Clinical Study Protocol

Protocol Title:	**FLUTicasone in Eosinophilic esophagitis (FLUTE): A Randomized, Double-blind, Placebo-controlled, Dose-ranging, and Maintenance Study of APT-1011 in Subjects with Eosinophilic Esophagitis**
Protocol Number:	**SP-1011-002**
IND Number:	**110889**
EudraCT Number:	**2016-004749-10**
Date of Protocol:	**16 Jul 2019 (Amendment 3.1)**
Product:	**APT-1011**
Study Phase:	**2b**
Sponsor:	**Adare Pharmaceuticals** **Princeton Pike Corporate Center** **1200 Lenox Drive, Suite 100** **Lawrenceville, New Jersey 08648 US**

SIGNATURES

PROTOCOL TITLE: FLUTicasone in Eosinophilic esophagitis (FLUTE): A Randomized, Double-blind, Placebo-controlled, Dose-ranging, and Maintenance Study of APT-1011 in Subjects with Eosinophilic Esophagitis

PROTOCOL NO: SP-1011-002

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| [redacted] | Signature | Date |

Medical Lead
Adare Pharmaceuticals

SYNOPSIS

Name of Sponsor/Company:	Adare Pharmaceuticals
Name of Finished Product:	APT-1011
Name of Active Ingredient:	fluticasone propionate
Title of Study:	FLUTicasone in Eosinophilic esophagitis (FLUTE): A Randomized, Double-blind, Placebo-controlled, Dose-ranging, and Maintenance Study of APT-1011 in Subjects with Eosinophilic Esophagitis
Protocol No:	SP-1011-002
Investigators and Sites:	Approximately 60 active sites
Study duration: FLUTE will be conducted in multiple parts: Screening (4 weeks), 4-week Single-Blind Placebo Run-in/Baseline Symptom Assessment, Part 1 (14-week induction), Part 2 Maintenance (Weeks 14 to up to Week 52) and a Follow-up Visit to be completed 2 weeks after the last dose of study drug. Subjects who complete all parts of FLUTE will be in the study for up to 62 weeks or until the last subject completes Week 28.	**Phase:** 2b

Objectives:

Primary: The primary objective of the study is to evaluate the efficacy (histological response) of APT-1011 in adults with eosinophilic esophagitis (EoE).

Secondary: The secondary objectives of the study are as follows:

- To define the dose-response of APT-1011;
- To select a dose(s) of APT-1011 for Phase 3;
- To evaluate the effect of APT-1011 on histology and endoscopic appearance;
- To evaluate maintenance of efficacy and long-term safety of APT-1011;
- To evaluate the population pharmacokinetics (PopPK) of APT-1011;
- To evaluate the effect of APT-1011 on dysphagia episodes.

Exploratory: The exploratory objectives of the study are as follows:

Study design:

Study design: This is a randomized, double-blind, placebo-controlled dose-ranging study of 4 total daily doses of APT-1011 versus placebo in 100 adult subjects (≥18 years of age) diagnosed with EoE.

During the single-blind run-in/baseline symptom assessment, the subjects will receive placebo 30 minutes after breakfast and hora somni (HS; at bedtime). Four doses of study drug will be administered: Placebo 30 minutes after breakfast and 1.5 mg HS APT-1011, 1.5 mg twice daily (BID) (30 minutes after breakfast and at bedtime; total daily dose of 3 mg) APT-1011, Placebo 30 minutes after breakfast and 3 mg HS (at bedtime), and 3 mg BID (30 minutes after breakfast and at bedtime; total daily dose of 6 mg) APT-1011, and matching placebo administered 30 minutes after breakfast and HS (at bedtime).

The 100 subjects will be randomized in a 1:1:1:1:1 to receive placebo or one of the active doses into Part 1 of the study. As described below, the treatment that a subject receives in Part 2 depends on their histologic response status at Week 12.

Randomization will occur in a double-blind manner using an integrated Interactive Web Response System (IWRS), and will be stratified by the presence or absence of a history of or current esophageal stricture and history of a prior positive steroid response to any corticosteroid treatment previously received to treat the subject's EoE captured with demography.

Efficacy (including sustained EoE response and patient-reported outcomes [PRO]), safety, and PK of APT-1011 will be examined.

FLUTE will be conducted in several parts (Screening [4 weeks], followed by a 4-week single-blind placebo run-in and Baseline Symptom Assessment, and 2 treatment parts [Part 1 and Part 2]), with a Follow-up Visit to occur 2 weeks after the final dose of study drug. The esophagogastroduodenoscopy (EGD) to determine eligibility must be performed prior to entry into the 4-week (28 day) single-blind placebo run-in/Baseline Symptom Assessment. To enter the 4-week Baseline Symptom Assessment, the subject must satisfy all eligibility criteria including the Global EoE score >3 (Inclusion Criterion #5), **except** those to be confirmed during this phase (Inclusion Criterion #7: evidence of EoE as defined by ≥15 PEAK eosinophils/high-power field [HPF]; Inclusion Criterion #8: in the daily diary, report episodes of dysphagia ≥3 days per 7 days during the last 14 days of the 4-week Baseline Symptom Assessment; Inclusion Criterion #9: completion of the daily diary on at least 5 out of each 7 days during the last 14 days of the Baseline Symptom Assessment; and Exclusion Criterion #24: a serum cortisol level <16 µg/dL (440 nmol/L) at 60 minutes with adrenocorticotropic hormone [ACTH] stimulation test using 250 µg cosyntropin administered intramuscularly [i.e., an abnormal result on the ACTH stimulation test]). The ACTH stimulation test should have been completed before entry into the 4-week Baseline Symptom Assessment, however the results of the test may be pending. The subjects will be dispensed placebo along with their electronic diary at the beginning of the 4-week placebo run-in/Baseline Symptom Assessment.

During the 4-week Baseline Symptom Assessment, baseline symptom severity will be determined and the ability of the subject to be compliant with diary entries will be assessed. The subjects must have ≥ 15 PEAK eosinophils/HPF on their esophageal biopsies to be randomized. In order to ensure that a diagnosis can be made, at least 5-6 biopsies from both the proximal and distal (~3 each) should be taken. The presence or absence of a history of or current esophageal stricture on the EGD along with a history of a prior positive response to any corticosteroid treatment previously received to treat the subject's EoE captured with demography will be stratification variables at randomization.

Following confirmation of these eligibility criteria, eligible subjects may be randomized as described above.

During treatment, all subjects will return to the site for scheduled visits and for unscheduled visits due to significant adverse events or worsening of symptoms including food impaction.

Definitions of Histologic Response, Histologic Non-response, and Treatment Failure

Response or non-responsive status will be assessed 2 weeks prior to the planned end of treatment for Part 1 (Week 12), and Part 2 (Weeks 26 and 52).

A histologic responder will be defined as a subject who achieves a histologic response of ≤6 peak eosinophils/HPF (as primary determinant). HPF will be defined as a standard area of 235 square microns in a

microscope with 40x lens and 22mm ocular.

A histologic non-responder will be defined as a subject who does not have a histologic response (i.e., do not achieve a histologic response of ≤6 peak eosinophils/HPF).

Subjects who develop food impaction with or without esophageal dilatation ANYTIME during the study will be considered treatment failures and complete early termination assessments and exit the study after the 2-week post-treatment follow-up period. Subjects who voluntarily withdraw from the study due to worsening symptoms before the week 12 evaluation or later in the study will also be considered treatment failures. Every effort should be made to perform an EGD in subjects wishing to withdraw due to worsening symptoms. They also must complete the early termination assessments and exit the study after a 2-week post-treatment follow-up period.

Part 1: Induction (Day 1 to Week 14)

During Part 1, subjects will be treated for 14 weeks with study drug. At Week 12, the subjects will undergo a response assessment, including EGD to assess endoscopic and histologic status.

Histologic responders and histologic non-responders (at Week 12) will enter Part 2.

Part 2: Maintenance (Week 14 to Week 52)

In Part 2, all subjects classified as histologic responders at Week 12 will continue to be treated according to the dosing group to which they were randomized for Part 1. Subjects may continue on this dose for up to 9 months after the completion of Part 1.

Subjects who are histologic non-responders at Week 12 will receive single-blind 3 mg BID in Part 2.

At Week 26, subjects will undergo a response assessment, including EGD to assess histologic response. Symptoms will also be assessed. The 14 days prior to Week 26 will be compared to the 14 days prior to Randomization. All subjects who are histologic non-responders will stop treatment at Week 28 and enter the 2-week follow-up and exit the study. Histologic responders will continue on the same dose.

Subjects who complete the study at Week 52 will undergo a response assessment, including EGD to assess endoscopic and histologic status. Symptoms will also be assessed. The 14 days prior to Week 52 will be compared to the 14 days prior to Randomization.

Subjects will complete a Follow-up Visit 2 weeks after the final dose of study drug.

Follow-up Visit

Subjects will complete a Follow-up Visit for 1 or more of the following reasons:

- Subject with histologic non-response at Week 26 including subjects on single-blind 3 mg BID;
- Subject completed treatment at Week 52 (following EGD);
- Subject experienced an adverse event (AE) requiring early discontinuation, including food impaction requiring EGD;
- Subjects with worsening symptoms who voluntarily withdraw during the study or who withdraw for any reason.

The Follow-up Visit will occur 2 weeks after the subject takes the final dose of study drug.

All subjects must have a final EGD within 3 weeks prior to completing the Follow-up Visit unless the subject withdraws consent or has a contraindication to EGD.

Schedules of events for each part of FLUTE are included in the protocol.

Pharmacokinetics

Sparse PK sampling will be performed to characterize fluticasone propionate (FP) exposure in the study population. PopPK analysis will be performed on sparse plasma concentration data.

Pharmacokinetic samples will be collected from subjects in all 5 dosing groups to maintain the blind. Samples collected from subjects in the placebo group will not be analyzed. Samples collected from the subjects on active doses will be analyzed for PopPK results.

For this sparse PK sampling, a pre-dose sample will be collected on Day 1. At Week 4, Week 8, and

Week 12, subjects must fast approximately 8 hours before the scheduled visits and will take their "after breakfast" dose as scheduled on the day of the visit (at the site and 2 samples will be taken during their scheduled visit: upon arrival to the site and approximately 1 to 1.5 hours after first sample (immediately prior to leaving the site). After arrival at the site and once samples for serum cortisol and sparse PK are drawn, the subject will eat breakfast and take their "after breakfast" dose approximately 30 minutes after breakfast. Site staff should document the time of the morning dose. Due to this variability, the sparse PK samples are expected to represent a large portion of the 12-hour post-dosing interval.	
Planned number of subjects:	Approximately 100 subjects will be randomized into Part 1 in a 1:1:1:1:1 fashion stratified by presence or absence of a history of or current esophageal stricture and a history of a prior positive steroid response to any corticosteroid treatment previously received to treat the subject's EoE. While both genders will be encouraged to enroll, it is expected that approximately 25% of subjects enrolled will be female. Although subjects are allowed to be up to 75 years old, it is expected that 5% of enrolled subjects will be geriatric (≥65 years). The protocol details the expected number of subjects who will participate in each part of the study. The final analysis for the primary endpoint will be performed when all randomized subjects have completed Week 12 of the study.
Diagnosis and main criteria for inclusion and exclusion:	**<u>Inclusion criteria</u>:** Subjects must satisfy all of the following criteria: **Before entering 4-week Baseline Symptom Assessment** 1. Male or female between ≥18 and ≤75 years of age at the time of informed consent; 2. Signed the informed consent form (ICF) and willing and able to adhere to all study procedures; 3. Diagnosis or presumptive diagnosis of EoE; • Diagnosis of EoE must be confirmed by symptoms, histology, and historical documentation of failed treatment on ≥8 weeks of high-dose proton pump inhibitors (PPI), as determined by the Investigator. High-dose PPI is defined as 20 to 40 mg BID of any marketed PPI, or alternatively this total dose administered once daily; maintenance doses of PPIs are not acceptable. *Note: Documentation of PPI failure prior to initial diagnosis or by documentation of PPI failure at the time of Screening is required. The subjects may be pre-screened but should not be consented, sign an ICF, or be offered participation in FLUTE if they have not met the diagnostic criteria for EoE that requires that they fail an 8-week trial of high-dose PPIs* ***except*** *those who have taken PPIs for 8 weeks will use the EGD within the study for this documentation. The Investigator and potential subject must make the decision to complete a PPI trial independent of any considerations of the study. There is insufficient time to do the 8-week trial within the current study. Should a subject be consented in error and screen fails due to this point, they may be re-screened as described in the protocol.* 4. Have a subject-reported history of ≥3 episodes of dysphagia (difficulty with food going down or an awareness of the sensation of food going down the esophagus) in the 7 days prior to

	Screening; 5. Have a 7-day Global EoE Symptom Score >3 at baseline (EoE score must remain >3 at each of Visits 1, 2 and 3 before randomization). This will be performed on paper during the Screening Visit. 6. Willing and able to adhere to study-related treatment regimens, procedures, and visit schedule. *Before randomization* 7. To be determined prior to randomization: have evidence of EoE, as defined by ≥15 PEAK eosinophils/HPF. In order to ensure that a diagnosis can be made, at least 5-6 biopsies should be taken including both proximal and distal specimens (~3 each); • No EGDs and biopsies performed outside FLUTE are acceptable for meeting eligibility criteria. • Optional biopsies may be taken and processed locally for local use, if specified in the local ICF. • Biopsies are to be obtained PRIOR to the 4-week Baseline Symptom Assessment. Eligibility from a histological perspective will be based solely on the central pathologist's assessment. 8. To be determined prior to randomization: in the daily diary, report at least 3 episodes of dysphagia (difficulty with food going down or an awareness of the sensation of food going down the esophagus) for each of the last 7 days during the last 14 days of the 4-week Baseline Symptom Assessment 9. To be determined prior to randomization: completion of the daily diary on at least 5 out of each 7 days during the last 14 days of the 4-week Baseline Symptom Assessment. **Exclusion criteria:** Subjects will not be entered in FLUTE for any of the following reasons: **Before entering 4-week Baseline Symptom Assessment** 1. Have known contraindication, hypersensitivity, or intolerance to corticosteroids (See Appendix 6 for signs and symptoms of adrenal suppression and hypercorticism); 2. Have any physical, mental, or social condition or history of illness or laboratory abnormality that in the Investigator's judgment might interfere with study procedures or the ability of the subject to adhere to and complete the study or increase the safety risk to the subject such as uncontrolled diabetes or hypertension; 3. Presence of oral or esophageal mucosal infection of any type; 4. Have any mouth or dental condition that prevents normal eating; 5. Have any condition affecting the esophageal mucosa or altering esophageal motility other than EoE, including erosive esophagitis (grade B or higher as per the Los Angeles Classification of Gastroesophageal Reflux Disease), hiatus hernia longer than 3 cm, Barrett's esophagus, and achalasia; 6. Use of systemic (oral or parenteral) corticosteroids within 60 days prior to Screening, use of inhaled/swallowed corticosteroids within 30 days prior to Screening, or extended use of high-potency dermal topical corticosteroids within 30 days prior to Screening; 7. Initiation of an elimination diet or elemental diet within 30 days

	before Screening (diet must remain stable after signing ICF); 8. Morning (0700 to 0800 hours, or as close to that window as possible) serum cortisol level ≤5 µg/dL (138 nmol/L) that is not responsive to ACTH stimulation; 9. Use of biologic immunomodulators in the 24 weeks prior to Screening (allergy desensitization injection or oral therapy is allowed as long as the course of therapy is not altered during the study period); 10. Use of calcineurin inhibitors or purine analogues (azathioprine, 6-mercaptopurine) in the 12 weeks prior to Screening; 11. Use of potent cytochrome P450 (CYP) 3A4 inhibitors (e.g., ritonavir and ketoconazole) in the 12 weeks prior to Screening; 12. Have a contraindication to or factors that substantially increase the risk of EGD or esophageal biopsy or have narrowing of the esophagus that precludes EGD with a standard 9 mm endoscope; 13. Have history of an esophageal stricture requiring dilatation within the previous 12 weeks prior to Screening; 14. Subjects who have initiated, discontinued, or changed dosage regimen of PPIs, H2 antagonists, antacids or antihistamines for any condition such as GERD or allergric rhinitis within 4 weeks prior to qualifying endoscopy. If already on these drugs, the dosage must remain constant throughout the study. 15. Subjects who are on a regimen of leukotriene inhibitors (e.g., montelukast) or oral cromolyn sodium for allergic rhinitis/asthma after ICF signature. 16. Infection with hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) (to be tested during Screening); • The following parameters will be utilized to determine hepatitis B and hepatitis C infection: positive for hepatitis B surface antigen [HBsAg], total hepatitis B core antibody [anti-HBc] positive alone if also hepatitis B virus (HBV) deoxyribonucleic acid (DNA) positive, or hepatitis C virus (HCV) antibody if also HCV ribonucleic acid (RNA) positive. Subjects who are positive for hepatitis B surface antibody, but negative for HBsAg and anti-HBc, will be eligible. • HIV 1 and HIV 2 will be tested by polymerase chain reaction (PCR). 17. Have gastrointestinal (GI) bleeding or documented active peptic ulcer within 4 weeks prior to Screening or between the Screening Visit and the Randomization Visit; 18. Have current (>30 days) chronic infection such as prior or active tuberculosis (TB), active chicken pox or measles or absence of prior measles, mumps and rubella (MMR) vaccine, immunosuppression, immunodeficiency, malignancy except treated non-melanoma skin cancer, or known severe bleeding disorder. Subjects with TB exposure or who live in high endemic areas should be assessed locally for TB before consideration for the study; 19. Have history or presence of Crohn's disease, celiac disease, or other inflammatory disease of the GI tract, including eosinophilic gastroenteritis; 20. Have current alcohol or drug abuse in the opinion of the Investigator. Chronic consumption of 3 or more standard drinks

	(≥42 g/L) per day is prohibited; 21. Female subjects who are pregnant, breastfeeding, or planning to become pregnant during the study; • Serum pregnancy test at Screening and urine pregnancy test during 4-week Baseline Symptom Assessment in women of childbearing potential must be negative. 22. Sexually active females of childbearing potential who do not agree to follow highly effective contraceptive methods through the Follow-up Visit; • For systemic contraceptives, use must be stable for ≥28 days prior to Screening. • Female subjects with surgical menopause or menopause confirmed by follicle-stimulating hormone/luteinizing hormone do not require contraception or pregnancy testing during the study. 23. Have received an investigational product, as part of a clinical trial within 30 days (or 5 half-lives) of Screening. Subjects who are currently on observational studies or enrolled in patient registries are allowed in this study. 24. A serum cortisol level <16 µg/dL (440 nmol/L) at 60 minutes with adrenocorticotropic hormone (ACTH) stimulation test using 250 µg cosyntropin administered intramuscularly (i.e., an abnormal result on the ACTH stimulation test).
Test product, dose and mode of administration:	APT-1011 is an orally disintegrating tablet that includes FP as its active ingredient. For the purposes of this protocol, the term study drug is used to refer to any blinded medication administered (i.e., any dosage of APT-1011 or placebo). Subjects will be instructed to take the study drug orally, with no water or other liquids. The tablet should be placed in the mouth and manipulated with the tongue until it disintegrates completely. It should be swallowed when fully disintegrated, without biting or chewing. No rinsing with water or liquids is to be allowed after administration. Dosing will occur in the morning ("after breakfast;" ≥30 minutes after breakfast) and at bedtime ("at bedtime;" ≥2 hours after the evening meal). The "at bedtime" dose of study drug will be administered immediately prior to sleep, while lying in bed. All eating, drinking, and tooth brushing should be completed prior to dosing. Study drug will be administered BID (30 minutes after breakfast and at bedtime) in all parts of the study. During the placebo run-in, the subjects will receive placebo BID. In the HS groups, the subjects will receive placebo in the morning 30 minutes after breakfast and their doses at bedtime. Placebo subjects after randomization will receive placebo BID. Subjects in the 1.5 mg BID APT-1011, 3 mg BID APT-1011, and placebo dosing groups will take the same study drug for the "after breakfast" and "at bedtime" doses. Subjects in the 1.5 mg HS and 3 mg HS APT-1011 groups will take placebo "after breakfast" and 1.5 mg or 3 mg APT-1011 "at bedtime." Subjects should refrain from oral intake of solids or liquids for ≥1 hour after dosing.

Reference therapy, dose, and mode of administration:	A comparator medication will not be administered in the current study.

Criteria for evaluation:

Efficacy will be assessed histologically (eosinophils per HPF), endoscopically (Eosinophilic Esophagitis Endoscopic Reference Score [EREFs]), clinically as an exploratory endpoint (via the PROSE completed for each dysphagia episode and at the end of each day), and the following additional patient-reported outcomes: Global EoE Symptom Score, Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC), 7-day Eosinophilic Esophagitis Activity Index (EEsAI) total and subscores, and subject's assessment of symptoms. Health Related Quality of Life (HRQoL) will be assessed as an exploratory endpoint by the Adult Eosinophilic Esophagitis Quality of Life Questionnaire (EoE-QoL-A).

Primary efficacy endpoint: The following primary efficacy endpoint will be evaluated at Week 12 to assess EoE response:

- Histology: percentage of subjects with ≤6 PEAK eosinophils/HPF after assessing at least 5-6 biopsies from the proximal and distal esophagus (~3 each) where the HPF area is 235 square microns (40 magnification lens with a 22 mm ocular).

Secondary efficacy endpoints: The following secondary efficacy endpoints will be evaluated:

- EoE sustained response: percentage of subjects who met the primary endpoint at Week 12 and maintained the primary endpoint at Week 26 and Week 52;
- Change from baseline EREFs at Week 12, Week 26, and Week 52;
  - Endoscopic changes will as per the EREFs evaluation based on the following endoscopic features: edema, rings, exudates, furrows, stricture, and several miscellaneous features (crepe paper esophagus, narrow caliber esophagus, and esophageal erosions).
- Percentage of subjects with a peak eosinophils/HPF number <1 and <15 at Week 12, Week 26, and Week 52;
- Change from baseline Global EoE Symptom Score assessed prior to randomization, which will be assessed for the 7-day period prior to the following study visits: Week 4, Week 8, Week 12, Week 14, Week 18, Week 22, Week 26, Week 28, Week 36, Week 44, and Week 52;
- Dysphagia: Change in the number of dysphagia episodes at baseline (14-day period prior to randomization) compared with the 14-day period prior to the time point of interest (Week 12, Week 26 and Week 52);
- Change from baseline 7-day EEsAI total score assessed prior to randomization to those assessed at Week 12, Week 26, and Week 52;
- Change from baseline 7-day EEsAI subscores to those assessed at Week 12, Week 26, and Week 52;
- Percentage of subjects with mean 7-day EEsAI total score <20 to those assessed at Week 12, Week 26, and Week 52;
- Change from baseline PGIS assessed prior to randomization to those assessed at Weeks 4, 8, 12, 14, 18, 22, 26, 28, 36, 44 and 52;
- PGIC at weeks 4, 8, 12, 14, 18, 22, 26, 28, 36, 44, and 52.
- Assessment of treatment failure and relapse, including:
  - Percentage of histologic non-responders by dose at Week 12, Week 26, and Week 52;
  - Percentage of subjects requiring emergency endoscopic food dis-impaction by dose before Week 14, between Week 14 and Week 28, and between Week 28 and Week 52;
  - Percentage of subjects requiring esophageal dilation by dosing group and part of the study;

Exploratory efficacy endpoints: The following exploratory efficacy endpoints will be evaluated:

- [redacted]

[redacted]

Safety variables:

Adverse events

Any AE or concurrent illness experienced by a subject during any portion of FLUTE must be described in detail and be fully evaluated by the Investigator. The Investigator is responsible for recording all AEs observed or reported during the study, regardless of causality and/or clinical significance.

Safety will be assessed by monitoring and recording all treatment-emergent adverse events (TEAEs), TEAEs leading to discontinuation, and serious adverse events (SAEs). All TEAEs will be coded using the current version of the Medical Dictionary for Regulatory Activities classification and classified by severity (mild, moderate, or severe). Relatedness to study drug (related or not related) will be reported for SAEs only by the Investigator. Treatment-emergent adverse events occurring within 3 days of a dose change will be attributed to the previous dose.

APT-1011 (fluticasone proprionate ODT) a minimally absorbed corticosteroid is expected to act topically in the esophagus. Because of this, there is potential for decreased efficacy if the subject swallows water soon after dosing. Since the use of fluticasone has only been rarely associated with oral candidiasis, there will be no need to do swish and spit since this could inadvertently be associated with swallowed water.

Oral and esophageal candidiasis will however be considered AEs of special interest. Subjects may remain in the study during the treatment for these AEs. The Investigator may allow swish and spit 30 minutes after dosing for these subjects. Subjects must be instructed not to swallow the rinsing water.

Symptoms of hypercorticism (See below) are also AEs of special interest.

Laboratory tests

Routine laboratory tests and assessments will be performed throughout the study, including hematology, blood chemistry, urinalysis, and electrocardiograms (ECGs). Clinically significant changes in laboratory tests or ECGs will be summarized.

Physical examination and vital signs

Physical examinations will be performed to document the baseline condition of the subject and to highlight changes related to AEs. Vital signs will also be assessed, and clinically significant deviations will be reported.

Cortisol-related findings

All subjects will undergo a 250 µg ACTH stimulation test during the Screening period. This test will also be administered at Week 12 (Visit 6), Week 26 (Visit 10), and Week 52 (Visit 14). It may also be performed in the event of clinical symptoms or a low cortisol result.

At all visits (scheduled or unscheduled), specific attention will be given to potential changes related to corticosteroids, as well as symptoms of hypercorticism (see Appendix 6). Should a subject undergo surgery or trauma during the study, particular care should be taken in observing subjects for evidence of inadequate adrenal response.

If hypercorticism or adrenal suppression are suspected, an adequate work-up should be performed to confirm or rule out these findings. Specifically, to monitor for hypothalamic pituitary adrenal (HPA) axis suppression of potential clinical concern, a 250 µg ACTH simulation test will also be performed after Screening if any of the following occur:

- During routine laboratory testing completed for the study, the subject has a morning serum cortisol level ≤5 µg/dL (138 nmol/L) (confirmed by 2 blood draws), including at the last on-treatment visit for a subject and, if applicable, Early Termination Visit;
- The subject reports symptoms of hypercorticism;
- The subject discontinues due to HPA axis suppression.

An abnormal result for the ACTH stimulation test is defined as serum cortisol level <16 µg/dL (440 nmol/L) at 60 minutes after treatment with 250 µg cosyntropin administered intramuscularly. This result is exclusionary if it occurs at Screening/4-week Baseline Symptom Assessment and requires follow-up through recovery of adrenal function if it occurs thereafter. Treatment for HPA axis suppression is discussion in the full protocol. The Sponsor will provide guidelines for safety follow-up and document of restoration of adrenal function in all subjects demonstrating evidence of hypercorticism or HPA axis suppression during the course of the study.

Electrocardiogram

Electrocardiograms signs will be assessed, and clinically significant deviations will be reported.

