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TITLE: Randomised clinical trial: the safety and tolerability of fluticasone propionate orally disintegrating tablets versus placebo for eosinophilic oesophagitis

Running Title: Eosinophilic oesophagitis fluticasone trial

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IH: study concept, review, and interpretation of data; writing of study report; and final approval. ES: study concept, analyses, review, and interpretation of data; writing of study report; and final approval; MCR: analyses, review, and interpretation of data; writing of study report; and final approval. GMC: review and interpretation of data; writing of study report, draft manuscript, and final approval; GE: review and interpretation of data, writing of study report, and final approval. AS: study concept, review and interpretation of data, writing of study report, and final approval. GWF: study concept, review and interpretation of data, writing of study report, and final approval.

All authors approved the final version of the manuscript, including the authorship list.

Conflict of Interest

IH has served as a consultant for Adare, Allakos, EsoCap, Receptos, Regeneron, and Shire Pharmaceuticals. He has received research funding from Adare, Allakos, Receptos, Regeneron, and Shire. GMC is a consultant for Adare. ES has served as a consultant for Adare, Aptalis, Novartis, Receptos, and Regeneron. MCR has no conflicts of interest to report. AS has served as consultant for AbbVie, Adare, Falk Pharma GmbH, MSD, Receptos, Regeneron, Novartis, Pfizer, Takeda, Vifor. He received research funding from Adare, Falk Pharma GmbH, Receptos, Regeneron. GWF has received research support from Allakos, Receptos/Celgene, and Regeneron. He has received research support and has served as a consultant for Adare and Shire/Takeda. GE has served as a consultant for and is currently employed by Adare.

SUMMARY

Background: APT-1011, a fluticasone propionate orally disintegrating tablet formulation, is under investigation for the treatment of eosinophilic oesophagitis (EoE).

Aims: To evaluate the safety and tolerability of APT-1011 administered to patients with EoE and to assess the effect on clinical symptoms of EoE, endoscopic appearance, and oesophageal eosinophilia.

Methods: A randomised, double-blind, placebo-controlled, multicentre, phase 1b/2a study was conducted at 7 medical centres in the US to evaluate the safety and tolerability of APT-1011 over 8 weeks in adults and adolescents with EoE. Participants were randomised to placebo (n=8), 1.5 mg APT-1011 BID (n=8) or 3.0 mg APT-1011 QD (n=8). Safety and tolerability were assessed as the primary outcome; histologic and endoscopic measures were assessed as exploratory outcomes.

Results: There were no deaths, serious treatment-emergent adverse events (TEAEs), severe TEAEs, or discontinuations from the study related to a TEAE. In one participant randomised to 1.5 mg APT-1011 BID, a reduction in cortisol was observed, but without evidence of adrenal insufficiency. Compared to placebo, treatment with APT-1011 resulted in greater reductions in oesophageal eosinophil counts, EoE Endoscopic Reference Score, patient global assessment, and symptom-based EoE activity index from baseline to end of treatment (Week 8).

Conclusions: APT-1011 was safe and well tolerated in adolescents and adults with EoE. Exploratory efficacy outcomes demonstrated improvement in histologic and endoscopic

findings as well evidence of symptom improvement. The results of this study support the continued development of APT-1011 for the treatment of EoE (NCT-01386112).

Keywords: eosinophilic oesophagitis; gastroesophageal reflux disease; oral topical corticosteroid; fluticasone propionate

Abbreviations: symptom-based Eosinophilic Esophagitis Activity Index (EEsAI); proton pump inhibitor (PPI); patient-reported outcomes (PRO); eosinophilic oesophagitis (EoE); Food and Drug Administration (FDA); United States (US); EoE Endoscopic Reference Score (EREFS); high-power field (HPF).

INTRODUCTION

Although currently classified as an orphan disease, EoE is an increasingly prevalent atopic condition characterised by symptoms of oesophageal dysfunction and infiltration of eosinophils into the oesophageal mucosa.[1–4] Untreated EoE can progress from inflammation to a mix of inflammatory and fibrostenotic disease with oesophageal remodelling that manifests by subepithelial fibrosis, oesophageal stricture formation, and reduced oesophageal distensibility.[5–8] In the United States (US) and several countries in Western Europe, EoE is now recognised as a leading cause of dysphagia and food impaction in adults.[9]

