Clinical and Regulatory Development

Biostatistics and Data Management

REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN

Title: A phase 2 Randomized, Double-Blind, Parallel, Placebo-Controlled Study of the Efficacy, Safety and Tolerability of Dupilumab in Adult Patients with Active Eosinophilic Esophagitis

Protocol: R668-EE-1324.04

Investigational product: Dupilumab (REGN668)

Sponsor: Regeneron Pharmaceuticals, Inc.

Statistician: [redacted]

Clinical Trial Manager: [redacted]

Clinical Study Director: [redacted]

Version/Date: Version 1 / 12Apr2017

The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AD	Atopic dermatitis
ADA	Anti-Drug Antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALT (SGOT)	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST (SGPT)	Aspartate aminotransferase
BUN	Blood urea nitrogen
CRF	Case report form
EEsAI	Eosinophilic Esophagitis Activity Index
EndoFLIP	Endolumenal functional lumen imaging probe
EoE	Eosinophilic esophagitis
EoE-EREFS	Eosinophilic Esophagitis-Endoscopic Reference Score
EoEHSS	Eosinophilic Esophagitis Histology Scoring System
EoE-QOL-A	Adult Eosinophilic Esophagitis Quality of Life (questionnaire)
ECG	Electrocardiogram
EOS	End of study EOT
	End of treatment
ET	Early termination
FAS	Full analysis set
HLT	High Level Term
ICF	Informed consent form
ICH	International conference on harmonization
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed effect model with repeated measures
PCSV	Potentially clinically significant value
PD	Pharmacodynamics
PK	Pharmacokinetic
PKAS	Pharmacokinetic analysis set
PPS	Per protocol set
PT	Preferred term

qw	Weekly
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis software
SC	Subcutaneous
SD	Standard deviation
SDI	Straumann Dysphagia Instrument
SOC	System organ class
TEAE	Treatment emergent adverse event
WHODD	World health organization drug dictionary

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying statistical approaches for the analysis of this study. The SAP is intended to be a comprehensive and detailed description of strategy and statistical techniques to be used to realize the analysis of data for R668-EE-1324 study.

This plan may be revised during the study to accommodate protocol amendments and to adapt to unexpected issues in study execution or data that affect planned analyses. The plan will be based on blinded data and will be finalized prior to the database lock.

1.1. Background and Rationale

Eosinophilic esophagitis (EoE) is an emerging, chronic, immune-/antigen-mediated disease characterized by esophageal dysfunction and eosinophil inflammation in the esophagus (Liacouras 2011, Weinbrand-Goichberg 2013, Zhang 2013). Adult patients with EoE have substantially impaired quality of life (QOL) due to dysphagia and the possible risk of food impaction (DeBrosse 2011, Falk 2014, Straumann 2008, Straumann 2003). Emergency endoscopy for prolonged food impactions is associated with a risk of severe esophageal injury. The prevalence of EoE in the general population was reported to range from 0.5 to 1 case per 100,000 persons (Dellon 2014a).

The pathogenesis of EoE is still unclear, however, growing evidence suggests that type 2 helper T cell (Th2)-mediated immune response plays an important role in the pathogenesis of EoE. Mutations in downstream Th2 functional genes including eotaxin-3 (chemokine [C-C motif] ligand [*CCL26*]), thymic and stromal lymphopoeitin (*TSLP*), and filaggrin (*FLG*) have been associated with EoE risk. Impaired barrier function of the esophageal epithelium is also thought to play a role in EoE pathogenesis. The data suggest that Th2 cytokines may be driving not only an inflammatory response, but also epithelial barrier dysfunction in the esophagus.

Consistent with the Th2-mediated inflammation observed in esophageal tissue, patients with EoE have high rates of comorbid Type 2 immune diseases, especially food allergies, atopic dermatitis (AD), asthma, and allergic rhinitis. The inflammatory damage to the esophageal epithelium results in symptoms of esophageal dysfunction, such as dysphagia. Chronic inflammation of the esophagus may also lead to remodeling, stricture formation, and fibrosis.

Current therapeutic approaches include chronic dietary elimination, swallowed topical formulation corticosteroids (not approved for the treatment of EoE in the US), and esophageal dilation. Although swallowed topical corticosteroids have been reported in clinical trials to induce partial clinical responses and histologic remission, they are not uniformly effective and can be associated with fungal infections as well as disease recurrence after discontinuation. There are currently no approved drug therapies for EoE.

Dupilumab is a human monoclonal antibody that targets the IL-4 receptor alpha subunit (IL-4Rα), a component of IL-4 receptors Type I and Type II, as well as the IL-13 receptor system. The binding of dupilumab to IL-4Rα results in blockade of the function of both IL-4 and IL-13 signal transduction. Dupilumab has demonstrated preliminary efficacy in 3 other Type 2/Th2 immune diseases: asthma, chronic sinusitis with nasal polyps, and moderate-to-severe

atopic dermatitis. Because IL-4 and IL-13 are likely key pathomechanisms in EoE, dupilumab treatment may improve inflammation and clinical symptoms.

This is a multicenter, randomized, double-blind, placebo-controlled, 2-arm, parallel-group, proof-of-concept study. This study will evaluate the effect of dupilumab on relieving EoE clinical symptoms and reducing esophageal inflammation in adults. Efficacy in this study will be assessed based on clinical signs and symptoms using the EoE-specific PROs currently in development, as well as on anatomical and histological findings from endoscopy with esophageal biopsies. The placebo control will provide a reliable reference for any apparent effects of the study treatment with active IL-4Rα inhibition. Repeat SC dose regimens as high as 300 mg qw (with or without a loading dose) for up to 16 weeks have previously been studied in phase 1, 2 and phase 3 clinical trials in healthy subjects as well as in patients with AD or asthma and were well tolerated. Therefore, a SC 600 mg loading dose followed by the repeat SC 300 mg qw dose, the highest SC repeat dose studied to date, was selected for this study.

1.2. Study Objectives

1.2.1. Primary Objective

The primary objective of the study is to assess the clinical efficacy of repeat SC doses of dupilumab, compared with placebo, to relieve symptoms in adult patients with active, moderate to severe EoE.

1.2.2. Secondary Objectives

The secondary objectives of the study are:

- To assess the safety, tolerability, and immunogenicity of SC doses of dupilumab in adult patients with active, moderate to severe EoE
- To assess the effect of dupilumab on esophageal eosinophilic infiltration
- To evaluate the PK of dupilumab in adult patients with EoE

1.2.3. Exploratory Objective

The exploratory objective of the study is to assess the effect of dupilumab on other esophageal biopsy pathologic features associated with EoE, as well as esophageal distensibility, which is reduced in EoE patients.

1.3. Modifications from the Statistical Plan in the Final Protocol

NA

1.4. Modifications from the Previously Approved SAP

NA

2. INVESTIGATIONAL PLAN

2.1. Study Design and Randomization

This is a phase 2, multicenter, double-blind, randomized, placebo-controlled study investigating the efficacy, safety, tolerability, PK, and immunogenicity of dupilumab in adult patients with EoE. Patients will be randomized in a 1:1 ratio to receive SC 600 mg dupilumab or SC placebo loading dose followed by weekly SC 300 mg dupilumab or SC placebo during the 12-week double-blind treatment phase. The randomization will be stratified by baseline Straumann Dysphagia Instrument (SDI) PRO score (≥5 and ≤7 versus >7).

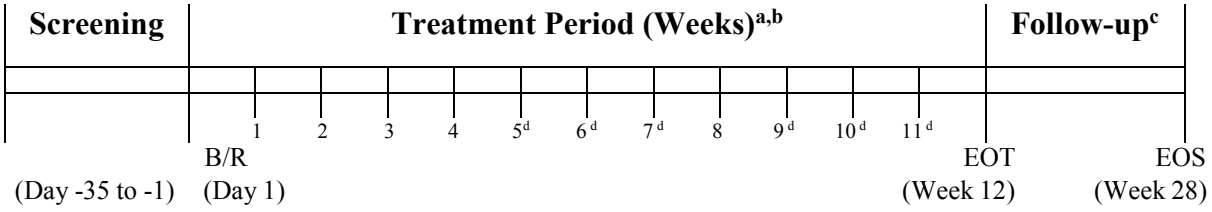
2.2. Sample Size and Power Considerations

The sample size calculations are based on the change from baseline in SDI score to week 12. The study of Straumann 2010 has a 2-week treatment period and the 3-point improvement from baseline is observed at end of week 2. A 3-point improvement from baseline is assumed for the study at both week 10 and week 12, so the power calculation for change from baseline in SDI score to week 12 is the same as the one at week 10. In the Straumann adult study, change from baseline in SDI score for active and placebo treatment group are -3.39 (2.46) [mean (maximum possible SD)] and -0.61 (2.19) [mean (maximum possible SD)] respectively.

A sample size of 18 patients per treatment arm will provide 94% power to detect a treatment effect, with an expected mean difference of 3 points in change from baseline to week 12 in SDI score between dupilumab and placebo at a 2-sided t-test with 5% significance level and an assumed SD of 2.46. Taking into account the assumed 15% dropouts, 22 patients per treatment arm will be enrolled.

2.3. Study Plan

The study will consist of 3 periods: screening, 12 week double-blind treatment, double-blind follow-up:



B/R = baseline/randomization; EOT = end of treatment; EOS = end of study.
Note: The scale is not linear.
[a] Patients will receive a weekly injection of study drug from day 1 through week 12 (with the last dose at week 11).
[b] Patients will be monitored at the study site for 30 minutes after each of the first 5 doses (visits 2 to 6) of study drug.
[c] Follow-up visits will occur every 4 weeks.
[d] Weeks 5, 6, 7, 9, 10, and 11 will be telephone visits.

After providing informed consent, patient eligibility will be assessed at the screening visit (to occur between day -35 and day -1). Patients who meet eligibility criteria will undergo day 1 baseline assessments. Patients will be randomized in a 1:1 ratio to receive dupilumab or placebo

during the 12-week double-blind treatment phase. After the 12-week double-blind treatment phase, patients will be followed off-study drug for an additional 16 weeks.

