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ESOPHAGUS

Fluticasone Propionate Orally Disintegrating Tablet (APT-1011) for Eosinophilic Esophagitis: Randomized Controlled Trial

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BACKGROUND & AIMS: **Topical steroids are effective treatments for eosinophilic esophagitis (EoE). The FLUTE (Fluticasone in EoE) trial evaluated safety and efficacy of APT-1011 (fluticasone propionate oral disintegrating tablet) vs placebo for treatment of EoE.**

METHODS: **In this randomized, double-blind, placebo-controlled, dose-finding, phase 2b trial, 106 adults with EoE received 1 of 4 APT-1011 doses or placebo for a 12-week induction period and 40 weeks of maintenance. Primary outcome was histologic response (≤6 eosinophils per high-power field) at Week 12. Secondary outcomes included endoscopic features and dysphagia frequency.**

RESULTS: **Histologic response rates were 0% for placebo, 80% for APT-1011 3 mg twice daily (BID), 67% for 3 mg at bedtime (HS), 86% for 1.5 mg BID, 48% for 1.5 mg HS ($P < .001$ for all groups vs placebo). At Week 12, mean Edema/Rings/Exudates/Furrows/Strictures (EoE Endoscopic Reference Score) total score (max, 9.0) improved from 4.5 to 2.3 for 3 mg BID, 5.3 to 2.1 for 3 mg HS, 4.6 to 1.7 for 1.5 mg BID, 5.3 to 2.9 for 1.5 mg HS vs 5.2 to 4.5 for placebo. Mean dysphagia frequency over 14 days improved from baseline to Week 12 with all active groups improving more than placebo. Improvements were sustained to Week 52. APT-1011 was safe and well-tolerated, with higher incidence of candidiasis noted at the higher twice daily doses.**

CONCLUSION: **APT-1011 dosing regimens were superior for histologic and endoscopic responses, and for reduction in dysphagia frequency vs placebo. Based on the symptom improvement and assessment of adverse events together with the histologic response rate, 3 mg once daily at bedtime dose showed the most favorable risk-benefit profile. ClinicalTrials.gov, Number: NCT03191864.**

Keywords: Eosinophilic Esophagitis; APT-1011; Fluticasone Propionate.

Eosinophilic esophagitis (EoE) is an immune-mediated chronic inflammatory esophageal disease.[1–4] The primary symptoms include dysphagia and food impaction in adolescents and adults.[2,5] Diagnosis is confirmed when at least 15 eosinophils per high-power field (eos/hpf) are found in an esophageal biopsy without other causes of eosinophilia.[4] Both the incidence and prevalence of EoE are rising rapidly throughout the world.[6–8]

Current nonpharmacologic therapeutic options include food elimination diets, but long-term adherence to this approach is difficult to maintain.[1,2,9] Oral budesonide therapy is available in Europe, and under

Abbreviations used in this paper: BID, twice daily; EEsAI, Eosinophilic Esophagitis Activity Index; EGD, esophagogastroduodenoscopy; EoE, eosinophilic esophagitis; EoE-QoL-A, EoE Adult Quality of Life Questionnaire; eos/hpf, eosinophils per high-power field; EREFS, Edema/Rings/Exudates/Furrows/Strictures (EoE Endoscopic Reference Score); FLUTE, Fluticasone in EoE; FP, fluticasone propionate; HS, hora somni (at bedtime); ODT, oral disintegrating tablet; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PPI, proton pump inhibitor; PROSE, Patient-Reported Outcome Symptoms of EoE; TEAE, treatment-emergent adverse event; U.S., United States.

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development in the United States (U.S.).[10] The most widely used pharmacologic treatments in the U.S. include proton pump inhibitors (PPIs) and topical corticosteroids, which are adapted from asthma medications that are swallowed rather than inhaled,[1,3,11,12] Relapse is common when any treatment for EoE is stopped, including topical steroids.[2,13–16] In addition, given potential concerns over adverse effects with long-term corticosteroid treatment, additional safety data for this drug class are needed.[1,17,18]

APT-1011 is an oral disintegrating tablet (ODT) formulation of fluticasone propionate (FP) that disintegrates on the tongue without water and is then swallowed to coat the esophagus.[12,19] APT-1011 was developed to mask the taste of a glucocorticoid with a rapidly dissolving ODT formulation for localized topical delivery of FP to the esophagus with minimal systemic exposure. Initial proof of concept was demonstrated in a small phase 1b/2a study, where improvements in histology, endoscopy, and symptoms were seen, compared with placebo.[19] The aim of this study, the FLUTE (Fluticasone in EoE) trial, was to evaluate the safety and efficacy of 4 doses of APT-1011 compared with placebo for induction of remission and maintenance treatment of EoE.

What You Need to Know

Background

Fluticasone propionate orally disintegrating tablet (APT-1011) was developed as an induction and maintenance treatment for eosinophilic esophagitis, an allergen-driven chronic inflammatory esophageal disease with no United States Food and Drug Administration–approved drug therapy.

Findings

The phase 2b FLUTE (Fluticasone in EoE) trial found that APT-1011 has efficacy for both short- and long-term treatment of eosinophilic esophagitis when compared with placebo. The 3-mg at bedtime arm had the most well-balanced efficacy/safety profile for both sustained response/remission (balancing histologic, symptomatic, and endoscopic data), and freedom from oropharyngeal/esophageal candidiasis over 52 weeks of treatment, and will be carried forward into the phase 3 studies.

Implications for patient care

This study is the most comprehensive dose-ranging study in the development of an orally disintegrating tablet for the topical treatment of eosinophilic esophagitis. It shows the benefit and safety profile of APT-1011, and that the drug should continue to undergo clinical development.

Methods

Study Design and Subjects

This was a multicenter, randomized, double-blind, placebo-controlled, dose-finding, phase 2b clinical trial. Adult patients (age ≥18 and ≤75 years) with a diagnosis of EoE were enrolled from 93 sites in 6 countries (U.S., Canada, Belgium, Switzerland, Spain, and Germany) from May 2017 to August 2018. The protocol and informed consent forms were submitted to the Institutional Review Boards/Independent Ethics Committees for approval. The International Council for Harmonization guidelines for Good Clinical Practices specify that the committee was to include persons of varying backgrounds (including peers of the responsible investigator and lay people) and exclude the responsible investigator as a voting member. The study was conducted according to the principles of the Declaration of Helsinki, and the International Council for Harmonization guidelines for Good Clinical Practices. The sponsor ensured that the study complied with all local, federal, or country regulatory requirements as applicable. All authors had access to the study data and reviewed and approved the final manuscript.

Subjects were eligible if they had a diagnosis of EoE, symptoms of dysphagia (defined as ≥3 episodes of dysphagia per week during the last 14 days of the 4-week baseline symptom assessment phase and a Global EoE Symptom Score of >3), and active esophageal eosinophilia (after evaluation of ≥5 biopsies from proximal and distal esophageal locations and at least 1 biopsy with peak count of ≥15 eos/hpf) after documentation of failed histologic response on ≥8 weeks of high-dose PPI. High-dose PPI was defined as 20 to 40 mg daily of any marketed PPI. Patients with a history of esophageal mucosal disease or known esophageal dysmotility unrelated to EoE were excluded from the study, with biopsies from the stomach and/or duodenum taken at screening if disease was suspected. Patients with a history of an esophageal stricture requiring dilation within the previous 12 weeks, or with a severe stricture or narrowing that precluded passage of a standard (8–10 mm) upper endoscope at screening were excluded. Patients with mild or moderate stricture(s) were not excluded. Corticosteroids, elimination diets or changes to diet, biologics, and immunomodulators were prohibited prior to screening and during the study. All patients were required to maintain a stable diet, and patients on a PPI were required to remain on a stable regimen.

Randomization, Interventions, and Study Conduct

Subjects were randomized in a 1:1:1:1:1 ratio to 1 of 4 APT-1011 regimens or matching placebo: 1.5 mg hora

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somni (at bedtime; HS) (placebo after breakfast); 1.5 mg twice daily (BID); 3 mg HS (placebo after breakfast); 3 mg BID; or placebo BID (HS and after breakfast). Randomization was stratified by current esophageal stricture(s) and a positive response to prior corticosteroid use. The randomization was created with a fixed block size of 5, without regard to geographical region or site. Subjects were randomized using an Interactive Web Response System. All study subjects, investigators, and study personnel were blinded through all study phases until after the analyses were completed.

The study drug was either active APT-1011 or a placebo disintegrating tablet indistinguishable from the active tablet in terms of size, color, texture, taste, and dispersibility. Subjects were instructed to take the study drug orally, with no water or other liquid. Subjects refrained from oral intake of solids or liquids for at least 1 hour after dosing.

The study was conducted in several parts: screening, baseline symptom assessment (a 4-week, single-blind, placebo run-in), 2 treatment parts (Part 1 and Part 2), and a follow-up visit 2 weeks after completion of study treatment. The single-blind run-in was implemented to enrich the population for symptoms and to determine the baseline dysphagia frequency using the Patient-Reported Outcome Symptoms of EoE (PROSE) tool.[20] Patients who did not meet the symptom threshold during the single blind phase were ineligible for study participation. Part 1 was the induction phase (Day 1 to Week 14), and Part 2 was the maintenance phase (Weeks 14 to 52). All responders at Week 12 were continued on the same blinded dosing regimen from Part 1 to Part 2. Full details of study design are in Supplementary Figure 1.

Outcomes

The primary efficacy outcome was histologic response at Week 12, defined as the percentage of subjects with $\leq$6 peak eos/hpf. Secondary efficacy outcomes included the percentage of responders with a sustained histologic response at Weeks 26 and 52; endoscopic severity measured by the change from baseline in the EREFS (Edema/Rings/Exudates/Furrows/Strictures [EoE Endoscopic Reference Score]) at Weeks 12, 26, and 52 (see Supplementary Material for scoring information); and the percentage of subjects with $<$1 and $<$15 eos/hpf at Weeks 12, 26, and 52. Secondary symptomatic outcomes included the change from baseline in the Global EoE Symptom Score (7-day recall) at multiple time intervals through Week 52 and the change in frequency of all reported dysphagia episodes for each day captured in an electronic diary (PROSE) over a 14-day period from baseline through Weeks 12, 26, and 52. Other symptom outcomes included the Eosinophilic Esophagitis Activity Index (EEsAI),[21] the Patient Global Impression of Severity (PGIS), and the Patient Global Impression of Change (PGIC) through Week 52.

Safety was evaluated by the frequency of treatment-emergent adverse events (TEAEs). Adverse events of special interest included oral and esophageal candidiasis and abnormalities of the hypothalamic-pituitary-adrenal axis as measured by morning cortisol and cortisol levels after adrenocorticotropic hormone stimulation.

Statistical Analysis and Sample Size Considerations

The primary outcome was analyzed using a stratified Cochran-Mantel-Haenszel test comparing the response rate for each APT-1011 dosing group with placebo using SAS Drug Development Software and analyzed by IQVIA. A gatekeeping strategy was used with tests performed in sequential order of doses to control type 1 error: 3 mg BID, 1.5 mg BID, 3 mg HS, and 1.5 mg HS. Each test was only performed if the previous test was significant at the 1-sided .05 significance level. The strata used in the stratified Cochran-Mantel-Haenszel test included history of or current presence of esophageal stricture (yes/no) and prior positive response to any corticosteroid treatment previously received to treat EoE (yes/no).

