STATISTICAL ANALYSIS PLAN

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

SAP Version and Date:

Version 1.0: 26 Jan 2021

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Phase: III

Version: 1.0

Date: 26-Jan-2021

Prepared by:

[redacted] BIOSTATISTICS
PPD
3900 N Paramount Parkway
Morrisville, NC 27560

Based on:

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REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
Version 1.0	26-Jan-2021	Not Applicable

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ABBREVIATIONS

ACTH	adrenocorticotropic hormone
AE	adverse event
AESI	AEs of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMD	bone mineral density
BMI	body mass index
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
[redacted]	[redacted]
EQ-5D-3L	EuroQol-5 Dimensions 3-level
EQ-5D	EuroQol
EQ-5D-3L	EuroQol-5 Dimensions 3-level EQ
EQ-5D-Y	EuroQol-5 Dimensions Youth
[redacted]	[redacted]
ET	early termination
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GDS	Global Drug Safety
GCP	Good Clinical Practice
GSL	Global Safety Lead
HIPAA	Health Insurance Portability and Accountability Act
[redacted]	[redacted]
HRQoL	health-related quality of life
hs	at bedtime
ICH	International Council for Harmonisation
IRB	Institutional Review Board
ITT	intent-to-treat

Med ID	medication identification
MedDRA	Medical Dictionary for Regulatory Activities
PBO	placebo
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
VAS	Visual Analog Scale

1. OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

The primary objective of this study is:

- *To evaluate the long-term safety and tolerability of BOS treatment*

1.1.2 Secondary Objective

Not applicable.

1.1.3 Exploratory Objectives

[redacted]

- [redacted]
- [redacted]

1.2 Endpoints

1.2.1 Primary Efficacy Endpoint

Not applicable.

1.2.2 Secondary Efficacy Endpoint

Not applicable.

1.2.3 Exploratory [redacted] Endpoints

[redacted]

- [redacted]
- [redacted]

1.2.4 Safety Endpoints

The safety endpoints of this study are:

- Adverse events (AEs)

- Physical examinations include specific assessments for signs of glucocorticoid excess (eg, moon faces, acne, hirsutism, mood swing, insomnia, and depression). Tanner staging assessments for all subjects <18 years of age until investigator confirms subject is post puberty.
- Vital signs (temperature, systolic and diastolic blood pressure, pulse, and respiratory rate)
- Height, weight and BMI
- 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.

1.2.5 Other Endpoints

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)*

1.3 Estimands

Not applicable.

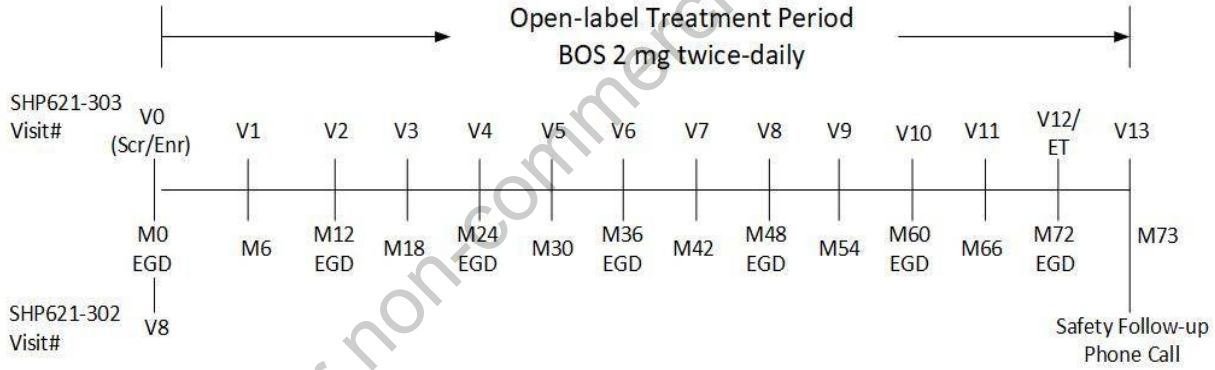
2. STUDY DESIGN

2.1 General Study Design

This is a Phase 3, multicenter, open-label study to evaluate the safety and tolerability of treatment administered twice daily of budesonide oral suspension (BOS; every morning [qAM] after meals [pc] and at bedtime [hs]) in adolescent and adults, aged 11 to 55 years, inclusive, 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.) (see Figure 1).

Figure 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.

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.

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

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 (i.e., positive result on serum pregnancy test) will not be replaced.

2.2 Randomization

Randomization is not applicable for this open-label single arm study.

2.3 Blinding

This is an open-label study. Blinding is not applicable.

2.4 Schedule of Assessments

Table 1 presents the schematic of the study design.

Table 1 Schedule of Assessment

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	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	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	
PGI-S	X	X	X	X	X	X	X	X	X	X	X	X	X	

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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**
Physical examination[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Tanner staging[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical laboratory[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													

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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**
BOS compliance assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	
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.

[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.

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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

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

[e] Endoscopy must include esophageal biopsies; gastric and duodenal biopsies may be done at the discretion of the investigator. 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. Endoscopy does not have to be completed at scheduled visit if unscheduled endoscopy was performed within 3 months of the scheduled visit (i.e., 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

Table 1 Schedule of Assessment

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

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.