Patients may receive concomitant medications (except for prohibited medications) as needed, at the discretion of the investigator, while continuing study treatment. Frequency of use and type of product will be documented. If medically necessary, rescue medications or emergency esophageal dilation may be provided to study patients. Patients receiving rescue therapy will be discontinued from study treatment. These patients will remain blinded and will be asked to return to the clinic for all remaining study treatment visits and participate in all follow-up assessments according to the visit schedule.

Efficacy, safety, and laboratory assessments will be performed at specified time points throughout the study. Samples for the assessments of dupilumab concentration and assessment of anti-drug antibody (ADA) response to dupilumab, as well as research samples will be collected at specified time points throughout the study. In response to AE's of special interest like anaphylaxis or hypersensitivity additional samples closer to the event may be collected and analyzed for ADA, based on the judgement of the medical investigator and/or medical monitor.

The end of the double-blind treatment period visit occurs at week 12, 1 week after the last dose of study drug. The maximum duration of the double-blind study is approximately 33 weeks including screening and follow-up.

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (1998), the following populations of analysis will be used for all statistical analyses.

3.1. The Full Analysis Set (FAS)

The full analysis set (FAS) includes all randomized patients. Efficacy analyses will be based on the treatment allocated by the IVRS/IWRS at randomization (as randomized). This is the primary analysis population for efficacy analyses.

3.2. Per Protocol Analysis Set (PPS)

The per protocol analysis set (PPS) includes all patients in the FAS except for those who are excluded from this analysis because of major efficacy-related protocol violations.

A major efficacy-related protocol violation is one that may affect the interpretation of study efficacy results. The criteria of major efficacy-related protocol deviation are defined as following:

- Any major violations of efficacy-related entry criteria
  - Inclusion criteria 2, 3, 5
  - Exclusion criteria 8, 12
- Patients who received <80% of the scheduled doses during the double blind treatment period

Final determination of the PPS will be made in the blinded manner prior to the database lock.

3.3. The Safety Analysis Set (SAF)

The safety analysis set (SAF) includes all randomized patients who receive any study drug, and will be analyzed as treated.

The actual treatment group as treated is defined by the following rules:

- For a patient randomized to dupilumab,
  - if the patient received all placebo injections, the actual treatment will be assigned as placebo
  - if the patient received at least one dupilumab injection, the actual treatment will be assigned as dupilumab
- For a patient randomized to placebo,
  - if the patient accidentally received one or more dupilumab injections, the actual treatment will be assigned as dupilumab; otherwise it will remain as placebo

The safety analyses will be based on the SAF.

For safety summaries, three analysis periods are defined as follows:

- Week 12 treatment period is defined as

  Day 1 from start of administration of the first dose of study drug through week 12 of the double-blind period (85 days starting from the first dose of study drug if the date of week 12 treatment visit is unavailable).

- Follow-up period is defined as from week 12 of the double-blind period to the last visit of the double-blind period.
- Overall study Period is defined as day 1 to the date of the end of study visit, consisting of both the treatment and follow-up periods

3.4. The Pharmacokinetic Analysis Set (PKAS)

The PK analysis set includes all randomized patients who received any study drug and who had at least one non-missing PK sample result following the first dose of study drug, and will be analyzed as the treated groups defined in the SAF.

3.5. The ADA Analysis Set (AAS)

The ADA analysis set includes all treated patients who received any study drug and had at least 1 non-missing ADA result in the ADA assay following the first dose of the study drug.

3.6. Subgroups

Subgroups are defined by key baseline factors recorded on the CRF and listed as follows

Subgroups to be considered for efficacy/safety analyses:

- Age group (≥18-<40, ≥40-<65, ≥65)
- Sex (Male, Female)
- Baseline weight group (<70 kg, ≥70-<100 kg, ≥100 kg)

93% patients enrolled for this study are white so no subgroup for ethnicity or race as all patients are not Hispanic or Latino

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic and Baseline characteristics variables will be summarized:

- Demographic variables: Age at screening with grouping (year; ≥18-<40, ≥40-<65, ≥65), Sex, Ethnicity with grouping (Hispanic or Latino, Not-Hispanic or Latino), Race with grouping (White, Black, Asian, Other), Baseline weight with grouping (kg, <70; ≥70-<100, ≥100), Height (m), and BMI (kg/m^2; <15, ≥15-<25, ≥25-<30, ≥30),
- Baseline characteristics: Age at EOE diagnosis, Duration of EoE, age at first esophageal dilation, number of documented dysphagia episodes, SDI PRO score, EEsAI PRO score, EoE-QOL-A PRO score, EoE-EREFS, distensibility plateau, peak eosinophils/hpf, EoEHSS stage, EoEHSS grade, allergic disease, peripheral eosinophil counts, serum total Immunoglobulin E (IgE).

4.2. Medical History and EoE Disease Medical History

Medical history will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to MedDRA version 19.1 at the coding of CRO. Information on conditions related to EoE includes diagnosis of EoE and EoE treatment history.

4.3. Pre-treatment/ Concomitant Medications and Procedures

Medications/Procedures will be recorded from the day of informed consent until the EOS visit. Medications will be coded to the ATC level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO Drug Dictionary (WHODD) version Sep 2016 at the coding of CRO Patients will be counted once in all ATC categories linked to the medication.

Pre-treatment medications/procedures: medications taken or procedures performed prior to administration of the first study drug.

Concomitant medications/procedures: medications taken or procedures performed following the first dose of study drug through the EOS visit.

Prohibited concomitant medications/procedures during week 12 treatment period Treatment with the following concomitant medications is prohibited:

- Medications used for the treatment of EoE .
- Allergen immunotherapy.
- Patients who are not using PPI in the 8 weeks prior to screening cannot start PPI therapy prior to EOT visit
- Treatment with a live (attenuated) vaccine
- Treatment with an investigational drug (other than dupilumab)

Treatment with the following concomitant procedures is prohibited:

- Major elective surgical procedures
- Esophageal dilation (considered rescue procedure)
- Diet change.

If medically necessary (eg, for treatment of intolerable EoE symptoms) patients may be rescued with a prohibited medication or procedure at the discretion of the investigator. Patients who receive rescue treatment with a prohibited medication or procedure through week 12 will be permanently discontinued from study drug.

Rescue treatments for EoE: Blinded adjudication of rescue treatments will be implemented before database locks by considering the type of medications. A predetermined algorithm for rescue medications listed in Appendix 10.6 will be used to programmatically search the concomitant medications (CMs). The rescue CMs will be reviewed and adjudicated by the medical monitor in a blinded fashion.

All patients will complete the schedule of study visits and assessments whether or not they complete study treatment. Investigators should make every attempt to conduct efficacy and safety assessments immediately before administering any rescue treatment. An unscheduled visit may be used for this purpose if necessary.

4.4. Efficacy Variables

Due to failure with electronic diaries, data from many patients are missing for the week 12 analysis. Week 10 timepoint is therefore chosen as endpoints for SDI and EEsAI in a blinded fashion prior to database lock to increase available data for analysis. Week 12 remains the endpoints for other efficacy endpoints.

4.4.1. Primary Efficacy Variables

The primary efficacy endpoint is the change in the Straumann Dysphagia Instrument (SDI) patient reported outcome (PRO) score from baseline to week 10.

Straumann Dysphagia Instrument (SDI)

The SDI is a PRO that has been used in clinical studies to determine the frequency and intensity of dysphagia. The SDI has a 1-week recall period. Frequency of dysphagia events is graded on a 5-point scale: 0 = none, 1 = once per week, 2 = several times per week, 3 = once per day, and 4 = several times per day, and intensity of dysphagia events is graded on a 6-point scale: 0 = swallowing unrestricted, 1 = slight sensation of resistance, 2 = slight retching with delayed passage, 3 = short period of obstruction necessitating intervention (eg, drinking, breathing), 4 = longer-lasting period obstruction only removable by vomiting, and 5 = long-lasting complete obstruction requiring endoscopic intervention. The SDI total score is the sum of scores of frequency of dysphagia and intensity of dysphagia, and ranges from 0 to 9. In the Straumann adult study of swallowed budesonide TCS (Straumann, Gastroenterology 2010), a clinical response (improvement) was defined as a decrease in SDI score of at least 3 points from baseline. SDI score is the sum of scores of frequency of dysphagia and intensity of dysphagia. SDI score will be set to missing if score of frequency of dysphagia or score of

intensity of dysphagia is missing. If intensity of dysphagia event is greater than 0 and frequency of dysphagia is 0, then frequency of dysphagia will be set to 1.

4.4.2. Secondary Efficacy Variables

The secondary endpoints are:

- Percent change in weekly Eosinophilic Esophagitis Activity Index (EEsAI) PRO score from baseline to week 10
- Change in weekly EEsAI PRO score from baseline to week 10
- Percent change in weekly EEsAI PRO score from baseline to week 12
- Change in weekly EEsAI PRO score from baseline to week 12
- Percent change in the SDI PRO score from baseline to week 10
- Percent change in the SDI PRO score from baseline to week 12
- Change in the SDI PRO score from baseline to week 12
- Change in EoE-QOL-A PRO score from baseline to week 12
- Percentage of patients with SDI PRO response at week 10; where response is defined as a decrease of at least 3 points on the SDI compared to baseline
- Percentage of patients who achieve ≥40% improvement in EEsAI score from baseline to week 10
- Percent change in overall peak esophageal intraepithelial eos/hpf (400X) from baseline to week 12
- Change in EoE-EREFs (endoscopy visual anatomical score) from baseline to week 12
- Percentage of patients with use of rescue medication or procedure (eg, esophageal dilation) through week 12
- Incidence of treatment-emergent AEs

Eosinophilic Esophagitis Activity Index (EEsAI) PRO

The EEsAI is a multimodular index in development at University Hospital Inselspital (Berne, Switzerland), a part of the international EEsAI study group. The EEsAI PRO module (questionnaire) used in this study includes items related to the intensity and frequency of dysphagia, and the influence of specific food groups on dysphagia symptoms. The PRO instrument contains 5 domains addressing symptoms while eating or drinking includes items on duration, frequency, and severity of dysphagia, time required for meal intake, dysphagia upon consuming liquids, and pain when swallowing. The visual dysphagia question (VDQ) addresses the severity of dysphagia when consuming food of 8 distinct consistencies. The 8 food consistencies and examples of foods to illustrate those consistencies are: (1) solid meat (such as steak, chicken, turkey, and lamb), (2) soft foods (such as pudding, jelly, and apple sauce), (3) dry rice or sticky Asian rice, (4) ground meat (hamburger and meatloaf), (5) fresh white untoasted bread or similar foods (such as doughnuts, muffins, and cake), (6) grits, porridge (oatmeal), or rice pudding, (7) raw fibrous foods (such as apples, carrots, and celery), and (8) French fries. The

behavioral adaptations (avoidance, modification, and slow eating [AMS] of various foods) are assessed in the context of consuming 8 distinct food consistencies. The total EEsAI PRO score ranges from 0 to 100. The details of the calculation are provided in Appendix 10.5 . The EEsAI PRO utilizes 24-hour and 1-week recall periods. Patients will electronically complete this questionnaire daily and weekly from the beginning of screening through end of study or early termination. EEsAI score will be set to missing if one of 5 domain scores is missing.