The sample size of a total of 100 patients was specified for the primary endpoint (20 in each treatment arm). The power for testing each active dose vs placebo, given a histologic response rate of 60% with active treatment and 10% with placebo for the primary endpoint (Part 1), was equal to 97.5% (1-sided type I error = .05). Additionally, the power for achieving statistical significance for all 3 of the highest active doses of 1.5 mg BID, 3 mg HS, and 3 mg BID via the gatekeeping hypothesis testing approach assuming independence was approximately .93. This sample size was considered sufficient to adequately evaluate the measurement properties of the PROSE tool and assess the amount of change that was clinically meaningful.

Results

Patient Flow and Baseline Characteristics

Of the 308 patients screened, 202 were screen failures. The primary reasons for screen failure included not meeting eligibility criteria for histology (34%), dysphagia episode frequency (25%), or diary compliance (10%). Of 106 patients who met eligibility criteria for randomization, 20 received 3 mg BID APT-1011, 22 received 3 mg HS APT-1011, 22 received 1.5 mg BID APT-1011, 21 received 1.5 mg HS APT-1011, and 20 received placebo (Supplementary Figure 2).

Treatment groups had similar baseline characteristics (Table 1). The mean age overall was 39 years; 68% were

Table 1. Baseline Patient Characteristics (Full Analysis Set)

Baseline characteristic	Randomized dosing group (full analysis set population)					Total (N = 103)
	APT-1011 3 mg BID (n = 20)	APT-1011 3 mg HS (n = 21)	APT-1011 1.5 mg BID (n = 22)	APT-1011 1.5 mg HS (n = 21)	Placebo (n = 19)	
Age at screening, *y*	36.8 ± 9.2	42.9 ± 11.5	41.3 ± 12.2	36.8 ± 11.7	38.6 ± 14.7	39.3 ± 12.0
Male	16 (80)	11 (52)	15 (68)	14 (67)	14 (74)	70 (68)
Race						
White	19 (95)	20 (95)	22 (100)	21 (100)	18 (95)	100 (97)
Black or African American	1 (5)	1 (5)	0	0	1 (5)	3 (3)
Ethnicity						
Hispanic or Latino	2 (10)	2 (10)	5 (23)	4 (19)	3 (16)	16 (15)
Not Hispanic or Latino	16 (80)	19 (90)	17 (77)	17 (81)	16 (84)	85 (83)
Other	2 (10)	0	0	0	0	2 (2)
Geographic region						
North America	13 (65)	17 (81)	16 (73)	15 (71)	16 (84)	77 (75)
Western Europe	7 (35)	4 (19)	6 (27)	6 (29)	3 (16)	26 (25)
BMI, *kg/m²*	25.5 ± 4.5	28.8 ± 6.9	27.39 ± 4.3	28.3 ± 5.2	28.4 ± 6.7	27.7 ± 5.6
History of atopy	18 (90)	17 (81)	20 (91)	20 (95)	13 (68)	88 (85)
PPI use[a]	13 (65)	12 (57)	18 (82)	12 (57)	14 (74)	69 (67)
History of esophageal stricture	8 (40)	8 (38)	10 (46)	11 (52)	9 (47)	46 (45)
Presence of esophageal stricture at screening	4 (20)	7 (33)	6 (27)	6 (29)	7 (37)	30 (29)
Presence of ≥ grade 2 rings at screening	6 (30)	8 (38)	10 (46)	10 (48)	9 (47)	43 (42)
Prior steroid response[b]	4 (20)	4 (19)	5 (23)	3 (14)	3 (16)	19 (18)
Baseline peak eosinophil count, *eos/hpf*	55.1 ± 21.3	65.3 ± 28.9	69.2 ± 33.3	56.2 ± 25.9	64.3 ± 33.4	62.1 ± 29.0
Baseline endoscopic severity, *EREFS*[c]	3.9 ± 1.7	4.7 ± 1.6	4.2 ± 1.8	4.7 ± 1.4	4.6 ± 1.3	4.4 ± 1.6
Dysphagia frequency over 14 days[d]	14.3 ± 10.2	12.7 ± 5.9	16.0 ± 11.4	11.5 ± 5.7	13.9 ± 8.4	13.7 ± 8.6
Baseline global EoE score	4.3 ± 1.9	5.1 ± 2.0	4.5 ± 2.1	5.1 ± 1.6	5.1 ± 1.7	4.8 ± 1.9

Note: Data are presented as mean ± standard deviation or number (%).
BID, Twice daily; *BMI*, body mass index; *EoE*, eosinophilic esophagitis; *eos/hpf*, eosinophils per high-power field; *EREFS*, Edema/Rings/Exudates/Furrows/Strictures (EoE Endoscopic Reference Score); *HS*, hora somni (at bedtime); *PPI*, proton pump inhibitor.
[a]PPI use for at least 30 days prior to signing of informed consent, with stable dose required throughout the study.
[b]Known prior response to topical corticosteroids based on medical history; number of subjects exposed to prior topical corticosteroids not known.
[c]EREFS scores 0 to 9, with 9 being the worst score. Scores evaluate edema, rings, exudates, furrows/fissures, and presence or absence of strictures.
[d]Dysphagia episode data were reported by subjects daily using an electronic diary, in real time and/or at the end of day.

male, and 86% had an atopic condition. At screening, 29% had an esophageal stricture, and 42% had ≥grade 2 ring(s). The average (± standard deviation) peak eosinophil count was 62.1 ± 29.0 eos/hpf, the mean EREFS was 4.4 ± 1.6, and the mean dysphagia frequency was 13.7 ± 8.6 episodes over 14 days. Over one-half of the randomized patients were on PPI treatment (67%).

Compliance with study medication was high in Part 1 (total APT-1011 compliance 80% and placebo compliance 73%). In Part 2, all subjects received APT-1011, with overall study medication compliance remaining high at 80% by Week 28 and 62% by Week 52.

Primary Outcome: Histologic Response

The primary endpoint of histologic response at Week 12 was higher for all dose groups compared with placebo: 80% for 3 mg APT-1011 BID, 67% for 3 mg HS, 86% for 1.5 mg BID, 48% for 1.5 mg HS, and 0% for placebo ($P < .001$ for all comparisons vs placebo;

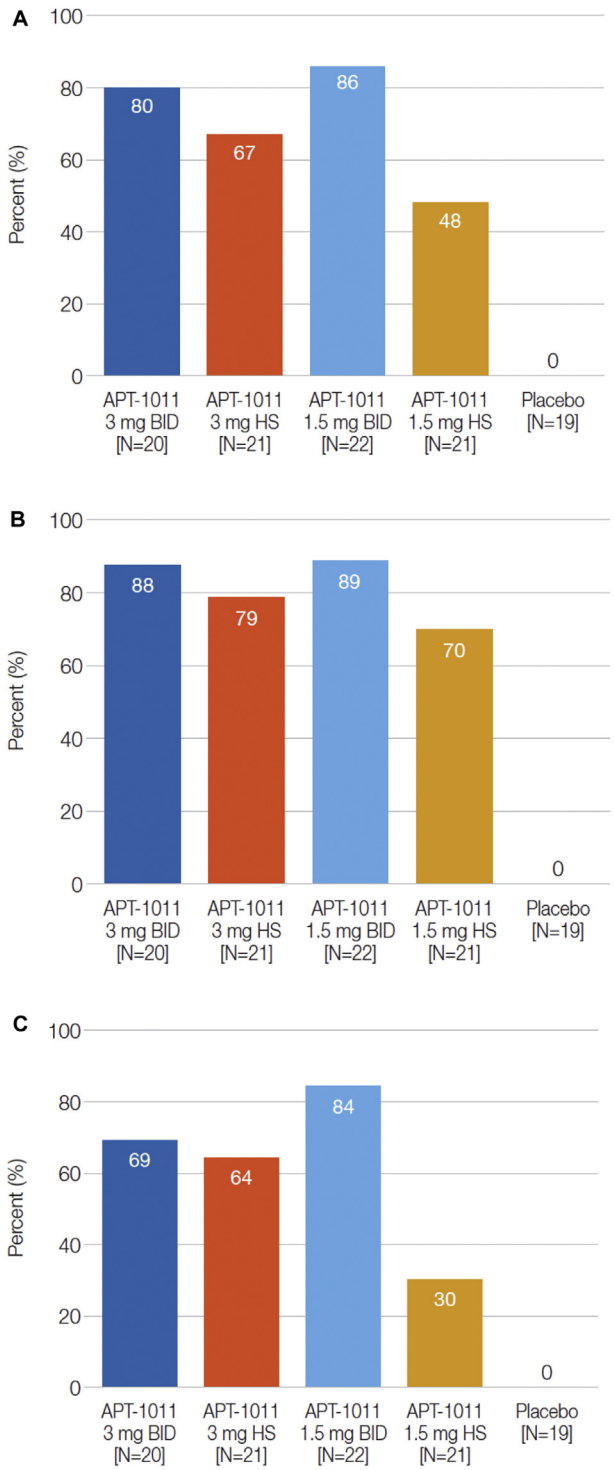

Figure 1. Histologic responders at Weeks 12 (*A*), 26 (*B*), and 52 (*C*) (full analysis set population).

Figure 1, *A*). Histologic response in Part 1 responders was maintained at Weeks 26 and 52 by: 88% and 69%, respectively, for 3 mg BID, 79% and 64% (3 mg HS), 89% and 84% (1.5 mg BID), and 70% and 30% (1.5 mg HS) (Figures 1, *B and C*).

Similar results were seen for secondary outcomes of <1 and <15 eos/hpf histologic thresholds (Supplementary Figures 3, *A and B*).

Secondary Outcome: Endoscopic Response

EREFS showed greater improvement compared with placebo for all APT-1011 dosing groups. At Week 12, mean EREFS total score improved from 4.5 to 2.3 for 3 mg BID ($P < .001$ compared with placebo), 5.3 to 2.1 for 3 mg HS ($P < .001$), 4.6 to 1.7 for 1.5 mg BID ($P < .001$), and 5.3 to 2.9 for 1.5 mg HS ($P = .004$), and 5.2 to 4.5 for placebo. Mean EREFS total scores were maintained below 2.0 for Part 1 histologic responders at Weeks 26 and 52 (Figure 2 and Supplementary Table 1).

Secondary Outcome: Symptom Metrics

The Global EoE Symptom Score showed greater improvement compared with placebo for all APT-1011 dosing groups, with nominal significance achieved by the 3-mg HS group (Supplementary Figure 4).

Mean dysphagia frequency showed greater improvement compared with placebo for all APT-1011 dosing groups. At Week 12, greater improvement in the APT-1011 treatment regimens, with the exception of 1.5 mg BID, was seen when compared with placebo: 14.3 to 5.6 for 3 mg BID ($P = .370$ compared with placebo), 12.7 to 3.6 for 3 mg HS ($P = .115$), 16.0 to 11.8 for 1.5 mg BID ($P = .753$), 11.5 to 3.8 for 1.5 mg HS ($P = .261$), and 13.9 to 9.1 for placebo. Lower mean dysphagia frequency was maintained through Week 52 (Figure 3).