[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.

[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. 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

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3. STATISTICAL HYPOTHESES AND DECISION RLUES

This section is not applicable because the statistical objective of this study does not involve any inference, but only estimation.

4. SAMPLE-SIZE DETERMINATION

The primary analysis for the study does not involve any statistical inference. Consequently, the sample size was determined based on feasibility considerations instead of a formal statistical evaluation. *Approximately 100 subjects who complete the SHP621-302 extension study are anticipated to enroll into this open-label continuation study*.

5. ANALYSIS SETS

5.1 Screened Set

The Screened Set will consist of all subjects who, upon completion of study SHP621-302, have signed informed consent and have conducted screening assessments.

5.2 Enrolled Set

The Enrolled Set will consist of all subjects who have signed informed consent excluding screen failures.

5.3 Safety Analysis Set

The safety set will consist of all subjects who received at least 1 dose of BOS. The Safety Set will be used for the primary safety analysis.

5.4 Full Analysis Set

The Full Analysis Set (FAS) will consist of all subjects who are enrolled in the study and receive at least 1 dose of BOS. [redacted]

5.5 Treatment Group

Based on treatment in SHP621-301, SHP621-302, and SHP621-303, the overall treatment integration can be categorized as the following:

A. BOS-BOS-BOS (subjects who were randomized to BOS treatment in SHP621-301, continuously randomized to BOS in SHP621-302, and enrolled in SHP621-303 with BOS)
B. BOS-PBO-BOS (subjects who were randomized to BOS treatment and fully responded to treatment in SHP621-301, randomized to placebo (PBO) in SHP621-302, and enrolled in SHP621-303 with BOS)
C. PBO-BOS-BOS (subjects who were randomized to placebo in SHP621-301, assigned to BOS in SHP621-302, and enrolled in SHP621-303 with BOS)
D. BOS-PBO-BOS-BOS (subjects who were randomized to BOS treatment and fully responded to treatment in SHP621-301, randomized to placebo treatment in SHP621-302, but relapsed during the randomized withdrawal and reinitiated treatment with BOS (intermittent therapy) in SHP621-302, and enrolled in SHP621-303 with BOS)

The majority of the data display will be presented by the following in SHP621-303:

- BOS-BOS: Group A, C and D
- PBO-BOS: Group B

- Total: Combine both BOS-BOS and PBO-BOS

6. STATISTICAL ANALYSIS

6.1 General Considerations

Continuous variables will be summarized using the following descriptive statistics: n, mean, SD, median, Q1, Q3, minimum, and maximum. Categorical and count variables will be summarized by the number of subjects (n) and the percent of subjects in each category.

Unless specified otherwise, min/max will be presented to the same decimal places as the raw data. Percentage, mean, and median will be presented to 1 more decimal place than the raw data. Standard deviation and standard error will be presented to 2 more decimal places than the raw data.

Body mass index (BMI) should be rounded to 1 decimal place for reporting.

Derived questionnaire scores, and other similar efficacy parameters recorded as integers, should be rounded to 1 decimal place for reporting.

Averaged laboratory and vital sign results eg, diastolic/systolic blood pressure and pulse (when taken in triplicate) should be rounded to 1 decimal place for reporting.

Baseline of this study is determined using the screening visit (Visit 0, also Visit 8 of SHP621-302) or the last observation prior to the first dose of BOS in SHP621-303, whichever is later.

Baseline of SHP621-302 is determined using the last assessment prior to the first dose of investigational product in SHP621-302.

Baseline of SHP621-301 is determined using the last assessment prior to the first dose of investigational product in SHP621-301.

Discontinuation of Study Treatment

6.2 Discontinuation of Study Treatment

In the disposition summary table, the number of subjects in each defined analysis set (i.e., Screened, Enrolled, FAS, and Safety) will be included. The number and percentage of subjects who completed each visit, who completed the study, and those who prematurely discontinued from the study will be presented for the Screened Set. The study completion includes the completion of the final protocol-defined assessment and follow-up visit or contact. Reasons for premature discontinuation from the study as recorded on the study completion page of the eCRF will be summarized (number and percentage). All subjects who prematurely discontinued will be listed by discontinuation reason for the Safety Set and the Screened Set.

The number of subjects who were screened, enrolled, and completed will be tabulated by site. In addition, the duration of enrollment, in days, will be summarized for each site. Duration of

enrollment will be calculated as (last date of contact for any subject at that site - the first date of informed consent for any subject at that site +1).

The number and percentage of subjects reporting any protocol deviations and the incidence of each deviation type will be summarized. All reported protocol deviations will be presented in a data listing with major/minor severity for the Screened Set. Protocol deviations will be summarized by deviation level (major or minor) and by type (International Council for Harmonisation [ICH]/Good Clinical Practice [GCP] or Protocol Deviation) within each deviation level. All protocol deviations related to the COVID-19 pandemic will be listed separately.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics

Demographic and other baseline characteristics will be summarized using descriptive statistics. The FAS will be used when summarizing demographic and baseline characteristics.

Continuous variables will be summarized by descriptive statistics including number of subjects, mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum. Categorical variables will be summarized by the count of subjects in each category and the percentage of subjects out of the total in the respective analysis set.