Derived weekly EEsAI score will be produced by average daily EEsAI score for each patient and calculated as the prorated average of the daily EEsAI score. For example, if there are 4 daily EEsAI score in a week, the prorated average = (score1 + score2 + score3 + score4)/4. A minimum of 4 days nonmissing daily score in a week is required to calculate the derived weekly score. If there are <4 days of daily score, the derived weekly score will be missing. Derived weekly EEsAI score will cover the same time period as the weekly EEsAI score.

Details for calculation EEsAI score can be found in Appendix 10.5.

Endoscopy with Esophageal Biopsies

Esophageal biopsies will be obtained by endoscopy at the screening and week 12 visits. A total of 9 mucosal pinch biopsies will be collected at each time point from 3 esophageal regions: 3 proximal, 3 mid, and 3 distal. Two samples from each region will be used for the histology. To participate in the study, patients must have a peak intraepithelial eosinophil count ≥15 eos/hpf (400X) in at least 2 of the 3 esophageal regions sampled. Peak esophageal eos/hpf (400X) will be determined for each of the 3 esophageal regions (proximal, mid, and distal) and overall at each time point. Mean peak of esophageal eos/hpf (400X) will be calculated from the peak count at each of the 3 esophageal regions for each patient at each time point.

EoE-EREFS

The EoE-EREFS (endoscopy visual anatomical score: Exudates, Rings, Edema, Furrows, Stricture) will be used to measure the endoscopically identified EoE esophageal mucosal inflammatory and remodeling features. This instrument includes a total of 12 items related to the presence and severity of esophageal features. The specific esophageal features include: rings (absent, mild, moderate, severe, not applicable); stricture (yes, no, not applicable); diameter of the stricture (if applicable); exudates (absent, mild, severe), furrows (absent, present); edema (absent, present). Total scores for edema, rings, furrows and exudate, stricture scores will be calculated, will range from 0 to 9. Also total scores excluding stricture and inflammation subscore (edema+exudate+furrows) and remodeling subscore (ring+stricture) will be calculated. Estimated diameter of stricture will be stratified into group (>=18 mm, 15-17, 12-14, 9-11, 6-8) and assigned severity scores from 0 to 4.

Adult Eosinophilic Esophagitis Quality of Life Questionnaire

The EoE-QOL-A questionnaire is a validated disease-specific measure of health-related quality of life in EoE patients. The instrument used in this study, the EoE-QOL-A v.3.0, includes 30 items related to 5 established domains such as social functioning, emotional functioning, and disease impact of daily life experiences. The EoE-QOL-A has a 1-week recall period. The items are graded on a 5-point scale from 1 to 5 as: ‘Not at All’=5, ‘Slightly’=4, ‘Moderately’=3, ‘Quite a bit’=2, and ‘Extremely’ =1.

Subscales	Score Range	Items
Eating/Diet Impact	0-40	Q2, Q9, Q16, Q24, Q25, Q26, Q27, Q28, Q29, Q30
Social Impact	0-16	Q14, Q17, Q19, Q22
Emotional Impact	0-32	Q1, Q5, Q6, Q7, Q11, Q13, Q21, Q23
Disease Anxiety	0-20	Q4, Q10, Q12, Q15, Q18,
Swallowing Anxiety	0-12	Q3, Q8, Q20
Overall Score	0-120	Q1-Q30

If less than 40% of EoE-QOL-A questionnaire for a domain are missing, the score for the domain will be imputed by a weighted average calculated by dividing sum of scores by the total number of items answered, recommended by the developer of the instrument. If more than 40% of questionnaire for a domain are missing, the total score for the domain will be set to missing.

This assessment will be recorded by the patient in a questionnaire at baseline and then monthly through end of study or early termination.

4.4.3. Exploratory Efficacy Variables

Exploratory efficacy variables include:

- Change in mean esophageal intraepithelial eosinophil counts (eos/hpf) [calculated using peak count from each esophageal site] from baseline to week 12
- Proportion of patients who achieve esophageal intraepithelial eosinophil count <1 eos/hpf at week 12
- Change in Collins Histology Score from baseline to week 12
- Change in esophageal distensibility plateau as measured by functional lumen imaging from baseline to week 12

Collins Histology Score

The Collins Histology Score, also known as the eosinophilic esophagitis histology scoring system (EoEHSS), is a method for evaluating the grade and stage of multiple pathologic features in esophageal biopsies from EoE patients (Collins et al. 2016). EoEHSS evaluates eight features: eosinophil density, basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, dilated intercellular spaces, surface epithelial alteration, dyskeratotic epithelial cells, and lamina propria fibrosis. Severity (grade) and extent (stage) of abnormalities were scored by a central, blinded pathologist for each parameter using a 4-point scale (0 normal; 3 maximum change). Composite scores for both grade and stage at 3 esophageal regions (proximal, mid, and distal) will be created by summing the individual 8 features scores. Due to anticipation of at least 50% missing data for LPF (lamina propria will likely be absent in at least 50% of biopsies), composite scores based on the other 7 features will be produced after excluding lamina propria score. An overall peak EoEHSS grade and stage score for a patient, as well as the peak grade and stage score for each individual region (proximal, mid and distal) will be generated.

Esophageal distensibility

The assessment of esophageal distensibility utilizing the endolumenal functional lumen imaging probe (EndoFLIP, Crospon, Ireland) will also be performed, with measurements taken as part of the endoscopy procedure performed at screening and week 12. The EndoFLIP device is a catheter based procedure that measures the cross sectional area at multiple sites along the esophagus with simultaneous intraluminal pressure recordings during volumetric distension of the esophagus. The analyses of cross sectional area versus pressure relationships of the esophagus allow for determination of esophageal compliance as well as the distensibility plateau (DP).

4.5. Safety Variables

4.5.1. Adverse Events and Serious Adverse Events Variables

Adverse events and serious adverse events will be collected from the time of informed consent signature and then at each visit until the end of the study. All adverse events are to be coded to a "Preferred Term", "High Level Term" and the associated primary "System Organ Class (SOC)" according to MedDRA version 19.1.

An **Adverse Event** is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product. An AE can, therefore, be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal (investigational) product.

AEs also include: any worsening (i.e., any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug; abnormal laboratory findings considered by the investigator to be clinically significant; and any untoward medical occurrence.

A **Serious Adverse Event** is any untoward medical occurrence that at any dose results in death; is life-threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/ incapacity; is a congenital anomaly/ birth defect; or is an important medical event.

The criteria for determining whether an abnormal laboratory, vital sign or ECG finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in dosing (outside of protocol-stipulated dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy

Treatment-emergent adverse events are defined as those that are not present at baseline or those that represent an exacerbation of a preexisting condition during the double blind period, follow up period.

4.5.2. Laboratory Safety Variables

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed by a central laboratory.

Blood samples for serum chemistry and hematology testing will be collected at time points according to the schedule in Appendix 10.2.

Blood Chemistry

Sodium	Total protein, serum	Total and indirect bilirubin
Potassium	Creatinine	Total cholesterol
Chloride	Blood urea nitrogen (BUN)	Low-density lipoprotein (LDL)
Carbon dioxide	AST	High-density lipoprotein (HDL)
Calcium	ALT	Triglycerides
Glucose	Alkaline phosphatase	Uric acid
Albumin	Lactate dehydrogenase (LDH)	CPK

Hematology with Differential

Hemoglobin	Differential:
Hematocrit	Neutrophils
Red blood cells (RBCs)	Lymphocytes
White blood cells (WBCs)	Monocytes
Red cell indices	Basophils
Platelet count	Eosinophils

Urinalysis

Urine samples for urinalysis will be collected to measure overall patient health at time points according to the schedule in Appendix 10.2.

Microscopic analysis will only be done in the event of abnormal dipstick results.

Color	Glucose	RBC
Clarity	Blood	Hyaline and other casts
pH	Bilirubin	Bacteria
Specific gravity	Leukocyte esterase	Epithelial cells
Ketones	Nitrite	Crystals
Protein	WBC	Yeast

4.5.3. Vital Sign Variables

The following vital signs parameters will be collected:

- Weight (kg) and height (cm)
- Respiratory rate (bpm)
- Heart rate (beats/min)
- Sitting systolic and diastolic blood pressures (mmHg)
- Body temperature (^{o}C)

Height is only measured at screening. Other vital signs are collected pre-dose at every scheduled and unscheduled clinic visit.

4.5.4. 12-Lead Electrocardiography (ECG) Variables

Standard 12-Lead ECG parameters include: Ventricular HR, PR interval, QRS interval, corrected QT interval (QTc Fridericia [QTcF] =QT/[$RR^{0.33}$] and QTc Bazett [QTcB]=QT/[$RR^{0.5}$]) ECG status: normal, abnormal not clinical significant or abnormal clinical significant. Electrocardiograms should be performed before blood is drawn during visits requiring blood draws. A standard 12-lead ECG will be performed at scheduled time points indicated in Appendix 10.2 Schedule of Events.

4.5.5. Physical Examination Variables

The physical examination variable values are dichotomized to normal and abnormal.

A thorough and complete physical examination will be performed at time points according to the schedule in Appendix 10.2.

4.5.6. Pharmacokinetic (PK) Variables

Samples for drug concentration will be collected at scheduled time points indicated in Appendix 10.2 Schedule of Events. Due to the sparse nature of the data, only descriptive analyses will be performed. Pharmacokinetic variables may include but not limited to C_{trough} over time, C_{last} and T_{last}.