The EEsAI total score demonstrated greater improvement compared with placebo for all APT-1011 dosing groups, with nominal significance for 3.0 mg BID and 3.0 mg HS (Supplementary Figures 5 and 6).

Post Hoc Analysis: Response in Patients with Fibrostenosis

A post hoc analysis conducted for the subgroup of patients with strictures and/or ≥grade 2 rings to evaluate treatment response for these features showed resolution of these features in patients receiving APT-1011, particularly 3 mg HS. Further, APT-1011 treatment had higher histologic (79% vs 0%; $P < .001$) and endoscopic (88% vs 38%; $P < .001$) response rates vs placebo, with comparable symptom response rates in these stricture/rings patients (Supplementary Table 2). Patients receiving APT-1011 also had lower rates of persistent stricture and/or rings at Week 12 vs placebo: stricture (21% vs 46%; $P = .075$), rings (7% vs 46%; $P < .001$), either stricture or rings (28% vs 77%; $P = .002$).

Safety and Adverse Events

Reports of TEAEs were similar across all treatment arms (Tables 2 and 3). There was one serious TEAEs in Part 1 of ureterolithiasis in the 3-mg HS group. In Part 2, there were 2 serious TEAEs of Hodgkin lymphoma (1.5 mg HS) and status epilepticus (3 mg HS).

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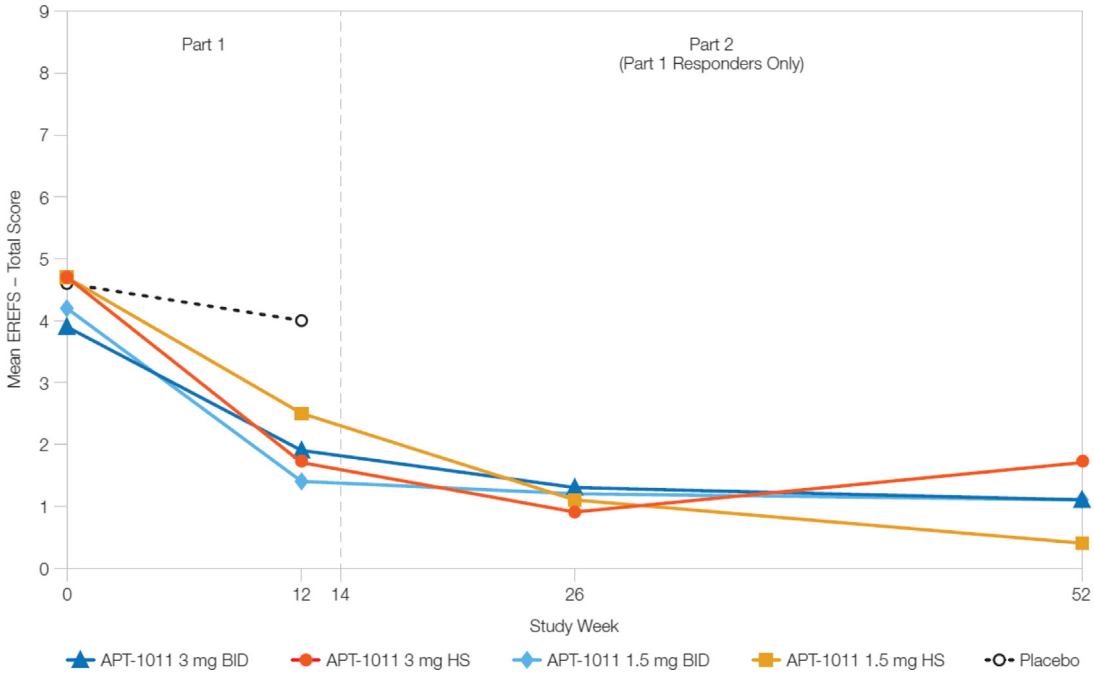

Figure 2. Mean EREFS scores at Week 12 through Week 52 (full analysis set population). Analysis after Week 12 based on histologic responder population at Week 12 only, continuing randomized dosage group from baseline. All histologic nonresponders at Week 12 were reallocated to receive 3 mg BID at Week 14 (when the responder status was determined based on histology results).

Nasopharyngitis was the most common TEAE in all groups through Part 1 and Part 2. Oral and esophageal candidiasis was more frequent in the BID dosing groups, with no events in the APT-1011 1.5-mg HS and placebo groups. For the 3-mg BID group, oral and esophageal candidiasis was 40% in Part 1 and 32% in Part 2, 18% and 16% for 1.5 mg BID, and 5% and 7% for 3 mg HS (same subject) (Supplementary Tables 3A and 3B). In Part 1, there were 3 TEAEs, and in Part 2, there were 5 TEAEs of low morning cortisol (Supplementary Tables 4A and 4B). In Part 2, there was 1 TEAE of adrenal suppression and another of abnormal adrenocorticotropic hormone test, both at Week 52 (3 mg HS and 3 mg BID, respectively); however, adrenal insufficiency was not confirmed. All cortisol test abnormalities resolved upon retesting, with no dose adjustment or interruption of treatment (Supplementary Tables 5A and 5B).

Discussion

Topical corticosteroids are recommended as a first-line treatment in EoE.[22,23] Emerging data indicate that

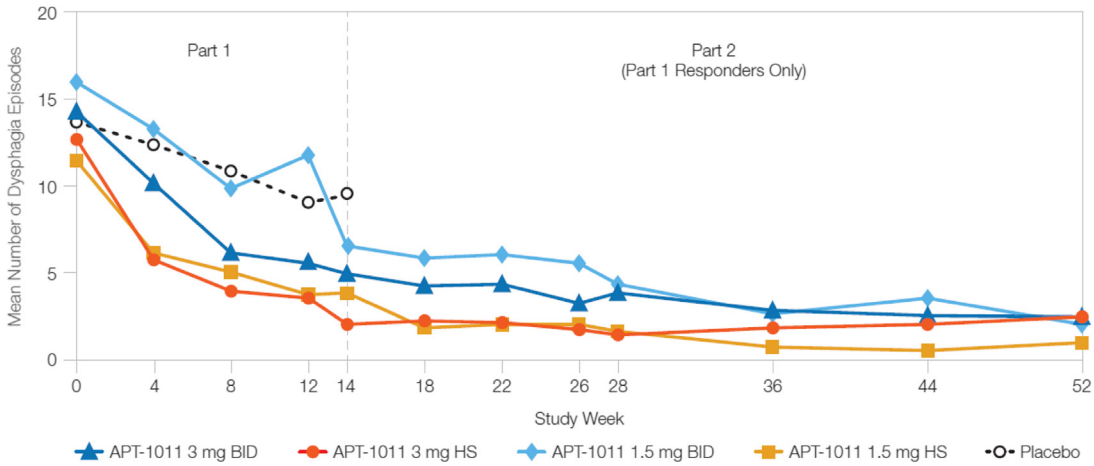

Figure 3. Mean number of dysphagia episodes over 52 weeks' treatment. The change in the number of dysphagia episodes at baseline (14-day period prior to randomization) was compared with the 14-day period prior to the time point of interest (Weeks 12, 26, and 52). Analysis after Week 12 based on histologic responder population at Week 12 only, continuing randomized dosage group from baseline. All histologic nonresponders at Week 12 were reallocated to receive 3 mg BID at Week 14 (when the responder status was determined based on histology results).

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Table 2. Overall Summary of Treatment-Emergent Adverse Events in Part 1 Safety Analysis Population

TEAE category	Double-blind dosing group					Total APT-1011[a] (N = 85)
	APT-1011 3 mg BID (n = 20)	APT-1011 3 mg HS (n = 21)	APT-1011 1.5 mg BID (n = 23)	APT-1011 1.5 mg HS (n = 21)	Placebo (n = 20)	
At least 1 TEAE[b]	17 (85)	16 (76)	17 (74)	13 (62)	13 (65)	63 (74)
Maximum severity of TEAE						
Mild	12 (60)	6 (29)	14 (61)	11 (52)	10 (50)	43 (51)
Moderate	5 (25)	9 (43)	3 (13)	1 (5)	3 (15)	18 (21)
Severe	0	1 (5)	0	1 (5)	0	2 (2)
TEAE related to study drug	10 (50)	4 (19)	5 (22)	2 (10)	4 (20)	21 (25)
TEAE leading to study discontinuation	1 (5)	0	2 (9)	0	2 (10)	3 (4)
Serious TEAE	0	1 (5)	0	0	0	1 (1)
TEAE resulting in death	0	0	0	0	0	0
TEAE of special interest[c]	7 (35)	1 (5)[d]	3 (13)	0	0	11 (13)

Note: Data are presented as number (%).
BID, Twice daily; *HS*, hora somni (at bedtime); *TEAE*, treatment-emergent adverse event.
[a]"Total APT-1011" refers to all subjects on active treatment.
[b]A TEAE is any adverse event that started or worsened in severity after the first dose of study drug in Part 1 of the study and prior to first dose of study drug in Part 2. Note: For maximum severity rows, if a subject had more than 1 TEAE, they were counted only once based on the maximum severity.
[c]TEAEs of special interest included events of candidiasis (oral, oropharyngeal, and esophageal) and events of abnormal morning cortisol; abnormal adrenocorticotropic hormone stimulation test; adrenal suppression.
[d]The TEAE of special interest was candidiasis.

esophageal-specific topical formulations have the potential to optimize treatment outcomes in EoE,[13,24–27] and preliminary investigations of FP orally disintegrating tablet (phase 2a) were promising.[19] In this phase 2b, randomized, placebo-controlled, dose-ranging study, the primary outcome of improved histologic responder rate at Week 12 was met with all doses of APT-1011, with the highest rates seen with a total daily dose of at least 3 mg APT-1011. Secondary outcomes demonstrated that APT-1011 improved endoscopic severity, with positive trends for symptoms. Moreover, the histologic, endoscopic, and symptomatic responses were sustained through Week 52. Overall, APT-1011 was safe and well-tolerated. Oral or esophageal candidiasis was noted predominantly at the higher doses administered twice daily.

Other formulations of corticosteroids have been developed to target topical administration directly to the esophageal mucosa and have been studied in controlled clinical trials. Budesonide has been studied in suspensions and oral dispersible tablet formulations with differing success rates for histologic remission, indicating the importance of formulation for achieving treatment goals.[16,26–28] When these formulations are studied as longer-term treatment, there can be a drop-off in efficacy.[15,29] Further, dosing regimens for EoE-specific budesonide formulations have focused only on twice-daily dosing.[30] There remains an unmet need for regimens that are less burdensome for patients while delivering adequate and effective corticosteroid to the esophageal mucosa with the potential to reverse long-term sequelae such as fibrostenosis.