Baseline characteristics will be obtained using assessments at the screening visit in SHP621-303.

The demographic characteristics to be summarized (in the order shown) are: age (years), age category (<18 years, ≥18 years), sex, ethnicity, and race.

The following baseline characteristics will be summarized in the order shown: weight (kg), height (cm), BMI (kg/m^2), Tanner stage, [redacted] final histology response in SHP621-302, treatment in SHP621-301, and treatment in SHP621-302.

If there are multiple measurements of weight and height collected on the same visit (e.g., adolescent subjects), the average of multiple measurements will be presented.

Age category is based on age at the SHP621-303 informed consent. Age is calculated as the difference between date of birth and date of the SHP621-303 informed consent:

- Age = (date of informed consent – date of birth+1)/365.25.

Height and weight will be used to calculate BMI using the formula below:

- BMI = weight [kg]/(height [m])^2.

Subject-level listings will generated displaying the demographics and baseline characteristics for each subject subjects.

6.3.2 General 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). Adverse events recorded during the SHP621-302 study may be added as medical history at the investigator's discretion. The medical history will be summarized by system organ class (SOC) and preferred term (PT) for the Safety Set. General medical history findings will also be listed for all subjects for the Safety Set. Medical history will be coded using MedDRA Version 18.0 or higher.

6.3.3 Interim EoE Medical History

The following information associated with interim EoE history will be recorded in the eCRF at the screening visit:

- Any changes in diet since the screening visit in the SHP621-302 study (yes/no answer).
- Any changes in medical treatment for EoE since the screening visit in the SHP621-302 study (yes/no answer).

Interim EoE history will be summarized and listed for the Safety Set.

6.4 Medication History and Concomitant Medications

The World Health Organization-Drug Dictionary (WHODRUG) as of March 2015 or higher version will be used to classify prior and concomitant medications by therapeutic class.

Both prior and concomitant medication usage and medical/surgical procedures will be summarized by the number and proportion of subjects in each treatment group receiving each medication/procedure for the Safety Set. Procedures can be counted both as prior and concomitant. Multiple medication/procedure received by a subject in the same category will be counted only once.

All prior and concomitant medications and medical/surgical procedures will be listed for the FAS.

6.4.1 Prior Medications

The prior medication is defined as any medication with the end date prior to the informed consent date of the SHP621-303 study.

Medical/surgical procedures performed prior and during the treatment period will be recorded on the eCRF, along with the date and reason for the procedure. The prior medical/surgical procedure is defined as any procedure with the start date prior to the informed consent date of the SHP621-303 study.

6.4.2 Concomitant Medications

Concomitant medication is defined as any medication with a start date prior to the date of the first dose of BOS in SHP621-303 (Visit 0) and continuing after the first dose of BOS in SHP621-303 (Visit 0) or with a start date between the dates of the first dose of BOS in SHP621-303 (Visit 0) and the Safety Follow-up Contact, or 31 days after the last dose of BOS for subjects who do not have a Safety Follow-up Contact.

The concomitant medical/surgical procedure is defined as any procedure with the start date between the first dose of BOS (Visit 0) and the last dose of BOS in SHP621-303.

6.5 Efficacy Analysis

There are no primary or secondary efficacy for SHP621-303. [redacted] The most recent non-missing measurement (scheduled or unscheduled) collected prior to first dose of investigational product administered (based on dates or date/times) will be used as the baseline for all efficacy analyses. The baseline of SHP621-301, the baseline of SHP621-302 , and the baseline of this SHP621-303 study will be used in the efficacy summary.

6.5.1 Primary Efficacy Endpoint Analysis

Not applicable.

6.5.2 Secondary Efficacy Endpoint Analysis

Not applicable.

6.5.3 Exploratory [redacted] Endpoints and Analyses

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

6.5.4 Subgroup Analyses

[redacted]

6.6 Safety Analysis

The safety analysis will be performed using the Safety Set. Safety variables include adverse events (AEs), physical examinations, tanner staging, 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 tests (hematology, chemistry, urinalysis; serum pregnancy test, if appropriate), and ACTH stimulation tests. To account for the effects of puberty in adolescent subjects (11–17 years of age, inclusive), BMD z-scores will be adjusted for height z-score using the Bone Mineral Density in Childhood Study. Continuous safety parameters will be descriptively summarized at baseline of SHP621-303 and for each postbaseline visit. The assessment done at screening visit (Visit 0) of the SHP621-303 study or the last assessment prior to the first dose of investigational product will be used as baseline of SHP621-303.

Both SHP621-301 and SHP621-303 study baselines will be used for safety analyses.

6.6.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 18.0 or higher.

All AEs will be collected from the time of the informed consent through the completion of the SHP621-303 study's post-treatment follow-up as described below. For eligible subjects from SHP621-302 who consent to participate in SHP621-303, AEs will be collected in the SHP621-302 clinical database up to the date of the first dose of SHP621-303 investigational product (i.e., Visit 0 in the SHP621-303 study) or the Safety Follow-up Contact for subjects who screen fail prior to enrolling in SHP621-303. Adverse events that have a start date on or after the informed consent of SHP621-303 study will be collected in the SHP621-303 database. Adverse events which start during SHP621-302 and remain ongoing until informed consent is signed for SHP621-303 will be recorded in the SHP621-302 clinical and safety databases and as ongoing AEs in the SHP621-303 database.