4.6. Antibody (ADA) Variable

ADA samples collected at day 1 (baseline) , Week 12 (EOT), Week 28 (EOS) and at early termination (ET) will be analyzed for ADA.

The variables include ADA response status and titer as follows:

- Total subjects negative in the ADA assay at all time points analyzed
- Total subjects with pre-existing immunoreactivity - defined as either an ADA positive response in the assay at baseline, with all post first dose ADA results negative, OR a positive response at baseline with all post first dose ADA results less than 4-fold over baseline titer levels.
- Total subjects with treatment-emergent response, defined as a positive response in the ADA assay post first dose when baseline results are negative or missing.

  The treatment emergent responses will be further characterized as Persistent, Indeterminate or Transient

  - Persistent Response – defined as a treatment emergent ADA response with two or more consecutive ADA positive sampling time points separated by greater than (>) 12-week period, with no ADA negative samples or any missing sample in between.
  - Indeterminate Response – defined as a treatment-emergent response with only the last collected sample positive in the ADA assay
  - Transient Response - defined as a treatment emergent ADA positive assay response that is not considered persistent or indeterminate.
- Total subjects with treatment-boosted response, defined as a positive response in the ADA assay post first dose that is greater than or equal to 4-fold over baseline titer levels, when baseline results are positive
- Titer Values (Titer value category)
  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤ 10,000)
  - High (titer >10,000)

ADA positive samples will be further characterized for presence of neutralizing antibody response in the NAb assay.

5. STATISTICAL METHODS

For continuous variables, descriptive statistics will include the following: the number of subjects reflected in the calculation (n), mean, median, standard deviation, Q1 and Q3, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

5.1. Demographics and Baseline Characteristics

Demographics and Baseline Characteristics will be summarized by treatment groups based on FAS. Listing of demographics and baseline characteristics will be presented.

5.2. Medical and EoE History

Medical history will be summarized by primary SOC and PT for each treatment group. The table will be sorted by decreasing frequency of SOC followed by PT based on the overall incidence across treatment groups.

Medical history will be listed, sorted by treatment groups based on the SAF.

5.3. Pre-treatment/Concomitant Medications/Procedures

Number and proportion of subjects taking prior/concomitant medications, prohibited medications/procedures and rescue medications/procedures will be summarized, sorted by decreasing frequency of ATC Level 2 and ATC level 4, based on the overall incidence for the dupilumab treatment group.

The procedure will be summarized by treatment group to MedDRA version 19.1 by system organ class (SOC) and preferred term (PT) and sorted by decreasing frequency of SOC and PT, based on the overall incidence for dupilumab treatment group.

Listing of pre-treatment medication and concomitant medications will include generic name and ATC levels 2 and 4, indication, study day onset (for medications started before treatment, the study day onset (defined as date of medication start - date of the first dose; for medications started on or after treatment, the study day onset = date of medication start - date of the first dose +1), the study end date (defined similarly as for study day onset), ongoing status, dose, frequency, route.

The detailed information of rescue medications/procedures including duration of use and incidence of use will be summarized. Kaplan Meier curves for time to first rescue use may be generated.

5.4. Subject Disposition

The following summaries by table will be provided:

- The total number of screened patients
- The total number of randomized patients: received a randomization number
- The total number of patients in each analysis set

- The total number of patients who discontinued the study treatment and the reasons for the discontinuation
- The total number of patients who discontinued the study, and the reasons for discontinuation
- Number of patients who entered into follow-up period.

The following listings will be provided:

- Listing of subject disposition including: date of randomization, date of the last visit, received dose, completed study drug or discontinued by reason, completed study or discontinued by reason
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized.
- A listing of patients prematurely discontinued from the study or treatment, along with reasons for discontinuation, summary tables of reasons will be provided
- Summary table with listing of protocol deviations will be provided

5.5. Dose administration

The compliance with protocol-defined study drug will be calculated as follows:

Treatment Compliance =

(Number of investigational product injections])/(Number of planned investigational product injections]) x 100%

Loading doses for the same patient will be counted as 1 study drug administration.

Summary of study drug administration will include the number of study drug doses administered and treatment compliance. The treatment compliance will be presented by the following specific ranges for each treatment group for the double blind period: <80% and ≥80%.

Listing of dose administration: including date/time, study day, number of injections, locations of injections, dosing information and whether or not the total dose is administered for each dose will be presented.

If subjects received treatment different from the randomized treatment or stopped treatment due to an AE, or overdosed, the listings will be provided.

5.6. Treatment Exposure and Observation Period

The duration of treatment during the study, in days, will be presented by treatment group and calculated as:

(Date of last study drug injection– date of first study drug injection) + 7

Note: exposure will be calculated based on the last study drug injection date and first study drug injection date, regardless of temporary dosing interruption.

The duration of exposure during the study will be summarized for each treatment group using number of patients, means, SD, minimums, Q1, medians, Q3, and maximums.

In addition, the duration of exposure will be summarized categorically by counts and percentages for each of the following categories and cumulatively by these categories as well:

≥ 7 days, ≥ 14 days, ≥ 21 days, ≥ 28 days, ≥ 35 days, ≥ 42 days, ≥49 days, ≥ 56 days, ≥ 63 days, ≥ 70 days, ≥ 77 days, ≥ 84 days.

The duration of observation period during the study, in days, is calculated as:

[Date of the last visit of double blind and follow up period – date of the first study injection] +1.

The duration of observation period will be summarized descriptively as a quantitative data (n, mean, SD, median, Q1 and Q3, minimum and maximum). In addition, the number (%) of subjects with observation periods will be presented by specific time periods. The time periods of interest is specified as: ≥ 8 days, ≥ 15 days, ≥ 22 days, ≥ 29 days, ≥ 36 days, ≥ 43 days, ≥50 days, ≥ 57 days, ≥ 64 days, ≥ 71 days, ≥ 78 days, ≥ 85 days, ≥113 days, ≥141 days, ≥169 days, ≥197 days.

5.7. Analyses of Efficacy Variables

5.7.1. Hypothesis Testing and Multiplicity Control

For all efficacy variables, the analysis will be a comparison of dupilumab and the placebo treatment groups. The following null and alternative hypotheses for the primary endpoint will be tested for dupilumab group and the placebo group:

Let μ_0 and μ_1 be the population mean of the primary endpoint at week 10 under placebo and dupilumab, respectively. The hypothesis that will be tested is "H0: $\mu 0 = \mu 1$" versus "H1: $\mu 0 \neq \mu 1$".

To account for the impact of rescue medication on the efficacy effect during 12 week double blinded period:

- Continuous efficacy endpoints: if a patient receives rescue medication, the data collected after rescue medication initiated will be treated as missing.
- Categorical efficacy endpoints: responder data will be counted as non-responders after use of rescue medication or procedure.

The analyses of efficacy variables are described in the subsections below and summarized in Appendix 10.1.

There will be no adjustment of multiplicity for the secondary efficacy endpoints in this proof-of-concept study.

The efficacy data endpoints for the follow-up period will be summarized descriptively. No formal statistical test will be performed for efficacy endpoints in the follow-up period.

5.7.2. Analysis of Primary Efficacy Variables

The change in the SDI score at week 10 from baseline will be analyzed in the full analysis set (FAS) using multiple imputation (MI), with an analysis of covariance (ANCOVA) model with treatment group as fixed effect, and the baseline SDI value as continuous covariate. (primary approach).

Due to the substantial imbalance at baseline in the number of patients in the two randomization strata (only 12.8% patients in the strata of baseline SDI > 7), the multiple imputation and ANCOVA model will not use randomization strata as a factor.

Patients' efficacy data through week 12 after rescue medication usage will be set to missing first, and then be imputed by the MI method.

Missing data from the FAS will be imputed 50 times to generate 50 complete data sets by using the SAS procedure MI following the 2 steps below:

Step 1: The monotone missing pattern is induced by Markov Chain Monte Carlo (MCMC) method in MI procedure. The monotone missing pattern means that if a patient has missing value for a variable at a visit, then the values at all subsequent visits for the same variable are all missing for the patient.

Step 2: The missing data at subsequent visits will be imputed using the regression method for the monotone pattern with adjustment for covariates including treatment groups, and baseline SDI score.

Data of each of the 50 complete datasets will be analyzed using an analysis of covariance (ANCOVA) model with treatment group as fixed effect, and the baseline SDI value as continuous covariate. SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from these multiple analyses using Rubin's formula.

The imputation model will include:

- The covariates included in the ANCOVA model, including the treatment group and the baseline SDI value.
- Observed efficacy values from every clinic visit up to week 10

The ANCOVA model will provide least-squares means at week 10, and at other time points for each treatment group, with the corresponding standard error, confidence interval, and the p-value for treatment comparisons. The graph of LS-mean +/- SE by visit will be provided.

Sensitivity analyses

In addition to the MI method described previously, sensitivity analyses for the primary efficacy endpoint will be conducted as described below:

1. The sensitivity analysis will use MI method, followed by ANCOVA based on all observed data no matter if rescue medication is used.
2. This sensitivity analysis will use ANCOVA model. The efficacy data will be set to missing after rescue medication is used. The post-baseline last-observed-case-forward (LOCF) method will then be used to impute missing values.
3. This sensitivity analysis will use ANCOVA model. The efficacy data will be set to missing after rescue medication is used. The post-baseline worst observation carried forward (WOCF) method will then be used to impute missing values.
4. This sensitivity analysis will use ANCOVA model, including all observed data, no matter if rescue medication is used.

5.7.3. Analyses of Secondary Efficacy Variables

The continuous secondary efficacy endpoints listed in Section 4.4.2 will be analyzed using the same approach as that used for the analysis of the primary endpoints. Inside step 2 of MI procedure, the missing data at subsequent visits will be imputed using the regression method for the monotone pattern with adjustment for covariates including treatment groups, baseline SDI score and relevant baseline value. Data of each of the 50 complete datasets will be analyzed using an analysis of covariance (ANCOVA) model with treatment group as fixed effect, and the baseline SDI value and relevant baseline value as continuous covariates.