Safety endpoints: The safety endpoints of interest are:

- Frequency of TEAEs;
- TEAEs leading to discontinuation;
- Treatment-emergent SAEs;
- Percentage of subjects with serum cortisol level ≤5 µg/dL (≤138 nmol/L) or abnormal ACTH stimulation test (serum cortisol <16 µg/dL [≤440 nmol/L] at 60 minutes);
- The number of subjects discontinuing for HPA axis suppression will be recorded.
- Frequency of oral and esophageal candidiasis.

Pharmacokinetic variables:

The following PopPK parameters will be estimated using sparse sampling, as data permit:

- Oral clearance;
- Volume of distribution.

Additional PopPK parameters will be estimated, as appropriate, based on the final structural PK model.

Statistical methods:

Sample size determination: Part 1 will include a sample size with a range of 100 subjects, in which 20 patients are randomized to 1.5 mg HS, 1.5 mg BID, 3 mg HS, 3 mg BID, and placebo (1:1:1:1:1). Based on these randomization ratios, approximately 80 % of all subjects in Part 1 will be treated with an APT-1011 dosing regimen and approximately 20% of all subjects in Part 1 will be treated with placebo.

Analysis populations:

- The All Enrolled Population includes all subjects who sign an ICF and are enrolled into the study.
- The Safety Population includes all subjects who receive ≥1 dose of the study drug.

- The Intent-to-treat (ITT) Population includes all subjects randomized.
  - A subject who is enrolled in the study and receives study drug, but fails to complete treatment will be considered a dropout.
- The Sparse PK Subgroup includes all subjects who have ≥1 quantifiable PK sample collected for sparse PK evaluations.

Additional analysis populations (e.g., Per Protocol Populations including subjects who complete Part 1, Part 2 Weeks 26 and 52) may be defined in the Statistical Analysis Plan (SAP).

Statistical methodology:

Subject characteristics

Baseline and demographic information will be summarized using descriptive statistics for continuous and ordinal variables (e.g., age, weight and height [Day 1 only]) and counts and percentages for categorical variables (presence or absence of esophageal strictures, prior response to steroids, sex and race). Body Mass Index (BMI) will be calculated on Day 1.

Primary efficacy analysis for Part 1

Let θ_j be the Cochran-Mantel-Haenzel common odds ratio comparing treatment vs. control for histologic response for dose j given randomization strata; with j=1,2,3,4 corresponding to APT-1011 3 mg BID, 1.5 mg BID, 3 mg HS, 1.5 mg HS doses, respectively. There are 4 hypotheses corresponding to the 4 active doses, which will be tested using a gatekeeping strategy to preserve Type I error for each analysis.

1) Primary Hypothesis #1

H_0: $\theta_1 \leq 1$

H_1: $\theta_1 \leq 1$

A stratified Cochran-Mantel-Haenzel test will be used to test primary hypothesis #1, i.e., 3 mg BID vs. placebo, using the randomization strata. If the corresponding one-sided p-value is less than or equal to 0.05, the null hypothesis will be rejected, and subsequently the following hypothesis will be tested:

2) Primary Hypothesis #2

H_0: $\theta_2 \leq 1$

H_1: $\theta_2 \leq 1$

A stratified Cochran-Mantel-Haenzel test will be used to test primary hypothesis #2, i.e., 3 mg HS vs. placebo. If the corresponding one-sided p-value is less than or equal to 0.05, the null hypothesis will be rejected, and subsequently the following hypothesis will be tested:

3) Primary Hypothesis #3

H_0: $\theta_3 \leq 1$

H_1: $\theta_3 \leq 1$

A stratified Cochran-Mantel-Haenzel test will be used to test primary hypothesis #3, i.e., 1.5 mg BID vs. placebo. If the corresponding one-sided p-value is less than or equal to 0.05, the null hypothesis will be rejected, and subsequently the following hypothesis will be tested:

4) Primary Hypothesis #4

H_0: $\theta_4 \leq 1$

H_1: $\theta_4 \leq 1$

A stratified Cochran-Mantel-Haenzel test will be used to test primary hypothesis #4, i.e., 1.5 mg HS vs. placebo. If the corresponding one-sided p-value is less than or equal to 0.05, the null hypothesis will be rejected.

Note the gatekeeping strategy only allows formal hypothesis testing of 1.5 mg HS or 1.5 mg BID if the higher doses meet statistical significance. Given prior studies with histologic endpoints, there is a strong rationale suggesting that higher doses will have a greater benefit on the primary efficacy endpoint of

histology.

Efficacy analysis for Part 2

Sustained EoE response will be assessed in subjects who complete both Part 1 and Part 2 and complete Week-26 and 52 evaluations. This will be assessed by the primary endpoint.

Other measures of efficacy will be assessed at Week 26.

Efficacy will be summarized for histologic non-responders from Part 1 who are treated in Part 2.

Other measures of efficacy will be assessed at Week 52.

The primary focus of Part 2 will be descriptive in nature.

Secondary and exploratory efficacy analysis

Formal statistical hypothesis testing will be used to evaluate treatment benefit with respect to the reduction in number of dysphagia episodes. For each dose that meets the criterion for statistical significance on the primary efficacy outcome, a Wilcoxon Rank-Sum test will be used to test whether the reduction in the number of dysphagia episodes from baseline is larger for the treatment group compared to the control. The hypothesis to be tested is:

H_0: $R_{1j}(x) \leq R_{0j}(x)$

H_1: $R_{1j}(x) > R_{0j}(x)$

Where $R_{ij}(x)$ is the distribution function for the reduction in number of dysphagia episodes for treatment group *i* (=0 for control, 1 for treatment) and dose *j*. Holm's step-down procedure will be used to control the overall Type I error at 0.05, where the number of doses considered for inferential testing is equal to the number of doses that meet statistical significance for the primary efficacy analysis.

Statistical tests to compare each APT-1011 dosing group with placebo will be performed for other secondary efficacy endpoints, but the corresponding p-values will be considered as descriptive rather than inferential. The secondary endpoints will be analyzed via a stratified Cochran-Mantel-Haenzel test for categorical endpoints and analysis of covariance or Wilcoxon Rank-Sum tests for change from baseline endpoints, except for the endpoint of time to relapse after initiation of double-blind treatment in Part 2, which will be analyzed using Kaplan-Meier methods.

As a secondary efficacy analysis, all 4 doses of active treatment will be pooled and compared to placebo with a stratified Cochran-Mantel-Haenzel test. Additionally, Bayesian hierarchical modeling will be used for both the primary efficacy endpoint and reduction in number of dysphagia episodes, in which dose-response modeling is used to estimate the difference between each active dose and placebo. Additionally, a logistic regression model using both dose and frequency and dose-frequency interaction will be used to analyze the primary endpoint. Subgroup analyses and regression models will also be conducted on primary and key secondary endpoints to assess regional effects and relationships with demographics (age, gender, race, ethnicity, PPI status, and strata variables).

Safety analyses

The incidence of TEAEs will be summarized by system organ class (SOC) and preferred term. Separate summaries by maximum severity (all AEs) and relationship to study drug (SAEs only) will be provided. The incidence of TEAEs leading to discontinuation from the study and treatment-emergent SAEs will also be summarized. In subjects who change dosing groups, the TEAEs will be attributed to actual dose at the time of the event.

Clinically significant changes of potential clinical interest in clinical tests will be summarized including hematology, chemistry, urinalysis, ECG, cortisol, vital signs, and bone mineral density. No statistical testing of safety endpoints will be performed. Shift tables may be produced, if needed. The number of subjects discontinuing due to HPA axis suppression or positive ACTH stimulation tests will be summarized.

Population pharmacokinetics

A PopPK analysis will be performed based on sparse plasma concentration data. It will be performed using the nonlinear mixed-effects software, NONMEM, Version 7.2.0 or later or other appropriate nonlinear mixed-effects modeling software. The structural PK model will include oral clearance and volume of

distribution as fixed-effect parameters. Additionally, the intersubject variability in the parameter estimates and the random residual error in the data will be estimated with appropriate error models. The optimal base model will be selected according to the standard criteria such as minimum objective function value and diagnostic plots. Evaluation of renal and hepatic functions and concomitant medications will be included in the PopPK model. A separate PopPK report will be generated as an appendix to the clinical study report.

Exploratory PK/PD analysis

[redacted]

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1.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACTH	adrenocorticotropic hormone
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
anti-HBc	total hepatitis B core antibody
AST	aspartate transaminase
AUC	area under curve
$AUC_{(0\text{-}12h)}$	area under the plasma concentration time curve from time 0 to the 12 hours post-dose
$AUC_{(0\text{-}24h)}$	area under the plasma concentration time curve from time 0 to the 24 hours post-dose
BID	twice daily
CL/F	oral clearance
C_{max}	maximum concentration
CMH	Cochran-Mantel-Haenzel
CR	concentration-response
CRA	Clinical Research Associate
CRO	contract research organization
CSR	clinical study report
CV%	coefficient of variation
CYP	cytochrome P450
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EEsAI	Eosinophilic Esophagitis Activity Index
EGD	esophagogastroduodenoscopy
EoE	eosinophilic esophagitis

EoE-QOL-A	Adult Eosinophilic Esophagitis Quality of Life Questionnaire
ePRO	electronic patient-reported outcome
EREFs	Eosinophilic Esophagitis Endoscopic Reference Score
FDA	Food and Drug Administration
FLUTE	FLUTicasone in Eosinophilic esophagitis
FP	fluticasone propionate
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HBC	hepatitis C virus
HIV	human immunodeficiency virus
HPA	hypothalamic adrenal
HPF	high-power field
HRQoL	Health Related Quality of Life
hs	hora somni (before sleep)
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	investigator site file
ITT	intent-to-treat
IV	intravenous(ly)
IWRS	Interactive Web Response System
LH	luteinizing hormone
n	number
PD	pharmacodynamics
PGIC	Patient Global Impression of Change

PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PopPK	population pharmacokinetics
PPI	proton pump inhibitor
PROSE	Patient Reported Outcomes Symptoms of EoE
QD	once daily
RAR	response adaptive randomization
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SFED	Six Food Elimination Diet
TB	tuberculosis
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
V/F	volume of distribution
WBC	white blood cell

2.0 INTRODUCTION

2.1 Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated, antigen-driven esophageal clinicopathologic disorder characterized by an eosinophilic-predominant inflammatory process.[1] It appears to represent a spectrum of disease that progresses from being predominantly characterized by inflammation to being predominantly characterized by stricture.

While EoE was initially described in 1978, it reached widespread awareness only in the past 15 years.[2] The disease is most prevalent in young, male Caucasians from urban or suburban areas. It exhibits seasonal variations in incidence, suggesting that both genetic and environmental factors may play a role in the pathophysiology.[3] The overall prevalence of EoE is 25.9 per 100,000 population in the United States (US). Of this population, approximately 38% are female, approximately 10% are elderly, and approximately 16% are children under 18 years of age.[4]

Updated guidelines for diagnosis from the 2013 American College of Gastroenterology Clinical Guideline[5] indicate that EoE is a clinicopathologic disorder, taking into account clinical and pathological information without parameters interpreted in isolation. The following parameters are considered:

- Clinical symptoms related to esophageal dysfunction;
- Eosinophil-predominant inflammation on esophageal biopsy, with peak esophageal mucosal eosinophil count per high-power field (HPF; standard area of 235 square microns; 40x magnification [0.3 mm^2]) number ≥15, shorten to peak eosinophils/HPF in this protocol;
    - This is defined as the peak eosinophils/HPF number in ~3 biopsies obtained from each the proximal and distal esophagus (5-6 total biopsies);
- Mucosal eosinophilia is confined to the esophagus and persists after a trial of proton pump inhibitors (PPIs).

The majority of adolescents and adults present clinically with dysphagia and/or food impaction.

Since patients with gastroesophageal reflux disease (GERD) have overlapping symptoms and may also have EoE, it is important to rule out GERD in the evaluation of patients with suspected EoE using a trial of PPIs.

Due to the overlapping symptoms with GERD, there is frequently considerable delay in diagnosis in both children and adults. The typical delay in diagnosis of EoE could give the false impression that the disease is different in adults when in fact the delay in diagnosis may just lead to an apparently more progressive disease in adults. Adults also are more able to adapt to dysphagia by modifying their food choices, including food consistency, compared with children; this case further delay diagnosis in adults. A review of untreated pediatric patients as young adults suggests that stricture in adults could be a result of lack of treatment in childhood.[27]

Consequences of EoE include dysphagia, tissue remodeling, food impaction, spontaneous perforation of the esophagus, and food intolerance and avoidance; the last consequence is especially common in the pediatric population. Tissue remodeling of the esophagus is part of the inflammatory process in EoE, akin to the airway remodeling in asthma.[6] Such remodeling leads to fibrosis and esophageal structural changes, including strictures, which affect most patients with EoE.[7] Food impaction, which may be associated with rings and strictures, has been commonly reported in both adults and children with EoE. While the majority of food impaction episodes are relieved by swallowing water or by regurgitation, 30% to 55% of adults require emergency esophagogastroduodenoscopy (EGD) to remove the food bolus with forceps.[8,9] In children, vomiting, food intolerance, and avoidance are common, with failure to thrive occurring in 5% to 19% of patients.[10] Malnutrition associated with EoE has not been documented.[11] Dysphagia and food impaction, which are typical in adults, do not typically appear until adolescence.[14]

While concerns have been raised about a possible increased risk of cancer due to the chronic inflammation that occurs in EoE, this potential risk has not been validated. There are also no data to suggest that EoE progresses to a more extensive eosinophilic disorder.

2.2 Current Therapeutic Options

The goal of treatment is to resolve symptoms of esophageal inflammation and to prevent complications, such as strictures, that lead to food impaction. The only widely advocated nonpharmacological approach is a food elimination diet that eliminates all intact protein by administering an amino acid-based formula to patients with known food allergies.[10] Another dietary approach is the use of the Six Food Elimination Diet (SFED) that eliminates cow's milk protein, soy, peanuts, wheat, egg, and seafood. After a patient has responded, the eliminated foods are re-introduced 1 by 1 to determine which are responsible for symptoms. In 1 study, this diet had demonstrated efficacy comparable with the elemental diet in children at a lower cost and improved compliance.[12] The SFED has recently been tested in adults with positive results.[18] Notably patient compliance with the severely restricted diet is poor, and this approach also requires multiple endoscopies to assess the esophagus with each change in diet. As such, this a dietary approach has not been widely adopted in adults.

Currently, there are no pharmacological treatments approved by the Food and Drug Administration (FDA) for patients with EoE, but there are several currently in clinically development. The most widely used drug treatment is topical corticosteroids delivered via metered dose inhalers, including fluticasone propionate (FP) and budesonide. Such treatments require that patients utilize a nasal formulation of corticosteroid orally (i.e., spray medication into the mouth and swallow). Additionally, there is a limit to the dose that can be practically administered by this route. Due to lack of regulatory approval for the EoE indication, patients may experience insurance and reimbursement issues if they do not have concurrent asthma. Systemic corticosteroids are used for the most severe cases of EoE.[1,19] There are significant concerns about corticosteroid side effects with long-term treatment with systemic corticosteroids. When corticosteroids are discontinued, the disease typically recurs and re-treatment is required.[10]

Proton pump inhibitors do also have some efficacy in some patients with EoE; the term "PPI-responsive EoE" is used to describe such patients.[16, 27]

In addition to corticosteroids and PPIs in some patients, small studies examining the use of other drugs directed towards the immune reactions thought to underlie EoE have been conducted; these have shown variable or no effects. Therefore, there is a significant unmet medical need for patients with EoE, an orphan disease associated with significant morbidity.

2.3 APT-1011

The active ingredient of the Fluticasone Propionate Oral Disintegrating Tablet (study drug; APT-011) is FP. This active ingredient has been reported to be effective in the treatment of EoE.[21,22,23,24,25]

The Investigator's Brochure (IB) presents additional information about the composition of APT-1011, as well as nonclinical data.

2.4 Summary of Clinical Data

Data from 3 clinical studies examining APT-1011 conducted to date are summarized below. Refer to the IB for additional details regarding these studies.

2.4.1 Study PR-021

Study PR-021 was a multisite, randomized, double-blind, placebo-controlled, safety and tolerability Phase 1/2a study in which subjects with EoE were treated for 8 weeks with 2 dosing regimens of oral APT-1011.

Twenty-four subjects with a mean age of 25.9 years (range 12 to 54 years) were randomized to placebo, APT-1011 1.5 mg twice daily (BID), or APT-1011 3 mg once daily (QD). One-third of the subjects were adolescents younger than 18 years old. Overall, 95.8% subjects were Caucasian and 62.5% were male.

2.4.1.1 Safety Findings

Treatment-emergent adverse events (TEAEs) that occurred in 2 or more subjects in any dosing group were decreases in blood cortisol, diarrhea, and nasopharyngitis (Table 2-1, in which APT-1011 is termed EUR-1100). All TEAEs were of mild severity except for 1 event of moderate fatigue in a subject treated with placebo. One subject experienced a significant adverse event (AE) of adrenal insufficiency (placebo dosing group), and another subject experienced decreased blood cortisol (APT-1011 1.5 mg BID dosing group). The proportion of subjects who shifted out of the normal laboratory reference range for serum cortisol at Week 8 was comparable among dosing groups.

Table 2-1 Summary of TEAEs Occurring in 2 or More Subjects in Any Dosing Group (PR-021 Safety Population)

	Placebo N = 8		EUR-1100 1.5 mg N = 8		EUR-1100 3.0 mg N = 8		EUR-1100 Total N = 16		All Subjects N = 24	
Preferred Term	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Any TEAE	6 (75.0)	15	6 (75.0)	9	6 (75.0)	17	12 (75.0)	26	18 (75.0)	41
Blood cortisol decreased	2 (25.0)	3	3 (37.5)	3	1 (12.5)	1	4 (25.0)	4	6 (25.0)	7
Diarrhoea	0	0	0	0	2 (25.0)	3	2 (12.5)	3	2 (8.3)	3
Nasopharyngitis	0	0	1 (12.5)	1	1 (12.5)	1	2 (12.5)	2	2 (8.3)	2

Abbreviations: n = number; N = total number; TEAE = treatment-emergent adverse event.

2.4.1.2 Exploratory Efficacy Findings

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2.4.2 Study PR-022

Study PR-022 was a 6-month, post-treatment observational study to evaluate the long-term safety of APT-1011 (following discontinuation of study drug) and to explore response duration, time to treatment failure, and relapse rates. Eligible subjects had to complete Study PR-021 and consent before entering Study PR-022. Relapse was defined as a significant worsening of

symptoms in the opinion of the Investigator. The frequency of dysphagia and its intensity were assessed at the time of relapse. Subjects with relapse underwent EGD at that time (rather than at the end of the study). At relapse, subjects could receive rescue therapy (i.e., standard of care).

Fourteen (58%) subjects who were considered responders at the completion of Study PR-021 enrolled into Study PR-022. Ten subjects who enrolled into Study PR-022 had been included in an active dosing group in Study PR-021. Based on the Investigator's independent assessment, 1 subject at Week 8 and no subjects after Week 12 were assessed as ongoing responders to the prior treatment with APT-1011. All 6 males and 8 females completed Study PR-022.

There were no post-treatment adverse events of special interest (AESIs), such as symptoms or signs of hypercorticism or adrenal insufficiency, that led to discontinuation from the study and no serious adverse events (SAEs). No event occurred in more than 1 subject. No events were judged to be treatment related and events were generally mild in severity.

2.4.3 Study PR-023

Study PR-023 was a Phase 1 open-label, randomized, parallel-group study to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), safety, and tolerability of APT-1011 administered orally at a dose of 3 mg BID or 6 mg QD for 4 days. Plasma PK of FP was evaluated at steady-state following treatment with either 3 mg BID or 6 mg QD APT-1011. The effect of food ingestion 30 minutes prior to a single 6-mg dose of APT-1011 was also explored. Safety, tolerability, and hypothalamic pituitary adrenal (HPA) axis function (as assessed by the cumulative cortisol suppression) were also assessed.

Following repeat-dose administration of APT-1011 (3 mg BID or 6 mg QD), apparent steady-state exposure of FP was attained within 4 days. There was no discernible difference between steady-state systemic exposure of APT-1011 at these 2 dosing regimens. Systemic exposure of FP was low following administration of (swallowed) FP at a total daily dose of 6 mg APT-1011. These data are consistent with a reported oral bioavailability of FP of <1%.

Administration of APT-1011 following a high-fat meal was associated with a decrease in both area under the plasma concentration time curve, from time 0 to the 24 hours post-dose ($AUC_{(0\text{-}24h)}$) and the maximum concentration (C_{max}) of FP observed after administration, indicating that food influences the absorption of oral FP. Administration of APT-1011 with food was associated with a 41% decrease in $AUC_{(0\text{-}24h)}$ for the full study population. These differences in the fed and fasted scenarios were not expected to be clinically meaningful.

Since steady-state was achieved within 4 days, the observed steady-state effects on cortisol levels (reflecting HPA axis suppression) could be determined during the study period. At Day 5 (steady-state), mean serum cortisol suppression was 5.51% (QD regimen) and 10.8% (BID

regimen) compared with Day 0. Urinary cortisol was substantially more variable than serum cortisol, but the trend for urinary cortisol changes was similar. On Day 5 (steady-state), mean urinary cortisol suppression was 1.1% (QD regimen) and 16% (BID regimen) compared with Day 0.

APT-1011 was generally well-tolerated under the dosing conditions (fasted and fed) and regimens (3 mg BID and 6 mg QD APT-1011 for 4 days) investigated. Four subjects experienced a total of 6 TEAEs during the repeat-dose period of the study. No TEAEs were experienced during the period in which the effect of food was studied. There were no AESIs, AEs leading to discontinuation, or SAEs.

2.5 Study Rationale and Risk-Benefit Analysis

The purpose of FLUTicasone in Eosinophilic esophagitis (FLUTE) is to examine 4 total daily doses of APT-1011 to define the exposure-response of APT-1011 and the minimum effective dose while minimizing any clinically significant HPA axis effects.

The current therapeutic landscape for EoE is described in Section 2.2. APT-1011 is expected to offer the following advantages for patients with EoE:

- Oral administration is generally more acceptable and more reliable in terms of accurate dose administration. Currently, the only available formulation of FP is a metered dose inhaler that is sprayed into the mouth and swallowed by the patient.
- Oral administration of APT-1011 has very low bioavailability (see Section 2.4.3) even compared with similar compounds such as budesonide, which further reduces its potential for systemic corticosteroid toxicity, while it may be more potent on a mg basis.

The current study represents the first dose-ranging study of APT-1011. Given its low bioavailability, it is considered unlikely that APT-1011 will have any significant systemic corticosteroid effects. However, these will be carefully monitored (see Section 6.3.4).

Selection of doses for FLUTE is discussed in detail in Section 5.5. The selected doses are largely based on the results of studies discussed in Section 2.4 and published information for other formulations of FP.

In terms of risk-benefit considerations, while the safety profile of APT-1011 is preliminary, that for FP has been reported for a variety of approved formulations. This includes liquid for oral inhalation (Flovent® HFA);[26] powder for oral inhalation (Flovent® Diskus); suspension for intranasal insufflation (Flonase®); and cream, lotion, and ointment for dermatologic use (Cutivate®). Due to the substantially lower systemic exposure expected following oral dosing

with APT-1011 (see Section 5.5), it is expected that APT-1011 will have a more favorable safety profile compared with inhaled Flovent® HFA.

Based on published studies of FP, several precautions should be noted until the safety profile of orally administered APT-1011 is established.[26] Most importantly, subjects treated with FP should be carefully observed for any evidence of systemic corticosteroid effects or clinically significant suppression of the HPA axis. Particular care should be taken in observing subjects post-operatively or during periods of stress for evidence of inadequate adrenal response. Side effects associated with HPA axis suppression will be captured in a specific electronic case report form (eCRF) and morning cortisol, serum glucose, and urine glucose will be monitored throughout FLUTE. Adrenocorticotropic hormone (ACTH) testing will also be performed.

In addition to concerns regarding cortisol-related findings, the IB includes warnings, precautions, and a list of possible AEs. Other expected safety risks for APT-1011 include the development of candidiasis of the mouth and/or throat due to local exposure of the oral and pharyngeal mucosa. Moreover, subjects taking medications that suppress the immune system are more susceptible to infections than healthy individuals. For example, chickenpox and measles can have a more serious or even fatal course in susceptible children or adults using corticosteroids. As such, subjects who have not previously contracted these diseases or have not been properly immunized should take particular care to avoid exposure. APT-1011 should be used with caution in individuals with active or quiescent tuberculosis infection of the respiratory tract; untreated systemic fungal, bacterial, viral or parasitic infections; or ocular herpes simplex. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known.

Due to the inhibitory effect of corticosteroids on wound healing, individuals who have experienced recent oropharyngeal ulcers, oropharyngeal surgery, or oropharyngeal trauma should not use APT-1011 until healing has occurred.

Since EoE typically relapses following the discontinuation of treatment, it is expected that FP in the form of APT-1011 would be used for extended periods of time. Some subjects have received inhaled FP on a continuous basis in a clinical study for up to 4 years. In clinical studies with subjects treated for 2 years with inhaled FP (Flovent® HFA), no apparent differences in the type or severity of adverse reactions were observed after long-term versus short-term treatment. Glaucoma increased intraocular pressure, and cataracts have been reported in subjects following long-term administration of inhaled corticosteroids, including FP.[26] Despite these studies, the long-term effects of topical FP are not fully known (e.g., impact of chronic use of FP on developmental or immunologic processes in the mouth, pharynx, trachea, and lung).

Although a formal Data Safety Monitoring Board is not planned, the study will be monitored continuously by the Medical Monitor and Sponsor. This will be supplemented by standard

pharmacovigilance efforts, including safety review meetings conducted not less frequently than every 3 months. This frequency is expected to be adequate given the projected enrollment rate.

Data are available regarding the exploratory efficacy of APT-1011 in the treatment of EoE in the Phase 1b/2a study and is presented in Section 2.4.1.2. Additionally, data from the interim analysis of this 2b FLUTE study shows that treatment with APT-1011 at all doses is safe and well-tolerated during Part 1 of the study (data not shown). The primary endpoint, that EoE histologic response rate at Week 12, was met at all APT-1011 doses verses placebo. The 3 mg HS dose has been chosen for future development due to best balance between efficacy and safety, i.e. Benefit: Risk Ratio and the added convenience of once a day dosing.

2.5.1 Rationale for Inclusion of Placebo

Since there are currently no drugs approved by the FDA for the treatment of EoE (i.e., no comparator available) and previous studies have demonstrated very high placebo response rates, it is critical to perform placebo-controlled studies to demonstrate efficacy in EoE.

Due to the high placebo rates, the study will utilize a 4-week single-blind placebo run-in period to not only establish the baseline symptoms for the study, but also to ensure that all subjects enrolled have sufficient severity of EoE to warrant inclusion in the study.