The FLUTE study is a dose-finding study to evaluate 3 total daily doses (1.5, 3, and 6 mg) and 2 different dosing regimens (BID and HS) of FP. The data suggest that APT-1011 at the 3-mg HS dose provides the best balance of safety and efficacy for inducing histologic remission, symptomatic improvement over 52 weeks, with lower rates of candidiasis. These data may indicate that 3 mg HS dose is the most optimal to achieve both sustained response/remission (balancing histologic, symptomatic, and endoscopic data), and freedom from oropharyngeal/esophageal candidiasis. Further, once daily dosing at bedtime has the potential to encourage better treatment compliance. In a post-hoc analysis of patients with strictures and/or grade 2 esophageal rings at baseline, APT-1011 demonstrated improvement or resolution of these features in most patients, particularly for the 3-mg HS dosing group. This is an important outcome as fibrostenosis has been linked to lower treatment responses.[31–33]

As swallowed corticosteroids can lead to systemic absorption, pharmacokinetic data and bioavailability for corticosteroids administered orally is of importance.[34] FP undergoes extensive first-pass metabolism to inactive metabolites, with bioavailability demonstrated as <1%.[35] Pharmacokinetic data of APT-1011, both from a phase 1 study and from the phase 2b study, show picograms per mL levels in plasma, well below those

Table 3. Overall Summary of TEAEs in Part 2 Safety Analysis Population

	Double-blind dosing group							
TEAE category	APT-1011 3 mg BID (n = 16)	APT-1011 3 mg HS (n = 14)	APT-1011 1.5 mg BID (n = 19)	APT-1011 1.5 mg HS (n = 10)	Placebo (n = 0)	Single-blind APT-1011 3 mg BID (n = 34)	Total APT-1011[a] 3 mg BID (n = 50)	Total (N = 93)
TEAE[b]	12 (75)	13 (93)	14 (74)	7 (70)	0	22 (65)	34 (68)	68 (73)
Mild	7 (44)	7 (50)	11 (58)	5 (50)	0	17 (50)	24 (48)	47 (51)
Moderate	5 (31)	5 (36)	3 (16)	1 (10)	0	5 (15)	10 (20)	19 (20)
Severe	0	1 (1)	0	1 (10)	0	0	0	2 (2)
TEAE related to study drug	8 (50)	2 (14)	5 (26)	0	0	6 (18)	14 (28)	21 (23)
TEAE leading to study discontinuation	0	0	0	1 (10)	0	0	0	1 (1)
Serious TEAE	0	1 (7)	0	1 (10)	0	0	0	2 (2)
Serious TEAE related to study drug	0	0	0	0	0	0	0	0
TEAE resulting in death	0	0	0	0	0	0	0	0
TEAE of special interest[c]	5 (31)	1 (7)[d]	3 (16)	0	0	2 (6)	7 (14)	11 (12)

Note: Data are presented as number (%).
BID, Twice daily; *HS*, hora somni (at bedtime); *TEAE*, treatment-emergent adverse event.
[a]"Total APT-1011" refers to all subjects on active treatment.
[b]A TEAE is any adverse event that started or worsened in severity after the first dose of study drug in Part 1 of the study and prior to first dose of study drug in Part 2. Note: For maximum severity rows, if a subject had more than 1 TEAE, they were counted only once based on the maximum severity.
[c]TEAEs of special interest included events of candidiasis (oral, oropharyngeal, and esophageal) and events of abnormal morning cortisol; abnormal adrenocorticotropic hormone stimulation test; adrenal suppression.
[d]The TEAE of special interest was candidiasis.

associated with systemic side effects and suppression of endogenous cortisol.[19,36]

The study limitations include the small sample size for each dosing regimen, and the study was not powered for the secondary outcomes. The maintenance phase of the study did not include a placebo comparator, and subjects exited the study at Week 28 if their histology indicated >6 eos/hpf at Week 26. Despite these limitations, nominally significant and numerical trends were sufficient to select 3 mg HS to take forward into phase 3. Strengths of the study included the rigorous design, the inclusion of validated metrics and outcomes consistent with U.S. Food and Drug Administration guidance for EoE drug development,[36] and the duration of the trial (52 weeks overall), with associated comprehensive safety data. The lack of histologic response with placebo is additionally validating, as multiple cohort studies have shown that EoE does not histologically remit.[26,37]

Conclusion

In sum, the potential benefit of APT-1011, an FP ODT formulation for the treatment of EoE, was demonstrated in this phase 2b study. This was the most comprehensive dose-ranging study in the development of topical preparations for the treatment of EoE, showing the benefit of once-daily dosing with comparable histologic responses to twice-daily dosing. With minimal to no systemic absorption of swallowed FP, the sustained benefits observed with long-term treatment, together with the safety profile, make APT-1011 a promising maintenance treatment.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2022.02.013.

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Conflicts of interest
These authors disclose the following: Evan S. Dellon, Alfredo J. Lucendo, Alain M. Schoepfer, Gary W. Falk, and Ikuo Hirano have received research funding from Adare/Ellodi. Evan S. Dellon, Christoph Schlag, Alain M. Schoepfer, Gary W. Falk, and Ikuo Hirano have received consulting fees from Adare/Ellodi. Gina Eagle, James Nezamis, Gail M. Comer, and Karol Knoop are employees of Ellodi.

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Data transparency statement
Data were collected by the investigators and the database was managed by Adare/Ellodi. All authors had access to the study data and reviewed and approved the final manuscript. All analyses for the primary and pre-specified secondary outcomes were performed masked to allocation.

Supplementary Methods

Study Conduct

Screening and Run-in Phase (Day -56 to Day -1). The study design is presented in Supplementary Figure 1. The screening period was 4 weeks and included the subject's undergoing esophagogastroduodenoscopy (EGD) to assess endoscopic and histologic status, followed by a 4-week, single-blind baseline symptom assessment placebo run-in phase, after which eligible patients were randomized. Symptoms were collected using an electronic diary. Dysphagia episodes were recorded in real time or at the end of day (24-hour recall), including severity ratings for 3 symptoms (difficulty, discomfort, and pain) based on a numerical rating scale (0–10). These data collectively were used to evaluate the Patient-Reported Outcome Symptoms of EoE (PROSE). The Global EoE and Patient Global Impression of Severity (PGIS) questionnaires were also completed during the placebo run-in phase.

The study drug, both placebo and active forms, were identical in size, volume, color, texture, appearance, taste (ie, tasteless), and dispersibility. The tablet was to be placed in the subject's mouth, and the subject manipulated the tablet with their tongue until the tablet disintegrated completely. It was to be swallowed when fully disintegrated without biting or chewing. No rinsing with water or liquids was allowed after administration. Dosing occurred in the morning ("after breakfast"; $\geq$30 minutes after breakfast) and at night ("at bedtime"; $\geq$2 hours after the evening meal). The "at bedtime" (hora somni [HS]) dose of study drug was administered immediately prior to sleep, while lying in bed. All eating, drinking, and tooth brushing was to be completed prior to dosing. For the HS-dosing groups, placebo was administered for the morning dose.

There were no stopping rules for this study, based on the very low systemic exposure of fluticasone propionate and no anticipated adverse events per package inserts for these other products, to necessitate stopping rules.

Part 1: Induction (Day 1 to Week 14). In Part 1 of the study, subjects received their randomized treatment for 14 weeks. At Week 12, the EGD was repeated to evaluate endoscopic and histologic outcomes. Symptoms were also assessed using the PROSE, Global EoE Symptom Score, EoE Adult Quality of Life Questionnaire (EoE-QoL-A), EEsAI, PGIS, and Patient Global Impression of Change (PGIC) questionnaires. The EoE-QoL-A and EEsAI questionnaires were collected at randomization and Week 12. The Global EoE, PGIS, and PGIC were collected at randomization and Weeks 4, 8, and 12. The PROSE was collected continuously from randomization through Week 14.

Analysis after Week 12 based on histologic responder population at Week 12 only, continuing randomized dosage group from baseline. All histologic nonresponders at Week 12 were reallocated to receive 3 mg BID at Week 14 (when the responder status was determined based on histology results).

Part 2: Maintenance (Week 14 to Week 52). In Part 2 of the study, all subjects who were classified as histologic responders at Week 12 (as defined below) continued to be treated according to the dosing group to which they were randomized in Part 1. Histologic nonresponders received single-blind 3 mg APT-2011 BID. At Week 26, the EGD was repeated to evaluate endoscopic and histologic status. All subjects classified as histologic nonresponders at Week 26 stopped study drug and exited the study after a 2-week follow-up period. For subjects who remained in the study, the EGD was repeated to evaluate endoscopic and histologic status at Week 52, followed by a 2-week off-study-drug period. EoE-QoL-A and EEsAI questionnaires were collected at Weeks 26 and 52. The Global EoE, PGIS, and PGIC were collected at randomization and Weeks 18, 22, 26, 28, 36, 44, and 52. The PROSE was collected continuously through Week 52.

Analysis Sets

- Enrolled: all subjects who signed the informed consent form
- Intent-to-treat: all subjects randomized to study drug (analyzed as randomized)
- Full analysis set: all subjects randomized who received at least 1 dose of study drug (analyzed as randomized)
- Safety set: all subjects who received at least 1 dose of study drug (analyzed as treated)

Outcomes

Pathologic Assessment. Esophageal biopsies were read by a central lab. The primary outcome of histologic response was defined as the percentage of subjects with $\leq$6 peak eosinophils per high-power field (eos/hpf) after assessing at least 5 to 6 biopsies from the proximal and distal esophagus (approximately 3 each) where the hpf area was 235 square microns (40-magnification lens with a 22-mm ocular).

Endoscopic Reference Score. The endoscopist recorded the observed EREFS, which assessed edema (0, 1), furrowing (0, 1, 2), exudates (0, 1, 2), rings (0, 1, 2, 3), and strictures (0, 1), as well as several other features, including crepe paper esophagus, narrow-caliber esophagus, and esophageal erosions. For this study, the EREFS score ranged from 0 to 9 (sum of edema, furrowing, exudates, rings, and strictures), with higher scores indicating increased endoscopic severity. Change from baseline in EREFS was evaluated at Weeks 12, 26, and 52 of the study.

Patient-Reported Outcome Symptoms of EoE (PROSE). The PROSE diary was used to collect dysphagia episodes in real time and at the end of day.

A daily diary was completed by the subject to assess the presence of dysphagia and questions related to its severity and associated pain. The diary was completed by the subject for each episode and daily (in the evening) throughout the study. The daily diary asked questions comprising the PROSE. The study was used to define the measurement properties and definitions of symptom responder and nonresponder for future studies as outlined in the exploratory endpoints. The change in the number of dysphagia episodes at baseline (14-day period prior to randomization) was compared with the 14-day period prior to the time point of interest (Weeks 12, 26, and 52).

These data were self-reported electronically by the subject, transferred automatically to the electronic patient-reported outcome vendor, and transmitted thereafter to Data Management.

Symptom Metrics. The secondary outcome of the Global EoE Symptom Score showed greater improvements compared with placebo for all APT-1011 dosing groups, with nominal significance achieved by the 3-mg HS group as compared with placebo. At Week 12, mean Global EoE Symptom Score improved from baseline for all APT-1011 treatment regimens: 5.8 to 4.0 for 3 mg BID ($P = .653$ compared with placebo), 6.0 to 3.0 for 3 mg HS ($P = .048$), 5.8 to 4.3 for 1.5 mg BID ($P = .672$), and 5.6 to 2.6 for 1.5 mg HS ($P = .067$). Placebo mean Global EoE Symptom Score changed from 5.6 at baseline to 3.9 at Week 12. Reduction in mean Global EoE Symptom Score was maintained with continued improvement through Week 52 (Supplementary Figure 4).