Due to the substantial imbalance at baseline in the number of patients in the two randomization strata (only 12.8% patients in the strata of baseline SDI > 7), the imputation and ANCOVA will not use randomization strata as a factor. Instead the model includes the baseline SDI score as a continuous covarate.

Categorical analyses will be performed on responder data. Comparisons between dupilumab and placebo will be done using the Fisher exact test. Patients with early withdrawals or use of rescue medication or procedure will be counted as non-responders.

5.7.4. Analyses of Exploratory Efficacy Variables

The exploratory efficacy endpoints listed in Section 4.4.3 will be analyzed in the same method as the analysis method used for primary endpoint and secondary endpoint.

5.7.5. Subgroup Analysis

Subgroups described in Section 3.6 for the primary and key secondary efficacy endpoints listed in Section 4.4.1 and Section 4.4.2 will be analyzed. The analysis method for the subgroup analysis will be conducted using the primary analysis of continuous and category endpoints described in Section 5.7.1 and Section 5.7.2. Interactions between the subgroups and treatment groups will also be tested.

5.8. Analysis of Safety Data

The summary of safety and tolerance will be performed based on SAF.

The safety analysis will be based on the reported AEs, clinical laboratory evaluations, physical examination, vital signs, and 12-lead ECG.

Thresholds for treatment-emergent Potentially Clinically Significant Values (PCSVs) in laboratory variables, vital signs and ECG are defined in Appendix 10.3. Treatment-emergent PCSV is any PCSV developed or worsened in severity compared to the baseline during the treatment and follow-up period.

The time interval to detect any event or abnormality is between the first injection of study medication and EOS.

5.8.1. Analysis of Adverse Events

The number and proportion of patients will be summarized separately for the week 12 treatment period, the follow-up period, and overall study period, described in Section 3.3. Adverse event (AE) incidence tables will be presented for each treatment group, including the number (n) and

percentage (%) of patients experiencing an AE, where multiple instances of the same event occur in the same patient the event will be counted only once for that patient. The denominator for computation of percentages is the number of patients in each treatment group.

The number and proportion of patients reporting TEAEs will be summarized, sorted by decreasing frequency of SOC and PT for the dupilumab group. The number and proportions of patients reporting TEAEs will also be summarized, sorted by decreasing frequency of SOC, HLT and PT for the dupilumab group.

Patient listings will be provided for all SAEs, death, and TEAEs leading to permanent treatment discontinuation.

The following variables will be included in the listing:

- Patient ID
- Treatment group
- Age/sex/race
- System Organ Class (SOC)
- High Level Term (HLT)
- Preferred Term (PT)
- Verbatim Term
- AE start date and end date/ongoing (using both calendar days and study days)
- AE Duration
- Relationship of AE to study drug: unrelated or related
- Action taken: Dose withdrawn temporarily, Dose reduced, Dose withdrawn permanently, Dose not changed, Not known or Not applicable
- Severity: using a 3–point scale (mild, moderate, or severe)
- Treatment: none, medication, surgery or others
- Outcome: recovered/resolved, recovered/resolved with sequelae, recovering/resolving, not recovered/not resolved, fatal or unknown

Overall TEAE summary

The overall summary of TEAEs will be provided with number and proportions of patients with any:

- TEAE
- TEAE related to study drug
- Serious TEAE
- TEAE of special interest (AESI)
- TEAE leading to death

- TEAE leading to permanent treatment discontinuation

AESI

- Anaphylactic reactions
- Acute allergic reactions that require immediate treatment
- Severe injection site reactions that last longer than 24 hours
- Mycosis fungoides
- Cutaneous T-cell dyscrasia
- Any severe infection
- Any infection requiring treatment with parenteral antibiotics
- Any infection requiring treatment with oral antibiotics/anti-viral/anti-fungal for longer than 2 weeks
- Any clinical endoparasitisis
- Any opportunistic infection
- Suicidal behavior

Appendix_10.5 provides a list of AESIs search criteria.

TEAE Incidence

Number and proportions of patients reporting TEAEs will be summarized for the following TEAEs:

- TEAEs
  - TEAEs by SOC/PT
  - TEAEs by SOC/HLT/PT
  - TEAEs by PT
  - TEAEs by SOC/HLT/PT with HLT ≥5% in any treatment groups
  - TEAEs by SOC/PT with PT ≥5% in any treatment groups
  - TEAEs by severity by SOC/PT
  - Severe TEAEs by SOC/PT
  - Severe TEAEs by SOC/HLT/PT
  - TEAEs related to study medication as assessed by the investigator by SOC/PT
  - Severe TEAEs related to study medication as assessed by the investigator by SOC/PT
  - TEAE of special interest/TEAE by category
- Serious TEAEs

  - Serious TEAEs by SOC/PT
  - Serious TEAEs by SOC/HLT/PT
  - Serious TEAEs related to study medication as assessed by the investigator by SOC/PT
- TEAEs leading to permanent discontinuation of study treatment by SOC/PT
- Death by SOC/PT

Summary of the most frequent (≥5%) TEAEs by SOC, HLT, PT, respectively, in the dupilumab groups and in the overall study population will be provided.

SAEs/AESI during the Week 12 treatment period, follow-up period, and overall period will be listed.

5.8.2. Analysis of Clinical Laboratory Measurements

Laboratory measurements include clinical chemistry, hematology and urinalysis results, and will be converted to standard international units and US conventional units. Summaries of laboratory variables will include:

- Descriptive statistics of laboratory result and change from baseline by visit
- The number (n) and percentage (%) of subjects with abnormal lab value during study whose screening and baseline values are normal (overall and per each lab parameter)
- The number (n) and percentage (%) of subjects with treatment-emergent PCSVs during study, depending on data
- Shift tables based on baseline normal/abnormal may be used to present the results for parameters of interest

Listing of all laboratory parameters value, normal range, abnormal flag and treatment-emergent PCSV by subject and visit will be provided.

5.8.3. Analysis of Vital Signs

Summaries of vital sign variables will include:

- Descriptive statistics of vital sign variable and change from baseline by visit
- The number (n) and percentage (%) of subjects with treatment-emergent PCSV, depending on data
- Shift tables based on baseline normal/abnormal may be used to present the results for parameters of interest

Listings will be provided with flags indicating the treatment-emergent PCSVs, depending on data.

5.8.4. Analysis of Physical Exams

The number (n) and percentage (%) of subjects with abnormal physical exams will be summarized at time points according to the schedule in Appendix 10.2. by treatment group. A summary of treatment-emergent abnormal findings will be provided.

5.8.5. Analysis of 12-Lead ECG

Summaries of 12-lead ECG parameters by treatment group will include:

- Each ECG parameter and change from baseline
- The number (n) and percentage (%) of subjects with PCSV, depending on data
- ECG status (i.e. normal, abnormal) summarized by a shift table

Listings will be provided with flags indicating PCSVs, depending on data.

5.9. Analysis of Pharmacokinetic Data

Due to the sparse nature of the drug concentration data, only descriptive analyses will be performed. Concentrations will be summarized at each time point. Pharmacokinetic variables may include but not limited to C_{trough} over time, C_{last} and T_{last}, as appropriate. Results will be described in the Clinical Pharmacology report.

No formal statistical analysis will be performed.

Impact of Drug Concentration on Safety and Efficacy

The association of drug concentration and efficacy and/or safety endpoints may be performed, as appropriate.

5.10. Analysis of ADA Data

The ADA variables described in Section 4.6 will be summarized using descriptive statistics by treatment arm in the ADA analysis set. Frequency tables of the proportion of patients with pre-existing immunoreactivity, treatment-emergent ADA response, persistent ADA response, and titers will be presented as absolute occurrence (n) and percent of patients (%), presented by treatment groups. Listing of all ADA titer levels and neutralizing antibody status will be provided for patients with a positive response in the ADA assay.

The following summaries will be performed on the AAS:

- Number (%) of patients with pre-existing immunoreactivity, treatment-emergent ADA, and persistent ADA response by treatment group
- Number (%) of patients with ADA peak titer achieved in each of the three ADA Titer value category (Low, Medium and High) as mentioned in Section 4.6, by treatment group
- ADA peak titers using descriptive statistics (median, minimum and maximum) for treatment-emergent and persistent ADA response by treatment group

- ADA titers using descriptive statistics (median, minimum and maximum) by treatment group and at each ADA time point analyzed
- Number (%) of patients with NAb status (negative or positive in the NAb assay) in treatment-emergent and persistent ADA response subjects by treatment group

Association between ADA variables (e.g. ADA peak titer, treatment-emergent, persistent ADA responses, and NAb status) and functional dupilumab concentrations may also be explored. plotting and comparing mean functional dupilumab concentrations over time by ADA response (treatment emergent and persistent) and NAb status and by peak titer category.

Impact of ADA on Safety and Efficacy

Analysis of the association of of treatment emergent and persistent ADA response and NAb status with safety endpoints may be performed on SAF.

The safety assessment will primarily focus on the following events:

- Hypersensitivity (SMQ: Hypersensitivity [Narrow])
- Anaphylaxis (SMQ: Anaphylaxis [Narrow])

Number (%) of patients with the above mentioned safety events will be summarized by treatment emergent, persistent ADA response status and neutralizing antibody status during the TEAE period.

Associations between ADA variables (e.g. ADA peak titer, treatment-emergent, persistent ADA responses and NAb status), and efficacy endpoints (clinical response) may be explored by plotting and comparing the mean % change from baseline in clinical response over time by ADA response (treatment emergent and persistent) and NAb status and by peak titer category.

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of study drug. If any randomized patients are not treated, the baseline will be the last value on or prior to the randomization. The following rules specify the determination by both date/time information:

1. For the AE, lab (including biomarker), drug concentration and ADA data, both date and time of the measurement will be used to determine baseline by comparing with the first injection date and time.
2. For other data except AE, lab (including biomarker), drug concentration or ADA, only date of the measurement will be used to determine baseline by comparing with the first injection date.

For the rescreened patients, all data from the same patient will be used to derive baseline regardless if the data is from the screen- failure subject ID or enrolled subject ID.

6.2. General Data Handling Conventions

For the laboratory safety variables and biomarker data, if the data below the lower limit of quantification (LLOQ) / limit of linearity, half of the lower limit value (i.e., LLOQ/2) will be used for quantitative analyses. For data above the upper limit of quantification (ULOQ) / limit of linearity, the upper limit value (i.e., ULOQ) will be used for quantitative analyses.