Pretreatment AEs are defined as AEs with a start date prior to the informed consent date of SHP621-303.

Treatment-emergent adverse events (TEAEs) 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 dies during the study (i.e., 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.

An overall summary of the number of participants in the Safety Set with AEs will be presented, including the number and percentage of participants with AEs, pretreatment AEs, any TEAEs, serious TEAEs, severe TEAEs, life-threatening TEAEs, TEAEs related to investigational product, TEAEs related to EoE, deaths and hospitalizations due to TEAEs, TEAEs leading to discontinuation of investigational product, and TEAEs leading to study discontinuation.

The number, and percentage of subjects reporting TEAEs will be tabulated by system organ class (SOC)/preferred term, and maximum severity. Serious TEAEs, TEAEs related to investigational product, and TEAEs related to EoE will also be summarized by SOC and preferred term. If more than 1 AE occurs with the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to investigational product.

The incidence of most common TEAEs (≥5% of subjects) will be summarized by preferred term.

6.6.2 Adverse Events of Special Interest

Adverse events of special interest (AESI) will be summarized. The AESIs are defined in Section 9.3. The following analyses for treatment-emergent AESIs will be performed for the Safety Set:

- Incidence of treatment-emergent AESIs
- Number and percentages of subjects by preferred terms
- Number and percentages of subjects by maximum severity
- Serious treatment-emergent AESIs
- Drug-related serious treatment-emergent AESIs
- Treatment-emergent AESIs leading to discontinuation of investigational product
- Treatment-emergent AESIs leading to death

6.6.3 Clinical Laboratory Variables

Descriptive statistics for clinical laboratory values (in both SI units and conventional units), changes from baseline of SHP621-303 and changes from baseline of SHP621-301 at each assessment time point, and shift tables from baseline of SHP621-303 as well as shift tables from baseline of SHP621-301 to each visit for quantitative variables will be presented for the following clinical laboratory variables. All laboratory data will also be listed.

Hematology	hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, erythrocyte count, leukocyte count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count.
Biochemistry	alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, total protein, albumin, glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, carbon dioxide.
Urinalysis	glucose, protein, specific gravity, pH, nitrite, bilirubin, ketones, hemoglobin, urobilinogen, and leukocyte esterase.
Other tests	urine pregnancy, morning cortisol (6:00-9:00 AM collection), ACTH stimulation testing (serum cortisol collections at 30 and 60 minutes after synthetic ACTH injection in addition to baseline collection at 6:00-9:00 AM).

Pregnancy test results will only be listed. Serum pregnancy tests are performed on all female subjects at Visit 8 of the SHP621-302 study. Urine pregnancy tests are performed on all female subjects at all visits starting with Visit 1 during the conduct of SHP621-303 study.

Adrenocorticotropic hormone stimulation testing (ACTH) 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 at the screening visit (Visit 0), Visit 2, Visit 4, Visit 6, Visit 8, Visit 10 and Visit 12. Unscheduled ACTH stimulation tests may be performed at the investigator's discretion between scheduled visits.

All laboratory data will be listed for the Safety Set.

6.6.4 Vital Signs

Descriptive statistics for vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, temperature, BMI, and weight) and their changes from baseline at each postbaseline visit and at the end of study will be presented. Weight will be collected at every visit for all subjects. Height for adolescents (11–17 years of age, inclusive, at the time of the SHP621-301 study consent) will be collected at every visit. Height for adults will be collected at Visits 2, 4, 6, 8, 10, and 12 only.

For adolescents (11–17 years of age, inclusive), 2 weight measurements per visit will be recorded, and 3 height measurements per visit using stadiometers will be collected. The average weight and average height per visit will be used in summary tables for adolescents.

For the growth parameters (height, weight, and BMI), the changes from baselines (both SHP621-301 and SHP621-303) will be summarized by age group (<18 years or ≥18 years, at the time of SHP621-301 informed consent). The z-scores for growth parameters will be summarized descriptively at each visit for adolescents based on the subject's age at each visit.

Z-scores will be derived using the CDC growth charts (Kuczmarski et al., 2002). A SAS program for the 2000 CDC Growth Charts will be used to derive the percentiles and z-scores (www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm).

All vital signs data will be listed for the Safety Set.

6.6.5 Physical Examination

Physical examination assessments at each visit will include specific assessments for signs of glucocorticoid excess (eg, moon faces, acne, hirsutism, mood swing, insomnia, and depression). Tanner staging assessments will be performed for all subjects <18 years of age until investigator confirms subject is post puberty. The number and percentage of subjects reporting symptoms described above will be presented by visit.