The mean EEsAI total score from baseline to Week 12 was as follows for APT-1011 treatment regimens: 59.1 to 36.3 for 3 mg BID ($P = .043$ compared with placebo), 57.4 to 34.4 for 3 mg HS ($P = .020$), 59.9 to 45.0 for 1.5 mg BID ($P = .195$), and 55.5 to 35.6 for 1.5 mg HS ($P = .079$). Placebo mean EEsAI total score changed from 56.0 at baseline to 45.1 at Week 12. Reduction in mean EEsAI total score was maintained with continued improvement through Week 52 (Supplementary Figure 5). At Week 12, the percentage of subjects with an EEsAI total score of <20 was 26% for the 3-mg BID dosing regimen, 30% (3 mg HS), 5% (1.5 mg BID), 22% (1.5 mg HS), and 12% (placebo). These percentages improved for Part 1 histological responders through Week 52 (Supplementary Figure 6). In addition, all APT-1011 dosing groups showed improvement in PGIS and PGIC (Supplementary Figure 7).

Safety Outcomes. Safety outcomes included treatment-emergent adverse events (TEAEs), severity, TEAE leading to discontinuation, abnormal serum cortisol and adrenocorticotropic hormone stimulation test results, and discontinuation due to hypothalamic-pituitary-adrenal axis suppression. Investigators were instructed to monitor for signs of hypercorticism, and a list of symptoms and signs was provided.

Statistical Analysis. Secondary analysis methods included Bayesian hierarchical modeling of the primary efficacy endpoint. Logistic regression models, including dose, frequency, and dose-frequency interaction, were used to model the dose response.

Continuous efficacy endpoints were summarized with descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) and, when analyzed, an analysis of variance was used. Discrete efficacy endpoints were tabulated by number and percentage of subjects within each category and analyzed using the Cochran Mantel-Haenszel test. There was no formal statistical testing on the safety outcomes.

Supplementary List of Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) Consulted During the Conduct of the Study

United States. Copernicus Group (CGIRB)
Western IRB (WIRB)
University of Utah
Northwestern Medicine
Mayo Clinic IRB
Henry Ford Health
BRANY
Weill-Cornell Medical College
Canada. Health Canada
European Union. *Spain.* Agencia Española de Medicamentos y Productos Sanitarios
CEIC Hospital de Madrid
Germany. Medizinische Fakultät der Christian-Albrechts-Universität zu Kiel
Belgium. Federal Agency for Medicines and Health Products
Switzerland. Swiss Agency for Therapeutic Products, Swissmedic

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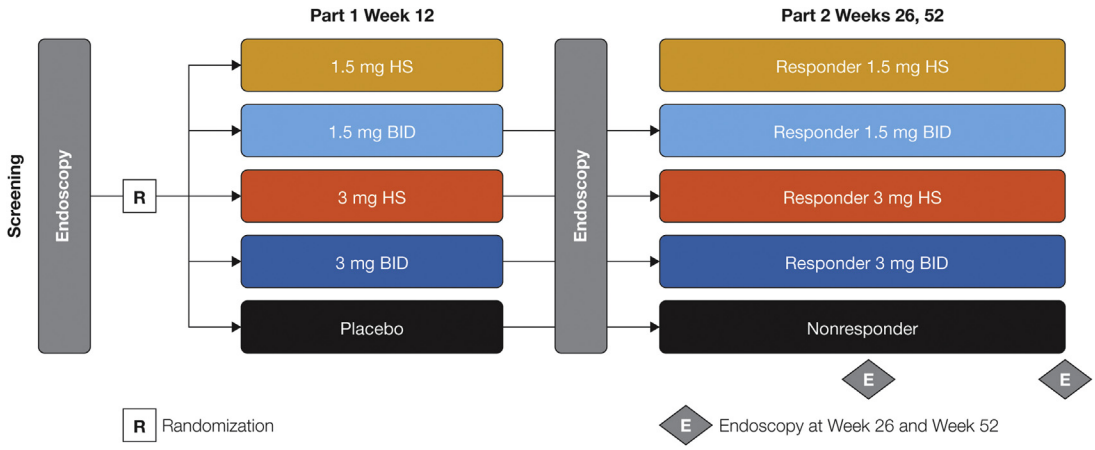
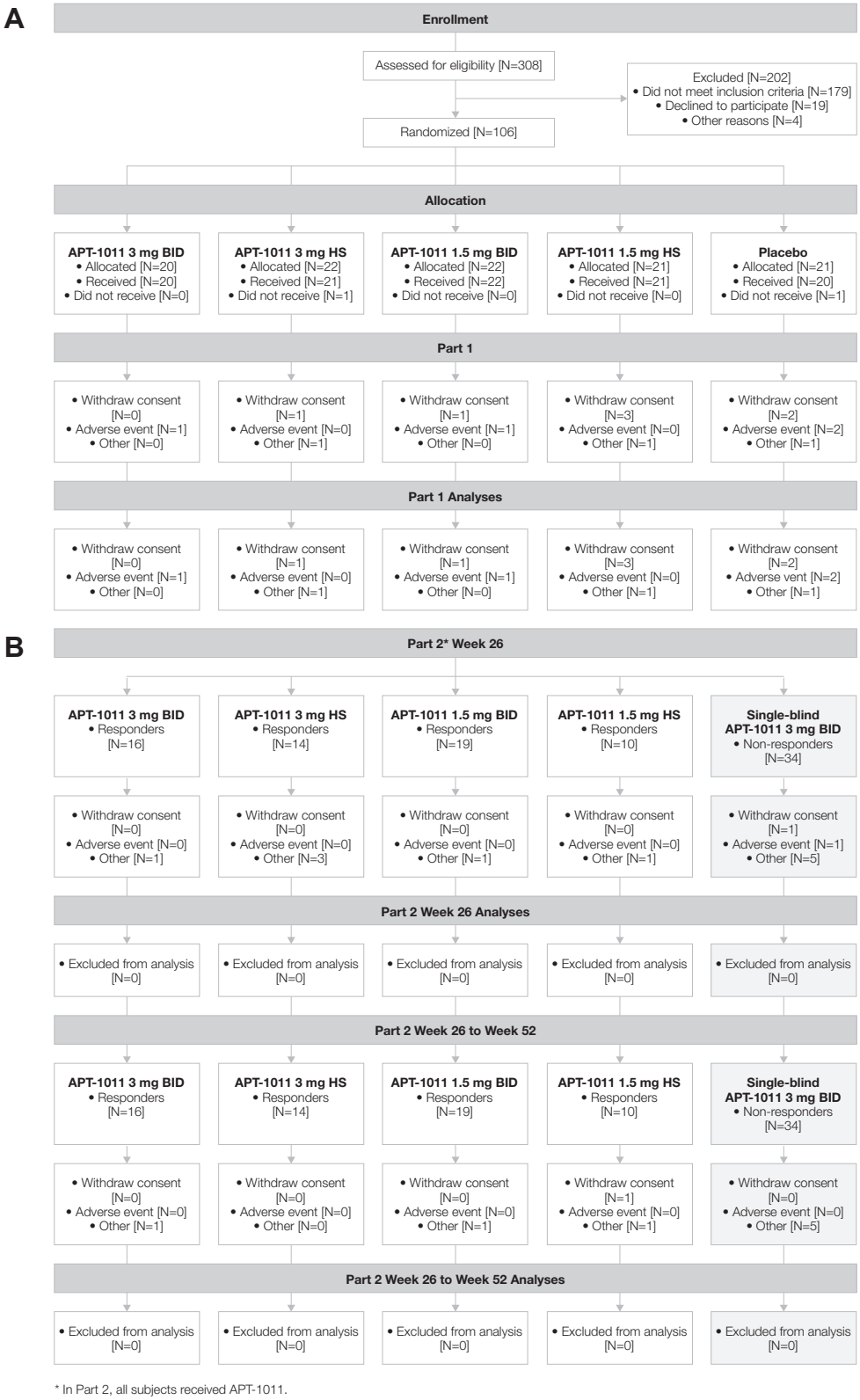
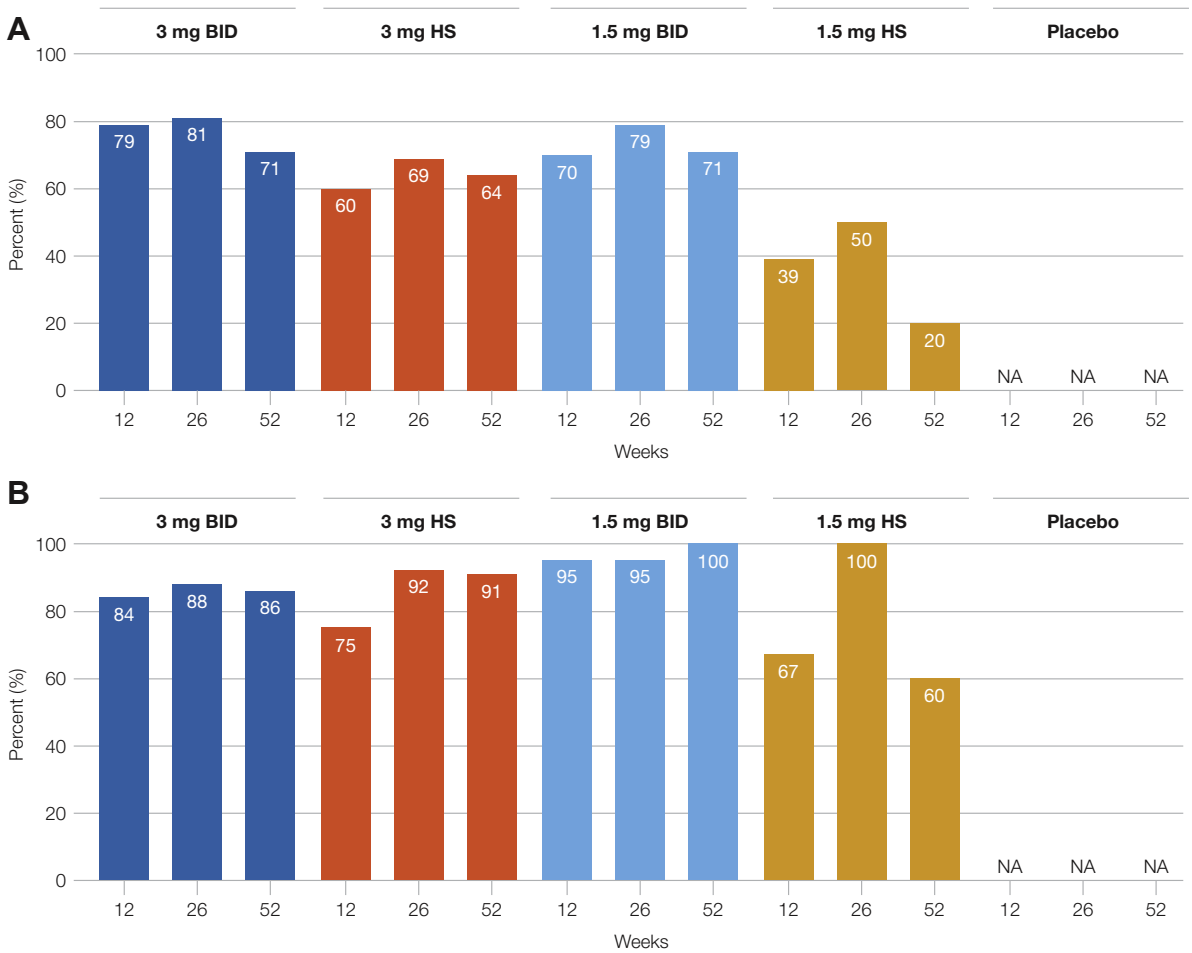