6.3. Data Handling Convention Missing Data

Missing data will not be imputed in listings. This section includes the methods for missing data imputation for some summary analyses, if necessary.

Adverse event

If the intensity of a TEAE is missing, it will be classified as “severe” in the frequency tables by intensity of TEAE. If the assessment of relationship of a TEAE to the investigational product is missing, it will be classified as “related” in the frequency tables by relation to the investigational product.

Adverse event start date

AE start date will be used for AE classification and analysis of AESIs. If AE start date is not complete, then the character variable will keep the original incomplete date, the numerical date variable will be imputed and an imputation flag will indicate which date component is missing.

If AE start day is missing, and AE start month and year are not missing: If AE start year is the same as first dose year and the AE start month is the same as the first dose month then impute AE start day using the day of first dose. If this leads to a date after the AE end date, use AE end

date instead. Otherwise impute the AE start day using the first day of the month. If this leads to a date before informed consent, the informed consent date will be used. Imputation flag is 'D'.

If AE start month is missing, and AE start year is not missing: If AE start year is less than the first dose year, use the informed consent day and month. If AE start year is equal to the first dose year, use the first dose day and month. If this leads to a date after the AE end date, use AE end date instead. If AE start year is after the first dose year, use 01 January. Imputation flag is 'M'.

If AE start year is missing: Impute AE start date using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Imputation flag is 'Y'.

Adverse event end date

The general recommendation is not to impute AE end date. However, since AE end date will be used for AE starting date imputation, In order to carry through the logic for programming, the following intermediate step will be used. Afterwards, only the original character/numeric date recorded in CRF will be kept in the final analysis dataset.

If AE end day is missing, and AE end month and year are not missing: Impute AE end date using the last day of the month. If this leads to a date after end of study follow up date, use the last study visit date instead.

If AE end month is missing, and AE end year is not missing: Impute AE end date using 31 December as the day and month. If this leads to a date after end of study follow up date, use the last study visit date instead.

If AE end year is missing: Impute AE end date using the end of follow up date.

Medication start and end date missing

To determine whether a medication is pre-treatment medication or concomitant medication or both, the missing medication start date is estimated as early as possible, and the missing medication end date is estimated as late as possible. If the medication start date is missing, the onset day will not be calculated in medication listings.

Prior medication start date

If start day is missing, and start month and year are not missing: Impute the start day using the first day of the month. Imputation flag is 'D';

If start month is missing, and start year is not missing: Impute the day and month using 01 January. Imputation flag is 'M'.

If start year is missing: Impute start date using 2 years before informed consent date. Imputation flag is 'Y'.

A special note: for start date with year missing, the general principle is not to impute. However in order to simplify the programming flow, the imputation is proposed to align with the protocol which specifies to collect up to 2 years prior medication. Since the start date of prior medication will not be used in any analysis, the rule will not impact the analysis result.

Prior medication end date

If end day is missing, and end month and year are not missing: Impute end date using the last day of the month. If this leads to a date on or after first dose intake date, use first dose intake date -1 instead. Imputation flag is 'D'.

If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month. If this leads to a date on or after first dose intake date, use first dose intake date -1 instead. Imputation flag is 'M'

If end year is missing: Impute end date using the first dose intake date –1. Imputation flag is 'Y'.

Concomitant medication start date

The imputation rule for concomitant medication start date is the same as AE start date.

Concomitant medication end date

If end day is missing, and end month and year are not missing: Impute end date using the last day of the month. If this leads to a date after end of study follow up date, use the last visit study date instead. Imputation flag is 'D'.

If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month. If this leads to a date after end of study follow up date, use the last study visit date instead. Imputation flag is 'M'.

If end year is missing: Impute date using the end of last study visit date. Imputation flag is 'Y'.

Medication coding

Medications whose ATC level 4 cannot be coded will be summarized by setting ATC4=ATC2 in the table programs. However, these uncoded ATC level 4 records still need to be confirmed with study DM and study MD.

PCSV

Patients who had post-baseline PCSV but missing baseline value will be regarded as having treatment emergent PCSV.

6.4. Analysis Visit Window

Data analyzed by-visit-analysis (including efficacy, laboratory data, visit sign, ECG, ADA) will be summarized by the study scheduled visits described Appendix 10.2, "Schedule of Event". The analysis visit windows will be exhaustive so that all available values obtained from unscheduled visits, early termination visit (ETV) and end of treatment (EOT)/end of study (EOS) have the potential to be summarized. No analysis visit windows will be applied for the study scheduled visits.

The following analysis visit windows will be used to map the unscheduled visits, ETV and EOT visits for weekly SDI and EEsAI, based on the study day during the double blind period:

Visit No.	visit	Targeted Study Days*	Analysis Window in Study Days
1	Screening	<1	<1
2	Baseline	1	1
3	Week 1	8	[2,11]
4	Week 2	15	[12,18]
5	Week 3	22	[19, 25]
6	Week 4	29	[26, 32]
7	Week 5	36	[33, 39]
8	Week 6	43	[40, 46]
9	Week7	50	[47, 53]
10	Week 8	57	[54, 60]
11	Week 9	64	[61, 67]
12	Week 10	71	[68, 74]
13	Week 11	78	[75, 81]
14	Week 12 (End of double blindTreatment)	85	[82, 88]
15	Week 13	92	[89, 95]
16	Week 14	99	[96, 102]
17	Week 15	106	[103, 109]
18	Week 16	113	[110, 116]
19	Week 17	120	[117, 123]
20	Week 18	127	[124, 130]
21	Week 19	134	[131, 137]
22	Week 20	141	[138, 144]
23	Week 21	148	[145, 151]
24	Week 22	155	[152, 158]
25	Week 23	162	[159, 165]
26	Week 24	169	[166, 172]
27	Week 25	176	[173, 179]
28	Week 26	183	[180, 186]
29	Week 27	190	[187, 193]
30	Week 28(End of follow-up period)	197	[>= 194]

*Study days are calculated from 1st day of dupilumab injection during the double blind period.

The following analysis visit windows will be used to map the unscheduled visits, ETV and EOT visits for EoE-QOL-A questionnaire, based on the study day during the double blind period:

Visit No.	visit	Targeted Study Days*	Analysis Window in Study Days
1	Screening	<1	<1
2	Baseline	1	1
3	Week 4	29	[2, 43]
4	Week 8	57	[44, 71]
5	Week 12 (End of double blindTreatment)	85	[72, 88]
6	Week 16	113	[89, 127]
7	Week 20	141	[128, 155]
8	Week 24	169	[156, 183]
9	Week 28 (End of follow-up period)	197	>=184

*Study days are calculated from 1st day of dupilumab injection during the double blind period.

The following analysis visit windows will be used to map the unscheduled visits, ETV and EOT visits for endoscopy related efficacy variables, based on the study day during the double blind period:

Visit No.	visit	Targeted Study Days*	Analysis Window in Study Days
1	Screening	<1	<1
2	Baseline	1	1
3	Week 12 (End of double blindTreatment)	85	[2, 99]

*Study days are calculated from 1st day of dupilumab injection during the double blind period.

The following analysis visit windows will be used to map the unscheduled visits, ETV and EOT visits for lab, based on the study day during the double blind period:

Visit No.	visit	Targeted Study Days*	Analysis Window in Study Days
1	Screening	<1	<1
2	Baseline	1	1
3	Week 2	15	[2, 22]
4	Week 4	29	[23, 43]
5	Week 8	57	[44, 71]
6	Week 12 (End of double blindTreatment)	85	[72, 88]
7	Week 16	113	[89, 127]
8	Week 20	141	[128, 155]
9	Week 24	169	[156, 183]

10	Week 28 (End of follow-up period)	197	>=184

*Study days are calculated from 1st day of dupilumab injection during the double blind period.

The following analysis visit windows will be used to map the unscheduled visits, ETV and EOT visits for vital sign, Physical examination and ECG, based on the study day during the double blind period:

Visit No.	Visit	Targeted Study Days*	Analysis Window in Study Days
1	Screening	<1	<1
2	Baseline	1	1
3	Week 12 (End of double blindTreatment)	85	[2, 88]
4	Week 28 (End of follow-up period)	197	>=88

*Study days are calculated from 1st day of dupilumab injection during the double blind period.

The following analysis visit windows will be used to map the unscheduled visits, ETV and EOT visits for body weight , based on the study day during the double blind period:

Visit No.	visit	Targeted Study Days*	Analysis Window in Study Days
1	Screening	<1	<1
2	Baseline	1	1
3	Week 1	8	[2,11]
4	Week 2	15	[12,18]
5	Week 3	22	[19, 25]
6	Week 4	29	[26, 43]
7	Week 8	57	[44, 71]
8	Week 12 (End of double blindTreatment)	85	[72, 88]
9	Week 16	113	[89, 127]
10	Week 20	141	[128, 155]
11	Week 24	169	[156, 183]
12	Week 28 (End of follow-up period)	197	>=184

*Study days are calculated from 1st day of dupilumab injection during the double blind period.

In general, the following order will be used to select the record for analysis at given visit:

1. Scheduled visit
2. Early termination (ET) or end of study (EOS), whichever comes first if scheduled visit not available
3. Unscheduled visit if both scheduled visit and ETV/EOT/EOS are not available

For the multiple measurements of the same test in the same window, the following rules will be used to pick up the analysis value:

- If multiple valid values of a variable within an analysis visit window, the closest from the target study day will be selected.
- If the difference is a tie, the value after the targeted study day will be used.
- If multiple available values of a variable exist within a same day, then the first value of the day will be selected.

Both scheduled and unscheduled measurements will be considered for determining abnormal/PCSV values from laboratory, vital sign or ECG as well as the baseline values.

For the ePRO data collected daily via IVRS, the analysis visit windows will be implemented following the procedures below:

Step 1: Derive the study day,

- If diary date ≥ 1st injection date, then diary study day=diary date – 1st injection date +1;
- Otherwise diary study day=diary date – 1st injection date

Step 2: Windows are defined as -6 to 1 = BL, 2 to 8 = week 1, 9 to 15 = week 2, etc, with 7 days interval between visit windows.

7. INTERIM ANALYSIS

No formal interim analysis is planned.