The exposure to placebo will be minimized by utilizing a relatively short (14-week) induction period (Part 1). Additionally, the FLUTE study allows subjects who are non-responsive to their randomized study drug including those on placebo to receive in a single-blind fashion, the highest dose of APT-1011 to be studied (3 mg BID) in Part 2, while other subjects remain on their current dose. At Week 26, subjects will undergo an EGD with biopsy to assess histologic response. Histologic non-responders will stop treatment and enter the follow-up period and exit the study. Histologic responders will continue on the same dose until Week 52.

3.0 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of the study is to evaluate the efficacy (histological response) of APT-1011 in adults with EoE.

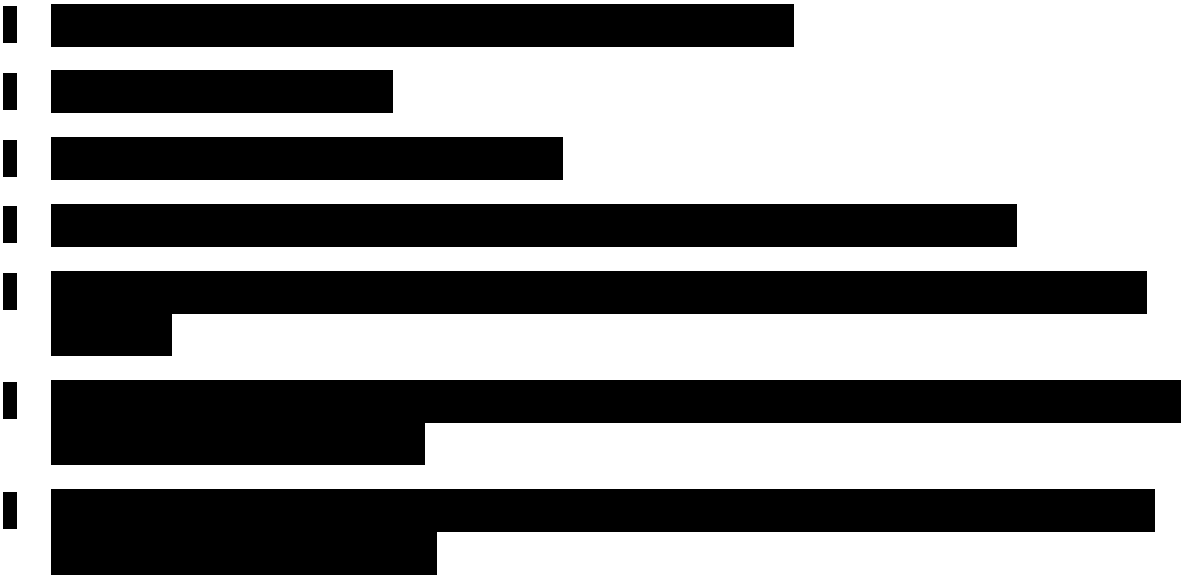
3.2 Secondary Objectives

The secondary objectives of the study are as follows:

- To define the dose-response of APT-1011;
- To select a dose(s) of APT-1011 for Phase 3;
- To evaluate the effect of APT-1011 on histology and endoscopic appearance;
- To evaluate maintenance of efficacy and long-term safety of APT-1011;
- To evaluate the population pharmacokinetics (PopPK) of APT-1011;
- To evaluate the effect of APT-1011 on dysphagia episodes.

3.3 Exploratory Objectives

The exploratory objectives of the study are as follows:



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4.0 INVESTIGATIONAL PLAN

4.1 Summary of Study Design

FLUTE is a randomized, double-blind, placebo-controlled dose-ranging study of 4 total daily doses of APT-1011 versus placebo in 100 adult subjects (≥18 years of age) diagnosed with EoE. During the single-blind run-in/baseline symptom assessment, the subjects will receive placebo 30 minutes after breakfast and HS (at bedtime). APT-1011 will be administered in 4 doses: Placebo 30 minutes after breakfast and 1.5 mg HS (at bedtime), 1.5 mg BID (30 minutes after breakfast and at bedtime; total daily dose of 3 mg), 3 mg HS (at bedtime), and 3 mg BID (30 minutes after breakfast and at bedtime; total daily dose of 6 mg), compared with matching placebo administered 30 minutes after breakfast and HS (at bedtime). The randomization scheme is discussed in Section 4.1.5.2. Efficacy (histological response), safety, and PK of APT-1011 will be examined.

FLUTE will enroll around 100 adult (≥18 years of age) subjects (see Section 8.1 for a discussion of the potential number of subjects to participate in each part).

FLUTE is planned to be performed at approximately 60 active sites in North America (US and Canada) and Western Europe (Belgium, Germany, Switzerland and Spain).

The study will be conducted in several parts (Screening, 4-week single-blind placebo run-in and Baseline Symptom Assessment, and 2 treatment parts [Part 1 and Part 2]) with a Follow-up Visit to occur 2 weeks after the final dose of study drug.

Subjects who enter and complete FLUTE will be in the study for up to 62 weeks or until the last subject completes Week 28.

4.1.1 Definitions of Histologic Response, Histologic Non-response, and Treatment Failure

The following definitions of histologic responders, histologic non-responders, and treatment failures will be used to classify subjects as needed throughout the study. Response or non-responsive status will be assessed 2 weeks prior to the planned end of treatment for Part 1 (Week 12) and Part 2 (Weeks 26 and 52).

Histologic Responder

A histologic responder will be defined as a subject who achieves a histologic response of ≤6 peak eosinophils/HPF (as primary determinant). HPF will be defined as a standard area of 235 square microns in a microscope with 40x lens and 22 mm ocular.

Histologic Non-responder

A histologic non-responder will be defined as a subject who does not have a histologic response (i.e., do not achieve a histologic response of ≤6 peak eosinophils/HPF).

Treatment Failure

Subjects who develop food impaction with or without esophageal dilatation ANYTIME during the study will be considered treatment failures and complete early termination assessments and exit the study after the 2-week post-treatment follow-up period. Subjects who voluntarily withdraw from the study due to worsening symptoms before the Week 12 evaluation or later in the study will also be considered treatment failures. Every effort should be made to perform an EGD in subjects wishing to withdraw due to worsening symptoms. They also must complete the early termination assessments and exit the study after a 2-week post-treatment follow-up period.

A brief overview of how responder status will be determined is discussed in Section 4.1.6; this will be fully described in the investigator site file (ISF).

4.1.2 Schedules of Events

During treatment, all subjects will return to the site for scheduled visits and for unscheduled visits should symptoms worsen between visits. The Schedules of Events, including procedures and assessments to be completed at each visit, are presented in Table 4-1 (Screening, 4-week single-blind placebo run-in/Baseline Symptom Assessment, and Part 1), Table 4-2 (Part 2), and Table 4-3 (Part 2 and Follow-up Visit).

When a specific visit is included in multiple Schedules of Events (e.g., Week 14 in Table 4-1 and Table 4-2), procedures and assessments will not be repeated and will be entered into a single eCRF.

Table 4-1 Schedule of Events (Screening, 4-week Placebo Run-in/Baseline Symptom Assessment, and Part 1)

Assessments and Procedures	VISIT								
	Visit 1 (Screening)	Visit 2 (4-week Baseline Symptom Assessment)	Visit 3 (Randomization)	Visit 4 (Week 4)	Visit 5 (Week 8)	Visit 6 (Week 12) (Response Assessment) [a]	Visit 7 (Week 14 [a])	Unscheduled Visit [b]	Early Termination Visit [c]
	DAY								
	-56 to -28	-28 to -1 (Site Visit to Occur Day -28)	1 ± 2	28 ± 2	56 ± 2	84 ± 2	98 ± 2		
ICF signed	X								
Confirm entry to 4-week Baseline Symptom Assessment [d]		X							
Inclusion/exclusion criteria	X	X	X [e]						
Demographics; medical, surgical, and medication history	X								
Concomitant medication(s)	X	X	X	X	X	X	X	X	X
Physical examination [f]	X		X	X	X	X	X	X	X
Vital signs [g]	X	X	X	X	X	X	X	X	X
Chemistry and hematology	X		X	X	X	X	X	X	X
HIV, HBV and HCV serology[h]	X								
HbA1C [i]	X								
Serum cortisol (morning fasting)	X[j]		X	X	X	X	X [k]	Optional	X

Assessments and Procedures	VISIT								
	Visit 1 (Screening)	Visit 2 (4-week Baseline Symptom Assessment)	Visit 3 (Randomization)	Visit 4 (Week 4)	Visit 5 (Week 8)	Visit 6 (Week 12) (Response Assessment) [a]	Visit 7 (Week 14 [a])	Unscheduled Visit [b]	Early Termination Visit [c]
	DAY								
	-56 to -28	-28 to -1 (Site Visit to Occur Day -28)	1 ± 2	28 ± 2	56 ± 2	84 ± 2	98 ± 2		
Urinalysis	X		X	X	X	X		X	X
12-lead ECG	X		X			X			X
PopPK [l]			X (pre-dose)	X	X	X			
EGD (with EREFs), including collection of multiple esophageal biopsies to be assessed histologically [m,n,o]	X					X			X [p]
Pregnancy test for women of childbearing potential (menopausal women FSH at Screening only) [q]	X (serum)	X (urine)	X (urine)	X (urine)	X (urine)	X (urine)	X (urine)	Optional	X (urine)
ACTH stimulation test (250 µg)	X [r]					X		Optional [s]	Optional [t]
AEs	X	X	X	X	X	X	X	X	X [u]
Global EoE Symptom Score	X[v]	X	X	X	X	X	X	Optional	X
7-day EEsAI			X			X			X
PGIC				X	X	X	X	Optional	X
PGIS		X	X	X	X	X	X	Optional [w]	X
EoE-QoL-A			X			X			X

Assessments and Procedures	VISIT								
	Visit 1 (Screening)	Visit 2 (4-week Baseline Symptom Assessment)	Visit 3 (Randomization)	Visit 4 (Week 4)	Visit 5 (Week 8)	Visit 6 (Week 12) (Response Assessment) [a]	Visit 7 (Week 14 [a])	Unscheduled Visit [b]	Early Termination Visit [c]
	DAY								
	-56 to -28	-28 to -1 (Site Visit to Occur Day -28)	1 ± 2	28 ± 2	56 ± 2	84 ± 2	98 ± 2		
Training for daily diary		X[x]							
Daily diary		X	X	X	X	X	X		X
Study drug dispensed		X	X	X	X	X	X		
Drug return and accountability and study drug compliance assessment			X	X	X	X	X		X
Reason for discontinuation									X

Abbreviations: ACTH = adrenocorticotropic hormone; AE = adverse event; ECG = electrocardiogram; eCRF = electronic case report form; EEsAI = Eosinophilic Esophagitis Activity Index; EGD = esophagogastroduodenoscopy; EoE = eosinophilic esophagitis; EoE-QoL-A = Adult Eosinophilic Esophagitis Quality of Life Questionnaire; EREFs = Eosinophilic Esophagitis Endoscopic Reference Score; FSH = follicle-stimulating hormone; HBV = Hepatitis B virus; HCA = Hepatitis C virus; HIV = human immunodeficiency virus; HPA = hypothalamic-pituitary-adrenal; ICF= informed consent form; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetic(s); popPK = population pharmacokinetic(s); SAE = serious adverse event.

[a] Data and samples collected for Week 14 in the Part 1 Schedule of Events will also apply for this visit in the Part 2 Schedule of Events (as applicable) and procedures will not be repeated. Histologic non-responders at Week 12 will receive single-blind 3 mg BID in Part 2.
[b] The reason for an unscheduled visit will guide procedures, at the discretion of the Investigator.
[c] The subject should be seen at the site within 7 days of determination of the need to discontinue. If this is not possible due to an SAE or other unforeseen circumstance, it may be completed with a phone visit with the subject or a family member. The eCRF should document why the subject was not available for an on-site visit.
[d] As described in Section 4.1.4, to enter the 4-week Baseline Symptom Assessment, subjects must meet all inclusion criteria including the Global EoE score >3 (Inclusion Criterion #5) **except** those to be assessed during the 4-week Baseline Symptom Assessment (Inclusion Criterion #7: evidence of EoE as defined by ≥15 PEAK eosinophils/HPF, Inclusion Criterion #8: in the daily diary, report episodes of dysphagia ≥3 days per 7 days during the last 14 days of the 4-week Baseline Symptom Assessment, Inclusion Criterion

#9: completion of the daily diary on at least 5 out of each 7 days during the last 14 days of the Baseline Symptom Assessment, and Exclusion Criterion #24: serum cortisol level <16 µg/dL (440 nmol/L) at 60 minutes with adrenocorticotropic hormone (ACTH) stimulation test using 250 µg cosyntropin administered intramuscularly [i.e., an abnormal result on the ACTH stimulation test]). The ACTH stimulation test should have been completed before entry into the 4-week Baseline Symptom Assessment, however the results of the test may be pending.

[e] Confirmation that the subject meets eligibility criteria include the following to be confirmed during the 4-week Baseline Symptom Assessment: Inclusion Criterion #7: evidence of EoE as defined by ≥15 PEAK eosinophils/HPF, Inclusion Criterion #8: in the daily diary, report episodes of dysphagia ≥3 days per 7 days during the last 14 days of the 4-week Baseline Symptom Assessment, Inclusion Criterion #9: completion of the daily diary on at least 5 out of each 7 days during the last 14 days of the Baseline Symptom Assessment, and Exclusion Criterion #24: serum cortisol level <16 µg/dL (440 nmol/L) at 60 minutes with ACTH stimulation test using 250 µg cosyntropin administered intramuscularly (i.e., an abnormal result on the ACTH stimulation test). The ACTH stimulation test should have been completed before entry into the 4-week Baseline Symptom Assessment, however the results of the test may be pending.

[f] Physical examination will include assessments of height at screening (Day 1 only), weight, general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological examination. Body Mass Index (BMI) will be calculated on Day 1.

[g] Vital signs to be collected include pulse, respiratory rate, temperature (°C; after a 5-minute rest in sitting position), and blood pressure (measured from the same arm throughout the study).

[h] HIV 1 and HIV 2 will be tested by polymerase chain reaction (PCR). The following parameters will be used to determine hepatitis B and hepatitis C infection: positive for hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (anti-HBc) positive alone if also hepatitis B virus (HBV) deoxyribonucleic acid (DNA) positive, or hepatitis C virus (HCV) antibody if also HCV ribonucleic acid (RNA) positive. Subjects who are positive for hepatitis B surface antibody, but negative for HBsAg and anti-HBc will be eligible (also see Section 6.3.2.4).

[i] HbA1C testing is optional for subjects with diabetes to assess level of control. This may be repeated as needed during the study (also see Section 6.3.2.4).

[j] To be drawn 0700 to 0800 hours, or as close to that window as possible. Subjects must be fasting for an 8-hour period prior to the serum cortisol assessments. Blood may be drawn for serum cortisol (morning fasting) ±3 days of scheduled visit to accommodate accurate timing. If desired, other blood draws scheduled for the visit may be done at the same time. If an ACTH test is scheduled for the visit, the serum cortisol assessment should occur at the same time. The pre-ACTH cortisol level can serve as the baseline serum cortisol level.

[k] If abnormal serum cortisol level is reported at the last on-treatment visit for a subject, additional monitoring and ACTH test may be required (see Section 6.3.4).

[l] Sparse PK samples will be performed in all subjects. A sample will be collected pre-dose on Day 1. At Week 4, Week 8, and Week 12, subjects must fast for 8 hours prior to the visit and will take their "after breakfast" dose at the site and 2 samples will be taken during their scheduled visit: upon arrival to the site and 1 to 1.5 hours after first sample (immediately prior to leaving the site). After arrival at the site and once samples for serum cortisol and sparse PK are drawn, the subject will eat breakfast and take their "after breakfast" dose approximately 30 minutes after breakfast. Site staff should document the time of the morning dose. The time of the "after breakfast" dose (day of the planned visit) and the time of the immediately preceding "at bedtime" dose (evening prior to planned visit) will be recorded. Actual PK sampling times will be documented.

[m] It is expected that the EGD will typically be performed during a separate time from other procedures for a given time point. Both EGD and any other procedures indicated for a study visit must be completed within the window for that study visit. For Screening, the EGD must be completed after the ICF is signed and ≥2 weeks before the date of expected randomization.

[n] During the EGD, the endoscopist will complete the EREFs and ~3 biopsies will be obtained from both the proximal and the distal esophagus (total of 5-6 biopsies). The pathologist will assess histology.

[o] The EGD to determine eligibility must be performed before entry into the 4-week (28 day) single-blind run-in/Baseline Symptom Assessment. Pathology for EGD biopsies may also be assessed during the 4-week Baseline Symptom Assessment (or earlier if possible).

[p] If the subject discontinues from the study due to lack of efficacy or other reasons, the Investigator may perform an EGD, if clinically indicated.

[q] A serum pregnancy test will be performed at Screening and urine pregnancy tests thereafter. Pregnancy testing in women of childbearing potential must be negative (see Section 6.3.2.1).

[r] All subjects undergo a 250 µg ACTH stimulation test as part of eligibility assessments. This evaluation will be completed during the Screening period. This must be performed before entry into the 4-week (28 day) single-blind run-in/Baseline Symptom Assessment. A positive ACTH stimulation test (serum cortisol level <16 µg/dL (440 nmol/L) at 60 minutes after treatment with 250 µg cosyntropin administered intramuscularly) will be exclusionary (see Exclusion Criterion #24: in Section 4.2.2).

[s] A 250 µg ACTH simulation test will be performed (at an unscheduled visit) to assess for HPA axis suppression of potential clinical concern as follows:

1) Any time a subject has a morning serum cortisol level ≤5 µg/dL (138 nmol/L) (confirmed by 2 blood draws)
2) Any time a subject reports symptoms of hypercorticism (Appendix 6)

[t] Subjects who discontinue from the study due to evidence of HPA axis suppression will undergo a 250 µg ACTH stimulation test at the Early Termination Visit.

[u] For the Early Termination Visit, the Investigator should record any occurrence of AEs (14 ± 5 days after discontinuation). Subjects discontinued for HPA issues should be followed until resolution.

[v] Global EoE symptom score at Screening will be completed on paper. EoE score must remain >3 at each of Visits 1, 2 and 3 before randomization, or the subject will be considered a screen failure.

[w] Only if visit is related to EoE change in symptoms.

[x] Recording in the daily diary will not start until 28 days prior to planned date of randomization.

Table 4-2 Schedule of Events (Part 2)

Assessments and Procedures	VISIT						
	Visit 7 (Week 14)	Visit 8 (Week 18)	Visit 9 (Week 22)	Visit 10 (Week 26) (Response Assessment) [a]	Visit 11 (Week 28 [a])	Unscheduled Visit [b]	Early Termination Visit [c]
	DAY						
	98 + 2	126 ± 2	154 ± 2	182 ± 2	196 ± 2		
Histologic Responder/Non-Responders in Part 1 (no contraindications to continue)	X						
Concomitant medication(s)	X	X	X	X	X	X	X
Physical examination [d]	X	X		X		X	X
Vital signs [e]	X	X	X	X	X	X	X
Chemistry and hematology	X	X	X	X		X	X
Serum cortisol (morning fasting) [f]	X	X	X	X	X [g]	Optional	X
Urinalysis		X	X	X		X	X
12-lead ECG				X			X
EGD (with EREFs), including collection of multiple esophageal biopsies to be assessed histologically [h, i]				X		X	X [j]
Urine pregnancy test for women of childbearing potential	X	X	X	X	X	Optional	X
ACTH stimulation test (250 µg) [k]				X		Optional [k]	Optional [l]
AEs	X	X	X	X	X	X	X [m]
Global EoE Symptom Score	X	X	X	X	X	Optional	X
7-day EEsAI				X			X
PGIC	X	X	X	X	X	Optional	X
PGIS	X	X	X	X	X	Optional [n]	X
EoE-QoL-A				X			X
Daily diary	X	X	X	X	X		X

Assessments and Procedures	VISIT						
	Visit 7 (Week 14)	Visit 8 (Week 18)	Visit 9 (Week 22)	Visit 10 (Week 26) (Response Assessment) [a]	Visit 11 (Week 28 [a])	Unscheduled Visit [b]	Early Termination Visit [c]
	DAY						
	98 + 2	126 ± 2	154 ± 2	182 ± 2	196 ± 2		
Study drug dispensed	X (if needed for dosing group change)	X	X	X	X		
Drug return and accountability and study drug compliance assessment		X	X	X	X		X
Reason for discontinuation							X

Abbreviations: ACTH = adrenocorticotropic hormone; AE = adverse event; ECG = electrocardiogram; eCRF = electronic case report form; EEsAI = Eosinophilic Esophagitis Activity Index; EGD = esophagogastroduodenoscopy; EoE = eosinophilic esophagitis; EoE-QoL-A = Adult Eosinophilic Esophagitis Quality of Life Questionnaire; EREFs = Eosinophilic Esophagitis Endoscopic Reference Score; HPA = hypothalamic-pituitary-adrenal; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; SAE = serious adverse event.

[a] Data and samples collected for Week 28 in the Part 1 Schedule of Events will also apply for this visit in the Part 2 Schedule of Events in Table 4-3 (as applicable) and procedures will not be repeated. At Week 26 subjects who are histologic non-responders will stop treatment at Week 28 and enter the 2- week Follow-up period. Histologic responders continue on the same dose.
[b] The reason for an unscheduled visit will guide procedures, at the discretion of the Investigator.
[c] The subject should be seen at the site within 7 days of determination of the need to discontinue. If this is not possible due to an SAE or other unforeseen circumstance, it may be completed with a phone visit with the subject or a family member. The eCRF should document why the subject was not available for an on-site visit.
[d] Physical examination will include assessments of weight, general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological examination.
[e] Vital signs to be collected include pulse, respiratory rate, temperature (°C; after a 5-minute rest in sitting position), and blood pressure (measured from the same arm throughout the study).
[f] To be drawn 0700 to 0800 hours, or as close to that window as possible. Subjects must be fasting for an 8 hour period prior to the serum cortisol assessments. Blood may be drawn for serum cortisol (morning fasting) ±3 days of scheduled visit to accommodate accurate timing. If desired, other blood draws scheduled for the visit may be done at the same time. If an ACTH test is scheduled for the visit, the serum cortisol assessment should occur at the same time. The pre-ACTH cortisol level can serve as the baseline serum cortisol level.
[g] If abnormal serum cortisol level is reported at the last on-treatment visit for a subject, additional monitoring and ACTH test may be required (see Section 6.3.4).

[h] It is expected that the EGD will typically be performed during a separate time from other procedures for a given time point. Both EGD and any other procedures indicated for a study visit must be completed within the window for that study visit. For Screening, the EGD must be completed after the ICF is signed and ≥2 weeks before the date of expected randomization.
[i] During the EGD, the endoscopist will complete the EREFs and ~3 biopsies will be obtained from both the proximal and the distal esophagus (total of 5-6 biopsies). The pathologist will assess histology.
[j] If the subject is discontinuation from the study due to lack of efficacy or other reasons, the Investigator may perform an EGD, if clinically indicated.
[k] A 250 µg ACTH simulation test will be performed (at an unscheduled visit) to assess for HPA axis suppression of potential clinical concern as follows:

1) Any time a subject has a morning serum cortisol level ≤5 µg/dL (138 nmol/L) (confirmed by 2 blood draws)
2) Any time a subject reports symptoms of hypercorticism (Appendix 6).

[l] Subjects who discontinue from the study due to evidence of HPA axis suppression will undergo a 250 µg ACTH stimulation test at the Early Termination Visit.
[m] For the Early Termination Visit, the Investigator should record any occurrence of AEs (14 ± 5 days after discontinuation). Subjects discontinued for HPA issues should be followed until resolution.
[n] Only if visit is related to EoE change in symptoms.

Table 4-3 Schedule of Events (Part 2 and Follow-up Visit)

Assessments and Procedures	VISIT						
	Visit 11 (Week 28)	Visit 12 (Week 36)	Visit 13 (Week 44)	Visit 14 (Week 52) (Response Assessment)	Unscheduled Visit [a]	Early Termination Visit [b]	Follow-up Visit
	DAY						
	196 + 2	252 ± 2	308 ± 2	364 ± 2			2 weeks after last dose of study drug
Histologic responders at Week 26 [c]	X						
Responder status				X			
Concomitant medication(s)	X	X	X	X	X	X	X
Physical examination [d]		X	X	X	X	X	X
Vital signs [e]	X	X	X	X	X	X	X
Chemistry and hematology		X	X	X	X	X	
Serum cortisol (morning fasting)[f]	X	X	X	X [g]	Optional	X	X
Urinalysis		X	X	X	X	X	
12-lead ECG				X	X	X	
EGD (with EREFs), including collection of multiple esophageal biopsies to be assessed histologically [h,i]				X [k]	X	X [j]	
Urine pregnancy test for women of childbearing potential	X	X	X	X	Optional	X	X
ACTH stimulation test (250 µg)				X	Optional [k]	Optional [l]	
AEs	X	X	X	X	X	X [m]	
Global EoE Symptom Score	X	X	X	X	Optional	X	
7-day EEsAI				X	X		
PGIC	X	X	X	X	Optional	X	
PGIS	X	X	X	X	Optional [n]	X	

Assessments and Procedures	VISIT						
	Visit 11 (Week 28)	Visit 12 (Week 36)	Visit 13 (Week 44)	Visit 14 (Week 52) (Response Assessment)	Unscheduled Visit [a]	Early Termination Visit [b]	Follow-up Visit
	DAY						
	196 + 2	252 ± 2	308 ± 2	364 ± 2			2 weeks after last dose of study drug
EoE-QoL-A			X		X		
Daily diary	X	X	X	X	X	X	
Study drug dispensed	X (if needed for dosing group change)	X	X				
Drug return and accountability and study drug compliance assessment	X	X	X		X	X	
Reason for discontinuation					X		

Abbreviations: ACTH = adrenocorticotropic hormone; AE = adverse event; ECG = electrocardiogram; eCRF = electronic case report form; EEsAI = Eosinophilic Esophagitis Activity Index; EGD = esophagogastroduodenoscopy; EoE = eosinophilic esophagitis; EoE-QoL-A = Adult Eosinophilic Esophagitis Quality of Life Questionnaire; EREFs = Eosinophilic Esophagitis Endoscopic Reference Score; HPA = hypothalamic-pituitary-adrenal; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; SAE = serious adverse event.

[a] The reason for an unscheduled visit will guide procedures, at the discretion of the Investigator.
[b] The subject should be seen at the site within 7 days of determination of the need to discontinue. If this is not possible due to an SAE or other unforeseen circumstance, it may be completed with a phone visit with the subject or a family member. The eCRF should document why the subject was not available for an on-site visit.
[c] Histologic responders will continue on the same dose. Histologic non-responders at Week 26 will stop treatment at Week 28 and enter the 2-week follow-up period.
[d] Physical examination will include assessments of weight, general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological examination.
[e] Vital signs to be collected include pulse, respiratory rate, temperature (°C; after a 5-minute rest in sitting position), and blood pressure (measured from the same arm throughout the study).
[f] To be drawn 0700 to 0800 hours, or as close to that window as possible. Subjects must be fasting for an 8 hour period prior to the serum cortisol assessments. Blood may be drawn for serum cortisol (morning fasting) ±3 days of scheduled visit to accommodate accurate timing. If desired, other blood draws scheduled

for the visit may be done at the same time. If an ACTH test is scheduled for the visit, the serum cortisol assessment should occur at the same time. The pre-ACTH cortisol level can serve as the baseline serum cortisol level.