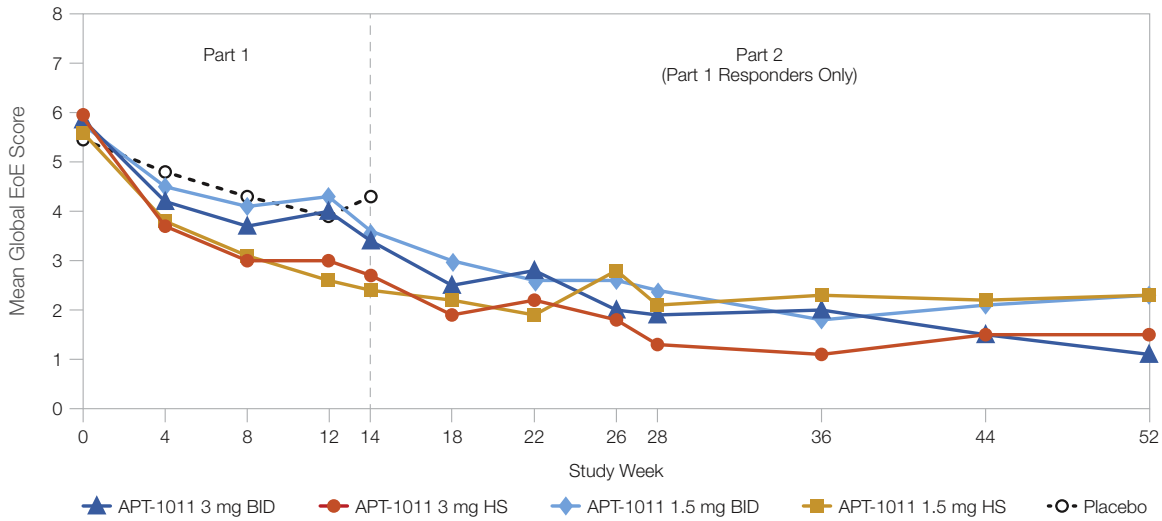
Supplementary Figure 1. Study design.



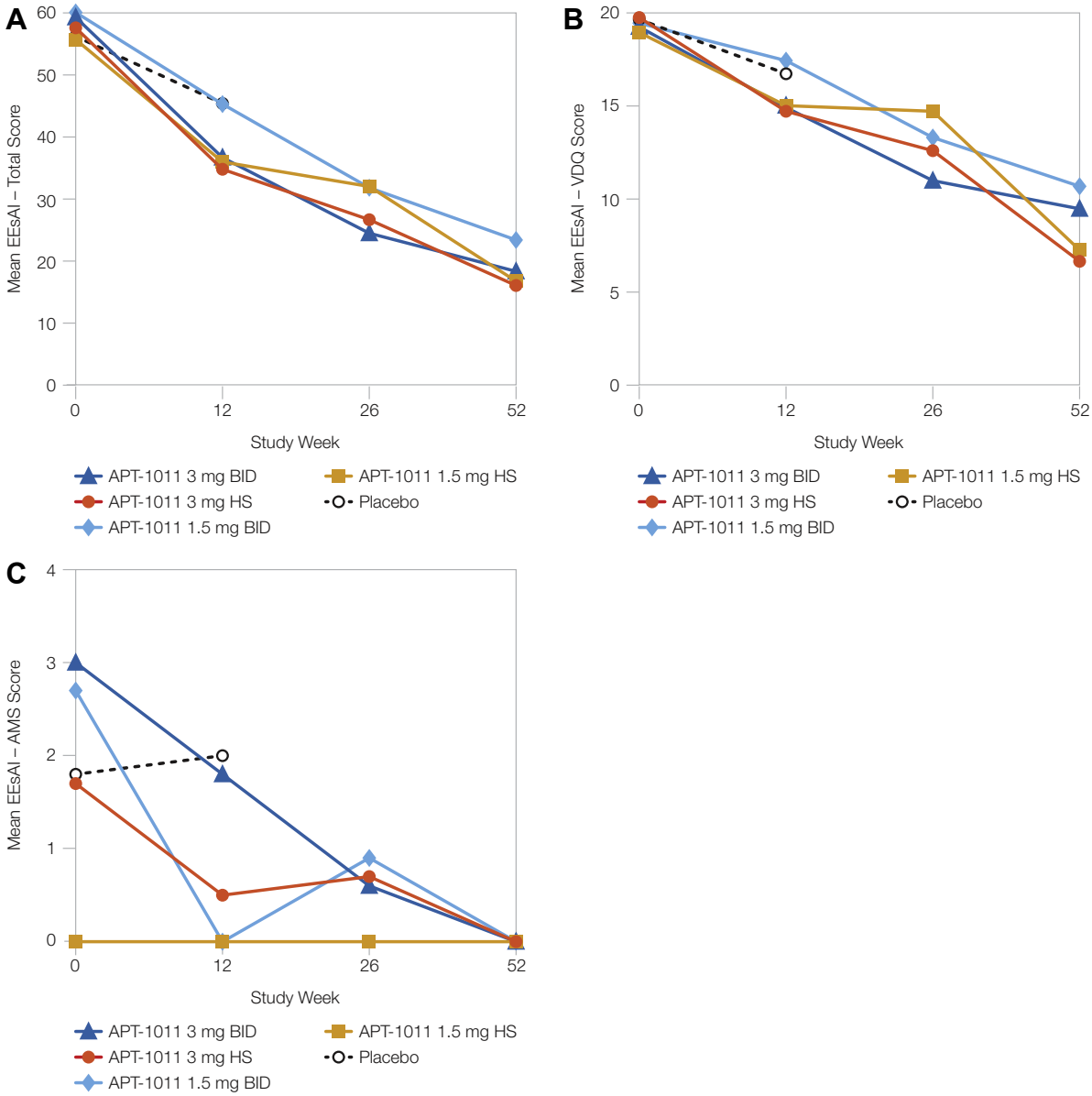
Supplementary Figure 2. Patient flow (intent-to-treat [ITT] population).



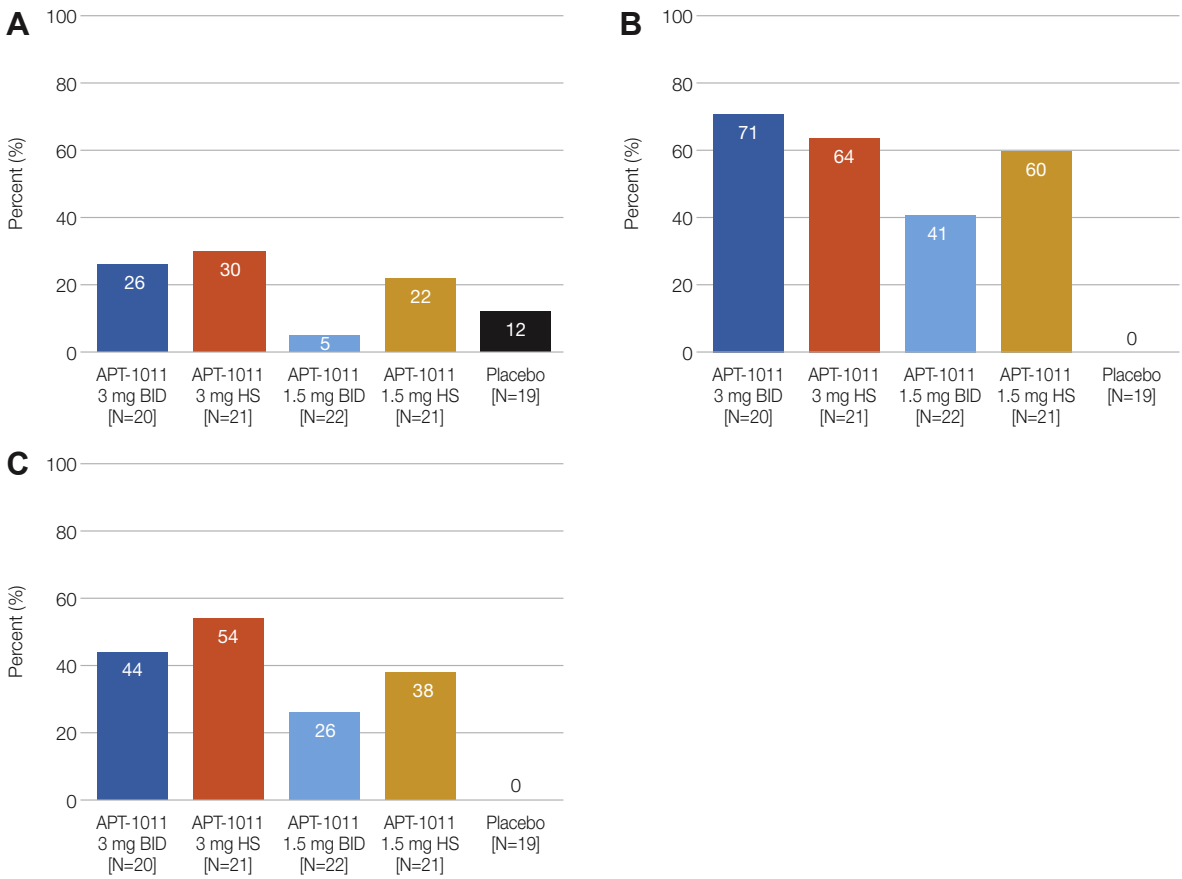
Supplementary Figure 3. *A*, Percentage of subjects with peak eos/hpf of <1 at Weeks 12, 26, and 52. *B*, Percentage of subjects with peak eos/hpf of <15 at Weeks 12, 26, and 52.