There will be 2 database locks for this study. The first database lock will occur when the last patient completes the week 12 visit. The analyses of primary and secondary efficacy endpoints at the first database lock are considered the final analyses. The second database lock will occur when the last patient completes the last visit of the study. For the first database lock, a designated unblinding team (eg, statisticians, SAS programmers, etc.) that is not involved in the conduct of the study will perform the analysis of week 12 outcomes. The study conduct will not be affected by the unblinded week-12 results. The analysis results will be made available only to a limited group of people who are not involved in the daily conduct of the study. Individuals involved in the continuing conduct of the study will remain blinded until after the final database lock. Following the second database lock, efficacy and safety results during the follow-up period will be summarized.

8. SOFTWARE

All analyses will be done using SAS Version 9.2 or above.

9. REFERENCES

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10. APPENDIX

10.1. Summary of Statistical Analyses

Efficacy Analysis:

Endpoint	Analysis Population	Primary Statistical Method	Supportive/Sensitive Statistical Method	Subgroup Analysis	Other Analyses
Change in the SDI score at week 10 from baseline	FAS	MI + ANCOVA	MI+ANCOVA regardless of rescue, ANCOVA on LOCF, WOCF and OC, and primary efficacy analysis on PPS	Yes	Line plot
Secondary continuous variables	FAS	MI + ANCOVA	NO	No	Line plot
Categorical variables	FAS	Fisher exact test / define missing as treatment failure		No	Histogram

Safety Analyses:

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Adverse Events	SAF	Descriptive statistics	No	No	No
Laboratory Measures	SAF	Descriptive Statistics	No	No	No
Vital sign	SAF	Descriptive Statistics	No	No	No
ECG	SAF	Descriptive Statistics	No	No	No

10.2. Schedule of Events

Table 1: Schedule of Events – Screening and Treatment Period

Study Procedures	Screening	Treatment Period												
In-Clinic Visit (V) or Telephone Visit (TV)	Screening V1	Baseline V2	V3	V4	V5	V6	TV7[1]	TV8[1]	TV9[1]	V10	TV11[1]	TV12[1]	TV13[1]	EOT V14
Week (Wk)			Wk1	Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8	Wk9	Wk10	Wk11	Wk12
Day (D)	D-35 to D-1	D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85
Visit Window in days (d)			±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d
Screening/Baseline:														
Informed consent[2]	X													
Inclusion/exclusion	X	X												
Medical history/demographics/height	X													
Randomization		X												
Treatment:														
Training for self-injection[3]		X	X	X	X	X								
Administer study drug		X[4]	X[4]	X[4]	X[4]	X[4]	X[1]	X[1]	X[1]	X[4]	X[1]	X[1]	X[1]	
Con meds/procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:[5]														
SDI/EEsAI (PRO)[6,7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EoE-QOL-A (PRO)[7,8]		X				X				X				X
EoE-EREFS[9]	X													X
Safety:[5]														
Weight	X	X	X	X	X	X				X				X
Vital signs	X	X[10]												X
Diet History	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination; ECG	X													X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Procedures	Screening	Treatment Period												
In-Clinic Visit (V) or Telephone Visit (TV)	Screening V1	Baseline V2	V3	V4	V5	V6	TV7[1]	TV8[1]	TV9[1]	V10	TV11[1]	TV12[1]	TV13[1]	EOT V14
Week (Wk)			Wk1	Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8	Wk9	Wk10	Wk11	Wk12
Day (D)	D-35 to D-1	D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85
Visit Window in days (d)			±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d
Laboratory Testing:[5]														
Hematology and serum chemistry	X	X		X		X				X				X
Coagulation[11]	X													X
Urinalysis	X	X				X				X				X
HBsAg and hepatitis C Ab	X													
Pregnancy testing	Serum	Urine				Urine				Urine				Urine
Serum FSH to confirm menopausal status	X													
Endoscopy with esophageal biopsies[12]	X[13]													X
Serum total IgE	X													
Research samples (serum/plasma)	X	X		X		X				X				X
[redacted]		X												
[redacted]	X	X												
PK and ADA Testing:[5]														
PK sample		X	X	X	X	X				X				X
ADA sample		X												X

ADA = anti-drug antibody; ECG = electrocardiogram; EEsAI = Eosinophilic Esophagitis Activity Index; EoE-EREFS = Eosinophilic Esophagitis-Endoscopic Reference Score; EoE-QOL-A = Adult Eosinophilic Esophagitis Quality of Life (questionnaire); EOT = end of treatment; PK = pharmacokinetic; PRO = patient-reported outcome; SDI = Straumann Dysphagia Instrument; TV = telephone visit; V = visit.

[1] The site will contact the patient by telephone to conduct these visits. The patient/caregiver will self-administer study drug outside clinic on these days. Patients will complete a dosing diary to document compliance with self-injection of study drug and to document any ISRs and concomitant medications. Patients may return to the clinic on a weekly basis if unable to self-administer study drug.

[redacted]

[3] Patients and/or caregivers will be trained on self-administration of study drug. Patients will be closely monitored at the study site at visits 2, 3, 4, 5, and 6 for a minimum of 30 minutes after the administration of study drug. In addition to the predose assessments, AEs will be assessed at 30 minutes (±10 minutes) postdose.
[4] On scheduled in-clinic study visit days, the study drug will be administered in the clinic (by site staff, the patient, or a caregiver).
[5] Assessments will be performed before the administration of study drug.
[6] Questionnaires will be completed before any other assessments or procedures.
[7] The SDI/EEsAI PROs should be done by the patient electronically, weekly for SDI, and daily and weekly for EEsAI from the beginning of screening through EOS or ET. Site should confirm patient compliance at each clinic visit.
[8] The EoE-QOL-A PRO should be recorded at baseline and then monthly through EOS or ET.
[9] EoE-EREFS should be completed when endoscopy with esophageal biopsies procedure is performed.
[10] Vital signs at predose and 30 (±10) minutes postdose.
[11] Coagulation tests should be performed before the procedure of endoscopy with esophageal biopsies on days the procedure is performed.
[12] The EndoFLIP procedure, with photographs, to measure esophageal distensibility will be performed during the endoscopy procedures.
[13] Screening endoscopy with esophageal biopsies, and photographs are to be performed during screening period to allow results to be available prior to day -1.

Table 2: Schedule of Events – Follow-up Period

Study Procedures	**Follow-Up Period**				**ET Visit** (if applicable)
In-Clinic Visit (V)	**V15**	**V16**	**V17**	**EOS Visit V18**	
Week (Wk)	**Wk16**	**Wk20**	**Wk24**	**Wk28**	
Day (D)	**D113**	**D141**	**D169**	**D197**	
Visit Window in days (d)	**±3 d**	**±3 d**	**±3 d**	**±3 d**	
Treatment:					
Concomitant medications/procedures	X	X	X	X	X
Efficacy:					
SDI/EEsAI (PRO)[1,2]	X	X	X	X	X
EoE-QOL-A (PRO)[1,3]	X	X	X	X	X
EoE-EREFS[4]					X
Safety:					
Weight	X	X	X	X	X
Diet History	X	X	X	X	X
Physical examination; ECG				X	X
Adverse events	X	X	X	X	X
Laboratory Testing:					
Hematology and serum chemistry	X	X	X	X	X
Coagulation					X
Urinalysis	X	X	X	X	X
Pregnancy testing		Urine		Serum	Serum
Endoscopy with esophageal biopsies[5]					X
Research samples (serum/plasma)		X		X	
PK and ADA Testing:					
PK sample	X	X	X	X	X
ADA sample[6]				X[6]	X[6]

ADA = anti-drug antibody; ECG = electrocardiogram; EEsAI = Eosinophilic Esophagitis Activity Index; EoE-EREFS = Eosinophilic Esophagitis-Endoscopic Reference Score; EoE-QOL-A = Adult Eosinophilic Esophagitis Quality of Life (questionnaire); EOS = end of study; ET = early termination; PK = pharmacokinetic; PRO = patient-reported outcome; SDI = Straumann Dysphagia Instrument.

[1] Questionnaires will be completed before any other assessments or procedures.

[2] The SDI/EEsAI PROs should be done by the patient electronically, weekly for SDI, and daily and weekly for EEsAI from the beginning of screening through EOS or ET. Site should confirm patient compliance at each clinic visit.

[3] The EoE-QOL-A PRO should be recorded at baseline and then monthly through EOS or ET.

[4] EoE-EREFS should be completed when endoscopy with esophageal biopsies procedure is performed.

[5] The EndoFLIP procedure, with photographs, to measure esophageal distensibility will be performed during the endoscopy procedures.

10.3. Criteria for Treatment-Emergent Potentially Clinical Significant Value (PCSV) for Dupilumab studies

Parameter	Treatment Emergent PCSV	Comments
Clinical Chemistry		
ALT*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
AST*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
Alkaline Phosphatase	>1.5 ULN and baseline ≤ 1.5 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007.
Total Bilirubin*	>1.5 and ≤ 2 ULN and baseline ≤ 1.5 ULN* >2 ULN and baseline ≤ 2.0 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤1.5, >1.5 to ≤2.0 and > 2.0 category for baseline vs. post baseline may be provided
Conjugated Bilirubin	(Direct Bilirubin >35% Total Bilirubin and Total Bilirubin >1.5 ULN) and (Direct Bilirubin <=35% Total Bilirubin or Total Bilirubin <=1.5 ULN) at baseline	Conjugated bilirubin dosed on a case-by-case basis.