[g] If abnormal serum cortisol level is reported at the last on-treatment visit for a subject, additional monitoring and ACTH test may be required (see Section 6.3.4).

[h] It is expected that the EGD will typically be performed during a separate time from other procedures for a given time point. Both EGD and any other procedures indicated for a study visit must be completed within the window for that study visit. For Screening, the EGD must be completed after the ICF is signed and ≥2 weeks before the date of expected randomization.

[i] During the EGD, the endoscopist will complete the EREFs and ~3 biopsies will be obtained from both the proximal and the distal esophagus (total of 5-6 biopsies). The pathologist will assess histology. The subject will be treated with study drug through completion of the EGD associated with the Week 52 visit.

[j] If the subject is discontinued from the study due to lack of efficacy or other reasons, the Investigator may perform an EGD, if clinically indicated.

[k] A 250 µg ACTH simulation test will be performed (at an unscheduled visit) to assess for HPA axis suppression of potential clinical concern as follows:

1) Any time a subject has a morning serum cortisol level ≤5 µg/dL (138 nmol/L) (confirmed by 2 blood draws)
2) Any time a subject reports symptoms of hypercorticism (Appendix 6).

[l] Subjects who discontinue from the study due to evidence of HPA axis suppression will undergo a 250 µg ACTH stimulation test at the Early Termination Visit.

[m] For the Early Termination Visit, the Investigator should record any occurrence of AEs (14 ± 5 days after discontinuation). Subjects discontinued for HPA issues should be followed until resolution.

[n] Only if visit is related to EoE change in symptoms.

4.1.3 Screening

The Screening Period is 4 weeks (28 days). Along with the reports confirming the subject's primary diagnosis of EoE, the Investigator will assess eligibility criteria (see Section 4.2.1 and Section 4.2.2) of the subject based on Screening results. The Global EoE score must be >3 for the subject to continue in the study.

The EGD procedures to determine eligibility (see Inclusion Criterion #7: have evidence of EoE, as defined by ≥15 PEAK eosinophils/HPF. In order to ensure that a diagnosis can be made, at least 5-6 biopsies should be taken including both proximal and distal specimens [~3 each]) will be completed during the Screening Period and the biopsies must be received by the central pathologist by the times noted in this inclusion criterion. EGD must be performed prior to Visit 2 (4-week Baseline Symptom Assessment).

ACTH stimulation test must also be performed prior to Visit 2 (4-week Baseline Symptom Assessment).

With Medical Monitor approval, a subject may be rescreened once if the previous reason for screen failure is no longer present or the subject withdrew due to personal or family reasons that have since resolved. If a subject is rescreened, a new informed consent form (ICF) will be signed and assigned a new number. All tests and assessments must be repeated. However, if the subject is being rescreened for reasons other than the esophagogastroduodenoscopy (EGD), then the EGD does not have to be repeated at rescreening, if the screening EGD occurred within the previous 6 weeks. Each subject will be reviewed and discussed on a case-by-case basis by the Medical Monitors on the study.

4.1.4 4-week Baseline Symptom Assessment (Placebo Run-in)

To enter this phase, subjects must:

- Meet all inclusion criteria that are possible to assess prior to the 4-week Baseline Symptom Assessment including the Global EoE score >3 (Inclusion Criterion #5; EoE score must remain >3 at each of Visits 1, 2 and 3 before randomization, or the subject will be considered a screen failure) except those to be assessed during the 4-week Baseline Symptom Assessment: Inclusion Criterion #7: evidence of EoE as defined by ≥15 PEAK eosinophils/HPF; Inclusion Criterion #8: in the daily diary, report episodes of dysphagia ≥3 days per 7 days during the last 14 days of the 4-week Baseline Symptom Assessment; Inclusion Criterion #9: completion of the daily diary on at least 5 out of each 7 days during the last 14 days of the Baseline Symptom Assessment;

- Meet no exclusion criteria that will be assessed prior to the 4-week Baseline Symptom Assessment (i.e., all except Exclusion Criteria #24: a serum cortisol level <16 µg/dL (440 nmol/L) at 60 minutes with adrenocorticotropic hormone [ACTH] stimulation test using 250 µg cosyntropin administered intramuscularly [i.e., an abnormal result on the ACTH stimulation test]). The ACTH stimulation test should have been completed before entry into the 4-week Baseline Symptom Assessment, however the results of the test may be pending.

The subject will complete a site visit at the beginning of the 4-week Baseline Symptom Assessment to complete procedures and assessments noted in Table 4-1.

During the 4-week Baseline Symptom Assessment, baseline symptom severity will be determined and the ability of the subject to be compliant with diary entries will be assessed. Pathology for EGD biopsies may also be assessed (or earlier if possible).

4.1.5 Randomization

4.1.5.1 Confirmation of Eligibility

To be eligible for randomization, subjects must satisfy all inclusion/exclusion criteria, including the following inclusion criteria that are expected to be confirmed during the 4-week Baseline Symptom Assessment: Inclusion Criterion #7: evidence of EoE as defined by ≥15 PEAK eosinophils/HPF; Inclusion Criterion #8: in the daily diary, report episodes of dysphagia ≥3 days per 7 days during the last 14 days of the 4-week Baseline Symptom Assessment; Inclusion Criterion #9: completion of the daily diary on at least 5 out of each 7 days during the last 14 days of the Baseline Symptom Assessment and Exclusion Criteria #24: a serum cortisol level <16 µg/dL (440 nmol/L) at 60 minutes with adrenocorticotropic hormone (ACTH) stimulation test using 250 µg cosyntropin administered intramuscularly (i.e., an abnormal result on the ACTH stimulation test). The ACTH stimulation test should have been completed before entry into the 4-week Baseline Symptom Assessment, however the results of the test may be pending.

If the Investigator confirms eligibility criteria are met, he or she will randomize the subject using the Interactive Web Response System (IWRS). The IWRS will confirm the eligibility of the subject pertaining to histology (i.e., confirm histological evidence of the EoE diagnosis as per Inclusion Criterion #7: evidence of EoE as defined by ≥15 PEAK eosinophils/HPF), and provide the randomization number to the Investigator and the Sponsor.

4.1.5.2 Randomization Scheme

A total of 100 adult subjects will be randomized to 1 of 4 doses of APT-1011 (1.5 mg HS, 1.5 mg BID, 3 mg HS, and 3 mg BID) or placebo. Subjects in the HS treatment groups will receive placebo 30 minutes after breakfast in order to maintain the blind.

Randomization will occur in a double-blind manner using an integrated IWRS, and will be stratified by the presence or absence of a history of or current esophageal stricture at Screening and history of a prior positive steroid response to any corticosteroid treatment previously received to treat the subject's EoE captured with demography. Randomization for subjects in Part 1 will be stratified by use, such that a comparable percentage of subjects during the study will be allocated to each of the 5 dosing groups.

4.1.6 Treatment

Figure 4-1 provides an overview of the treatment each subject will receive is determined throughout FLUTE (based on responder status). Symptom improvement or deterioration will be assessed on an ongoing basis.

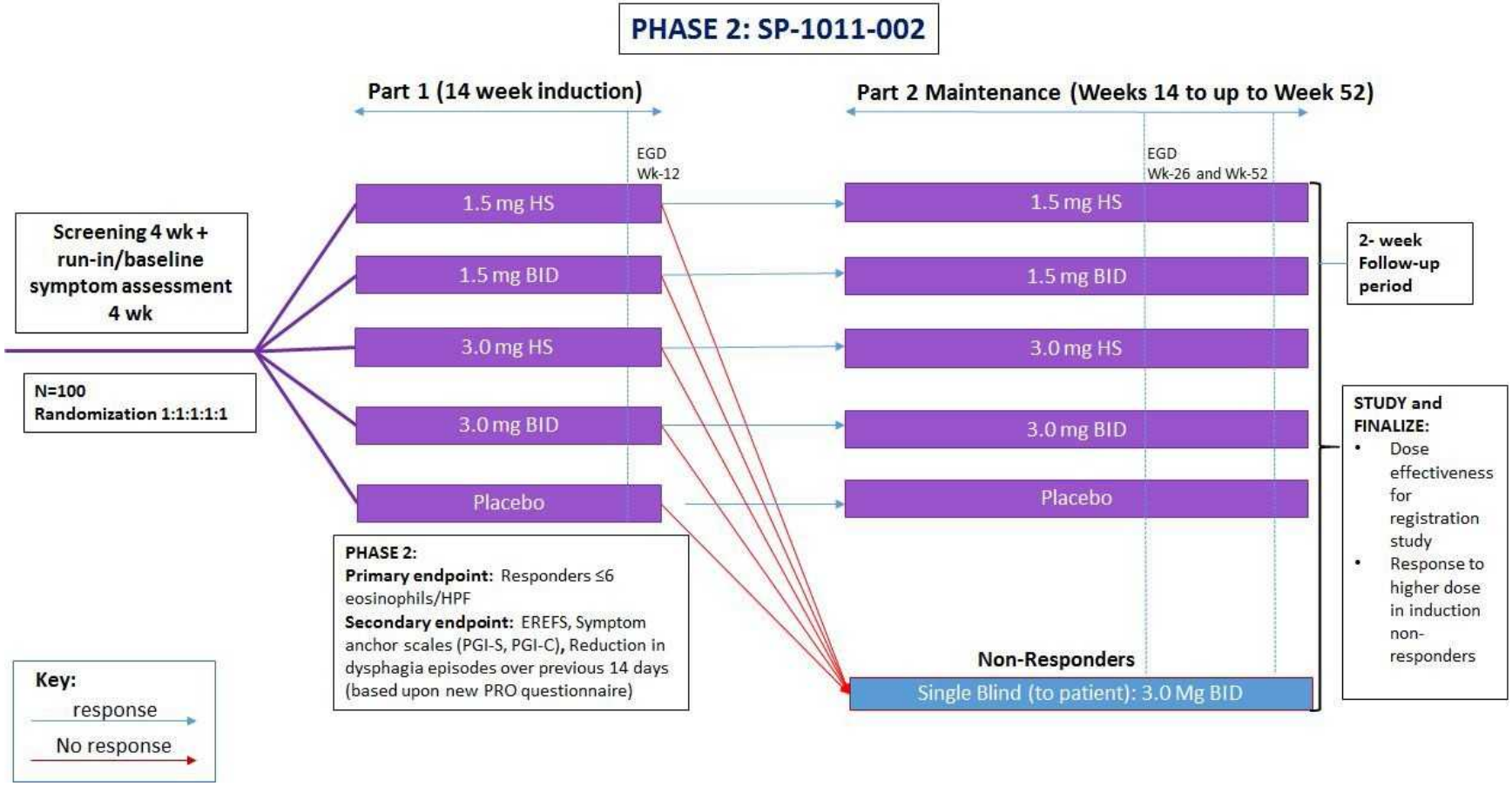


Figure 4-1 Study Schematic

Abbreviations: BID = twice daily; EGD = esophagogastroduodenoscopy; EREFs = Eosinophilic Esophagitis Endoscopic Reference Score; HS = hora somni (before sleep); PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PRO = Patient Reported Outcomes; Wk = Week.

4.1.6.1 Part 1: Induction (Day 1 to Week 14)

During Part 1, subjects will receive their randomized treatment for 14 weeks.

At Week 12, the subjects will undergo a response assessment, including EGD to assess endoscopic and histologic status. The process overview in Section 6.2 will be followed to determine responder status (as defined in Section 4.1.1) and inform the site thereof. Symptoms will also be assessed. The 14 days prior to Week 12 will be compared to the 14 days prior to Randomization.

Histologic responders and non-responders (at Week 12) will enter Part 2 (see Section 4.1.6.2).

4.1.6.2 Part 2: Maintenance (Week 14 to Week 52)

In Part 2, all subjects classified as histologic responders at Week 12 will continue to be treated according to the dosing group to which they were randomized for Part 1. Subjects may continue on this dose for up to 9 months after the completion of Part 1.

Subjects who are histologic non-responders (see Section 4.1.1) at Week 12 will receive single-blind 3 mg BID in Part 2.

At Week 26, subjects will undergo an EGD with biopsy, to assess histologic response. The process overview in Section 6.2 will be followed to determine responder status (as defined in Section 4.1.1) and inform the site thereof. Symptoms will also be assessed. All subjects classified as histologic responders will continue to be treated according to the dosing group to which they were randomized for Part 1 up to Week 52. The 14 days prior to Week 26 will be compared to the 14 days prior to Randomization.

Subjects who are histologic non-responders (see Section 4.1.1) at Week 26 will stop treatment at Week 28 and enter the 2-week follow-up period and exit the study.

Subjects who complete the study at Week 52 will undergo a response assessment, including EGD to assess endoscopic and histologic status. The process overview in Section 6.2 will be followed to determine responder status (as defined in Section 4.1.1) and inform the site thereof. Symptoms will also be assessed. The subject will be treated with study drug through completion of the EGD associated with the Week 52 visit. The 14 days prior to Week 52 will be compared to the 14 days prior to Randomization.

Subjects will complete a Follow-up Visit 2 weeks after the final dose of study drug (see Section 4.1.8).

4.1.7 Early Termination Procedures

Reasons for early termination are discussed in Section 4.2.3.

The subject should be seen at the site within 7 days of determination of the need to discontinue. If this is not possible due to an SAE or other unforeseen circumstance, it may be completed with a phone visit with the subject or a family member. The eCRF should document why the subject was not available for an on-site visit.

If the subject withdraws consent, the date of and the reason for withdrawing consent only will be collected. Otherwise, the Investigator will make all reasonable effort to complete as much as possible of the procedures for the Early Termination Visit.

The Investigator must complete the eCRF up to the time study drug is terminated (and follow-up, if applicable).

4.1.8 Follow-up Visit

Subjects will complete a Follow-up Visit for 1 or more of the following reasons:

- Subject with histologic non-response at Week 26 including subjects on single-blind 3 mg BID;
- Subject completed treatment at Week 52 (following EGD);
- Subject experienced an AE requiring early discontinuation, including food impaction requiring EGD;
- Subjects with worsening symptoms who voluntarily withdraw during the study or who withdraw for any reason.

The Follow-up Visit will occur 2 weeks after the subject takes the final dose of study drug.

All subjects must have a final EGD within 3 weeks prior to completing the Follow-up Visit unless the subject withdraws consent or has a contraindication to EGD.

4.2 Selection of Study Population

To qualify for FLUTE, each subject must meet all inclusion criteria and none of the exclusion criteria, including assessments that confirm EoE diagnosis.

While both genders will be encouraged to enroll, it is expected that approximately 25% of subjects enrolled will be female. Although subjects are allowed to be up to 75 years old, it is expected that approximately 5% of enrolled subjects will be geriatric (≥65 years). It is not required that these estimates are reflected in the enrolled population for the study.

4.2.1 Inclusion Criteria

Subjects must satisfy all of the following criteria:

Before Entering 4-week Baseline Symptom Assessment

1. Male or female between ≥18 and ≤75 years of age at the time of informed consent;
2. Signed the ICF and willing and able to adhere to all study procedures;
3. Diagnosis or presumptive diagnosis of EoE;
    - Diagnosis of EoE must be confirmed by symptoms, histology, and historical documentation of failed treatment on ≥8 weeks of high-dose PPI, as determined by the Investigator. High-dose PPI is defined as 20 to 40 mg BID of any marketed PPI or alternatively this total dose administered once daily; maintenance doses of PPIs are not acceptable.

    Note: Documentation of PPI failure prior to initial diagnosis or by documentation of PPI failure at the time of Screening is required. The subjects may be pre-screened but should not be consented, sign an ICF, or be offered participation in FLUTE if they have not met the diagnostic criteria for EoE that requires that they fail an 8-week trial of high-dose PPIs ***except*** *those who have taken PPIs for 8 weeks will use the EGD within the study for this documentation. The Investigator and potential subject must make the decision to complete a PPI trial independent of any considerations of the study. There is insufficient time to do the 8-week trial within the current study. Should a subject be consented in error and screen fails due to this point, they may be re-screened (see Section 4.1.3).*
4. Have a subject-reported history of ≥3 episodes of dysphagia (difficulty with food going down or an awareness of the sensation of food going down the esophagus) in the 7 days prior to Screening;
5. Have a 7-day Global EoE Symptom Score >3 at baseline (EoE score must remain >3 at each of Visits 1, 2 and 3 before randomization). This will be performed on paper during the Screening Visit.
6. Willing and able to adhere to study-related treatment regimens, procedures, and visit schedule.

Before Randomization

7. To be determined prior to randomization: have evidence of EoE, as defined by ≥15 PEAK eosinophils/HPF. In order to ensure that a diagnosis can be made, at least 5-6 biopsies should be taken including both proximal and distal specimens (~3 each);

- No EGDs and biopsies performed outside FLUTE are acceptable for meeting eligibility criteria.
- Optional biopsies may be taken and processed locally for local use, if specified in the local ICF.
- Biopsies are to be obtained PRIOR to the 4-week Baseline Symptom Assessment. Eligibility from a histological perspective will be based solely on the central pathologist's assessment.

8. To be determined prior to randomization: in the daily diary, report episodes at least 3 episodes of dysphagia (difficulty with food going down or an awareness of the sensation of food going down the esophagus) for each of the last 7 days during the last 14-days of the 4-week Baseline Symptom Assessment;
9. To be determined prior to randomization: completion of the daily diary on at least 5 out of each 7 days during the last 14 days of the 4-week Baseline Symptom Assessment.

4.2.2 Exclusion Criteria

Subjects will not be entered in FLUTE for any of the following reasons:

Before Entering 4-week Baseline Symptom Assessment

1. Have known contraindication, hypersensitivity, or intolerance to corticosteroids (See Appendix 6 for signs and symptoms of adrenal suppression and hypercorticism);
2. Have any physical, mental, or social condition or history of illness or laboratory abnormality that in the Investigator's judgment might interfere with study procedures or the ability of the subject to adhere to and complete the study or increase the safety risk to the subject such as uncontrolled diabetes or hypertension;
3. Presence of oral or esophageal mucosal infection of any type;
4. Have any mouth or dental condition that prevents normal eating;
5. Have any condition affecting the esophageal mucosa or altering esophageal motility other than EoE, including erosive esophagitis (grade B or higher as per the Los Angeles Classification of Gastroesophageal Reflux Disease), hiatus hernia longer than 3 cm, Barrett's esophagus, and achalasia;
6. Use of systemic (oral or parenteral) corticosteroids within 60 days prior to Screening, use of inhaled/swallowed corticosteroids within 30 days prior to Screening, or extended use of high-potency dermal topical corticosteroids within 30 days prior to Screening;

7. Initiation of an elimination diet or elemental diet within 30 days before Screening (diet must remain stable after signing ICF);

8. Morning (0700 to 0800 hours, or as close to that window as possible) serum cortisol level ≤5 µg/dL (138 nmol/L) that is not responsive to ACTH stimulation;

9. Use of biologic immunomodulators in the 24 weeks prior to Screening (allergy desensitization injection or oral therapy is allowed as long as the course of therapy is not altered during the study period);

10. Use of calcineurin inhibitors or purine analogues (azathioprine, 6-mercaptopurine) in the 12 weeks prior to Screening;

11. Use of potent cytochrome P450 (CYP) 3A4 inhibitors (e.g., ritonavir and ketoconazole; see Appendix 2) in the 12 weeks prior to Screening;

12. Have a contraindication to or factors that substantially increase the risk of EGD or esophageal biopsy or have narrowing of the esophagus that precludes EGD with a standard 9 mm endoscope;

13. Have history of an esophageal stricture requiring dilatation with the previous 12 weeks prior to Screening;

14. Subjects who have initiated, discontinued, or changed dosage regimens of PPIs, H2 antagonists, antacids or antihistamines, for any condition such as GERD or allergric rhinitis within 4 weeks prior to qualifying endoscopy. If already on these drugs, the dosage must remain constant during the study.

15. Subjects who are on a regimen of leukotriene inhibitors (e.g., montelukast) or oral cromolyn sodium for allergic rhinitis/asthma after ICF signature.

16. Infection with hepatitis B, hepatitis C, or human immunodeficiency virus (to be tested during Screening);

    - The following parameters will be utilized to determine hepatitis B and hepatitis C infection: positive for hepatitis B surface antigen [HBsAg], total hepatitis B core antibody [anti-HBc], positive alone if also hepatitis B virus (HBV) deoxyribonucleic acid (DNA) positive, or hepatitis C virus (HCV) antibody if also HCV ribonucleic acid (RNA) positive. Subjects who are positive for hepatitis B surface antibody, but negative for HBsAg and anti-HBc, will be eligible;

    - Human immunodeficiency virus (HIV) 1 and HIV 2 will be tested by polymerase chain reaction (PCR).

17. Have gastrointestinal (GI) bleeding or documented active peptic ulcer within 4 weeks prior to Screening or between the Screening Visit and the Randomization Visit;

18. Have current chronic (>30 days) infection such as prior or active tuberculosis (TB), active chicken pox or measles or absence of prior measles, mumps and rubella (MMR) vaccine, immunosuppression, immunodeficiency, malignancy except treated non-melanoma skin cancer, or known severe bleeding disorder. Subjects with TB exposure or those who live in high endemic areas should be assessed locally for TB before consideration for the study;

19. Have history or presence of Crohn's disease, celiac disease, or other inflammatory disease of the GI tract, including eosinophilic gastroenteritis;

20. Have current alcohol or drug abuse in the opinion of the Investigator. Chronic consumption of 3 or more standard drinks (≥42 g/L) per day is prohibited;

21. Female subjects who are pregnant, breastfeeding, or planning to become pregnant during the study;

    - Serum pregnancy test at Screening and urine pregnancy test during 4-week Baseline Symptom Assessment in women of childbearing potential must be negative.

22. Sexually active females of childbearing potential who do not agree to follow highly effective contraceptive methods (see Section 5.8.4) through the Follow-up Visit;

    - For systemic contraceptives, use must be stable for ≥28 days prior to Screening.
    - Female subjects with surgical menopause or menopause confirmed by follicle-stimulating hormone (FSH)/luteinizing hormone (LH) do not require contraception or pregnancy testing during the study.

23. Have received an investigational product as part of a clinical trial within 30 days (or 5 half-lives, whichever is longer) of Screening. Subjects who are currently on observational studies or enrolled in patient registries are allowed in the study.

24. A serum cortisol level <16 µg/dL (440 nmol/L) at 60 minutes with ACTH stimulation test using 250 µg cosyntropin administered intramuscularly (i.e., an abnormal result on the ACTH stimulation test).

4.2.3 Early Termination of Subjects

Subjects have the right to discontinue from FLUTE at any time for any reason without penalty or prejudice. The Investigator also has the right to discontinue subjects from the study if he or she feels it is in the best interest of the subject or if the subject is uncooperative or noncompliant.

Should a subject decide to discontinue, all efforts will be made to complete all the early discontinuation procedures as thoroughly as possible.

Subjects who discontinue following prestudy evaluations (i.e., screening procedures and during the 4-week Baseline Symptom Assessment), but before receiving any study drug will be considered screen failures. Only data pertaining to Screening and the reason for screen failure will be included in the database. No additional data will be collected from the time of consent withdrawal.

The following reasons for discontinuation will be considered for FLUTE:

- Female subject becomes pregnant;
- Violation of inclusion/exclusion criteria and the Sponsor requires the subject to discontinue;
- Subject withdraws consent and/or chooses to discontinue participation for personal reasons;
- Subject chooses to discontinue, or is discontinued by the Investigator or the Sponsor, due to an AE;
- Subject participates in Part 2 and is classified as a histologic non-responder at Week 26 (see Section 4.1.1).
- Subject uses a prohibited medication (see Section 5.8.1) and the Sponsor requires subject to discontinue;
- In the Investigator or Sponsor's judgment, discontinuation from the study is in the subject's best interest (e.g., SAE [dependent on Investigator clinical judgment], an immediate medical or surgical procedure is required that would compromise the subject's continued participation, intercurrent illness that compromises participation, lack of adequate therapeutic response as outlined in the protocol [relapse; see discussion in Section 4.1.6], or unacceptable risk);
    - Subjects who are discontinued due to lack of efficacy will receive treatment as per Section 5.9.
- Subject is uncooperative or does not comply with protocol requirements (e.g., failure to return for scheduled visits, failure to complete study evaluation tools, failure to return study drug, etc.).
    - Failure or inability to comply with EGD requirements are included in this reason for discontinuation.
    - This may also include serious protocol violation(s).

- Subjects for whom an AE(s) associated with HPA axis suppression are reported are not required to be discontinued. The Investigator must consult with the Sponsor to discuss and receive approval for any such subjects to continue in the study following the AE(s) associated with HPA axis suppression.

All reasonable efforts must be made to contact subjects who fail to return for scheduled visits and to encourage them to comply with all the procedures. All attempts to contact subjects either by phone, courier, and/or email must be clearly documented.

For any subject who discontinues, procedures to be completed are described in Section 4.1.7.

Subjects who are discontinued from the study will not be replaced.

4.2.4 Termination of the Study

The Sponsor may terminate FLUTE for safety, ethical, or administrative reasons at any time. In such cases, the termination procedures set forth in the individual agreement with the clinical sites will be followed. The Investigator will notify the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of study termination and reason(s) for termination.

The Sponsor will notify the regulatory authorities in all countries where FLUTE is being conducted regarding the rationale for the termination of the study.

5.0 STUDY TREATMENTS

5.1 Treatments Administered

APT-1011 will be provided as blinded tablets in dosage strengths of 1.5 and 3.0 mg to achieve the following dosing groups: 1.5 mg HS, 1.5 mg BID, 3 mg HS and 3 mg BID. Matching placebo will be provided similarly. For the purposes of this protocol, the term study drug is used to refer to any blinded medication administered (i.e., any dosage of APT-1011 or placebo).

Timing of and instructions for dosing are discussed in Section 5.6.

5.2 Identity of Investigational Product and Placebo

APT-1011 includes FP as its active ingredient. Dosage strengths to be administered in FLUTE are discussed in Section 5.1. It is manufactured and packaged by Patheon Pharmaceuticals. The Sponsor will be responsible for ensuring that study drug is manufactured in accordance with current Good Manufacturing Practice.

Information regarding the composition of APT-1011 may be found in the IB.

Matching placebo tablets will also be provided to subjects in the 1.5 mg HS, 3 mg HS and placebo dosing groups. Placebo tablets are identical in composition to APT-1011 except they exclude the active ingredient.

5.3 Packaging and Labeling

Tablets of APT-1011 are packaged into 30-count, 30 cc high-density polyethylene bottles with a child-resistant closure, foil induction seal, 0.5 g silica desiccant pouch, and approximately 6 inches of 12/g yard rayon coil.

Each study drug package for a specific subject will contain 2 bottles that are logically color-coded with either a yellow label with a sun logo (“after breakfast” dose) or a blue label with a moon logo (“before bedtime” dose). For blinding purposes, study drug will be provided to the site packaged in Study Medication Kits, identified by a randomization number.

