduled endoscopies may be performed to assess relapse or to determine whether modifications to the BOS dosing regimen are needed. Added language indicating that if unscheduled EGDs are performed within 3 months of Visit 8 or ET, the Visit 8 (or ET) EGD does not need to be performed if discussed prospectively with the medical monitor.		Table 1-1, Footnote e
Added footnote 'n': **Dual-energy X-ray absorptiometry scans should be performed using the same machine and software as used in the SHP621-301 and SHP621-302 studies.**		Table 1-1, Footnote n
Edited footnote 'o' to clarify that investigational product may be provided at unscheduled visits to assess subjects for treatment interruption or re-initiation.		Table 1-1, Footnote o
Continued participation in the study (ie, completion of scheduled study		Synopsis: Methodology;

Summary of Change(s) for Protocol Amendment 1		
Amendment Number 1	**Amendment Date 27 Jun 2017**	**Global Amendment**
Description of Change		**Section(s) Affected by Change**
assessments) is required to resume BOS treatment. Subjects who are discontinued from the study may not reinitiate BOS treatment.		Section 3.1: Study Design and Flow Chart
No fixed duration of subject participation is specified. Subjects **may participate in the study** ~~will continue to receive open label treatment~~ for up to 4 years or until commercial product is available.		Section 3.2: Duration and Study Completion Definition
If **the investigator adjusts** BOS **treatment at their discretion** ~~for potential reinitiation at a later date~~ **by interrupting treatment (allowable for up to 6 months prior to restarting treatment, see Section 3.1),**-the subject may continue in the study (ie, complete study assessments as scheduled). **If the investigator adjusts BOS treatment at their discretion by decreasing the frequency of BOS dose from 2 mg twice-daily to 2 mg once-daily, the duration of dose regimen change does not impact continued study participation. Subjects with BOS treatment interruptions greater than 6 months should be discontinued after completing the Visit 8/Early Termination evaluations**.		Section 4.5: Discontinuation of Subjects
~~Dose interruptions starting at the time of completion of the SHP621-302 study, due to administrative or other reasons, will be permitted; however, dosing should be reinitiated within 3 months of completion of treatment in SHP621-302 unless discussed prospectively with the medical monitor.~~ At the investigator's discretion, **changes to the dosage regimen are allowable. BOS treatment may be changed from twice-daily administration (2 mg twice-daily) to once-daily administration (qAM, pc). In addition, BOS treatment may be interrupted by stopping and planning to reinitiate investigational product treatment** up to 6 months **later (see Section 3.1). In these instances, investigational product treatment will be stopped while the subject remains in the study and continues to have other protocol assessments. Investigational product must be resumed within 6 months and multiple treatment interruptions are permitted (ie, 3 months on and 3 months off treatment). BOS** ~~may also be stopped (allowable up to 6 months) and/or stopped and restarted at the investigator~~'s discretion. ~~D~~**d**ose **regimen changes and dose** interruptions must be recorded by the subject and study site. Continued participation in the study is required to resume BOS. **Dose interruptions starting at the time of completion of the SHP621-302 study, due to administrative or other reasons, will also be permitted; however, dosing should be reinitiated within 3 months of completion of treatment in SHP621-302 unless discussed prospectively with the medical monitor (eg, in instances when SHP621-302 investigational treatment was completed more than 3 month prior to the investigator's site initiation in this study). In such instances, the visit schedule in this study will be based off the final treatment evaluation visit (Visit 8) in SHP621-302, regardless of dose interruption at the time of completion of SHP621-302 or timing of consent to participate in this study. Unscheduled safety and efficacy assessments may be required and should be discussed prospectively with the medical monitor prior to dispensing study drug considering the time off of investigational treatment and the study schedule (see Table 1 1).**		Section 6.2.3: Dosing

Summary of Change(s) for Protocol Amendment 1		
Amendment Number 1	**Amendment Date** **27 Jun 2017**	**Global Amendment**
Description of Change		**Section(s) Affected by Change**
Dose interruptions starting at the time of completion of the SHP621-302 study, due to administrative or other reasons, will be permitted; however, dosing should be reinitiated within 3 months of completion of treatment in SHP621-302 unless discussed prospectively with the medical monitor **(eg, in instances when SHP621-302 investigational treatment was completed more than 3 months prior to the investigator's site initiation in this study). In such instances, unscheduled safety and efficacy assessments may be required prior to dispensing study drug considering the time off of investigational treatment and the study schedule (see Table 1-1).**		Section 7.1.1: Screening/Enrollment/Visit 0 (Month 0) Section 6.2.3: Dosing
The subject will continue with the twice-daily (morning and evening) dosing regimen **unless otherwise instructed by the investigator (see Section 6.2.3).**		Section 7.1.1.1: Screening/ Enrollment Visit (Visit 0)/Visit 8 of SHP621-302 Study
At the investigator's discretion, **the dose regimen may be changed from twice-daily to once-daily (qAM, pc) or** ~~administration~~ may be stopped (allowable up to 6 months) and/or stopped and reinitiated (Section 6.2.3).		Section 7.1.2: Open-label Treatment Period (Visits 1-8)
Edited text describing vital signs assessments to indicate that vital signs may be assessed after the subject has been resting for at least 5 minutes.		Section 7.1.2.1: Visits 1, 3, 5, 7 (Months 6, 18, 30, 42); Section 7.1.2.2: Visits 2, 4, 6 (Months 12, 24, 36); Section 7.1.2.3: Visit 8 (Month 48) or Early Termination; 7.2.1.4, Vital Signs
Investigators may perform an unscheduled EGD to evaluate subjects in their determination to interrupt or restart treatment, or to change the BOS dose (see Section 3.1). An unscheduled EGD may replace a scheduled interim EGD if it occurs within 3 months of the latter (ie, 3 months before or after Visit 2, 4, or 6). If an unscheduled EGD is performed within 3 months of Visit 8 or ET, the Visit 8 (or ET) does not need to be completed if discussed prospectively with the medical monitor and determined to be unnecessary.		Section 7.2.1.1: Esophagogastroduodenoscopy with Esophageal Biopsy and Histopathologic Evaluation

Appendix 2 Scales and Assessments

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

Full Title of Scale/Assessment	Completed By
EQ-5D-3L (for subjects ≥18 years) EQ-5D-Y (for subjects 11-17 years of age, inclusive)[a]	Subject
PedsQL-EoE (subjects 11-17 years of age, inclusive)[b]	Subject and parent or legal guardian
EoE-QoL-A (subjects ≥18 years of age)	Subject
PGI-S	Subject
Tanner Staging Assessment	Site
[redacted]	Site

EoE-QoL-A=Adult Eosinophilic Esophagitis Quality of Life; EQ-5D=EuroQol; [redacted]; PedsQL-EoE=Pediatric Quality of Life Inventory – EoE; PGI-S=Patient Global Impression of Severity

[a] Subjects 11 to 17 years of age, inclusive, at the time of consent into the SHP621-301 study, will complete the EQ-5D-Y throughout study participation; subjects ≥18 years of age (at the time of consent into the SHP621-301 study) will complete the EQ-5D-3L.

[b] Subjects 11 to 17 years of age, inclusive, at the time of consent into the SHP621-301 study will complete the PedsQL-EoE throughout study participation.

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 Patient Global Impression of Severity

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

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