Parameter	Treatment Emergent PCSV	Comments
ALT and Total Bilirubin	(ALT>3 ULN and TBILI>2 ULN) and baseline (ALT <=3 ULN **or** TBILI <=2 ULN)	Concept paper on DILI – FDA draft Guidance Oct 2007.
CPK*	>3 and ≤ 10 ULN and baseline ≤ 3ULN* >10 ULN and baseline ≤ 10ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤3, >3 to ≤10, and > 10 category for baseline vs. post baseline may be provided
Creatinine	≥150 µmol/L (Adults) and baseline < 150 µmol/L >=30% change from baseline and <100% change from baseline ≥100% change from baseline	Benichou C., 1994. 3 independent criteria
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L and <=408 µmol/L at baseline <120 µmol/L and >= 120 µmol/L at baseline	Harrison- Principles of internal Medicine 17th Ed., 2008. Two independent criteria
Blood Urea Nitrogen	≥17 mmol/L and <17 mmol/L at baseline	Two independent criteria
Chloride Hypochloremia Hyperchloremia	 <80 mmol/L and baseline ≥ 80 mmol/L >115 mmol/L and baseline ≤ 115 mmol/L	Two independent criteria
Sodium Hyponatremia Hypernatremia	 ≤129 mmol/L and baseline > 129 mmol/L ≥160 mmol/L and baseline <160 mmol/L	Two independent criteria
Potassium Hypokalemia Hyperkalemia	 <3 mmol/L and baseline ≥ 3 mmol/L ≥5.5 mmol/L and baseline <5.5 mmol/L	FDA Feb 2005. Two independent criteria
Total Cholesterol	≥7.74 mmol/L and < 7.74 mmol/L at baseline	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L and < 4.6 mmol/L at baseline	Threshold for therapeutic intervention.
Glucose Hypoglycaemia Hyperglycaemia	 (≤3.9 mmol/L and <LLN) and (>3.9 mmol/L or >=LLN) at baseline ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted) and < 11.1 mmol/L (unfasted); <7 mmol/L (fasted) at baseline	 ADA May 2005. ADA Jan 2008.
HbA1c	>8% and <= 8% at baseline	

Parameter	Treatment Emergent PCSV	Comments
Albumin	≤25 g/L and >25 g/L at baseline	
CRP	>2 ULN or >10 mg/L (if ULN not provided) and <=2 ULN or <=10 mg/L (if ULN not provided) at baseline	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L and >=3.0 Giga/L at baseline (Non-Black); <2.0 Giga/L and >=2.0 Giga/L at baseline (Black) ≥16.0 Giga/L and < 16 Giga/L at baseline	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L and <= 4.0 Giga/L at baseline	
Neutrophils	<1.5 Giga/L and >=1.5 Giga/L at baseline (Non-Black); <1.0 Giga/L and >=1.0 Giga/L at baseline (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L <= 0.7 Giga/L at baseline	
Basophils	>0.1 Giga/L <= 0.1 Giga/L at baseline	
Eosinophils	(>0.5 Giga/L and >ULN) and (<=0.5 Giga/L or <= ULN at baseline)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L and > 115 g/L at baseline for male; ≤95 g/L and> 95 g/L at baseline for Female. ≥185 g/L and <185 g/L at baseline for Male; ≥165 g/L and < 165 g/L at baseline for Female Decrease from Baseline ≥20 g/L	Three criteria are independent. Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v and > 0.37 v/v at baseline for Male ; ≤0.32 v/v and > 0.32 v/v at baseline forFemale ≥0.55 v/v and < 0.55 v/v at baseline for Male ; ≥0.5 v/v and < 0.5 v/v at baseline for Female	Two Criteria are independent
RBC	Female <3 Tera/L and baseline ≥3 Tera/L ≥6 Tera/L and baseline < 6 Tera/L Male <4 Tera/L and baseline ≥4 Tera/L ≥7 Tera/L and baseline < 7 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L and >=100 Giga/L at baseline ≥700 Giga/L and < 700 Giga/L at baseline	International Consensus meeting on drug-induced blood cytopenias, 1991. Two independent criteria

Parameter	Treatment Emergent PCSV	Comments
Urinalysis		
pH	≤4.6 and > 4.6 at baseline ≥8 and < 8 at baseline	Two independent criteria
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.
ECG		Ref.: CPMP 1997 guideline.
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
PR	≥220 ms and increase from baseline ≥20 ms	
QRS	≥120 ms & < 120 ms at baseline	
QTc Borderline Prolonged* Additional	<u>Absolute values (ms)</u> Borderline: 431-450 ms and < 431ms at baseline for Male; 451-470 ms and < 451 ms at baseline for Female Prolonged: >450 to <500 ms and <= 450 ms at baseline for Male; >470 to <500 ms and <= 470 ms at baseline for Female ≥500 ms and < 500 ms at baseline <u>Increase from baseline</u> Borderline: Increase from baseline 30-60 ms Prolonged: Increase from baseline >60 ms	To be applied to any kind of QT correction formula. *QTc prolonged and ΔQTc>60 ms are the PCSA to be identified in individual subjects/patients listings. 5 independent criteria

10.4. Search Criteria for TEAE of Special Interest/TEAE Syndrome

AESI	Search Criteria
Anaphylactic reactions	Narrow SMQ for "anaphylactic reaction"
Acute allergic reactions that require treatment	• Narrow SMQ for "hypersensitivity" • TEAE occurred due to the medication taken and recoded on ConMed CRF page *Note: Blinded manual adjudication of relevant PTs will be required by the study medical monitor, before database locks*
Severe ISRs that last longer than 24 hours	-HLT = Injection site reactions - Severity = "severe"
Mycosis fungoides or other forms of cutaneous T cell lymphoma	-HLT = "Mycosis fungoides" • Includes LLT = Sezary syndrome • Includes LLT = Cutaneous T-cell lymphoma -PT = "Cutaneous T-cell dyscrasia
Any severe infection	-SOC = Infections and infestations -Severity = "severe
Any infection requiring treatment with parenteral antibiotics	-SOC = Infection and infestations -Action taken for AE = "medication" - ConMed: ATC3= "Antiinfectives" during the TEAE course (between start and stop dates), Route = IV, IM
Any infection requiring treatment with oral antibiotic/anti-viral/anti-fungal for longer than 2 weeks	-SOC = Infection and infestations -Action taken for AE = "medication" -Check CM: ATC3= "Antiinfectives" during the TEAE course (between start and stop dates), Route = PO and Treatment duration >14 days
Any clinical endoparasitosis	-HLT = Cestode infections -HLT = Helminthic infections NEC -HLT = Nematode infections -HLT = Trematode infection
Any opportunistic infection[a]	The following HLTs plus PTs -HLT = Pneumocystis infection -HLT* = Fungal infections NEC -HLT* = Pseudallescheria infections -HLT = Herpes viral infections -HLT = Paracoccidioides infections

	-HLT = Sporothrix infections -HLT = Cryptosporidia infections -HLT* = Trypanosomal infections -HLT* = Campylobacter infections -HLT* = Shigella infections -HLT* = Vibrio infections Plus the following PTs -Polyomavirus-associated nephropathy -BK virus infection -Cytomegalovirus infection -Post transplant lymphoproliferative disorder -Progressive multifocal leukoencephalopathy -*Bartonellosis -Blastomycosis -Toxoplasmosis -Coccidioidomycosis -Histoplasmosis -*Aspergillus infection -Systemic candida -Oropharyngeal candidiasis -Cryptococcosis -Listeriosis -Tuberculosis -Nocardiosis -Mycobacterial infection -*Salmonellosis -*Hepatitis B -Herpes zoster -*Strongyloidiasis -Microsporidia infection -Visceral leishmaniasis -*Hepatitis C *Note: *Blinded manual adjudication of relevant PTs under each of HLTs listed above will be required by the study medical monitor, before database locks*
Suicidal behavior	Include the following PTs -Completed suicide -Suicidal ideation

[a] The definition of opportunistic infections is referring to the recent consensus guidance for opportunistic infections in the setting of biologic therapy (K L Winthrop et al, 2015)

10.5. EEsAI Score

The tables and fomular below are used to calculate the EEsAI score.

Weekly EEsAI score

Item	Score (total set to 100)
Frequency of trouble swallowing	
Never	0
1–3 times/wk	15
4–6 times/wk	27
Daily	31
Duration of trouble swallowing	
<=5 min	0
>5 min	6
Pain when swallowing	
No	0
Yes	15
VDQ score	
0	0
0.1–2.5	12
2.6–5.0	19
5.1–7.5	21
7.6–10.0	23
AMS score	
0	0
0.1–2.5	0
2.6–5.0	0
5.1–7.5	9
7.6–10.0	25
Total	100

Daily EEsAI score

Item	Score (total set to 100)
Frequency of trouble swallowing	
Never	0
Present	11
Duration of trouble swallowing	
<=5 min	0
>5 min	14
Pain when swallowing	
No	0
Yes	6
VDQ score	
0	0
0.1–2.5	1
2.6–5.0	17
5.1–7.5	27
7.6–10.0	51
AMS score	
0	0
0.1–2.5	0
2.6–5.0	0
5.1–7.5	2
7.6–10.0	18
Total	100

1. VDQ score - one should get a number from 0 to 10.

$VDQ = 10 * (N1 * 1 + N2 * 2 + N3 * 3)/(D * 3)$

Where:
1. N1 = number of food consistencies graded with ‘Mild difficulties’
2. N2 = number of food consistencies graded with ‘Moderate difficulties’
3. N3 = number of food consistencies graded with ‘Severe difficulties’
4. D = number of relevant food consistencies (different than ‘Not applicable’)

2. AMS score - one should get a number from 0 to 10.

$AMS = 10 * (N1 * 1 + N2 * 2 + N3 * 3 + N4 * 5)/(D * 5)$

Where:
1. N1 = number of food consistencies with ‘Yes’ to ‘Eating slowly’ only
2. N2 = number of food consistencies with ‘Yes’ to ‘Modification’ only
3. N3 = number of food consistencies with ‘Yes’ to both ‘Eating slowly’ and ‘Modification’
4. N4 = number of food consistencies with ‘Yes’ to ‘Avoidance’ only
5. D = number of relevant food consistencies (different than ‘Not applicable’)

10.6. Medication for RESCUE TREATMENTS

The medications given post-baseline are considered rescue Medication.

Therapeutic Class	Chemical Class	
ANTINEOPLASTIC AGENTS	MONOCLONAL ANTIBODIES	Check if patient took Omalzumab (Anti IgE)
CORTICOSTEROIDS FOR SYSTEMIC USE	GLUCOCORTICOIDS	Except route of administration as topical
DRUGS FOR ACID RELATED DISORDERS	PROTON PUMP INHIBITORS	
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	GLUCOCORTICOIDS	Except route of administration as topical
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	LEUKOTRIENE RECEPTOR ANTAGONISTS	
IMMUNOSUPPRESSANTS	INTERLEUKIN INHIBITORS	Check if patient took Anti IL5

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