Study drug will be supplied by the Sponsor in sufficient quantities to allow for the treatment of all subjects participating in FLUTE.

Study drug must be stored at room temperature (according to the US Pharmacopeia definition) at 25°C (77°F), with excursions permitted between 15°C and 30°C (59°F and 86°F). Study drug

must be protected from moisture. Care should be taken to avoid excessively shaking the bottles as tablets may break.

The labeling will comply with applicable regulatory requirements, including provision of the following information: pharmaceutical dosage form and route of administration; quantity of the dosage unit; protocol number; subject identifier; subject randomization number; lot number; re-assay/expiration date; caution statements regarding investigational use, access to children, and return of medication; storage conditions; Sponsor information; and directions for use).

5.4 Method of Assigning Subjects to Dosing Group

Randomization will be managed by the IWRS. To randomize a subject, the site staff will access the IWRS via the web to enroll and obtain randomization information. Site staff will then dispense the randomized treatment allocation of study drug, which corresponds to the allocation number as assigned by the IWRS. The IWRS will provide the Subject Medication Kit of the blinded study drug to be dispensed.

The randomization code will be held by the clinical supplies vendor.

The randomization scheme is discussed in Section 4.1.5.2.

5.5 Selection of Doses in the Study

A formal dose-ranging study for FP in EoE has not been performed previously. Selection of the dose in FLUTE is based on safety, PK (as a major determinant of safety), and efficacy considerations.

Since the safety of APT-1011 depends in part on systemic exposure, the bioavailability of oral FP is an important factor in determining the dose range to be studied. Orally administered and inhaled FP each have low bioavailability compared with intravenous (IV) administration (<1% and approximately 26%, respectively). This means the relative bioavailability of orally administered FP compared with an equivalent dose of inhaled FP is <3%.

The PK of FP may also be impacted by potential drug interactions. Specifically, a study in healthy subjects has shown that ritonavir (a highly potent CYP3A4 inhibitor) can significantly increase systemic FP exposure (area under the curve [AUC]), resulting in significantly reduced serum cortisol concentrations. As such, the current study excludes subjects on potent CYP3A4 inhibitors such as ritonavir and ketoconazole. The consumption of grapefruit is also prohibited since this contains a potent CYP3A4 inhibitor.

In Study PR-021 (doses of 1.5 mg BID and 3 mg QD) and Study PR-022 (observational follow-up), APT-1011 was generally well-tolerated with relatively few and largely mild TEAEs reported. Adrenal and cortisol-related AEs were rare.

In published results, 1.7 mg of FP administered orally (typically 2 sprays of 880 mcg each) by metered dose inhaler demonstrates clinical efficacy.[21,22] The planned 1.5 mg HS dosing group closely approximates this 1.7 mg dose.

The doses of APT-1011 to be evaluated in FLUTE range from the expected minimally efficacious dose to the highest dose studied in Study PR-023 that is expected to avoid HPA axis suppression.[20] The maximum total daily dose of 6 mg administered as 3 mg BID was chosen as it allows for assessment of safety and efficacy over a 4-fold dose range while maintaining anticipated mean serum cortisol suppression below 20%.

5.6 Selection and Timing of Dose for Each Subject

The dose to be administered for each subject for Part 1 will be as per randomization (see Section 5.4). For Part 2, the dose to be administered for each subject depends on their histologic responder status (see Section 4.1.6).

Subjects will be instructed to take the study drug orally, with no water or other liquids. The tablet should be placed in the mouth, and manipulated with the tongue until it disintegrates completely. It should be swallowed when fully disintegrated without biting or chewing. No rinsing with water or liquids is to be allowed after administration.

Dosing will occur in the morning ("after breakfast;" ≥30 minutes after breakfast) and at bedtime ("at bedtime;" ≥2 hours after the evening meal). The "at bedtime" dose of study drug will be administered immediately prior to sleep, while lying in bed. All eating, drinking, and tooth brushing should be completed prior to dosing. Table 5-1 summarizes the dosage strength to be taken for the "after breakfast" and "at bedtime" doses for each dosing group.

Study drug will be administered BID (30 minutes after breakfast and at bedtime) in all parts of the study. During the placebo run-in, the subjects will receive placebo BID. In the HS groups, the subjects will receive placebo in the morning 30 minutes after breakfast and their doses at bedtime. Placebo subjects after randomization will receive placebo BID.

Subjects in the 1.5 mg BID APT-1011, 3 mg APT-1011, and placebo dosing groups will take the same study drug for the "after breakfast" and "at bedtime" doses. Subjects in the 1.5 mg HS and 3 mg HS APT-1011 groups will take placebo "after breakfast" and 1.5 mg or 3 mg APT-1011 "at bedtime".

Subjects should refrain from oral intake of solids or liquids for ≥1 hour after dosing.

Table 5-1 Blinded Dosing Regimens by Dosing Group

Dose	Dosing Group				
	1.5 mg HS APT-1011	**1.5 mg BID APT-1011**	**3 mg HS APT-1011**	**3 mg BID APT-1011**	**Placebo**
"After breakfast"	Placebo	1.5 mg APT-1011	Placebo	3.0 mg APT-1011	Placebo
"At bedtime"	1.5 mg APT-1011	1.5 mg APT-1011	3.0 mg APT-1011	3.0 mg APT-1011	Placebo

Abbreviations: BID = twice daily; HS = hora somni (before sleep).
Note: To maintain the blind, all tablets will be labeled for "after breakfast" or "at bedtime" administration (see Section 5.7).

5.7 Blinding

This study is randomized, double-blind, and placebo-controlled with limited access to the randomization code. The investigational product and placebo tablets will be identical in physical appearance. The treatment each subject will receive will not be disclosed to the Investigator, site staff, subject, Sponsor, or any Sponsor designees. The treatment codes will be held by the clinical supplies vendor and randomization will be completed by the IWRS.

Several areas of study operationalization are of particular concern:

- As discussed in Section 4.1.6, subjects may be assigned to single-blind treatment at various time points in the study (Week 14 and potentially following relapse depending upon the clinical circumstances at any time after Week 14). This includes subjects who are determined to be histologic non-responders or who relapse. For subjects who are assigned to single-blind treatment with 3 mg BID APT 1011 (regardless of reason), the previous randomized dosing group assignment will continue to remain blinded.
    - As discussed in Section 4.1.6, subjects who exhibit a sustained response to study drug (when assessed at Week 12 and Week 26) will continue to be treated according to the dosing group to which they were randomized for Part 1.
- The central pathologist will communicate histology responder status from a histological perspective to the IWRS vendor. The corresponding overall responder status (i.e., also accounting for worsening of symptoms [i.e., dysphagia] and food impaction) will be communicated in a blinded fashion to the sites by the IWRS vendor.
- Subjects in the 1.5 mg HS, 3 mg HS APT-1011 and placebo dosing groups will undergo PK sampling to avoid breaking the blind.
- Cortisol suppression was reported in 1 subject taking placebo and 1 subject taking APT-1011 1.5 mg BID in Study PR-021 (see Section 2.4.1.1). As such, the occurrence of such an event

does not necessarily indicate that a subject is being treated with APT-1011. However, it is possible that cortisol laboratory values could unblind site staff. As such, these values will be blinded at all time points after randomization. Programmed alerts will prompt the site should a low-level cortisol laboratory value necessitate an ACTH stimulation test.

- A blinded pharmacist at each site will manage distribution and accountability of study drug. To maintain the blind, the bottle containing the study drug will be labeled for "after breakfast" or "at bedtime" administration. See Table 5-1 for a description of the study drug to be contained in "after breakfast" and "at bedtime" bottle for each dosing group.

5.7.1 Breaking the Blind

At the site, the blind may be broken only in emergency cases in which knowledge of treatment would impact the medical care of the subject. **The Investigator and/or site staff should discuss possible unblinding with the Medical Monitor before unblinding, if at all possible.** Adverse event(s) associated with HPA axis suppression are not expected to require subject unblinding. The Investigator and/or site staff must inform the Sponsor within 24 hours of any unblinding that occurs. The pharmacovigilance group may also break the blind for subjects who experience a suspected unexpected serious adverse reaction.

The process for breaking the blind will be handled through the IWRS. Investigators are strongly discouraged from requesting the blind be broken for an individual subject, unless there is a subject safety issue that requires unblinding and would change subject management. Any site that breaks the blind under inappropriate circumstances may be asked to discontinue its participation in FLUTE. If the blind is broken, it may be broken for only the subject in question.

The Sponsor and contract research organization (CRO) must be notified immediately if a subject and/or Investigator is unblinded during the course of the study. Pertinent information regarding the circumstances of unblinding of a subject's treatment code, including the date, time and reason for unblinding must be documented in the subject's source documents.

5.8 Prior and Concomitant Treatments

The brand name (or, if unknown, the generic name), dose, dose unit (or dosage form if compound), frequency, route of administration, duration of use (start date and, if applicable, stop date), and indication for all medications taken within 30 days prior to signing the ICF, all concomitant medications that are ongoing at the time of the ICF signature, and all concomitant medications taken during the course of the study must be documented on the eCRF. Medications should be recorded whether or not they are allowed or prohibited. Medications include IV fluid, herbal, vitamins, and any other over-the-counter medicines.

Medication history will be collected with particular attention to prior histological response to high-dose PPI and prohibited medications. Of particular note, the use of systemic, oral, or parenteral corticosteroids in the 60 days prior to the start of participation in the study must be documented in the eCRF (see also Exclusion Criterion #6 in Section 4.2.2). Use of, discontinuation or change in dosage regimens of PPIs, H2 antagonists, antacids, antihistamines, leukotriene inhibitors (e.g., montelukast), or oral cromolyn sodium for any condition such as GERD or allergic rhinitis/asthma within 4 weeks prior to qualifying endoscopy was not allowed (see also Exclusion Criteria #14 and #15 in Section 4.2.2).

5.8.1 Exclusionary Medications and Dietary-related Issues

Use of the following medications or dietary-related issues is exclusionary (see Section 4.2.2); their use is also prohibited during the study:

- Use of systemic (oral or parenteral) corticosteroids within 60 days prior to Screening, use of inhaled/swallowed corticosteroids within 30 days prior to Screening, or extended use of high-potency dermal topical corticosteroids within 30 days prior to Screening;
- Initiation of an elimination diet or elemental diet within 30 days before Screening (diet must remain stable after signing ICF);
- Use of biologic immunomodulators within the 24 weeks prior to Screening (allergy desensitization injection therapy is allowed as long as the course of therapy is not altered during the study period);
- Use of calcineurin inhibitors or purine analogues (azathioprine, 6-mercaptopurine) within the 12 weeks prior to Screening;
- Use of potent CYP3A4 inhibitors (e.g., ritonavir and ketoconazole) in the 12 weeks prior to Screening;
- Initiation, discontinuation, or change in dosage regimen of PPIs, H2 antagonists, antacids or antihistamines for any condition such as GERD or allergric rhinitis within 4 weeks prior to qualifying endoscopy. If already on these drugs, the dosage must remain constant during the study
- Use of leukotriene inhibitors or oral cromolyn sodium for allergic rhinitis/asthma after ICF signature;
- Have current alcohol or drug abuse in the opinion of the Investigator. Chronic consumption of 3 or more standard drinks (≥42 g/L) per day is prohibited;

- Participation in a clinical study involving an investigational product within 30 days of Screening.

5.8.2 Excluded Concomitant Medications and Dietary-related Issues

The following medications/therapies and foods are prohibited during the study:

- Initiation of new PPI therapy or alteration of existing PPI therapy is not allowed during the study (see Section 5.8.3 about continuation of existing PPI therapy);
- Initiation, discontinuation or change in dosage regimen of H2 antagonists, antacids or antihistamines for any condition such as GERD or allergic rhinitis within 4 weeks prior to qualifying endoscopy is not allowed during the study;
- Consumption of grapefruit juice (during treatment);
- Potent CYP3A4 inhibitors (e.g. ritonavir and ketoconazole);
- Additionally, as detailed in Section 5.8.1, the following exclusionary concomitant medications are also prohibited during the study: corticosteroids; elimination diet, elemental diet, biologic immunomodulators, calcineurin inhibitors or purine analogues (azathioprine, 6-mercaptopurine), current alcohol or drug abuse, or other investigational product.
    - Short-duration corticosteroid use to treat specific AEs will be captured as a protocol deviation and subjects may remain in the study per the discretion of the Investigator. All concomitant corticosteroid use will be captured on a specific eCRF.

The eligibility or continued participation of subjects using any of these prohibited medications may be revised by the Sponsor based on the impact on subject safety and efficacy or safety parameters.

Any prohibited medication taken should be recorded in the eCRF.

5.8.3 Allowed Medications, Adjunctive Therapy, and Procedures

Treatment with PPIs may be continued during the study only if the subject was taking such therapy at the time of signing the ICF. Subjects on PPI may either discontinue them after the EGD or reduce the dose as long as this is before the 4-week Baseline Symptom Assessment. The subject must remain on a stable dose after this allowed dose change. Once a PPI is stopped, it may not be restarted.

Acceptable contraceptive methods are discussed in Section 5.8.4.

An adjunctive therapy/procedure is defined as any procedure or intervention (e.g., psychotherapy, surgery, dental work, acupuncture, physiotherapy, chiropractic, osteopathy, mass therapy) used to treat an illness. Although diagnostic tests or procedures (e.g., chest X-rays, electrocardiogram [ECG]) are not considered therapies, these will be recorded for the assessment of the burden of illness. Adjunctive procedures expected for the study include EGD, endoscopic dis-impaction, and esophageal dilatation. Diet therapies (elimination diets) are not included as allowed adjunctive therapies.

5.8.4 Acceptable Contraception

Fluticasone propionate is classified as a pregnancy category C medication under the FDA regulations. This means that it may not be safe for use during pregnancy, although the full risks are not currently known. Current regulations and guidelines pertaining to pharmaceutical industry require properly documenting and monitoring exposure to any investigational or marketed drugs under clinical research during pregnancy of study subjects and/or their partner.

5.8.4.1 Female Subjects

Female subjects of childbearing potential who have had their first menses must use a highly effective method of birth control during the study and for 30 days after the last dose of study drug[28]. Medically acceptable regimens to prevent pregnancy must be followed. These include:

- Systemic contraceptives (e.g., oral contraceptives, injectable contraceptives, implantable/insertable hormonal contraceptive products, or transdermal patches);
    - For systemic contraceptives, use must be stable for ≥28 days prior to Screening.
- Intrauterine/intravaginal methods (e.g., vaginal contraceptive ring, intrauterine system with hormone release, or copper intrauterine device);
- Bilateral tubal occlusion;
- Vasectomized partner;
- Sexual abstinence.

Female subjects of childbearing potential will have a urine pregnancy test at every visit. Documentation of ongoing contraception or exemption will be completed at each visit.

Should a pregnancy occur during the course of the study, the participating female subject will be discontinued from the study and monitored throughout the course of pregnancy and outcome (see Section 4.2.3).

All female subjects of childbearing potential will be informed about these requirements in the ICF.

5.8.4.1.1 Exemptions from Contraception for Female Subjects

Subjects who are sexually inactive, had a documented tubal ligation, are at no risk of becoming pregnant, or who have a monogamous partner who is surgically sterilized may be exempted from contraception at the discretion of the Investigator. Additionally, female subjects of non-childbearing potential may be exempted from contraception at the discretion of the Investigator; this may include females who:

- Are diagnosed infertile;
- Have undergone a surgical procedure (total abdominal hysterectomy and or oophorectomy);
- Have undergone menopause (defined as 12 consecutive months without menses and substantiated by an appropriate FSH/LH test for subjects <65 years of age).
    - An allowance will be made for subjects taking hormone replacement therapy.

The exemption will be documented.

5.8.4.2 Male Subjects

Male subjects who participate in the study or their female partners of childbearing potential will be advised to use highly effective birth control. Participating male subjects will be advised to discuss the use of highly effective birth control methods (described in Section 5.8.4.1) and the potential risks to the unborn child in the event of pregnancy with their female partners for the duration of the study. This discussion will be documented within the source document. Subjects will also be informed about this potential risk in the ICF.

Should a case of pregnancy in a partner of a male subject occur during the study, the male subject may remain in the study. Should she agree, the pregnant partner will be monitored during the pregnancy course until delivery; this will require the signature of a specific ICF.

5.9 Medical Care of Subjects after End of Study

The Sponsor will not provide any additional care to subjects after they leave the study because such care should not differ from what is normally expected for subjects with EoE.

Should a subject be discontinued from the study because of lack of efficacy, the subject will receive standard treatment as per the Investigator's clinical judgment.

5.10 Treatment Compliance

The prescribed dosage, timing, and mode of administration of the study drug may not be changed. Any departures from the intended regimen must be recorded in the eCRF.

At each visit, prior to dispensing study drug, previously dispensed study drug will be retrieved by the Investigator or designee and compliance assessed. Subjects exhibiting poor compliance as assessed by tablet counts should be counseled on the importance of good compliance to the study dosing regimen.

Noncompliance is defined as taking less than 80% or more than 120% of study drug during any evaluation period (visit to visit).

5.11 Study Drug Accountability

A qualified individual (pharmacist or authorized study personnel) designated by the Investigator will dispense study drug only to randomized subjects. This individual will be instructed to maintain the blind if involved in the assessment of subjects or otherwise involved in the analysis of the study. The subject will be instructed to return all unused bottles or opened bottles with unused tablets to this assigned individual. Study drug supplies must not be loaned or dispensed by the Investigator to another site or used for any purpose other than the study.

Upon receiving the study drug supplies, the qualified individual must complete, sign, and return to the Sponsor the form acknowledging the receipt of the study drug. The qualified individual is responsible to maintain and keep current study drug inventory and dispensing records for all study drug dispensed. A copy of this record must be kept on-site and be available to the Clinical Research Associate (CRA). Any discrepancies or deficiencies are to be recorded and explained.

During the study, the CRA will periodically check the inventory/dispensing record for the complete accountability of study drug supplies. Upon successful completion of the check, all empty bottles along with the study drug inventory/dispensing record must be returned to the Sponsor for final reconciliation.

5.11.1 Disposition of Unused Study Drug

At the end of treatment or at the time of premature discontinuation, the subject will return all remaining full and empty study drug containers to the site. The qualified individual must record the returned quantities on the inventory/dispensing record.

Before returning the study drug to the Sponsor, study drug reconciliation must be performed by the Investigator or designee and verified by the CRA. Any discrepancies will be explored and explained.

Exceptionally, the Sponsor may ask the CRA to instruct the Investigator or designee to destroy or make arrangement for the destruction of the study drug or other material locally. In this case, the Sponsor will be provided with a destruction certificate or any relevant document confirming the destruction.

The CRA will return study drug and accountability forms to the Sponsor. The returned quantities have to be recorded on the appropriate documents and the study drug must be stored in a controlled room under restricted access until its destruction.

When all study drugs have been returned, reconciliation will be performed by the Sponsor. Any discrepancies will be explored and explained.

Study drug destruction should occur after the product approval. It will be performed as per Sponsor procedures. If needed, a quantity of study drug will be retained for authorities' inspections or requests.

6.0 EFFICACY, SAFETY, AND PHARMACOKINETIC ASSESSMENTS

The procedures and assessments described in this section will be performed at the time point(s) described in the Schedules of Events in Section 4.1.2.

6.1 Demographics and Medical, Surgical and Medication Histories

Baseline and demographic data to be collected include age, gender, height at screening (Day 1 only), weight, race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander or Other), ethnicity (Hispanic or Latino, Not Hispanic or Latino, or Other), smoking status, presence and absence of esophageal strictures, and history of a positive steroid response.

6.2 Efficacy and Patient-reported Outcome Assessments

6.2.1 Esophagogastroduodenoscopy

For the purposes of the current study, it is expected that the esophagus will be the focus of EGD procedures.

Whenever possible, the same endoscopist should be used for all EGDs performed for the study.

6.2.1.1 Multiple Esophageal Biopsies

About 3 biopsies will be obtained from both the proximal and the distal esophagus (total of 5-6 biopsies) during the EGD. Care should be taken to obtain biopsies that are of sufficient size and are opaque. Additional attempts should be made if suboptimal biopsies are taken. It is suggested that biopsies be obtained 1 at a time to achieve optimal results.

All biopsies should be stored at room temperature. Other details regarding biopsy handling and shipping are provided in the Central Pathology Laboratory Operations Manual.

Eosinophilic Esophagitis Histology

A central pathologist will evaluate all esophageal biopsies and count the peak number of eosinophils/HPF. Forms to be used for the histology portion of analysis are found in the Central Pathology Laboratory Operations Manual. This number will also be captured in the clinical database.

The pathologist will notify the IWRS vendor of subject eligibility (at baseline), or responder status (at other time points from histology perspective; see also Section 5.7). From a histological perspective, the eligibility requirements are described in Inclusion Criterion # 7 (have evidence of EoE, as defined by ≥15 PEAK eosinophils/HPF) in Section 4.2.1 and the responder definition is descried in Section 4.1.1.

6.2.1.2 Eosinophilic Esophagitis Endoscopic Reference Score

The endoscopist will record the observed Eosinophilic Esophagitis Endoscopic Reference Score (EREFs)[27] that assesses edema, furrowing, exudates, rings, strictures, several miscellaneous features, and physician assessment of overall disease activity (absent; mild; moderate; severe) at each EGD. The EREFs has been shown to be a reliable diagnostic tool to both diagnose EoE and to assess the response to treatment.[27,30,31]

The endoscopist will complete a worksheet for the EREFs, and data will be transferred to the appropriate eCRF by the site clinical staff/study coordinator. The worksheet should be retained at the site as a source document.

The EREFs may be found in Appendix 3; this also includes an endoscopy atlas.

6.2.2 Daily Diary

A daily diary will be completed by the subject to assess the presence of dysphagia and questions related to its severity and associated pain. The diary will be completed by the subject for each episode and daily (in the evening) throughout the study. The daily diary will ask questions comprising the PROSE. The study will be used to define the measurement properties and definitions of symptom responder and non-responder for future studies as outlined in the exploratory endpoints (Section 3.3).

These data will be self-reported electronically by the subject, transferred automatically to the electronic patient-reported outcome (ePRO) vendor, and transmitted thereafter to Data Management.

English screenshots of the daily diary will be submitted in a separate file.

6.2.3 Global Eosinophilic Esophagitis Symptom Score

For the Global EoE Symptom Score, the subject will respond to the following:

> On a scale from 0 to 10 (0 representing no symptoms and 10 representing most severe symptoms), how severe were your eosinophilic esophagitis symptoms over the past 7 days? Please think of all your symptoms due to eosinophilic

esophagitis and make an overall statement by selecting 1 of the numbers. In the past 7 days:

0 1 2 3 4 5 6 7 8 9 10

No symptoms ---------- Most severe symptoms

Except for the Screening Visit where this will be collected on paper and stored as a source document, these data will be self-reported electronically by the subject, transferred automatically to the ePRO vendor, and transmitted thereafter to Data Management. This will be collected at all visits except at an unscheduled visit where it is optional and at the final Follow-up visit.

6.2.4 7-day Eosinophilic Esophagitis Symptom Assessment Index

Symptoms will be assessed using the 7-day EEsAI questionnaire[32,33] periodically and both total and subscores will be calculated. The subscores will include symptoms such as dysphagia, food avoidance and modification, and painful swallowing (odynophagia).

Additional questions used as anchors for the 7-day EEsAI score will also be assessed (i.e., assessments described in Section 6.2).

The 7-day EEsAI may be found in Appendix 4.

These data will be self-reported on paper by the subject and entered onto an eCRF by the site on Day 1, Week 12, Week 26 and Week 52 or Early Termination Visit.

6.2.5 Patient Global Impression of Change (PGIC)

The following Patient Global Impression of Change (PGIC) questions will be asked to examine the subject's assessment of symptoms:

Compared with the beginning of the study, before you started the treatment, your EoE symptoms today are:

- Much worse;
- Moderately worse;
- A little worse;
- Stayed the same;
- A little improved;
- Moderately improved;
- Much improved.

Please think of all your symptoms due to EoE and make an overall statement by choosing 1 of the options above.

Compared with the beginning of the study, before you started the treatment, your difficulty with food or pills going down today is:

- Much worse;
- Moderately worse;
- A little worse;
- Stayed the same;
- A little improved;
- Moderately improved;
- Much improved.

Please think of your difficulty with food or pills going down and make an overall statement by choosing 1 of the options above.

This will be performed at all regular visits beginning with Week 4. These data will be self-reported electronically by the subject, transferred automatically to the ePRO vendor, and transmitted thereafter to Data Management.

6.2.6 Patient Global Impression of Severity (PGIS)

The following questions about Patient Global Impression of Severity (PGIS) will be asked to examine the subject's assessment of severity:

Please choose the response that best describes the severity of your EoE symptoms over the past 7 days (check one response):

- None
- Mild
- Moderate
- Severe
- Very Severe

Please think of all your symptoms due to EoE and make an overall statement of their severity by choosing 1 of the options above.

Please choose the response that best describes the severity of your difficulty with food or pills going down over the past 7 days (check one response):

- None
- Mild
- Moderate
- Severe
- Very Severe

Please think of your difficulty with food or pills going down and make an overall statement of its severity by choosing 1 of the options above.

This will be collected at all visits beginning with the dispensing of the daily diary. These data will be self-reported electronically by the subject, transferred automatically to the ePRO vendor, and transmitted thereafter to Data Management.

6.2.7 Adult Eosinophilic Esophagitis Quality of Life Questionnaire

The Adult Eosinophilic Esophagitis Quality of Life Questionnaire (EoE-QOL-A)[29] is an assessment that may be administered directly to subjects to determine how EoE impacts their quality of life.[29] It includes 30 questions on a 5-point Likert scale; questions represent 5 factors: eating/diet impact, social impact, emotional impact, disease anxiety, and choking anxiety and has been validated to correlate with established health-related quality of life measures. Higher scores indicate better quality of life.

The EoE-QOL-A may be found in Appendix 5.

This will be assessed on Day 1 and on Weeks 12, 26, 52 and the Early Termination visit. These data will be self-reported electronically by the subject, transferred automatically to the ePRO vendor, and transmitted thereafter to Data Management.

6.2.8 Efficacy Endpoints

6.2.8.1 Primary Efficacy Endpoint

The following primary efficacy endpoint will be evaluated at Week 12 to assess EoE response:

- Histology: percentage of subjects with ≤6 PEAK eosinophils/HPF after assessing at least 5-6 biopsies from the proximal and distal esophagus (~3 each) where the HPF area is 235 square microns (40 magnification lens with a 22 mm ocular).