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

DXA (also referred to as DEXA) scans for determination of BMD and body composition will be performed in subjects aged 11–17 years, inclusive, at the screening visit (Visit 0), Visit 2, Visit 4, Visit 6, Visit 8, Visit 10, and Visit 12. The sites for DXA measurement will be the lumbar spine (L1–L4 preferred) and total body less head. To account for the effects of puberty in adolescent subjects (11–17 years of age, inclusive), BMD z-scores will be adjusted for height in the following manner. The subject's height is compared to the 50th percentile on the CDC growth chart. The age on the CDC growth chart where the subject's height is equal to the 50th percentile height on the growth chart will be used in lieu of the subject's actual age to calculate a "height-adjusted" BMD z-score. For example, if a 10-year-old boy is 125 cm tall, according to the CDC growth chart for boys aged 2–20 years, 125 cm is the median height for a 7.5-year-old boy. When calculating the height-adjusted BMD z-score, an age of 7.5 years will be used rather than the boy's actual age of 10 years. Mean z-scores at scheduled assessments and mean within-subjects changes from baselines (both SHP621-301 and SHP621-303) will be calculated for the DXA z-scores.

Summary of baselines (both SHP621-301 and SHP621-303) and change from baselines of z-scores adjusted for height at Visit 0 (Month 0), Visit 2 (Month 12), Visit 4 (Month 24), Visit 6 (Month 36), Visit 8 (Month 48), Visit 10 (Month 60), and Visit 12 (Month 72) will be presented in a table by location of DXA. Measurements at each scheduled visit will also be listed.

6.6.7 Extent of Exposure and Compliance

Exposure to Investigational Product:

Exposure to investigational product for the Safety Set will be summarized in terms of treatment duration, which is calculated as the number of weeks from the date of first dose of investigational product taken to the date of the last dose of investigational product taken excluding treatment interruption, inclusively. BOS treatment may be adjusted by a dose regimen change between 2 mg twice-daily and 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). BOS treatment may be interrupted by stopping and planning to reinitiate investigational product treatment up to 6 months. Investigational product must be resumed within 6 months and multiple treatment interruptions are permitted throughout study participation (i.e., 3 months on and 3 months off treatment). 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.

For all treated subjects, including those who terminated early, treatment exposure is the duration between the first dose date and last dose date excluding all treatment interruptions:

- Duration of the 1st interruption (days) = Last date of 1st treatment interruption – First date of 1st treatment interruption +1
- Duration of the 2nd interruption (days) = Last date of 2nd treatment interruption – First date of 2nd treatment interruption +1
- Duration of the nth interruption (days) = Last date of nth treatment interruption – First date of nth treatment interruption +1
- Total days of treatment interruption = Duration of the 1st interruption + Duration of the 2nd interruption + … + Duration of the nth interruption
- Duration of exposure (days) = Last dose date - First dose date + 1 - Total days of treatment interruption
- Length of Exposure (weeks) = Duration of exposure (days)/7

In addition, total dose administered (mL) and average daily dose will be calculated and summarized:

- Actual Average Daily Dose (mL/day) = Sum of the doses (mL)/Duration of exposure (days).

Continuous variables will be summarized by descriptive statistics (n, mean, SD, Q1, Q3, minimum, median, and maximum) for total dose, duration of exposure and average daily dose. Categorical variables will be summarized by the number of subjects in each category and the percentage of subjects out of the total for categories of length of exposure in weeks (0 to ≤24, >24 to ≤48, >48 to ≤72, >72 to ≤96, >96 to ≤120, >120 to ≤168, >168 to ≤216, >216 to ≤264, and >264) for all subjects in the Safety Set.

A listing will be created by subject number and visit giving the date and time of dose administration for the Safety Set.

Measurements of Treatment Compliance:

Compliance with investigational product will be assessed across all study visits. Subjects will be instructed to bring any remaining investigational product and empty bottles to each study visit. Designated site staff will evaluate compliance by questioning the subject and evaluating the amount of investigational product remaining. The subject will be questioned regarding any discrepancies. 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.

When a bottle is returned, the site will measure the amount of investigational product remaining in the bottle in centimeters and the remaining amount will be recorded as 9.375 cm if the

measured amount in the bottle is >9.375 cm. The volume taken in mL for each bottle will be determined in centimeters based on the equation below:

- Volume in mL = 210 cm^3 – [22.4 cm^2 × height of remaining product cm].

The percent compliance at each study visit will be determined as follows:

- (volume of investigational product taken in all returned bottles)/(expected volume of investigational product to be taken).

Compliance rate calculation will be based on the actual dose regimen.

Subjects will be considered compliant with investigational product if they received no less than 70% and no more than 130% of the intended dosing as assessed during the treatment period.

Study drug exposure and overall compliance will be summarized for the Safety Set. The number and percentage of subjects whose compliance is <70% or >130% as well as between 70% and 130% will be summarized. The overall approximate compliance rates will be summarized using descriptive statistics for the Safety Set.

6.7 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

Not applicable.

6.8 Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis

Not applicable.

6.9 Other Analyses

All other analyses will be performed using the FAS. [redacted]

6.9.1 Health-related Quality of Life Analyses

Adult Eosinophilic Esophagitis Quality of Life Questionnaire

The EoE-QoL-A will be performed in subjects ≥18 years of age at all scheduled visits, from screening visit (Visit 0) to the last visit in the treatment period.

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 swallowing anxiety.

Results of the EoE-QoL-A questionnaire will be summarized for each of the 5 scales/30 questions by presenting number of subjects and percentages at all scheduled visits.