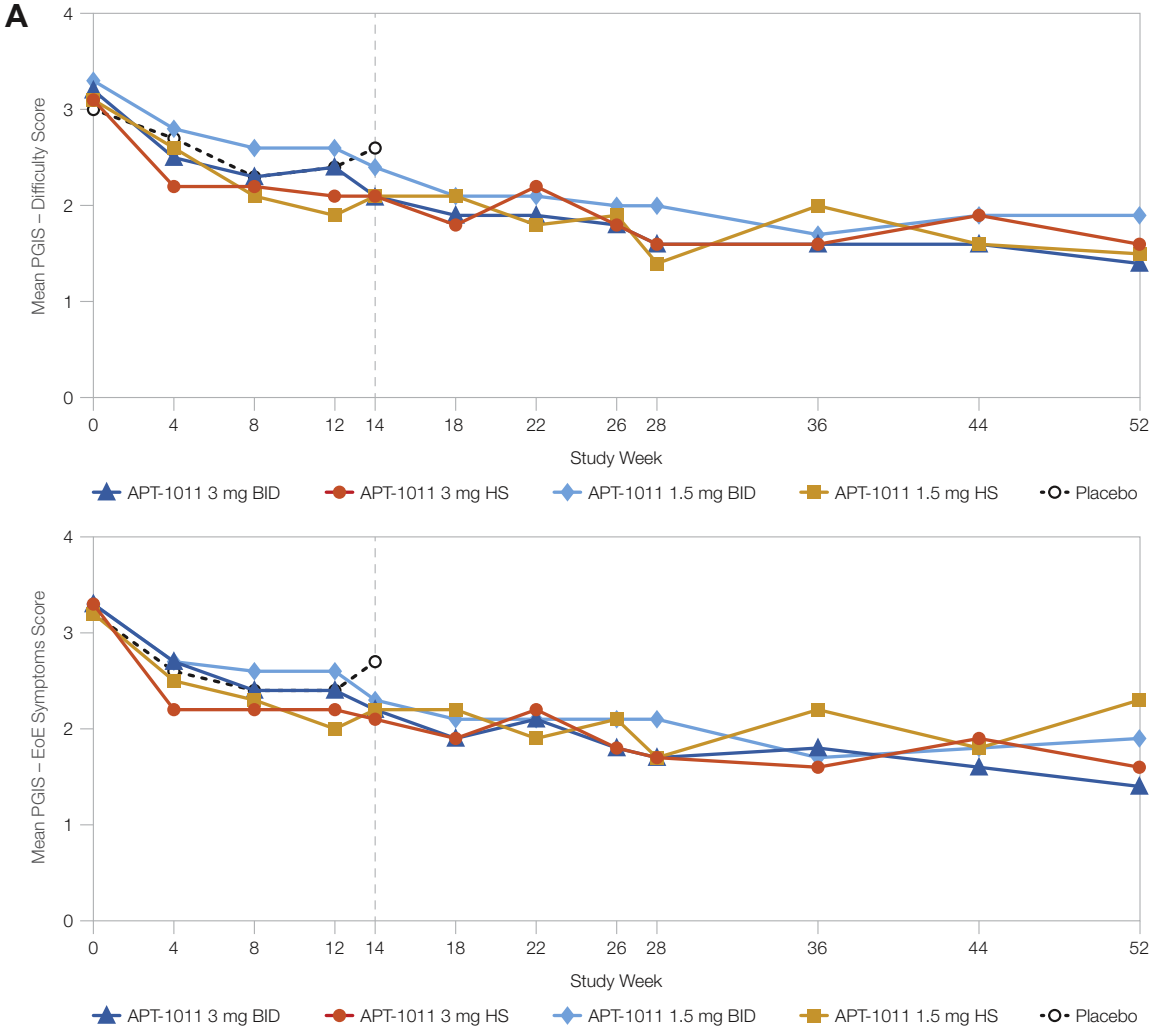
Supplementary Figure 4. Mean Global EoE Symptom Score over 52 weeks' induction and maintenance. Analysis after Week 12 based on histologic responder population at Week 12 only, continuing randomized dosage group from baseline. All histologic nonresponders at Week 12 were reallocated to receive 3 mg BID at Week 14 (when the responder status was determined based on histology results). Change from baseline Global EoE Symptom Score assessed prior to randomization, which was assessed for the 7-day period prior to the following study visits: Weeks 4, 8, 12, 14, 18, 22, 26, 28, 36, 44, and 52.



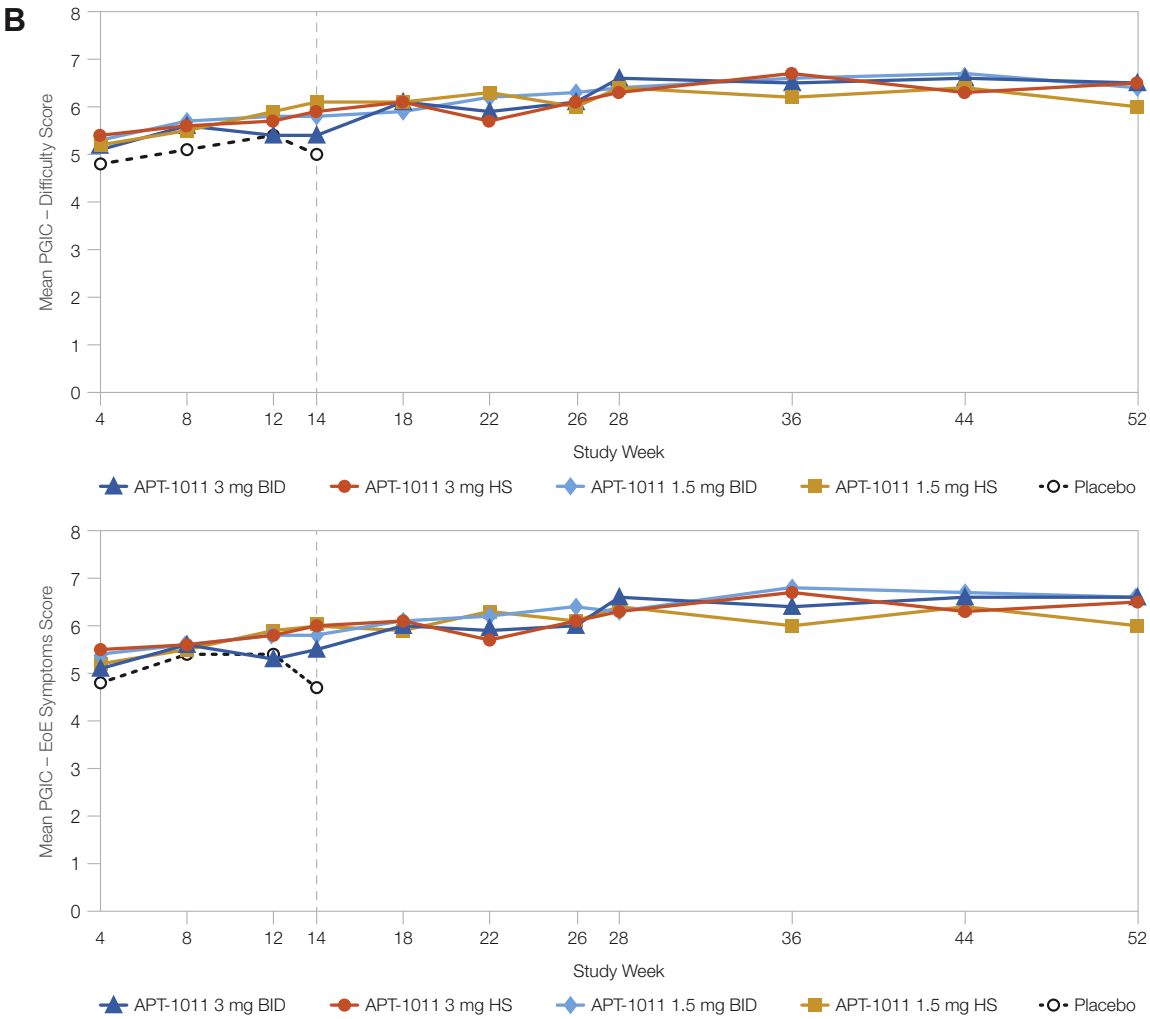
Supplementary Figure 5. Change from baseline 7-day EEsAI total score assessed prior to randomization to those assessed at Weeks 12, 26, and 52. *A*, Mean EEsAI Total Score. *B*, Mean EEsAI VDQ Score. *C*, Mean EEsAI AMS Score.



Supplementary Figure 6. Percentage of subjects with mean 7-day EEsAI total score of <20 at Weeks 12, 26, and 52. *A*, Mean 7-day EEsAI total score of <20 at Week 12. *B*, Mean 7-day EEsAI total score of <20 at Week 26. *C*, Mean 7-day EEsAI total score of <20 at Week 52.



Supplementary Figure 7. *A*, Change from baseline in mean PGIS assessed prior to randomization at Weeks 4, 8, 12, 14, 18, 22, 26, 28, 36, 44, and 52. *Panel 1*, Mean PGIS – Difficulty Score. *Panel 2,* Mean PGIS – EoE Symptoms Score. *B*, Mean PGIC assessed at Weeks 4, 8, 12, 14, 18, 22, 26, 28, 36, 44, and 52. *Panel 1*, Mean PGIC – Difficulty Score. *Panel 2*, Mean PGIC – EoE Symptoms Score.



Supplementary Figure 7. Continued.

Supplementary Table 1. Baseline and Change From Baseline in EREFS Total Score (Corrected) at Week 12 (Full Analysis Set)

Statistic[a]	APT-1011 3 mg BID (n = 20)	APT-1011 3 mg HS (n = 21)	APT-1011 1.5 mg BID (n = 22)	APT-1011 1.5 mg HS (n = 21)	Placebo (n = 19)
Number of patients	19	20	20	18	17
Baseline visit mean[b]	4.5	5.3	4.6	5.3	5.2
Mean change from baseline	−2.2	−3.2	−2.9	−2.4	−0.7
Standard deviation	1.84	2.28	1.92	1.85	1.31
Median change from baseline	−2.0	−3.0	−2.5	−2.0	−1.0
Minimum, maximum	−5, 1	−7, 0	−7, −1	−6, 1	−3, 2
LS mean difference compared with placebo	−1.66	−2.34	−2.40	−1.43	
90% confidence interval of LS mean difference	−2.52 to −0.80	−3.19 to −1.49	−3.25 to −1.55	−2.30 to −0.56	
1-sided *P* value	< .001	< .001	< .001	.004	

BID, Twice daily; *EREFS*, Edema/Rings/Exudates/Furrows/Strictures (EoE Endoscopic Reference Score); *HS*, hora somni (at bedtime); *LS*, least squares.
[a]LS mean differences, 90% confidence intervals, and 1-sided *P* values for comparisons of each APT-1011 dose group to placebo at Week 12 are from an analysis of covariance model including dosing group, history of or current presence of esophageal stricture (yes/no), prior positive steroid response to any corticosteroid treatment previously received to treat eosinophilic esophagitis (yes/no), geographic region (North America/Western Europe), history of asthma/allergy (yes/no), and proton pump inhibitor status (continuing into the study/not continuing into the study) as factors and EREFS at baseline as a covariate.
[b]The mean baseline value of subjects with data at the visit and at baseline.

Supplementary Table 2. Post Hoc Analysis: Response in Patients With Fibrostenosis

Dosing group	APT- 1011 3 mg BID	APT- 1011 3 mg HS	APT- 1011 1.5 mg BID	APT- 1011 1.5 mg HS	APT- 1011 Total	Placebo	*P* Value[a]
Subjects with strictures and/or grade 2 rings at baseline	n = 7	n = 11	n = 12	n = 13	n = 43	n = 13	
Stricture at Week 12, %	29	9	42	8	21	46	.075
Stricture and grade 2 rings at Week 12, %	0	0	0	0	0	15	.009
Stricture or grade 2 rings at Week 12, %	29	18	50	15	28	77	.002
Subjects with new strictures and/or rings at Week 12, %	0	0	0	0	0	8	.355

BID, Twice daily; *HS*, hora somni (at bedtime).
[a]*P* value from Cochran-Mantel-Haenszel test comparing APT-1011 total with placebo for those subjects with strictures and/or grade 2+ rings at baseline.