6.2.8.2 Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be evaluated:

- EoE sustained response: percentage of subjects who met the primary endpoint (histology) at Week 12 and maintained the primary endpoint at Week 26 and Week 52;
- Change from baseline EREFs at Week 12, Week 26, and Week 52;
    - Endoscopic changes will as per the EREFs evaluation based on the following endoscopic features: edema, rings, exudates, furrows, stricture, and several miscellaneous features (crepe paper esophagus, narrow caliber esophagus, and esophageal erosions);
- Percentage of subjects with a peak eosinophils/HPF number <1 and <15 at Week 12, Week 26, and Week 52;
- Change from baseline Global EoE Symptom Score assessed prior to randomization, which will be assessed for the 7-day period prior to the following study visits: Week 4, Week 8, Week 12, Week 14, Week 18, Week 22, Week 26, Week 28, Week 36, Week 44, and Week 52;

- Dysphagia: Change in the number of dysphagia episodes at baseline (14-day period prior to randomization) compared with the 14-day period prior to the time point of interest (Week 12, Week 26 and Week 52).
- Change from baseline 7-day EEsAI total score assessed prior to randomization to those assessed at Week 12, Week 26, and Week 52;
- Change from baseline 7-day EEsAI subscores to those assessed at Week 12, Week 26, and Week 52;
- Percentage of subjects with mean 7-day EEsAI total score <20 to those assessed at Week 12, Week 26, and Week 52;
- Change from baseline PGIS assessed prior to randomization at Weeks 4, 8, 12, 14, 18, 22, 26, 28, 36, 44, and 52;
- PGIC at Weeks 4, 8, 12, 14, 18, 22, 26, 28, 36, 44, and 52.
- Assessment of treatment failure and relapse, including:
    - Percentage of histologic non-responders by dose at Week 12, Week 26, and Week 52;
    - Percentage of subjects requiring emergency endoscopic food dis-impaction by dose before Week 14, between Week 14 and Week 28, and between Week 28 and Week 52;
    - Percentage of subjects requiring esophageal dilation by dosing group and part of the study.

6.2.8.3 Exploratory Efficacy Endpoints

The following exploratory efficacy endpoints will be evaluated:

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

The populations to be analyzed are described in Section 8.2 and will be detailed in the Statistical Analysis Plan (SAP). Subgroup analyses may be performed based upon age, gender, PPI status, and other study subpopulations.

6.3 Safety

6.3.1 Adverse Events

Definition of AE

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment.

All AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities. A TEAE will be an AE that occurs after the first dose of study drug is administered.

Figure 6-1 illustrates the decision-making process the Investigator should follow in determining how to document an AE for the purposes of FLUTE.

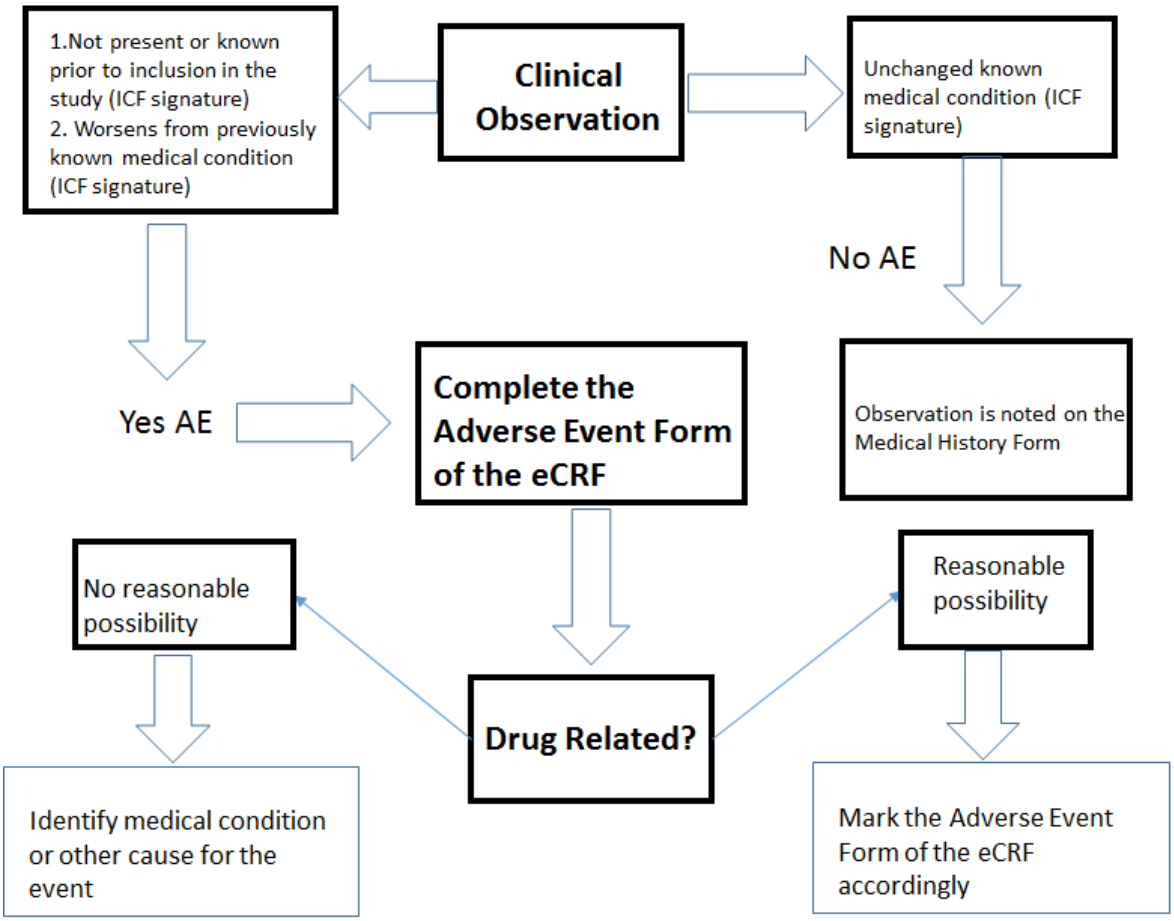


Figure 6-1 AE Documentation Decision Tree

Abbreviations: AE = adverse event; eCRF = electronic case report form; ICF = informed consent form.

Definition of SAE

An SAE is any untoward medical occurrence (whether considered to be related to study drug or not) that at any dose:

- Results in death;
- Is life-threatening;
    - The subject is at a risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization;
    - Hospitalization or prolongation of hospitalization not associated with an AE are not considered SAEs, including admission due to pre-existing condition that did not worsen

during the study and pre-planned admission (e.g., due to pre-existing condition that did not worsen during the study).

- Results in persistent or significant disability/incapacity;
- Is a congenital abnormality/birth defect;
- Other:
    - Medically significant events, which do not meet any of the criteria above, but may jeopardize the subject and may require medical or surgical intervention to prevent 1 or more of the other serious outcomes listed in the definition above. Examples of such events are blood dyscrasias (e.g., neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization.
    - For the purposes of the study, the suspected transmission of infectious agents will be considered an SAE as a medically significant event.

Death and surgery should not be reported as an event; these are viewed as an outcome of an event, rather than the event itself. In cases where the cause of death is unknown, death may be initially reported as an event. Every attempt should be made to submit a follow-up report identifying the cause of death.

Definition of Adverse Event of Special Interest

For the purposes of the study, the primary AESIs will be those related HPA axis suppression. Subjects will be observed carefully for any evidence of systemic corticosteroid effects such as hypercorticism and adrenal suppression. Serum cortisol levels will be measured and will be the primary evaluator of any potential HPA axis suppression (see Section 6.3.4). Oral and esophageal candidiasis will however be considered AEs of special interest. Subjects may remain in the study during the treatment for these AEs. The Investigator may allow swish and spit 30 minutes after dosing for these subjects. Subjects must be instructed not to swallow the rinsing water. Adverse events related to such effects will be considered AESIs for the purposes of the study.

6.3.1.1 Severity and Relationship of Adverse Events

Severity

The severity of the all AEs will be characterized as “mild, moderate, or severe” according to the following definitions:

- Mild events are usually transient and do not interfere with the subject’s daily activities;

- Moderate events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities;
- Severe events interrupt the subject's usual daily activity.

Relationship (Serious Adverse Events Only)

Documentation for SAEs only will involve the Investigator making a causality assessment. To promote consistency among Investigators, the guidelines in Table 6-1 should be taken into consideration, along with good clinical judgment, when determining the relationship of study drug to AE.

Table 6-1 Relatedness of SAEs

Not related	• The SAE is definitely not associated with study drug AND/OR; • The SAE does not follow a reasonable temporal sequence from study drug administration AND/OR; • The SAE does not disappear or decrease on discontinuation of the study drug (dechallenge) and/or does not reappear or increase on repeated exposure (rechallenge) AND/OR; • The SAE is reasonably explained by known characteristics of the subject's clinical state, history, environment, other therapy administered to the subject (drug or nondrug) AND/OR; • The SAE may be caused by reasons other than administration of the study drug.
Related	• The SAE follows or may follow a reasonable temporal sequence from study drug AND/OR; • The SAE disappears or abates upon discontinuation of study drug (dechallenge) and/or reappears or increases on repeated exposure (rechallenge) AND/OR; • The SAE cannot be reasonably explained by known characteristics of the subject's clinical state, history, environment, other therapy administered to the subject (drug or nondrug) AND/OR; • Previous experience with the study drug or related compounds resulted in a similar event AND/OR; • The SAE is a known effect of APT-1011.

Abbreviation: SAE = serious adverse event.

6.3.1.2 Recording and Reporting of Adverse Events

An AE must be promptly documented and recorded on the Adverse Events eCRF. The Investigator is responsible for recording all AEs observed or reported during the study, regardless of causality and/or clinical significance.

At each study visit, after the subject has had an opportunity to spontaneously mention any problems, the Investigator or designee should inquire about AEs by asking the appropriate open questions. In addition to straightforward subject observation (e.g., headache, nausea, etc.), AEs will also be documented from any data collected in the eCRF (e.g., laboratory values, physical examination findings, etc.) or other documents (e.g., subject diaries) that are relevant to subject safety.

The Adverse Event eCRF will record the following information.

- Name of the AE;
    - Investigators should use correct medical terminology/concepts when recording AEs in the Adverse Event eCRF, avoiding colloquialisms and abbreviations.
    - Only 1 AE term should be recorded in the event field on the Adverse Event eCRF. If several conditions meet the criteria for AE reporting, each condition should be reported in the separate eCRF.
    - If known, a diagnosis should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only hepatic injury or hepatitis rather than jaundice and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be separately recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be replaced by a single AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis. Signs/symptoms of the reported AE should be described in the eCRF description field.
- Date of onset of the AE;
- Intensity (mild, moderate, or severe);
- Date of resolution (or statement that the event is ongoing);
- Action taken;
    - Concomitant medication or adjunctive therapy/procedure given will be recorded on the concomitant medication form or adjunctive therapy/procedure form of the eCRF, respectively.
- Subject outcome;
- Whether the event meets the definition of an SAE.

The CRA will check the completeness and accuracy of the Adverse Events eCRF. Wherever possible, all AEs regardless of the seriousness must be followed through resolution.

6.3.1.2.1 Timing of Expected Reporting of Adverse Events

All AEs should be reported from the time of signature on the ICF to the last study visit.

All SAEs should be reported from the time of signature of the ICF to 30 days after the last study procedure or study drug administration.

6.3.1.2.2 Expedited and Other Notable Reporting of Nonserious Adverse Events

In addition to the expedited reporting requirements for SAEs, the following events will be recorded and reported within 24 hours to the Sponsor (similar to reporting requirements for SAEs to the Sponsor [see Section 6.3.1.3]):

- Any pregnancy that occurs in subjects or their partners during the study;
    - Follow-up should be completed to collect information about the course of the pregnancy, delivery, and condition of the newborn and this information provided to the Sponsor in a timely manner. If the newborn is healthy, additional follow-up is not needed. In case of a health problem in the newborn, follow-up must be performed.
- Drug abuse, misuse, and overdose with or without AEs (an overdose is a dose higher than that prescribed by a health care professional for clinical reasons);
    - The Investigator will use their clinical judgement to decide whether a dose was an overdose.
- Inadvertent or accidental exposure to the study drug with or without an AE;
- Any other medication errors (including dispensing errors such as inadvertent use of expired medication and dosing errors) with or without an AE.

Specific forms for reporting these events will be included in the ISF. These data will also be recorded in the eCRF.

6.3.1.3 Reporting of Serious Adverse Events to the Sponsor

Serious adverse events will be monitored by the Sponsor in real time throughout the study.

All SAEs, regardless of relationship to study drug, must be reported by the Investigator to the Sponsor by completing the electronic Serious Adverse Event eCRF within 24 hours of awareness. This includes SAEs occurring as soon as the subject signs the ICF (i.e., pretreatment SAEs). The Serious Adverse Event eCRF should be completed as thoroughly as possible, given the information available and time constraints, and then signed electronically by the Investigator.

In case of unavailability of the electronic capture (EDC) database, the SAE should still be reported to the Sponsor within 24 hours of awareness using the paper Serious Adverse Events Form provided in the ISF. The paper Serious Adverse Events Form should be faxed or emailed to the Sponsor or designee.

If any follow-up information is received after the last study procedure or last study drug administration, this information will not be recorded in the eCRF but should be provided to the Sponsor using the paper Serious Adverse Events Form. Additionally, any new spontaneously reported SAEs that occur within 30 days after the last study procedure or study drug administration should be recorded in the paper Serious Adverse Events Form.

6.3.1.4 Reporting of Serious Adverse Events to Regulatory Authorities and Investigators

In addition to these reporting requirements of SAEs to the Sponsor or designee, every Investigator is expected to know, understand, and follow reporting procedures according to their local reporting requirements and IRB/IEC requests.

Investigators will be notified by the Sponsor or designee of all SAEs that require prompt submission to their IRB/IEC. Investigators should provide written documentation of IRB/IEC notification for each report to the Sponsor or designee. The Sponsor or designee will ensure that all SAEs are reported to the appropriate regulatory authorities.

6.3.1.5 Follow-Up of Adverse Events

Any AEs observed from Screening up to the end of the study will be followed up to resolution. Resolution means that the subject has returned to a baseline state of health or the Investigator does not expect any further improvement or worsening of the AE. All AEs that occur after the subject completes the study should also be reported to the Sponsor or designee within 30 days of the last dose of study drug.

6.3.1.5.1 Nonserious Adverse Events

Whenever possible, all AEs that occur during the study, regardless of the seriousness, must be followed to satisfactory resolution or until the Investigator or designee deems the event to be chronic or not clinically significant or the subject to be stable.

6.3.1.5.2 Serious Adverse Events

A subject experiencing 1 or more SAEs will receive treatment and follow-up after evaluation by the Investigator, or will be referred to another appropriate physician for treatment and follow-up. Discontinuation from the study and all therapeutic measures will be at the discretion of the Investigator.

The clinical condition of subjects who have had an SAE must be followed until all parameters, including laboratory values, have either returned to normal or to baseline value or are otherwise explained or judged acceptable by the Investigator. Follow-up and/or final reports, including information on the action taken and the outcome, must be sent to the Sponsor.

In the event of death, any post-mortem findings (including histopathology and autopsy reports) must be provided to the Sponsor.

6.3.1.5.3 Adverse Events of Special Interest

The primary AESIs for FLUTE are events related HPA axis suppression (see Section 6.3.4).

APT-1011 (fluticasone proprionate ODT) a minimally absorbed corticosteroid is expected to act topically in the esophagus. Because of this, there is potential for decreased efficacy if the subject swallows water soon after dosing. Since the use of fluticasone has only been rarely associated with oral candidiasis[34,35,36,37] there will be no need to do swish and spit since this could inadvertently be associated with swallowed water.

Oral and esophageal candidiasis will however be considered AESIs. Subjects may remain in the study during the treatment for these AESIs. The Investigator may allow swish and spit 30 minutes after dosing for these subjects. Subjects must be instructed not to swallow the rinsing water.

These will be followed until resolution or until judged to be acceptable by the Investigator.

6.3.2 Clinical Laboratory Evaluations

Blood and urine samples are to be taken as close as possible to 0800 hours. The blood draw for morning serum cortisol may be drawn ±3 days of scheduled visit to accommodate accurate timing. Other laboratory blood draws scheduled for the visit may be done at the same time.

Q2 Solutions will be the responsible central laboratory.

Clinical laboratory tests will be reviewed for results of potential clinical significance at all time points throughout the study. The Investigator will be required to comment on any laboratory values outside the normal reference range, as well as evaluate any change in laboratory values. Laboratory values substantially out of range and within laboratory alert ranges should be evaluated promptly.

Laboratory values outside the normal range that are considered clinically significant by the Investigator upon repeat testing and are significantly changed from baseline, should be considered an AE. If the abnormal laboratory value is consistent with a current diagnosis, it may be documented accordingly. All laboratory value abnormalities that require medical treatment should be considered an AE.

6.3.2.1 Serum Chemistry

The following will be assessed: sodium, potassium, chloride, calcium, magnesium, phosphorus, blood urea nitrogen, creatinine, glucose, albumin, total protein, alkaline phosphatase, total

bilirubin, direct bilirubin (if total bilirubin >1.5 mg/dL), aspartate transaminase (AST), alanine transaminase (ALT), and 5'-nucleotidase (if alkaline phosphatase exceeds upper limit of normal (ULN).

Elevated liver function tests potentially meeting Hy's Law must be evaluated immediately, and the Sponsor must be notified of a potential case immediately to obtain further instructions. For the purposes of FLUTE, Hy's Law parameters will be ALT or AST ≥3x ULN and total bilirubin ≥2x ULN. A true Hy's Law case with this elevation of liver enzymes without an alternative explanation other than drug-induced liver disease should be reported as an SAE. All potential Hy's Law cases will be followed until resolution.

6.3.2.2 Hematology

The following will be assessed: red blood cell (RBC) count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell (WBC) count and differential, absolute neutrophil count, and platelet count.

6.3.2.3 Urinalysis

The following will be assessed: dipstick-measured pH, specific gravity, total protein, ketones, glucose, nitrite, leukocyte esterase activity, bilirubin, and microscopic analysis (RBC, WBC, and urinary casts).

6.3.2.4 Other Laboratory Evaluations

Pregnancy Test

Females of childbearing potential are required to be tested for pregnancy by the urine β-human chorionic gonadotropin test. Serum pregnancy test should be completed at Screening and urine pregnancy test thereafter.

Follicle-stimulating Hormone and Luteinizing Hormone

Females of non-childbearing potential ≤65 years of age will be tested for FSH/LH to confirm menopause.

Once non-childbearing potential and/or menopause is confirmed, further pregnancy tests are not required.

Serum Cortisol (Morning Fasting)

Subjects must be fasting for an 8-hour period prior to the serum cortisol assessments.

See also Section 6.3.4.

ACTH Stimulation Test (250 µg)

If any subject's morning serum cortisol is <5 µg/dL at Screening, falls to below that level during the study, and/or there are signs and symptoms of hypercorticism, an ACTH stimulation test (60 minute with 250 µg, following the procedure from a commercialized test kit) will be required to rule out or confirm adrenal suppression.

This test will also be performed at Screening prior to Visit 2 (4-week Baseline Symptom Assessment), as well as at Visit 6 (Week 12), Visit 10 (Week 26) and Visit 14 (Week 52). It may also be performed in the event of clinical symptoms or a low cortisol result.

See also Section 6.3.4.

Serology

HIV 1 and HIV 2 DNA by PCR will be performed at Screening. Subjects with positive results will be excluded. HBsAg, anti-HBs and total anti-HBc (if positive, HBV DNA will be done) will assessed. Subjects with positive HBsAg, positive anti-HBc with positive HBV DNA) will be excluded. Anti-HBs positive alone, which is indicative of prior cleared infection or vaccination is allowed.

Anti-HCV will be confirmed by HCV RNA. Subjects with positive HCV RNA will be excluded.

HbA1C

HbA1C should be performed on all subjects with diabetes during Screening to assess level of control. This may be repeated as needed throughout the study.

6.3.3 Physical Examination and Vital Signs

Physical examinations will be used to detect and evaluate AEs, but are not a safety variable for analysis.

Physical examination will include assessments of weight, general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and age-appropriate neurological examination. Genitourinary and rectal examinations are not required unless there is a specific complaint.

Vital signs to be collected include pulse (after a 5-minute rest in sitting position), respiratory rate, temperature (°C), and blood pressure (after a 5-minute rest in sitting position and measured from the same arm throughout the study).

6.3.4 Cortisol-related Findings

All subjects will undergo a 250 µg ACTH stimulation test during the Screening period.

At all visits (scheduled or unscheduled), specific attention will be given to potential changes related to corticosteroids, as well as symptoms of hypercorticism (Appendix 6). Should a subject undergo surgery or trauma during the study, particular care should be taken in observing subjects for evidence of inadequate adrenal response. These assessments must be documented in the eCRF.

If hypercorticism or adrenal suppression are suspected, an adequate work-up should be performed to confirm or rule out these findings. Specifically, to monitor for HPA axis suppression of potential clinical concern, a 250 µg ACTH stimulation test will be performed after Screening if any of the following occur:

- During routine laboratory testing completed for the study, the subject has a morning serum cortisol level ≤5 µg/dL (≤138 nmol/L) (confirmed by 2 blood draws), including at the last on-treatment visit for a subject (ACTH stimulation test to be completed at an unscheduled visit);
    - See Section 6.3.4.1 for a discussion of the expected management/treatment of abnormal serum cortisol levels for the purposes of the study.
- The subject reports symptoms of hypercorticism (Appendix 6) (ACTH stimulation test to be completed at an unscheduled visit if needed).
- The subject discontinues due to HPA axis suppression (ACTH stimulation test to be completed at the Early Termination Visit).

An abnormal result for the ACTH stimulation test is defined as serum cortisol level <16 µg/dL (440 nmol/L) at 60 minutes after treatment with 250 µg cosyntropin administered intramuscularly. This result is exclusionary (see Section 4.2.2) if it occurs at Screening/4-week Baseline Symptom Assessment and requires follow-up through recovery of adrenal function if it occurs thereafter. The Sponsor will provide guidelines for safety follow-up (see Section 6.3.4.1) and document of restoration of adrenal function in all subjects demonstrating evidence of hypercorticism or HPA axis suppression during the course of the study.

Any clinical (Appendix 6) or laboratory abnormalities reflecting potential cortisol issues (such as abnormal morning cortisol, urinary glucose, or elevated serum glucose and results of ACTH stimulation test) will also be reported on a cortisol-specific eCRF. Changes fulfilling the definition of an AE, including laboratory values related to cortisol, will be reported as AEs in the eCRF.

All subjects will have an ACTH stimulation test performed at Screening, Week 12 (Visit 6), Week 26 (Visit 10), Week 52 (Visit 14), and at the end of treatment. It may also be performed in the event clinical symptoms or a low cortisol result.

6.3.4.1 Management

If the subject has serum cortisol ≤5 µg/dL (138 nmol/L) and

- The subject is asymptomatic: An ACTH stimulation test will be performed within the following week to confirm adequacy of adrenal reserve. The ACTH stimulation test may be performed at any time of the day and does not require subjects to be in fasting state. If the test suggests adrenal insufficiency (i.e., minimum cortisol value <16 µg/dL [440 nmol/L] before or 30 minutes after ACTH injection), the subject will be prescribed CORTEF® (hydrocortisone oral) 10 mg/day in the morning and be referred to an endocrinologist for further monitoring and management. The Investigator will maintain contact with the subject and endocrinologist on a biweekly basis until adrenal insufficiency is resolved or determined to be unrelated to study participation. If the test does not suggest adrenal insufficiency, no further follow-up is required.
- The subject is symptomatic (Appendix 6): The subject will be prescribed CORTEF® (hydrocortisone oral) 10 mg/day in the morning and be referred to an endocrinologist for further monitoring and management. The Investigator will maintain contact with the subject and endocrinologist on a biweekly basis until adrenal insufficiency is resolved or determined to be unrelated to study participation.

6.3.5 Electrocardiogram

A standard 12-lead ECG will be performed with the subject sitting for ≥5 minutes prior to the assessment.

6.3.6 Safety Endpoints

The safety endpoints of interest are:

- Frequency of TEAEs;
- TEAEs leading to discontinuation;
- Treatment-emergent SAEs;
- Percentage of subjects with serum cortisol level ≤5 µg/dL (≤138 nmol/L) or abnormal ACTH stimulation test (serum cortisol <16 µg/dL [≤440 nmol/L] at 60 minutes);
- The number of subjects discontinuing for HPA axis suppression will be recorded.

- Frequency of oral and esophageal candidiasis.

6.4 Pharmacokinetics

Sparse PK sampling (all subjects) will be performed to characterize FP exposure in the study population. PopPK analysis will be performed based on sparse plasma concentration data.

Pharmacokinetic samples will be collected from subjects in all 5 dosing groups to maintain the blind (see Section 5.7). Samples collected from subjects in the placebo dosing group will not be analyzed. Samples collected from subjects in the 1.5 and 3 mg HS, 1.5 and 3 mg BID dosing groups will be analyzed for PopPK results. As part of the PopPK modeling, renal and hepatic function as well as concomitant medications will be considered.

6.4.1 Sparse Pharmacokinetic Sampling

Sparse PK samples (all subjects) will be performed in all subjects enrolled in FLUTE. The main study ICF will include consent for sparse PK sampling.

The following PK samples will be collected for all subjects for sparse PK sampling:

- Day 1: pre-dose;
- Week 4, Week 8, and Week 12: Subjects will take their "after breakfast" dose as scheduled on the day of the visit at the site and 2 samples will be taken during their scheduled visit:

    1. Subjects must fast approximately 8 hours before the scheduled visits.
    2. Upon arrival to the site: After arrival at the site and once samples for serum cortisol and sparse PK are drawn, the subject will eat breakfast and take their "after breakfast" dose approximately 30 minutes after breakfast. There are no requirements for the time duration between when the "after breakfast" dose is administered and this first sample to be collected on-site. The "at bedtime" must not have been taken at the time of sampling.
    3. Approximately 1 to 1.5 hours after first sample (immediately prior to leaving the site). This sample must be collected ≥1 hour after the first sample at a given site; there is no maximum time duration between the first and second sample to be collected.

Site staff should document the time of the morning dose. Due to this variability, the sparse PK samples are expected to represent a large portion of the 12-hour post-dosing interval.

6.4.2 Methods for Pharmacokinetic Sampling

Samples of whole blood will be obtained in a Vacutainer® containing sodium fluoride/potassium oxalate anticoagulant for the determination of PF in human plasma.

The following information will be captured for blood sample collection in each subject's eCRF:

- Subject's number;
- Time and date of each blood sample collected for PK analysis;
- Time and date of subject's most recent ingestion of food prior to dose administration;
- Time and date of administration of the "after breakfast" dose (day of the planned visit);
- Time and date of administration of the immediately preceding "at bedtime" dose (evening prior to the planned visit).

If a subject refuses blood collection for PK analysis, this will not be considered a protocol violation as the PK analysis is a secondary objective.

6.4.3 Pharmacokinetic Variables

The following PopPK parameters will be estimated using sparse sampling, as data permit:

- Oral clearance (CL/F);
- Volume of distribution (V/F).

Additional PopPK parameters will be estimated, as appropriate, based on the final structural PK model.

A PopPK approach will be used to analyze sparse PK samples.

6.5 Appropriateness of Measurements

All assessments will be performed using methods that are considered standard and appropriate with the exception of the dysphagia instrument which is being developed. Data from FLUTE will provide validation information, such as test-retest validity and responsiveness to change. The instrument will be validated with the results of the current study. Screenshots will be submitted in a separate document.