Summary of change from baseline at all scheduled visits in EoE-QoL-A total score and each of the subscales will also be presented. Refer to Section 9.4 for derivation of EoE-QoL-A subscale scores.

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 at all scheduled visits, from screening visit (Visit 0) to Visit 12.

Subjects who turn 18 over the course of the study (i.e., after providing consent for SHP621-303), 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-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.

Results of both EQ-5D-3L and EQ-5D-Y descriptive system instruments will be summarized separately on each question by presenting number of subjects and percentages for all visits. Visual Analog Scale (VAS) at baseline and at each scheduled visit, and change from baseline at each scheduled visit will be summarized using the following descriptive statistics: the number of subjects, mean, standard deviation, standard error, minimum value, 25th percentile, median, 75th percentile, and maximum value.

Descriptive summary of EQ-5D-3L composite index score at each scheduled visit from screening and change from baseline at each scheduled visit will also be presented. Refer to Section 9.6 for derivation of EQ-5D-3L composite index score.

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 at all scheduled visits, from screening visit (Visit 0) to Visit 12. 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). 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).

Results of the PedsQL-EoE report (adolescents and parents separately) questionnaire will be summarized for each of the 7 scales/questions by presenting number of subjects and percentages for all visits.

Summary of change from baseline at all visits in PedsQL-EoE total score (adolescents and parents separately) and each of subscales will also be presented. Refer to Section 9.5 for derivation of PedsQL-EoE total and subscale scores.

Patient Global Impression of Severity (PGI-S)

The PGI-S is a global index that can be used to rate the severity of a specific condition - in this case, dysphagia in EoE. The PGI-S will be performed in all subjects at every visit starting at screening visit (Visit 0) through the last visit in the open-label treatment phase. Subjects will be asked to rate the severity of their dysphagia over the last 7 days using a 5-point scale at each visit:

- No dysphagia (0)
- Mild dysphagia (1)
- Moderate dysphagia (2)
- Severe dysphagia (3)
- Very severe dysphagia (4)

Change from baseline in PGI-S value at each assessment visit will be calculated as PGI-S at each assessment visit. Negative change from baseline value will indicate an improvement of dysphagia symptoms while a positive change from baseline value will indicate worsening of the symptoms.

Responses of the PGI-S will be summarized by presenting number of subjects and percentages by visit. Frequency of PGI-S at baseline and each postbaseline assessment and the change from baseline values will be summarized.

6.10 Interim Analyses

No interim analyses are planned.

Details on the statistical methods used for interim summaries generated for inclusion in regulatory filings (including safety updates) are provided in a separate Integrated Summary of Safety Statistical Analysis Plan (ISS SAP).

6.11 Data Monitoring Committee/Internal Review Committee/Other Data Review Committees

Not applicable.

7. REFERENCES

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8. CHANGES TO PROTOCOL PLANNED ANALYSES

Not applicable.

9. APPENDIX

9.1 Changes from the Previous Version of the SAP

Not applicable.

9.2 Data Handling Conventions

9.2.1 General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: n, mean, SD, median, Q1, Q3, minimum, and maximum. Categorical and count variables will be summarized by the number of subjects (n) and the percent of subjects in each category.

Unless specified otherwise, min/max will be presented to the same decimal places as the raw data. Percentage, mean, and median will be presented to 1 more decimal place than the raw data. Standard deviation and standard error will be presented to 2 more decimal places than the raw data.

BMI should be rounded to 1 decimal place for reporting.

Derived questionnaire scores, and other similar efficacy parameters recorded as integers, should be rounded to 1 decimal place for reporting.

Averaged laboratory and vital sign results eg, diastolic/systolic blood pressure and pulse (when taken in triplicate) should be rounded to 1 decimal place for reporting.

9.2.2 Definition of Baseline

Baseline of SHP621-303 is determined using the screening visit (Visit 0, also Visit 8 of SHP621-302) or the last observation prior to the first dose of BOS in SHP621-303, whichever is later.

Baseline of SHP621-302 is determined using the last assessment prior to the first dose of investigational product in SHP621-302.

Baseline of SHP621-301 is determined using the last assessment prior to the first dose of investigational product in SHP621-301.

9.2.3 Definition of Visit Windows

Visit window will be applied for unscheduled assessments of EGD with [redacted] and biopsy. If the scheduled visits are missing for endoscopy, then the most closest unscheduled endoscopy which within 3 months will be mapped to the scheduled visits.

9.2.4 Repeated or Unscheduled Assessments of Safety Parameters

For safety parameters, the early termination visits will be mapped to the next scheduled visits. The last visits per subject will be summarized in “End of Study” visit, including both last visits

of completers and early termination visits. Repeated or unscheduled assessments of safety parameters will be handled as follows:

If a subject has repeated assessments before the start of investigational product, then the results from the final assessment made prior to the start of investigational product will be used as baseline. If end of study assessments are repeated or unscheduled, the last post-baseline assessment will be used as the end of study assessment for generating descriptive statistics. If a subject has repeated assessments between the start of investigational product in the treatment period and the end of study visit, the assessments of unscheduled visits will be excluded in the table summary. However, all assessments will be presented in the data listings.