Supplementary Table 3A. TEAE of Candidiasis in Part 1[a]

	Double-blind dosing group					Total
	APT-1011 3 mg BID (n = 20)	APT-1011 3 mg HS (n = 21)	APT-1011 1.5 mg BID (n = 23)	APT-1011 1.5 mg HS (n = 21)	Placebo (n = 20)	APT-1011 (N = 85)
Esophageal candidiasis	6 (30)	0	2 (9)	0	0	8 (9)
Oral/oropharyngeal candidiasis	2 (10)	1 (5)	2 (9)	0	0	5 (6)

[a]The number of subjects who discontinued due to an adverse event of candidiasis was 2 (1 in the 1.5-mg BID group and 1 in the 3-mg BID group). All other subjects continued study drug, received anti-fungal medication, and reported resolution of the candidiasis. The subject receiving 3 mg HS in Part 1 who developed candidiasis is the same subject receiving 3 mg HS in Part 2 who reported it again.

Supplementary Table 3B. TEAE of Candidiasis in Part 2[a]

	Double-blind dosing group							
	APT-1011 3 mg BID (n = 16)	APT-1011 3 mg HS (n = 14)	APT-1011 1.5 mg BID (n = 19)	APT-1011 1.5 mg HS (n = 10)	Placebo (n = 0)	Single-blind APT-1011 3 mg BID (n = 34)	Total APT-1011 3 mg BID (n = 50)	Total (N = 93)
Esophageal candidiasis	3 (19)	0	1 (5)	0	0	1 (3)	4 (8)	5 (5)
Oral/oropharyngeal candidiasis	2 (13)	1 (7)	2 (11)	0	0	1 (3)	3 (6)	5 (5)

Note: Data are presented as number (%).
BID, Twice daily; *HS*, hora somni (at bedtime); *TEAE*, treatment-emergent adverse event.
[a]The number of subjects who discontinued due to an adverse event of candidiasis was 2 (1 in the 1.5-mg BID group and 1 in the 3-mg BID group). All other subjects continued study drug, received anti-fungal medication, and reported resolution of the candidiasis. The subject receiving 3 mg HS in Part 1 who developed candidiasis is the same subject receiving 3 mg HS in Part 2 who reported it again.

Supplementary Table 4A. TEAEs[a] in ≥1 Subject and ≥10% of APT-1011 Dosing Group During Part 1 by System Organ Class and Preferred Term Safety Analysis Population

System organ class preferred term	Double-blind dosing group					Total APT-1011 (N = 85)
	APT-1011 3 mg BID (n = 20)	APT-1011 3 mg HS (n = 21)	APT-1011 1.5 mg BID (n = 23)	APT-1011 1.5 mg HS (n = 21)	Placebo (n = 20)	
At least 1 TEAE	17 (85)	16 (76)	17 (7)	13 (62)	13 (65)	63 (74)
Number of TEAEs	44	35	34	40	27	153
At least 1 TEAE by system organ class and preferred term						
Infections and infestations	14 (70)	8 (38)	10 (44)	4 (19)	3 (15)	36 (42)
Nasopharyngitis	0	2 (10)	3 (13)	3 (14)	2 (10)	8 (9)
Esophageal candidiasis	6 (30)	0	2 (9)	0	0	8 (9)
Oral candidiasis	2 (10)	1 (5)	2 (9)	0	0	5 (6)
Vulvovaginal mycotic infection	2 (10)	0	0	0	0	2 (2)
Gastrointestinal disorders	5 (25)	9 (43)	6 (26)	3 (14)	4 (20)	23 (27)
Investigations	3 (15)	1 (5)	3 (13)	1 (5)	3 (15)	8 (9)
Musculoskeletal and connective tissue disorders	2 (10)	1 (5)	2 (9)	3 (14)	0	8 (9)
Back pain	2 (10)	1 (5)	0	2 (10)	0	5 (6)
Nervous system disorders	3 (15)	2 (10)	1 (4)	2 (10)	2 (10)	8 (9)
Headache	3 (15)	1 (5)	1 (4)	1 (5)	2 (10)	6 (7)
Injury, poisoning, and procedural complications	2 (10)	2 (10)[b]	1 (4)	1 (5)	0	6 (7)
Respiratory, thoracic, and mediastinal disorders	1 (5)	0	1 (4)	4 (19)	2 (10)	6 (7)
Psychiatric disorders	2 (10)	1 (5)	0	1 (5)	0	4 (5)

Note: Data are presented as number (%).
BID, Twice daily; *HS*, hora somni (at bedtime); *TEAE*, treatment-emergent adverse event.
[a]A TEAE was any adverse event that started or worsened in severity after the first dose of study drug in Part 1 of the study and prior to first dose of study drug in Part 2.
[b]One patient reported a laceration of his index finger; 1 patient reported a hamstring tear.

Supplementary Table 4B. TEAEs in ≥1 Subject and ≥10% of APT-1011 Dosing Group During Part 2 by System Organ Class and Preferred Term Safety Analysis Population

System organ class preferred term	Double-blind dosing group					Single-Blind APT-1011 3 mg BID (n = 34)	Total APT-1011 3 mg BID (n = 50)	Total (N = 93)
	APT-1011 3 mg BID (n = 16)	APT-1011 3 mg HS (n = 14)	APT-1011 1.5 mg BID (n = 19)	APT-1011 1.5 mg HS (n = 10)	Placebo (n = 0)			
At least 1 TEAE	12 (75)	13 (93)	14 (74)	7 (70)	0	22 (65)	34 (68)	68 (73)
Number of TEAEs	54	35	39	30	0	63	117	221
At least 1 TEAE by system organ class and preferred term								
Infections and infestations	11 (69)	6 (43)	12 (63)	6 (60)	0	9 (27)	20 (40)	44 (47)
Nasopharyngitis	5 (31)	0	1 (5)	2 (20)	0	4 (12)	9 (18)	12 (13)
Esophageal candidiasis	3 (19)	0	1 (5)	0	0	1 (3)	4 (8)	5 (5)
Oral candidiasis	2 (13)	0	2 (11)	0	0	1 (3)	3 (6)	5 (5)
Upper respiratory tract infection	2 (13)	1 (7)	2 (11)	0	0	0	2 (4)	5 (5)
Gastroenteritis	1 (6)	0	2 (11)	1 (10)	0	0	1 (2)	4 (4)
Pharyngitis	2 (13)	0	1 (5)	0	0	0	2 (4)	3 (3)
Viral upper respiratory tract infection	0	2 (14)	0	0	0	1 (2)	1 (2)	3 (3)
Influenza	0	0	2 (11)	0	0	0	0	2 (2)
Gastrointestinal disorders	4 (25)	2 (14)	5 (26)	3 (30)	0	13 (38)	17 (34)	27 (29)
Musculoskeletal and connective tissue disorders	5 (31)	1 (7)	4 (21)	3 (30)	0	2 (6)	7 (14)	15 (16)
Back pain	1 (6)	0	2 (11)	0	0	1 (3)	2 (4)	4 (4)
Pain in extremity	2 (13)	0	0	1 (10)	0	0	2 (4)	3 (3)
Investigations	4 (25)	4 (29)	1 (5)	1 (10)	0	4 (12)	8 (16)	14 (15)
Cortisol decreased	1 (6)	1 (7)	0	1 (10)	0	2 (6)	3 (6)	5 (5)
Nervous system disorders	1 (6)	4 (28)	2 (10)	2 (20)	0	2 (6)	3 (6)	11 (12)
Headache	1 (6)	2 (14)	1 (5)	1 (10)	0	2 (6)	3 (6)	7 (8)
Respiratory, thoracic, and mediastinal disorders	2 (13)	2 (14)	1 (5)	2 (20)	0	1 (3)	3 (6)	8 (9)
Injury, poisoning, and procedural complications	2 (13)	3 (21)	0	0	0	2 (6)	4 (8)	7 (8)
Reproductive system and breast disorders	1 (6)	2 (14)	1 (5)	1 (10)	0	2 (6)	3 (6)	7 (8)
Skin and subcutaneous tissue disorders	2 (13)	1 (7)	0	1 (10)	0	3 (9)	5 (10)	7 (8)

Supplementary Table 4B. Continued

System organ class preferred term	Double-blind dosing group					Single-Blind APT-1011 3 mg BID (n = 34)	Total APT-1011 3 mg BID (n = 50)	Total (N = 93)
	APT-1011 3 mg BID (n = 16)	APT-1011 3 mg HS (n = 14)	APT-1011 1.5 mg BID (n = 19)	APT-1011 1.5 mg HS (n = 10)	Placebo (n = 0)			
General disorders and administration site conditions	2 (13)	1 (7)	0	0	0	2 (6)	4 (8)	5 (5)
Psychiatric disorders	2 (13)	1 (7)	0	0	0	1 (3)	3 (6)	4 (4)
Anxiety	2 (13)	0	0	0	0	0	2 (4)	2 (2)
Metabolism and nutrition disorders	1 (6)	2 (14)	0	0	0	0	1 (2)	3 (3)
Vascular disorders	0	1 (7)	2 (11)	0	0	0	0	3 (3)
Hypertension	0	1 (7)	2 (11)	0	0	0	0	3 (3)

Note: Data are presented as number (%).
BID, Twice daily; *HS*, hora somni (at bedtime); *TEAE*, treatment-emergent adverse event.

Supplementary Table 5A. Subjects With Abnormal Cortisol and ACTH Stimulation Test Results in Part 1 (Safety Analysis Population)

Double-blind dosing group	APT-1011 3 mg BID (n = 20)	APT-1011 3 mg HS (n = 21)	APT-1011 1.5 mg BID (n = 23)	APT-1011 1.5 mg HS (n = 21)	Placebo (n = 20)
Serum cortisol level ≤5 μg/dL (≤138 nmol/L)	0	0	0	0	0
Abnormal ACTH stimulation test result: serum cortisol level <16 μg/dL (≤440 nmol/L)	0	0	0	0	0
Discontinued due to HPA axis suppression	0	0	0	0	0
Discontinuation due to abnormal ACTH stimulation test result	0	0	0	0	0

Supplementary Table 5B. Subjects With Abnormal Cortisol and ACTH Stimulation Test Results in Part 2 (Safety Analysis Population)

Double-blind dosing group	APT-1011 3 mg BID (n = 16)	APT-1011 3 mg HS (n = 14)	APT-1011 1.5 mg BID (n = 19)	APT-1011 1.5 mg HS (n = 10)	Placebo (n = 0)	Single-blind APT-1011 3 mg BID (n = 34)
Serum cortisol level ≤5 μg/dL (≤138 nmol/L), n (%)	6 (38%)	4 (29%)	1 (5%)	4 (44%)	0	10 (32%)
Abnormal ACTH stimulation test result: serum cortisol level <16 μg/dL (≤440 nmol/L), n (%)	4 (25%)	1 (8%)	2 (11%)	0	0	3 (10%)
Discontinued due to HPA axis suppression, n (%)	0	0	0	0	0	0
Discontinuation due to abnormal ACTH stimulation test result, n (%)	0	0	0	0	0	0

Note: Data are presented as number (%).
ACTH, Adrenocorticotropic hormone; *BID*, twice daily; *HPA*, hypothalamic-pituitary-adrenal axis; *HS*, hora somni (at bedtime).