7.0 QUALITY CONTROL AND QUALITY ASSURANCE

According to the Guidelines of Good Clinical Practice (GCP), the Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written standard operating procedures.

Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Investigator meeting(s);
- Central laboratories for clinical laboratory parameters and ECGs;
- Site initiation visit;
- Early site visits following enrollment;
- Routine monitoring;
- Ongoing site communication and training;
- Data management quality control checks;
- Continuous data acquisition and cleaning;
- Internal review of data;
- Quality control check of the final clinical study report (CSR).

In addition, Sponsor and/or designee clinical quality assurance department may conduct periodic audits of the study processes, including, but not limited to site, site visits, central laboratories, vendors, clinical database, and final CSR. When audits are conducted, access must be authorized for all study related documents including medical history and concomitant medication documentation to authorized Sponsor representatives and regulatory authorities.

7.1.1 Monitoring

The Sponsor has engaged the services of a CRO to perform all clinical monitoring functions within this clinical study. The CRA will establish and maintain regular contact between the Investigator and the Sponsor.

The CRA will evaluate the competence of each site, informing the Sponsor about any problems relating to facilities, technical equipment, or medical staff. During the study, the CRAs will check that written informed consent has been obtained from all subjects correctly and that data are recorded correctly and completely. The CRAs are also entitled to compare entries in eCRFs with corresponding source data and to inform the Investigator of any errors or omissions. The CRAs will also monitor adherence to the protocol at the site. They will arrange for the supply of study drug and ensure appropriate storage conditions are maintained.

Monitoring visits will be conducted according to all applicable regulatory requirements and standards. Regular monitoring visits will be made to each site while subjects are enrolled in the study. The CRA will make written reports to the Sponsor on each occasion contact with the Investigator is made, regardless of whether it is by phone or in person.

During monitoring visits, entries in the eCRFs will be compared with the original source documents (source data verification). The current study will utilize a Data-driven Trial Execution model; as such, not all data in the eCRF will be source verified.

7.1.1.1 Source Documents

The following are considered to be source data:

- Medical and clinical charts;
- Nursing notes;
- Medical and study-related correspondence regarding the subject;
- Subject progress notes;
- ECG tracings;
- X-ray reports;
- EREFs worksheet;
- Peak eosinophil count;
- Histology results (pdfs);
- Laboratory reports;
- Study worksheets.

In some cases, the eCRF, or part of the eCRF may also be considered source documents. In such cases, a document should be available at the Investigator's site as well as at Adare Pharmaceuticals, and clearly identify those data that will be recorded in the eCRF. The eCRF

will stand as the source for these documents. The eCRFs for the 7-day EEsAI will also be considered as source documents.

All individual entries in the source documents require signatures and dates by the Investigators. All typed or dictated documents and computer printouts must be signed and dated by the Investigator to confirm review. If the site uses electronic (paperless) hospital reporting systems, the CRA must be provided access to verify the source data. In the case that access cannot be provided, the Investigator must sign and date a hard copy of this data for this to be considered a source document.

Draft and/or fax copies of laboratory preliminary reports must be initialed and dated, and need to be retained in site files. Final laboratory reports should be signed and dated by the Investigator to confirm review. Original laboratory reports should be kept in site files.

7.1.1.2 Protocol Deviation Definition and Process

A protocol deviation is an excursion (generally unplanned) from the expected conduct of the study that is inconsistent with the protocol, ICF, or study agenda.

At each visit, subjects who fail to adhere to treatment will be assessed on whether or not the lack of adherence to dosing regimen was due to AEs. The Investigator should make every effort to ensure that visits occur at the appropriate intervals.

The Investigator must notify the Medical Monitor and/or clinical study manager of any protocol deviation. Protocol deviations will be documented in the Clinical Trial Management System and evaluated and categorized by the Medical Monitor. Protocol deviations including the reason for any out of window study visits, will be documented in the subject source records.

Protocol deviations must be reported to the IRB/IEC per local requirements.

7.1.2 Data Management and Coding

An EDC system will be used for the study. Data collection will be completed by authorized site staff designated by the Investigator. Appropriate training and security measures will be completed with the Investigator and all authorized site staff prior to the study being initiated and any data being entered into the system for any study subjects.

A completion guideline will be developed to provide guidance to site personnel on how to record data in the eCRF.

All data must be entered in English. The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the subject's visit. To avoid inter-observer variability, every effort

should be made to ensure that the same individual who made the initial baseline determinations completes all efficacy and safety evaluations. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, the Investigator should indicate this in the eCRF. The Investigator will be required to electronically sign off on the clinical data.

The CRA will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections, and alterations are to be made by the responsible Investigator or his/her designee. The CRA cannot enter data in the eCRFs. Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the site staff responsible for entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the CRA or data manager will raise a query in the EDC application. The appropriate site staff will answer queries sent to the Investigator. This will be audit trailed by the EDC application meaning that the name of site staff, time, and date stamp are captured.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria, and all records covering the subject's participation in the study. They include laboratory notes, ECG results, memoranda, pharmacy dispensing records, subject files, etc.

The Investigator is responsible for maintaining source documents. These will be made available for inspection by the CRA at each monitoring visit. The Investigator must submit a completed eCRF for each subject who receives study drug, regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and randomization number. Any personal information, including subject name, should be removed or rendered illegible to preserve individual confidentiality.

The eCRF records will be automatically appended with the identification of the creator, by means of their unique UserID. Specified records will be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique UserID and password; date and time stamps will be added automatically at time of electronic signature. If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software

procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

A detailed Data Management Plan will be developed to ensure the quality of the data. The eCRF will be validated through extensive data checking and query processing capabilities. Capabilities will include generating open queries and routing answers.

7.1.3 Quality Assurance Audit

The Sponsor has instituted a quality assurance program to ensure that all aspects of the study have been conducted according to GCP, International Council for Harmonisation (ICH) guidelines, and applicable laws and regulations. This may include an audit by the Sponsor or designee and/or regulatory agency representatives at any time. The Investigator must agree to the audit of study-related records by regulatory agency and/or the Sponsor or designee and provide direct access to source data/documents along with adequate space to conduct such an audit. The Investigator must adhere to these principles, in addition to any applicable or local requirements.

8.0 STATISTICS

8.1 Determination of Sample Size

Part 1 includes a sample size with 100 subjects, in which 20 patients are randomized each to 1.5 mg HS, 1.5 mg BID, 3 mg HS, 3 mg BID, and placebo in the ratio 1:1:1:1:1. See also the discussion of randomization in Section 4.1.5.2.

8.1.1 Expected Number of Subjects by Part

The following assumptions were used:

- The 1:1:1:1:1 (1.5 mg HS: 1.5 mg BID: 3 mg HS, 3 mg BID: placebo) randomization ratios will remain constant throughout the study.
- Based on these randomization ratios, approximately 80% of all subjects in Part 1 will be treated with an APT-1011 dosing regimen and approximately 20% of all subjects in Part 1 will be treated with placebo.
- Based upon the PR-021 study, which had slightly different histologic response criteria, it is expected that approximately 60% of patients on active treatment are expected to be a histologic responder compared to 10% on placebo. The lowest dose may be less effective.
    - Assuming a 60% histologic response rate for the 3 highest active doses of 1.5 mg BID, 3 mg HS, 3 mg BID, a 20% response rate for 1.5 mg HS, and a 10% response rate for placebo, it is expected that overall approximately 50% of active treatment will be responders at Week 12 (40 out of 80).
    - It is expected that at Week 26 an additional 20% will drop out who were previously responders and of the PART 1 non-responders that 40% will still be non-responders.
    - After Week 26, of the remaining subjects, it is expected that approximately 20% will dropout before Week 52.

  Given these assumptions, it is expected that approximately 42 patients will be responders and complete Week 26, and about 34 of those responders will complete Week 52.

  The power for testing each active dose versus placebo given a histologic response rate of 60% active treatment and 10% placebo for the primary endpoint (Part 1) is equal to 97.5% (one-sided Type I error = 0.05). Additionally, the power for achieving statistical significance for all 3 of the highest active doses of 1.5 mg BID, 3 mg HS, 3 mg BID via the gatekeeping hypothesis testing approach assuming independence is approximately 0.93.

Due to lack of previous data, estimating power for the secondary endpoint of reduction in number of dysphagia episodes is difficult. We expect that majority of control group will range between 25-35 dysphagia episodes per week at baseline. We expect a placebo effect corresponding to a 20-30% reduction, implying a reduction of 5-10 episodes. If we assume that the range of reduction for patients in control group is 0 to 15 episodes (and a normal distribution), this would correspond to a standard deviation of approximately 15/6=2.5 episodes. We also expect treatment group to also have 25-35 dysphagia episodes per week at baseline, and a reduction of 30-60% with treatment, implying a reduction of 7 to 21 episodes. If we assume that the range of reduction for patients in treatment group is 0 to 30 episodes (and a normal distribution), this would correspond to a standard deviation of approximately 30/6=5 episodes. Given the uncertainty of these estimates, our conservative approach assumes standard deviations of 4.5 and 7.5 for control and treatment group (respectively) for the reduction in number of dysphagia episodes. Given these assumptions, we have 80% power for 20 active dose patients vs. 20 control patients to detect a mean difference in reduction between groups of 5.0 episodes. This calculation is for a single active arm vs. control and does not factor in the multiplicity of having 4 potential doses to test. Assuming independence, a conservative Bonferonni approach would provide 80% power for a mean difference in reduction between groups of 6.3 episodes per arm, indicating the study is powered for an effect size of 5.0 to 6.3 episodes in reduction of dysphagia episodes for each of the doses.

The study has other important objectives which require sufficient sample size. The sample size of a total of 100 subjects as specified for the primary endpoint is considered sufficient to adequately evaluate the measurement properties of the new PRO instrument, and assess the amount of change that is clinically meaningful and to establish cut offs for Response and Relapse.

8.2 Analysis Populations

- The All Enrolled Population includes all subjects who sign an ICF and are enrolled in the study.
- The Safety Population includes all subjects who receive ≥1 dose of the study drug.
- The Intent-to-treat (ITT) Population includes all subjects randomized. This is the primary analysis population for efficacy.
    - A subject who is enrolled in the study and receives study drug, but fails to complete treatment will be considered a dropout.
- The Sparse PK Subgroup includes all subjects who have ≥1 quantifiable PK sample collected for sparse PK evaluations.

Additional analysis populations (e.g., Per Protocol Populations including subjects who complete Part 1, Part 2, and/or single-blind treatment) may be defined in the SAP.

8.3 Summary Statistics

Summary statistics will be presented in tabular form by dosing group and subgroups (including at least the stratification factors described in Section 4.1.5.2) for each part of the study. Analyses by gender, and region (North America versus Western Europe, or site will be done as appropriate.

Continuous variables will be summarized using descriptive statistics (number [n], mean, standard deviation [SD], coefficient of variation [CV%; as appropriate], median, minimum, maximum, and geometric mean and geometric CV% [as appropriate for PK parameters]). Categorical variables will be summarized by presenting the number (frequency) and percentage in each category.

8.4 Data Handling and Data to be Analyzed

The data will be inspected for inconsistencies by performing validation checks.

All details regarding the statistical analysis and the preparation of tables, listings, and figures will be described in the SAP and approved by the Sponsor before database lock.

8.5 Missing Data

Frequencies and comparisons of missing data by randomization and study visit will be summarized. Sensitivity analyses will be conducted for assessing the impact of missing data, including multiple imputation and tipping point analyses for the comparison of the dose with maximum utility versus placebo.

8.6 Subject Disposition

The subject disposition will be summarized using descriptive statistics.

8.7 Subject Characteristics

Baseline and demographic information will be summarized using descriptive statistics for continuous and ordinal variables (e.g., age, weight, height [Day 1 only]) and counts and percentages for categorical variables (e.g., sex, race, presence or absence of esophageal strictures, and prior response to steroids). Body Mass Index (BMI) will be calculated on Day 1.

8.8 Efficacy Analyses

8.8.1 Efficacy Analysis for Part 1

The primary efficacy endpoints for Part 1 is detailed in Section 6.2.8.

Let θ_j be the Cochran-Mantel-Haenzel common odds ratio comparing treatment vs. control for histologic response for dose j given randomization strata; with j=1,2,3,4 corresponding to APT-1011 3 mg BID, 1.5 mg BID, 3 mg HS, 1.5 mg HS doses, respectively. There are 4 hypotheses corresponding to the 4 active doses, which will be tested using a gatekeeping strategy to preserve Type I error for each analysis.

1) Primary Hypothesis #1

H_0: $\theta_1 \leq 1$

H_1: $\theta_1 \leq 1$

A stratified Cochran-Mantel-Haenzel test will be used to test primary hypothesis #1, i.e., 3 mg BID vs. placebo, using the randomization strata. If the corresponding one-sided p-value is less than or equal to 0.05, the null hypothesis will be rejected, and subsequently the following hypothesis will be tested:

2) Primary Hypothesis #2

H_0: $\theta_2 \leq 1$

H_1: $\theta_2 \leq 1$

A stratified Cochran-Mantel-Haenzel test will be used to test primary hypothesis #2, i.e., 3 mg HS vs. placebo. If the corresponding one-sided p-value is less than or equal to 0.05, the null hypothesis will be rejected, and subsequently the following hypothesis will be tested:

3) Primary Hypothesis #3

H_0: $\theta_3 \leq 1$

H_1: $\theta_3 \leq 1$

A stratified Cochran-Mantel-Haenzel test will be used to test primary hypothesis #3, i.e., 1.5 mg BID vs. placebo. If the corresponding one-sided p-value is less than or equal to 0.05, the null hypothesis will be rejected, and subsequently the following hypothesis will be tested:

4) Primary Hypothesis #4

H_0: $\theta_4 \leq 1$

H_1: $\theta_4 \leq 1$

A stratified Cochran-Mantel-Haenzel test will be used to test primary hypothesis #4, i.e., 1.5 mg HS vs. placebo. If the corresponding one-sided p-value is less than or equal to 0.05, the null hypothesis will be rejected.

Note the gatekeeping strategy only allows formal hypothesis testing of 1.5 mg HS or 1.5 mg BID if the higher doses meet statistical significance. Given prior studies with histologic endpoints, there is a strong rationale suggesting that higher doses will have a greater benefit on the primary efficacy endpoint of histology.

8.8.2 Efficacy Analysis for Part 2

Sustained EoE response will be assessed in subjects who complete both Part 1 and Part 2 and complete Week 26 evaluations. This will be assessed by the primary endpoint.

Other measures of efficacy will be assessed at Week 26 as indicated in Section 6.2.8.2.

Efficacy will be summarized for non-responders from Part 1 who are treated in Part 2.

Sustained EoE response will be assessed in subjects who complete Part 1, and Part 2 and also complete Week 52 evaluations. This will be assessed by the primary endpoint.

Other measures of efficacy will be assessed at Week 52 as indicated in Section 6.2.8.2.

The primary focus of Part 2 will be descriptive in nature.

8.8.3 Secondary and Exploratory Efficacy Analysis

Statistical tests to compare each APT-1011 dosing group with placebo will be performed for the secondary efficacy endpoints, but the corresponding p-values will be considered as descriptive rather than inferential. The secondary endpoints will be analyzed via a Cochran-Mantel-Haenzel test for categorical endpoints and analysis of covariance for change from baseline endpoints, except for the endpoint of time to relapse after initiation of double-blind treatment in Part 2, which will be analyzed using Kaplan-Meier methods.

As a secondary efficacy analysis, all 4 doses of active treatment will be pooled and compared to placebo with a one-sided test of two proportions.

[redacted] Additionally, a logistic regression model using both dose and frequency and dose-frequency interaction will be used to analyze the primary endpoint. Formal statistical hypothesis testing will be used to

evaluate treatment benefit with respect to the reduction in number of dysphagia episodes. For each dose that meets the criterion for statistical significance on the primary efficacy outcome, a Wilcoxon Rank-Sum test will be used to test whether the reduction in the number of dysphagia episodes from baseline is larger for the treatment group compared to the control. The hypothesis to be tested is:

H_0: $R_{1j}(x) \leq R_{0j}(x)$

H_1: $R_{1j}(x) > R_{0j}(x)$

Where $R_{ij}(x)$ is the distribution function for the reduction in number of dysphagia episodes for treatment group *i* (=0 for control, 1 for treatment) and dose *j*. Holm's step-down procedure will be used to control the overall Type I error at 0.05, where the number of doses considered for inferential testing is equal to the number of doses that meet statistical significance for the primary efficacy analysis.

Statistical tests to compare each APT-1011 dosing group with placebo will be performed for other secondary efficacy endpoints, but the corresponding p-values will be considered as descriptive rather than inferential. The secondary endpoints will be analyzed via a stratified Cochran-Mantel-Haenzel test for categorical endpoints and analysis of covariance or Wilcoxon Rank-Sum tests for change from baseline endpoints, except for the endpoint of time to relapse after initiation of double-blind treatment in Part 2, which will be analyzed using Kaplan-Meier methods.

As a secondary efficacy analysis, all 4 doses of active treatment will be pooled and compared to placebo with a stratified Cochran-Mantel-Haenzel test. Additionally, Bayesian hierarchical modeling will be used for both the primary efficacy endpoint and reduction in number of dysphagia episodes, in which dose-response modeling is used to estimate the difference between each active dose and placebo. Additionally, a logistic regression model using both dose and frequency and dose-frequency interaction will be used to analyze the primary endpoint. Subgroup analyses and regression models will also be conducted on primary and key secondary endpoints to assess regional effects and relationships with demographics (age, gender, race, ethnicity, PPI status, and strata variables).

8.9 Safety Analyses

The incidence of TEAEs will be summarized by system organ class and preferred term using the current version of the Medical Dictionary of Regulatory Activities. Separate summaries by maximum severity (for all AEs) and relationship (for SAEs only) to study drug will be provided. The incidence of TEAEs leading to discontinuation from the study and treatment-emergent SAEs

will also be summarized. In subjects who change dosing groups, the TEAEs will be attributed to the actual dose at the time of the event.

Clinically significant changes of potential clinical interest in clinical tests will be summarized including hematology, chemistry, urinalysis, ECG, cortisol, vital signs, and bone mineral density. No statistical testing of safety endpoints will be performed. Shift tables may be produced, if needed. The number of subjects discontinuing due to HPA axis suppression or positive ACTH stimulation tests will be summarized.

8.10 Pharmacokinetic and Pharmacodynamic Analyses

Sparse PK sampling (all subjects) will be performed to characterize FP exposure in the study population.

8.10.1 Population Pharmacokinetics

A PopPK analysis will be performed based on sparse plasma concentration data and will be described in a separate report. It will be performed using the nonlinear mixed-effects software, NONMEM, Version 7.2.0 or later (Pharmaceutical Product Development LLC, Wilmington, North Carolina) or other appropriate nonlinear mixed-effects modeling software. The structural PK model will include CL/F and V/F as fixed-effect parameters. Additionally, the intersubject variability in the parameter estimates and the random residual error in the data will be estimated with appropriate error models. The optimal base model will be selected according to the standard criteria such as minimum objective function value and diagnostic plots. The relevant information from bioanalytical and clinical databases (e.g., dosing times and sampling times) will be extracted and integrated for generation of the PopPK input files. All possible attempts will be made to capture missing information. Any additional information obtained regarding missing data and the procedures followed to handle any missing data will be documented and discussed in the CSR. After the final model is constructed, secondary parameters such as AUC and C_{max} will be calculated to characterize the extent of FP systemic exposure for the range of dosing regimens. Additional simulations may be performed, as necessary, to inform decision making for future studies. The output from the final population models including appropriate diagnostic plots, listings, and summaries of PK parameters will be generated. Evaluation of renal and hepatic functions and concomitant medications will be included in the PopPK model. In addition, graphical and tabular presentations of any PK simulations will be produced. A separate PopPK report will be generated as an appendix to the CSR.

Previous serial PK data for APT-1011 (Study PR-023) may be included in this analysis to facilitate development of a base PK model.

Population PK parameters to be estimated are detailed in Section 6.4.3.

8.10.2 [redacted]

[redacted]

8.11 Interim Analyses

The final analysis for the primary endpoint will be performed when all randomized subjects have completed Week 12 of the study. Safety through Week 12 will be assessed at this time. The final safety analysis will be performed when all randomized subjects have exited or completed the study.

9.0 ETHICS

9.1 Institutional Review Board or Independent Ethics Committee

The protocol and the ICFs for FLUTE must be submitted to the IRB/IEC for approval. Written documentation of approval of the protocol, any protocol amendment(s), and the ICF must be approved before starting the study. When necessary, an extension or renewal of the IRB/IEC approval must be obtained and also forwarded to the Sponsor.

Upon approval and before study start, the following IRB/IEC approval documentation must be sent to the Sponsor:

- A list on institution letterhead of IRB/IEC members, their representative capacity, and their affiliation;
- A signed and dated letter on institution letterhead documenting IRB/IEC approval of the protocol (indicating its title and number) and the ICF;
- If applicable, a signed and dated letter on institution letterhead documenting the IRB/IEC approval of amendment(s) to the protocol (indicating its title and number) and/or the ICF.

The ICH guidelines for GCP specify the committee should include persons of varying backgrounds (including peers of the responsible Investigator and lay people) and must exclude the responsible Investigator as a voting member.

9.2 Ethical Conduct of the Study

FLUTE will be conducted according to the principles of the Declaration of Helsinki (Seoul, October 2008), and the ICH guidelines for GCP. The Sponsor will ensure that the study complies with all local, federal, or country regulatory requirements as applicable.

9.3 Subject Information and Informed Consent

Prior to any evaluations performed for FLUTE, the Investigator or designee must explain the study to the subject in simple terms and in sufficient detail to allow for her/his informed decision to participate. The following items must be described fully to each subject prior to obtaining consent:

- Statement that the study involves research and an explanation of the purposes of the research;
- Statement that stress steroids may be required during significant medical illnesses;

- Expected duration of the subject's participation;
- Description of the procedures to be followed (including requirements for sparse sampling) and identification of any procedures that are experimental;
- Description of any reasonable foreseeable risks or discomforts to the subject;
- Description of any benefits to the subject that may reasonably be expected from the research;
- Availability of alternative treatment and disclosure of alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- Statement describing the extent, if any, to which confidentiality of records, lab samples, and genetic materials identifying the subject will be maintained;
- Statement that the Sponsor and the worldwide regulatory agency may inspect study records;
- Explanation of whom to contact for answers to pertinent questions about the research and research subject's rights;
- Explanation of whom to contact in the event of a research-related injury to the subject;
- Statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled;
- Consequences of a subject's decision to discontinue from the research and procedures for orderly termination of participation by the subject;
- Anticipated circumstance under which the subject's participation may be terminated by the Investigator without regard to the subject's consent;
- Any additional costs (e.g., travel expenses) to the subject that may result from participation in the research;
- Statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject;
- Approximate number of subjects involved in FLUTE;
- Any other country-specific and ICH/GCP requirements.

The Investigator must adopt a standardized approach for obtaining the ICF(s) from each subject. Written informed consent using the ICF(s) must be obtained from the subject by the Investigator before the subject enters the study.

If the subject understands the requirements of the study and agrees to participate, the subject will sign the ICF(s). The ICF(s) must also be signed by the Investigator or designee. All signatures must be dated.

The original, signed, and dated ICF(s) should be maintained with the source documents and be available for monitoring by the Sponsor or designee for review. A copy of the signed and dated ICF(s) must be given to the subject before the subject starts the study.

Should the Investigator decide to modify the ICF(s), the modified version must be approved, in writing, by the Sponsor prior to its submission to the IRB/IEC. Should the IRB/IEC request modifications, the revised version of the ICF(s) must be submitted to and approved by the Sponsor prior to study initiation.

9.4 Protocol Amendments and Other Changes in Study Conduct

Any change or addition to this protocol requires a written protocol amendment that must be approved by the Sponsor and Investigator before implementation. Any substantial changes will be made as formal amendments to the protocol and will be submitted to each participating site for appropriate review by an IRB/IEC and to regulatory authorities.

Examples of amendments requiring such approval are:

- Any increase in study drug dosage or duration of exposure of subject to the study drug beyond that in the current protocol;
- Any significant increase in the number of subjects to be enrolled in the study;
- Any significant change in the design of the protocol (such as the addition or removal of a dosing group);
- Addition or deletion of a test procedure for safety monitoring;
- An increase in the number of invasive procedures to which subjects are exposed;
- Generally, any change that may affect subject management, subject safety, scope of the investigation, the scientific quality of the study, clinical procedures, or outcomes assessment.

A copy of the written approval of the IRB/IEC, which becomes part of the protocol, must be given to the Sponsor or designee.

The above requirements for approval should not prevent any immediate action from being taken by the Investigator or by the Sponsor in the interests of preserving the safety of all subjects included in FLUTE. If an immediate change to the protocol is felt to be necessary by the Investigator and is implemented by him/her for safety reasons, the Sponsor should be notified and the IRB/IEC at the clinical site should be informed within 10 working days.

Amendments affecting only administrative aspects of FLUTE do not require formal protocol amendments or IRB/IEC approval, but the IRB/IEC of each clinical site must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB/IEC approval that can be treated as administrative amendments include:

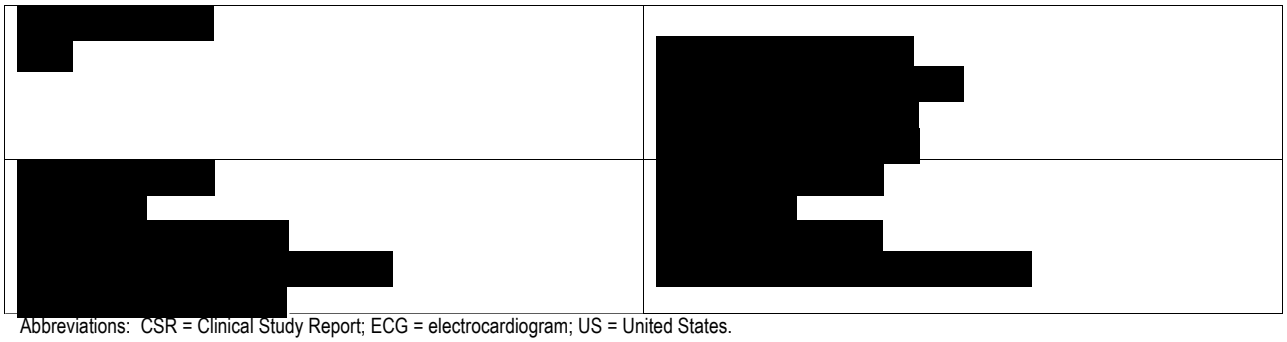
- Changes in the staff used to monitor study;
- Minor changes in the packaging or labeling of study drug.

Any deviation from the specific requirements of the protocol must be discussed in advance with the Medical Monitor and will require prior approval (see also Section 7.1.1.2). Any unforeseen changes in study conduct will be recorded in the CSR.

10.0 STUDY ADMINISTRATION

10.1 Administrative Structure

Table 10-1 Administrative Structure



Abbreviations: CSR = Clinical Study Report; ECG = electrocardiogram; US = United States.