9.2.5 Missing Date of Investigational Product

When the date of the last dose of investigational product is missing for a subject in the Safety Set, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, then the last visit date when investigational product was returned will be used in the calculation of treatment duration.

9.2.6 Missing Date Information for Prior or Concomitant Medications (Therapies/Procedures)

For prior or concomitant medications (and/or therapies/procedures), including rescue medications, incomplete (i.e., partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first.

Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing day and month

- If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields.
- If the year of the incomplete start date is before the year of the date of the first dose of investigational product, then December 31 will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of investigational product, then the day of the date of the first dose of investigational product will be assigned to the missing day.
- If either the year is before the year of the date of the first dose of investigational product or if both years are the same but the month is before the month of the date of the first dose of investigational product, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the date of the first dose of investigational product or if both years are the same but the month is after the month of the date of the first dose of investigational product, then the first day of the month will be assigned to the missing day.

Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of investigational product is missing, it will be replaced with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the same as the year as of the date of the last dose of investigational product, then the day and month of the date of the last dose of investigational product will be assigned to the missing fields.
- If the year of the incomplete stop date is before the year of the date of the last dose of investigational product, then 31 December will be assigned to the missing fields.
- If the year of the incomplete stop date is after the year of the date of the last dose of investigational product, then 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of investigational product, then the day of the date of the last dose of investigational product will be assigned to the missing day.

- If either the year is before the year of the date of the last dose of investigational product or if both years are the same but the month is before the month of the date of the last dose of investigational product, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the last dose of investigational product or if both years are the same but the month is after the month of the date of the last dose of investigational product, then the first day of the month will be assigned to the missing day.

9.2.7 Missing Date Information for Adverse Events

For AEs, the default is to only impute incomplete (i.e., partially missing) start dates. Incomplete stop dates may also be imputed when calculation of the duration of an AE is required per the protocol. If imputation of an incomplete stop date is required, and both the start date and the stop date are incomplete for a subject, the start date will be imputed first.

Incomplete Start Date

Follow the same rules as in Section 9.2.6.

Incomplete Stop Date

Follow the same rules as in Section 9.2.6.

9.2.8 Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of investigational product, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the first dose of investigational product, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while both the actual and the imputed values will be used in data listings.

9.2.9 Missing Relationship to Investigational Product for Adverse Events

If the relationship to investigational product is missing for an AE starting on or after the date of the first dose of investigational product, a causality of "Related" will be assigned. The imputed values for relationship to investigational product will be used for incidence summaries, while both the actual and the imputed values will be presented in data listings.

9.2.10 Character Values of Clinical Laboratory Variables

If the reported value of a clinical laboratory variable cannot be used in a statistical analysis due to, for example, an alpha character string being reported for a numerical variable, the appropriately determined coded value will be used in the statistical analysis. However, the actual values as reported in the database will be presented in data listings.

Table 2 Examples for Coding of Special Character Values for Clinical Laboratory

Clinical Laboratory Test	Possible Results (in SI units)	Possible Results (in conventional units)	Coded Value for Analysis
Chemistry: ALT	<5 U/L	<5 U/L	0
Chemistry: AST	<5 U/L	<5 U/L	0
Chemistry: Total Bilirubin	<2 umol/L	<0.15 mg/dL	0
Urinalysis: Glucose	≥50 mg/dL	≥50 mg/dL	Positive
	≤0 mg/dL	≤0 mg/dL	Negative
Urinalysis: Ketones	>0 mg/dL	>0 mg/dL	Positive
Urinalysis: Protein	>0 mg/dL	>0 mg/dL	Positive
Urinalysis: pH	≥9.0	≥9.0	9.0

9.3 AESI Categories

The following AESIs are categorized with preferred terms (SOC where applicable) and will be summarized:

- Infections:
  - System Organ Classes of infections and infestations
  - Candidiasis related: oesophageal 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, paraesthesia, hypoaesthesia, 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: oedema peripheral, peripheral swelling, hypertension, palpitations

- Fractures: foot fracture, hand fracture, spinal fracture, upper limb fracture, humerus fracture, rib fracture, wrist fracture

- GI effects:
  - Oesophagitis pain, oesophagitis, vomiting, nausea, diarrhoea, abdominal pain, abdominal pain upper, constipation, abdominal distention, abdominal discomfort, hiatus hernia, dyspepsia, gastritis, gastritis erosive, chronic gastritis, dry mouth, erosive oesophagitis, and gastroesophageal reflux disease, mouth ulceration, gastric ulcer, duodenal ulcer, erosive duodenitis, mouth ulceration, esophageal ulcer, hepatic steatosis.

9.4 Calculation of Adult Eosinophilic Esophagitis Quality of Life (EoE-QOL-A) Subscale Scores

Adult Eosinophilic Esophagitis Quality of Life Questionnaire Standard Version (30 items)

The responses will be changed to a numeric equivalent using the following transformation: Not at all=4, Slightly=3, Moderately=2, Quite a Bit=1, Extremely=0.

Subscales will be the sum of set questions:

Eating/Diet Impact will be the sum of: Q2, Q9, Q16, Q24, Q25, Q26, Q27, Q28, Q29, Q30 and it will have a score range from 0–40.

Social Impact will be the sum of: Q14, Q17, Q19, Q22 and it will have a score range from 0–16.

Emotional Impact will be the sum of: Q1, Q5, Q6, Q7, Q11, Q13, Q21, Q23 and it will have a score range from 0–32.

Disease Anxiety will be the sum of: Q4, Q10, Q12, Q15, Q18 and it will have a score range from 0–20.

Swallowing Anxiety will be the sum of: Q3, Q8, Q20 and it will have a score range from 0–12. To compute subscale score, a weighted total sum will be used. Sum up the value of the response for each of the questions in that subscale and then divide by the total number of questions answered for that subscale.

9.5 Calculation of Pediatric Quality of Life – EoE (PedsQL-EoE, subjects 11–17 years of age) Subscale Scores

Pediatric Quality of Life – EoE Questionnaire

The responses will be transformed to a numeric equivalent using the following reverse scoring transformation: NEVER=100, ALMOST NEVER=75, SOMETIMES=50, OFTEN=25, ALMOST ALWAYS=0.

We will create dimensions by combining different questions to form the dimensions (Symptoms I, Symptoms II, Treatment, Worry, Communication, Food and Eating, Food Feelings, and Feeding Tube). Feeding Tube dimension will not be used for reporting or analyses.

SYMPTOMS I will be the sum of CRF questions ("Burning in chest", "Chest pain, ache, or hurt", "Feel like Throwing up", "Food coming back up throat", "Stomach aches or belly aches", "Throwing up").

SYMPTOMS II will be the sum of CRF questions ("Need drink to help swallow food", "Needing more time to eat", "Trouble swallowing", "food stuck in throat or chest").

TREATMENT will be the sum of CRF questions ("Getting allergy testing", "Getting an endoscopy", "Going to the doctor", "Not wanting to take medicines", "Remembering to take medicines").

WORRY will be the sum of CRF questions ("Getting allergy testing", "Getting an endoscopy Worry", "Getting sick in front of other people", "Going to the doctor", "Having EoE", "other people think about me because of EoE").

COMMUNICATION will be the sum of CRF questions ("Tell people about EoE", "Telling adults how feels", "Telling nurses how feels", "Telling friends how feels", "Telling parents how feels").

FOOD AND EATING will be the sum of CRF questions ("following diet restriction", "not eating same as family", "not eating same as friends", "sneaking food")

FOOD FEELINGS will be the sum of CRF questions ("Feeling Mad", "Feeling Sad", "Worry about foods allergic too").

FEEDING TUBE will be the sum of CRF questions ("Remember to use feeding tube", "Using a feeding tube").

The dimension score will not be calculated if more than 50% of the items in the scale are missing. To compute dimension score, a weighted total sum will be used. Sum up the value of the response for each of the questions in that dimension and then divide by the total number of questions answered for that dimension.

A total score will be the sum of all the items scores except for FEEDING TUBE.

Symptoms total scale score will be calculated as the sum of items scores when dimensions in Symptoms I and II divided by the number of items answered.

9.6 Calculation of the EQ-5D Score

ED-5D 3L and ED-5D Y Composite Index Score for US-Based Population

The US population-based EQ-5D index score ranges from -0.11 to 1.0 on a scale where

0.0 = death and 1.0 = perfect health. The negative index scores are regarded as worse than death. The calculations of the EQ-5D index scores are based on a regression equation derived from a large-scale survey of the general adult US population (Shaw et al., 2005). The regression equation for scoring is as follows:

X = 1 - 0.146 *MO2 - 0.558 *MO3 - 0.175 *SC2 - 0.471* SC3 - 0.140 *UA2 - 0.374 *UA3 - 0.173* PD2- 0.537* PD3 - 0.156* AD2 - 0.450* AD3 + 0.140 *D1 - 0.011 *I2-squared + 0.122* I3 + 0.015 *I3- squared

Where X is the US EQ-5D index score, and the independent variables are listed below

MO2: 1 if mobility is level 2; 0 otherwise

MO3: 1 if mobility is level 3; 0 otherwise

SC2: 1 if self-care is level 2; 0 otherwise

SC3: 1 if self-care is level 3; 0 otherwise

UA2: 1 if usual activities is level 2; 0 otherwise

UA3: 1 if usual activities is level 3; 0 otherwise

PD2: 1 if pain/discomfort is level 2; 0 otherwise

PD3: 1 if pain/discomfort is level 3; 0 otherwise

AD2: 1 if anxiety/depression is level 2; 0 otherwise

AD3: 1 if anxiety/depression is level 3; 0 otherwise

D1: number of dimensions beyond the first in level 2 or level 3 (i.e., 0 if 0, 1 if 1 dimension in level 2 or 3 or number of dimensions in level 2 or level 3 minus 1 otherwise)

I2-squared: squared number of dimensions beyond the first in level 2

I3: number of dimensions beyond the first in level 3

I3-squared: squared I3

9.7 Analysis Software

Statistical analyses will be performed using Version 9.4 (or newer) of SAS® on a suitably qualified environment.

10.0 ELECTRONIC SIGNATURE

[redacted]

16-Feb-2021 | 13:53:22 JST

[redacted] PhD
[redacted] Statistical and Quantitative Sciences-GI
Takeda

Date