10.2 Data Handling and Record Keeping

It is the Investigator's responsibility to maintain essential study documents (protocol and protocol amendments, completed eCRFs, signed ICFs, relevant correspondence, and all other supporting documentation). The site should plan on retaining such documents for approximately 15 years after study completion. The site should retain such documents until ≥2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or ≥2 years after the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the study is being conducted. Subject identification codes (subject names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to the Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to the Sponsor. The Investigator must contact the Sponsor prior to disposing of any study records.

10.3 Direct Access to Source Data/Documents

The Investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each subject randomized into FLUTE.

The Investigator will allow the Sponsor, designee, and authorized regulatory authorities to have direct access to all documents pertaining to the study, including individual subject medical records, as appropriate.

10.4 Investigator Information

10.4.1 Investigator Obligations

The Investigator agrees to conduct the clinical study in compliance with this protocol after the approval of the protocol by the IRB/IEC in compliance with local regulatory requirements. The Investigator and the Sponsor will sign the protocol to confirm this agreement (Appendix 1).

10.4.2 Protocol Signatures

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative. By signing the protocol, the Investigator confirms in writing that he/she has read, understands, and will strictly adhere to the study protocol and will conduct the study in accordance with ICH Tripartite Guidelines for GCP and applicable regulatory requirements. The study will not be able to start at any site where the Investigator has not signed the protocol.

10.4.3 Publication Policy

The Sponsor designs and conducts clinical studies in an ethical and scientifically rigorous manner to determine the benefits, risks, and value of pharmaceutical products. The Sponsor is responsible for receipt and verification of data from all research sites for the sponsored studies, to ensure the accuracy and integrity of the entire study database, which is owned by the Sponsor.

The Sponsor is committed to ensure that publication of all of its clinical studies results in biomedical journals are done in a timely manner, regardless of the study results. Publications should follow the guidelines established by the International Committee of Medical Journal Editors (ICMJE) and published in its Uniform Requirements of Manuscripts Submitted to Biomedical Journals (http://www.icmje.org) is committed to ensuring that authorship for all publications comply with the criteria defined by the ICMJE.

Clinical studies may involve already marketed products and/or investigational products. The Sponsor is committed to the timely submission and registration on a public database (e.g., http://clinicaltrials.gov) of summary information concerning all clinical studies that the Sponsor is conducting. These clinical studies will involve use of the Sponsor's marketed or investigational products. The Sponsor is also committed to the timely submission and posting of summary results of all clinical studies conducted in subjects involving the use of the Sponsor's products that are approved for marketing, or that are investigational products whose development programs are discontinued, regardless of outcome.

10.5 Financing and Insurance

The Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the subjects participating in the study. The terms of the insurance will be kept in the study files.

11.0 REFERENCES

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APPENDIX 1: SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: FLUTicasone in Eosinophilic esophagitis (FLUTE): A Randomized, Double-blind, Placebo-controlled, Dose-ranging, and Maintenance Study of APT-1011 in Subjects with Eosinophilic Esophagitis

PROTOCOL NO: SP-1011-002

This protocol is a confidential communication of the Sponsor. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the site in which the study will be conducted. Return the signed copy to the Sponsor or designee

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Site: _____

_____

_____

APPENDIX 2: STRONG CYTOCHROME P450 3A4 INHIBITORS

- Boceprevir;
- Clarithromycin;
- Conivaptan;
- Grapefruit juice;
- Indinavir;
- Itraconazole;
- Ketoconazole;
- Lopinavir/ritonavir;
- Mibefradil;
- Nefazodone;
- Nelfinavir;
- Posaconazole;
- Saquinavir;
- Telaprevir;
- Telithromycin;
- Voriconazole.

APPENDIX 3: EOSINOPHILIC ESOPHAGITIS ENDOSCOPIC REFERENCE SCORE AND ENDOSCOPY ATLAS

Endoscope Type

Olympus	○	Pentax	○	Fujinon	○
Adult	○	Pediatric	○		

Feature/Location

Please select a grade for each feature/location

	LOCATION			
…….	Proximal Esophagus		Distal Esophagus	
Edema (mucosal "pallor", decreased clarity or absence of vascular markings)	○	Grade 0: absent	○	Grade 0: absent
	○	Grade 1: present	○	Grade 1: present
…….				
Rings (fixed esophageal rings, "Trachealization," corrugations)	○	Grade 0: none (normal)	○	Grade 0: none (normal)
	○	Grade 1: mild (subtle circumferential ridges)	○	Grade 1: mild (subtle circumferential ridges)

	○	Grade 2: moderate (distinct rings that do not impair passage of a standard diagnostic adult upper endoscope (diameter 9-10 mm))	○	Grade 2: moderate (distinct rings that do not impair passage of a standard diagnostic adult upper endoscope (diameter 9-10 mm))
	○	Grade 3: severe (distinct rings that do not permit passage of a diagnostic	○	Grade 3: severe (distinct rings that do not permit passage of a diagnostic

.....

Exudates (also referred to as white spots, plaques)	○	Grade 0: none	○	Grade 0: none
	○	Grade 1: mild (lesions involving <10% of the esophageal surface area)	○	Grade 1: mild (lesions involving <10% of the esophageal surface area)
	○	Grade 2: severe (lesions involving >10% of the esophageal surface area)	○	Grade 2: severe (lesions involving >10% of the esophageal surface area)

.....

Furrows (also referred to as vertical lines, longitudinal furrows)	○	Grade 0: absent	○	Grade 0: absent
	○	Grade 1: mild (vertical lines without visible depth)	○	Grade 1: mild (vertical lines without visible depth)
	○	Grade 2: severe (vertical lines with depth or indentation of the mucosa)	○	Grade 2: severe (vertical lines with depth or indentation of the mucosa)
Stricture	○	Grade 0: absent	○	Grade 0: absent
	○	Grade 1: present	○	Grade 1: present
	____	Diameter (mm)	____	Diameter (mm)
	____	Length (cm)	____	Length (cm)

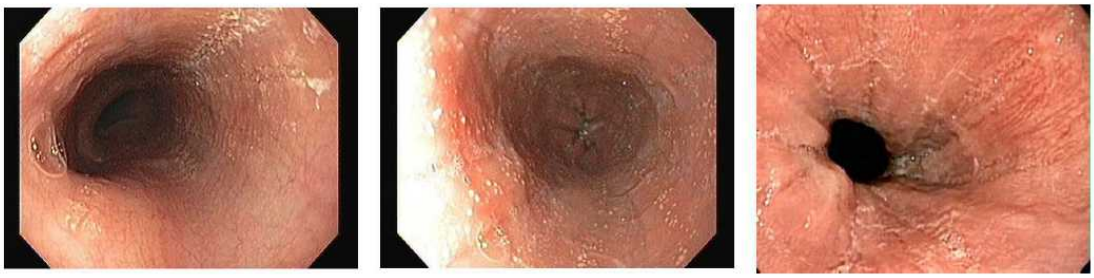
Miscellaneous Features

Crepe Paper Esophagus (mucosal tearing or laceration upon passage of endoscope)	○	Grade 0: None
	○	Grade 1: Present
Narrow Caliber Esophagus (reduced luminal diameter involving greater than 50% of the esophageal length)	○	Grade 0: None
	○	Grade 1: Present
Esophageal erosions (Los Angeles Classification)	○	Normal (No erosions/mucosal breaks)
	○	Grade A: One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds
	○	Grade B: One (or more) mucosal break more than 5 mm long, that does not extend between the tops of two mucosal folds
	○	Grade C: One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference
	○	Grade D: One (or more) mucosal break which involves at least 75% of the esophageal circumference

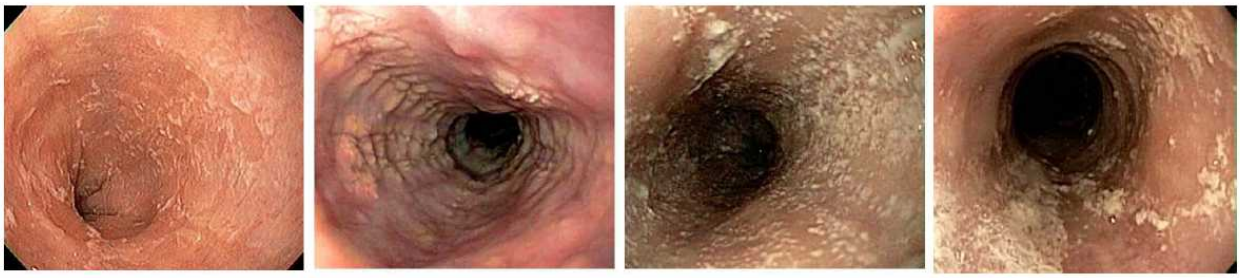
Endoscopy Atlas (Hirano 2013)

White Exudates (Plaques)

Mild: Scattered lesions occupying<10% of surface area

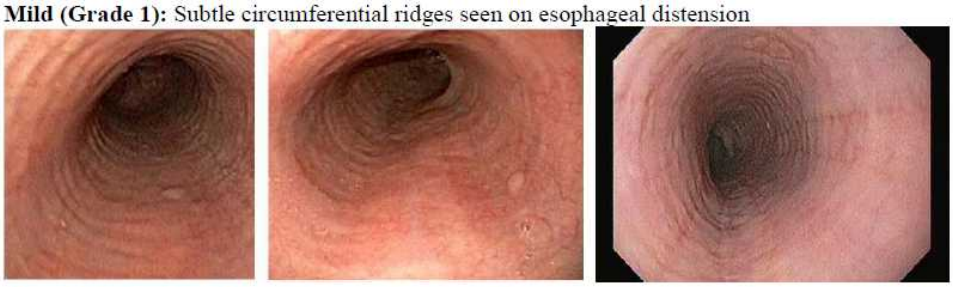


Severe: involving >10% of surface area of esophagus

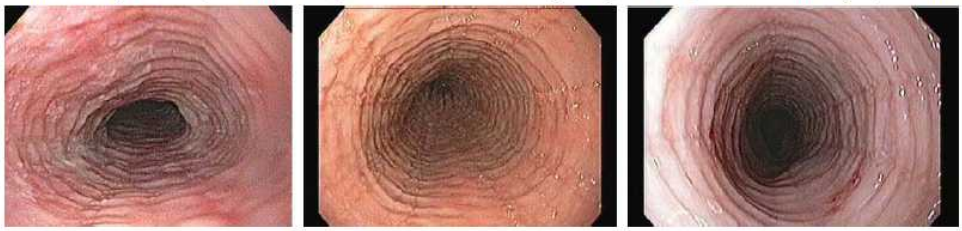


Fixed Esophageal Rings ***((Evaluate during air insufflation))*** *Persistent concentric rings. Also referred to as "corrugated esophagus", "corrugated rings", "ringed esophagus" or"trachealization"*

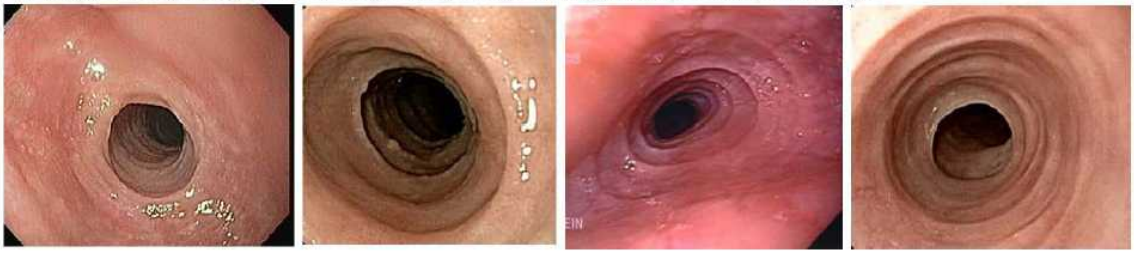
Mild (Grade 1): Subtle circumferential ridges seen on esophageal distension



Moderate (Grade 2): Distinct rings that do not occlude passage of diagnostic endoscope (8-9mm diameter)



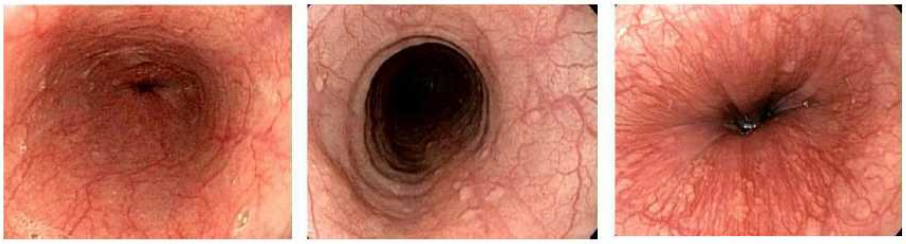
Severe (Grade 3): Rings that do not permit passage of diagnostic (8-9 mm) endoscope



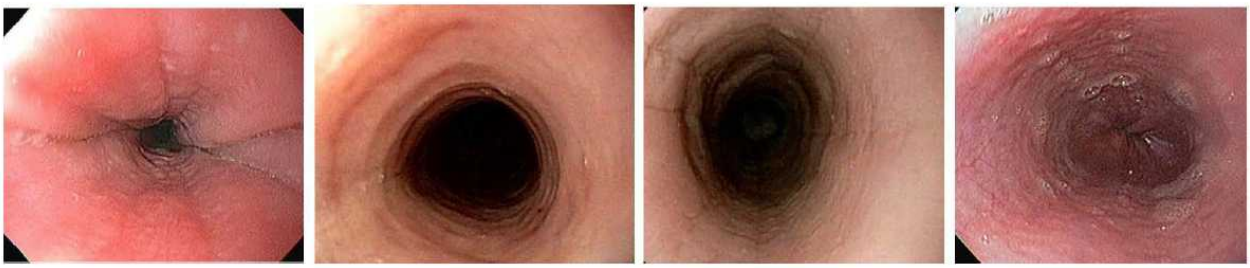
EoE Endo Atlas

Decreased Vascular Pattern ("Edema") ***(Evaluate during air insufflation)***

Normal: Distinct vasculature

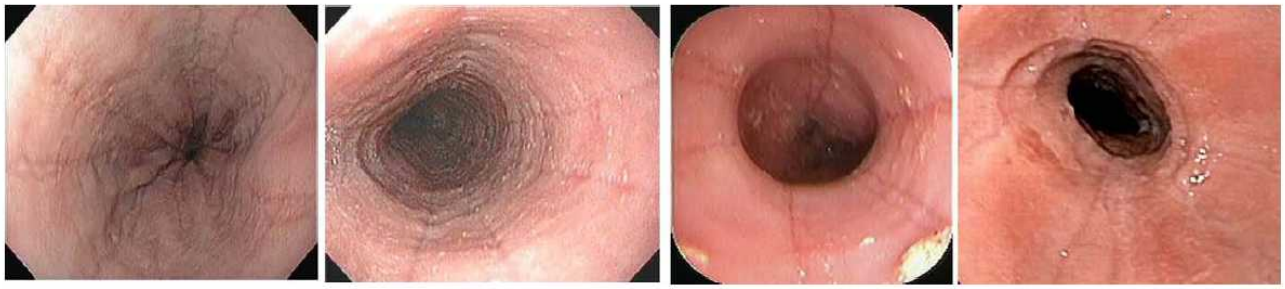


Decreased: Loss of clarity or absence of vascular markings

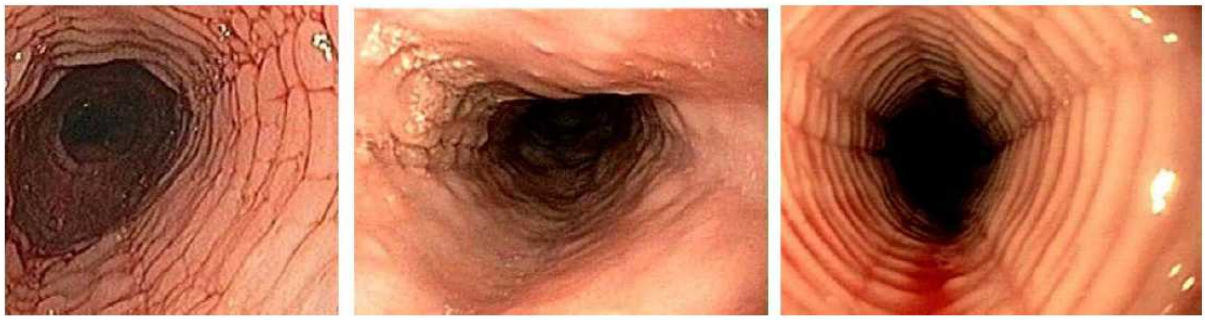


Furrows *(Vertical lines) evaluate during air insufflation)*

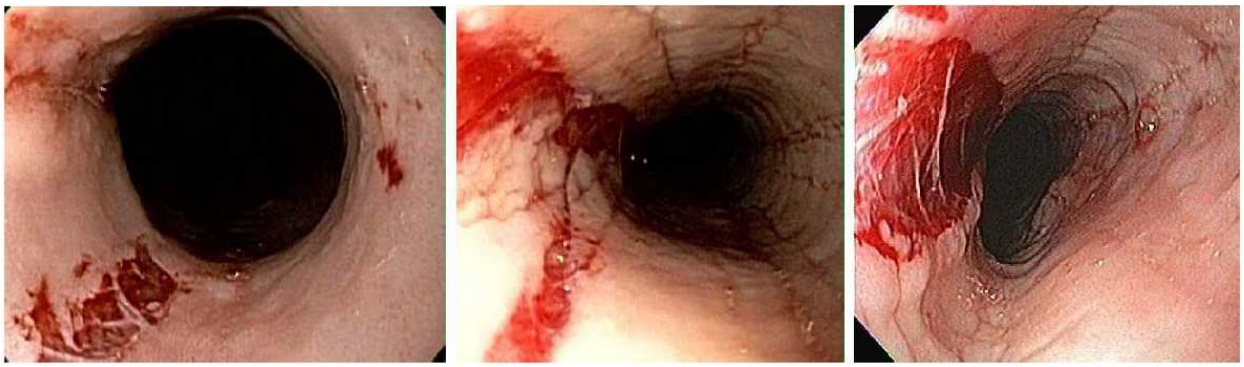
Mild: vertical lines without visible depth



Severe: Vertical lines with clear depth (indentation) into the mucosa



Crepe Paper Esophagus: Mucosal fragility or laceration upon passage of diagnostic endoscope (not with esophageal dilation)



7-DAY RECALL EOSINOPHILIC ESOPHAGITIS SYMPTOM ENT INDEX

you some questions about your disease. It is easy to miss a question, so please check e any out as you go. Thank you for helping us with this study!

either one of the following methods:

appropriate box: ☒ OR by writing on the line.

vered question 2 A-H one or several times with "Don't know", please explain for each
I do not eat French fries

O EOSINOPHILIC ESOPHAGITIS

estions are related to your eosinophilic esophagitis (EoE) symptoms, not related to problems that occur during a occal throat infection or mononucleosis), nor to problems that occur, for instance, if a fishbone is stuck in your to ask you about problems that occur while you are eating (questions 1 to 10).

ulties chewing (for example, your teeth need filling, or you have false teeth, or your jaw is injured)?

2)

	A	B	C	D	E	F	G	H
								
	Solid meat (steak, chicken, turkey, lamb)	**Soft foods** (pudding, jelly, apple sauce)	**Dry rice** (grains don't stick) **or sticky Asian rice,** without sauce	**Ground meat** (hamburger, meat loaf)	**Fresh white untoasted bread** or similar foods (donut, muffin, cake)	**Grits, porridge (oatmeal), rice pudding**	**Raw, fibrous foods**, not grated (apple, carrot, celery)	**French fries** without sauce or ketchup
Severe difficulties (for example: will not pass at all)	☐	☐	☐	☐	☐	☐	☐	☐
Moderate difficulties (for example: will need to be washed down with liquid)	☐	☐	☐	☐	☐	☐	☐	☐
Mild difficulties (for example: will pass with further swallows)	☐	☐	☐	☐	☐	☐	☐	☐

Today, how difficult would it be to swallow the foods shown above? Please check only one box per food consistency.

Please imagine what would typically happen if you were to eat those foods right now.

Important: please imagine eating it without modification such as blending, mashing, cutting in tiny pieces, dunking in liquid.

No difficulties	☐	☐	☐	☐	☐	☐	☐	☐
Don't know *Please explain at the end of the table (question #3)*	☐	☐	☐	☐	☐	☐	☐	☐

3) If you have answered question 2 A-H one or several times with "Don't know", please explain for each food why.

_____

4)

	A	B	C	D	E	F	G	H
								
	Solid meat (steak, chicken, turkey, lamb)	**Soft foods** (pudding, jelly, apple sauce)	**Dry rice** (grains don't stick) **or sticky Asian rice,** without sauce	**Ground meat** (hamburger, meat loaf)	**Fresh white untoasted bread** or similar foods (donut, muffin, cake)	**Grits, porridge (oatmeal), rice pudding**	**Raw, fibrous foods**, not grated (apple, carrot, celery)	**French fries** without sauce or ketchup
Now, we would like to know, in the past <u>7 days</u>, did you... *Please tell us now about your regular eating habits.*								
4) <u>Avoid</u> this food <u>altogether</u> because of your EoE? (for example, because it would not pass at all)	☐ Yes (If yes, skip to next food group) ☐ No	☐ Yes (If yes, skip to next food group) ☐ No	☐ Yes (If yes, skip to next food group) ☐ No	☐ Yes (If yes, skip to next food group) ☐ No	☐ Yes (If yes, skip to next food group) ☐ No	☐ Yes (If yes, skip to next food group) ☐ No	☐ Yes (If yes, skip to next food group) ☐ No	☐ Yes (If yes, skip to next food group) ☐ No
5) <u>Eat</u> this food?	☐ No (If no, skip to next food group) ☐ Yes	☐ No (If no, skip to next food group) ☐ Yes	☐ No (If no, skip to next food group) ☐ Yes	☐ No (If no, skip to next food group) ☐ Yes	☐ No (If no, skip to next food group) ☐ Yes	☐ No (If no, skip to next food group) ☐ Yes	☐ No (If no, skip to next food group) ☐ Yes	☐ No (If no, skip to next food group) ☐ Yes

6) <u>Modify</u> this food? (for example, put it in blender, cut in tiny pieces, dunk in liquid, mash it)	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
7).<u>Eat this food slower</u> than other people eating that same food? (for example, because you chew for long time)	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No

8) In the past 7 days, how often have you had trouble swallowing (not associated with cold symptoms, such as sore throat)**?** *Please tick only one box per time period.*

☐ Never
☐ Once to 3 times per week
☐ 4 to 6 times per week
☐ Daily

9) In the past 7 days, typically, how long did an episode of trouble swallowing last?

☐ Less than 15 seconds
☐ 16 to 59 seconds
☐ 1 to 5 minutes
☐ Longer than 5 minutes
☐ In the past 7 days, I have not had any trouble swallowing

10) In the past 7 days, has it been painful to swallow?

☐ Yes
☐ No

Thank you for completing this questionnaire!

APPENDIX 5: ADULT EOSINOPHILIC ESOPHAGITIS QUALITY OF LIFE

Please think about your life over the past week (7 days) and look at the statements below. Each statement has 5 responses. For each statement, please check the response that best describes your experiences with living with eosinophilic esophagitis (EoE).

	Not at All	Slightly	Moderately	Quite A Bit	Extremely
During the past week…..					
1. I find EoE to be a stressful disease.					
2. I have to be cautious about eating because I have EoE.					
3. I feel panicked or out of control when I have difficulty swallowing.					
4. I worry about the side effects of my EoE medications long-term.					
5. Because of EoE, my daily life feels abnormal.					
6. I feel helpless because of my EoE.					
7. I find myself getting nervous or anxious before a meal.					
8. I fear that I will not be able to breathe when I have difficulty swallowing.					
9. I find it embarrassing when I have to make special requests at restaurants.					
10. I worry about having to be on an EoE treatment for the rest of my life.					
11. I feel like my life is less enjoyable because of my EoE.					
12. I worry about never identifying the cause of my EoE.					
13. I feel frustrated that I have EoE.					
14. I try to hide my difficulty swallowing so that other people do not realize what is happening.					
15. I worry that EoE will get worse or turn into something else.					

	Not at All	Slightly	Moderately	Quite A Bit	Extremely
16. I feel frustrated that I cannot eat what I want because of my EoE.					
17. I worry that I cause my family members anxiety when I have a swallowing episode.					
18. I have anxiety because EoE is a relatively new disease.					
19. I feel frustrated when people think I cause my own choking episodes by eating too fast or taking too big bites.					
20. I worry about when the next swallowing episode will occur.					
21. I have a difficult time explaining EoE to my family in order to ease their concerns.					
22. I feel embarrassed if I need to spend a long time in the bathroom trying to resolve a swallowing episode.					
23. I feel isolated from others because of my EoE.					
24. I worry about never being able to eat normally because of my EoE.					
Only answer the following questions if you are on an elimination diet (six food elimination, elemental formula diet, allergy testing based elimination diet) as treatment for EoE.					
25. I worry when I'm out that I won't find something to eat.					
26. I worry about eating out for fear of contamination.					
27. I spend a lot of time planning my meals.					
28. I find it troublesome to read food labels and shop at special stores.					
29. I find myself spending more money on food because of EoE.					
30. I have difficulty finding foods I can eat because of my EoE.					

Scoring Instructions:

The EoE-QOL-A yields an overall score and 5 subscale scores. Higher scores denote better quality of life. Each item ranges from 0 to 4 as follows: Not at all = 4, Slightly = 3, Moderately = 2, Quite a Bit = 1, Extremely = 0. There is a standard version and a standard + dietary restrictions version of the EoE-QOL-A.

Standard Version (24-item)

	Score Range	Items
Overall Score:	0-96	Q1-Q24
Subscales:		
Eating/Diet Impact:	0-16	Q2, Q9, Q16, Q24
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

Standard Version + Dietary Restrictions (30-item)

	Score Range	Items
Overall Score:	0-120	Q1-Q30
Subscales:		
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

APPENDIX 6: SYSTEMIC CORTICOSTEROID EFFECTS

Adrenal Insufficiency or Suppression

- Decreased ability to respond to emotional or physical stress;
- Fatigue;
- Joint pains (arthralgias);
- Low blood pressure (hypotension), which may cause light-headedness or fainting when standing after sitting or lying down;
- Muscle pain (myalgias);
- Nausea and vomiting;
- Shock;
- Weakness;
- Hypoglycemia (low blood sugar);
- Low serum cortisol level;
- Low sodium;
- Abnormal responses to ACTH stimulation test.

Hypercorticism

- Increased appetite;
- Weight gain;
- Water and salt retention, leading to swelling and edema;
- High blood pressure;
- Diabetes;
- Slowed healing of wounds;
- Osteoporosis;
- Cataracts;

- Acne;
- Muscle weakness;
- Thinning of the skin;
- Increased susceptibility to infection;
- Stomach ulcers;
- Increased sweating;
- Mood swings;
- Psychological problems, such as depression;
- Cushing syndrome: obesity around the waist and moon face (moon facies);
- Hirsutism;
- Insomnia.