Currently, there are no US Food and Drug Administration (FDA)-approved pharmacologic treatments for EoE, so all pharmaceutical treatments are currently being used off-label.[10] Elimination diets are considered a first-line treatment option for EoE but can adversely affect meal-related quality of life and have demonstrated limited sustained adherence in some studies.[11,12] Common first-line treatments for EoE are swallowed topical corticosteroids, such as fluticasone propionate or budesonide.[1,13,14] In clinical practice in the US, the available aerosolised or nebulised corticosteroids, designed for airway delivery, are ingested by patients. Alternatively, liquid preparations of topical corticosteroids, designed for nebuliser use, have been mixed into a viscous slurry and swallowed by patients.[3,15] While the initial results of swallowed aerosolised corticosteroid treatment for EoE have demonstrated efficacy, variation in dose, administration technique, and/or compliance can affect the outcomes of therapy.[3] Additionally, administration of swallowed aerosolised topical corticosteroids may be suboptimal for treatment of EoE, as the aerosolised preparation is delivered to both the lungs and the oesophagus.[16] Oral drug delivery and formulation can also have an effect on relevant outcomes, such as complete histologic remission, as seen with a swallowed viscous liquid vs a swallowed, nebulised preparation of budesonide (64% vs 27%).[16]

APT-1011 is a fluticasone propionate tablet that dissolves in the mouth and is swallowed without liquids. APT-1011 was developed to specifically address the unmet therapeutic need for EoE. The objectives of this proof-of-concept study were to evaluate the safety and tolerability of 2 dosing regimens of APT-1011 administered orally to patients with EoE and to assess the effect of APT-1011 on clinical symptoms of EoE, endoscopic appearance, and oesophageal mucosal eosinophil count.

METHODS

A randomised, double-blind, placebo-controlled, multicentre, phase 1b/2a study was conducted at 7 medical centres in the US to evaluate the safety and tolerability of APT-1011 (Adare Pharmaceuticals, Inc, Lawrenceville, NJ [formerly Aptalis Pharma US, Inc.]) over 8 weeks in adults and adolescents with EoE (ClinicalTrials.gov registration #NCT01386112). The study was conducted in accordance with the principles set forth in the Declaration of Helsinki and in compliance with International Conference on Harmonization—Good Clinical Practice standards. The study protocol was approved by Copernicus Group Independent Review Board (protocol #PR-021; 01 September 2011).

Eligibility Criteria

Eligible patients between 12 and 55 years age had histologically confirmed EoE (oesophageal mucosal peak eosinophil count ≥ 24 per high-power field (HPF) [HPF; radius=0.275 mm; 400×] in at least 1 biopsied site, within 30 days prior to and 21 days after the screening visit), histologically confirmed prior treatment failure of a high-dose proton pump inhibitor (PPI), defined as peak eosinophil counts ≥24 per HPF after 8 weeks of 2× standard PPI dose per investigator, and at least one of the following symptoms: chest pain or discomfort, dysphagia, or food impaction continuously or intermittently present within 30 days prior to the screening visit. Specific symptom severity was not required for this study. Females of childbearing potential must have agreed to use adequate contraception during the study and could not be pregnant or lactating at time of enrolment. Written informed consent was obtained from each participant or caregiver/parent/guardian at screening.

Patients were excluded from participating in the study if they met any of the following criteria: presence of any condition, other than EoE, that affected the oesophageal mucosa or motility; any contraindication to completing oesophagogastroduodenoscopy, including stricture that blocked the passage of a standard endoscope; history or presence of Crohn's disease, celiac disease, or other gastrointestinal inflammatory disease; use of systemic, inhaled, intranasal, or high-potency dermal topical corticosteroids during the 30 days prior to enrolment; morning serum cortisol level ≤ 5 μg/dL; or use of anti-inflammatory or immunosuppressant drugs.

Randomisation

Participants were randomised 1:1:1 to APT-1011 at 1.5 mg BID, APT-1011 at 3.0 mg QD, or placebo by a blinded study coordinator, according to a computer-generated list of randomisation numbers, with a block size of 3. A unique randomisation number was assigned to each participant in sequential order of enrolment. All study site personnel, including the endoscopist, the central pathologist, the participants/caregivers, and the sponsor, were blinded to the treatment groups.

Interventions

Participants were given 2 bottles—1 for the morning dose, and 1 for the evening dose—and were instructed to take their morning dose at least 30 minutes before food intake and their evening dose at least 30 minutes after a meal. Participants were instructed not to drink or eat for 30 minutes after each dose. The placebo group had a placebo tablet in both morning and evening bottles; the APT-1011 1.5 mg BID group had a 1.5-mg fluticasone propionate tablet in both morning and evening bottles; and the

APT-1011 3.0 mg QD group had a placebo tablet in the morning bottle, and a 3.0-mg fluticasone propionate tablet in the evening bottle. Participants were instructed to place the tablet on the tongue until it dissolved completely and to swallow until it was completely ingested (i.e. no visible drug), then to thoroughly rinse mouth with water (i.e., rinse and spit) to remove any residual fluticasone propionate from the oral cavity. Participants were allowed to continue PPI therapy if they met the histology inclusion criteria above (oesophageal mucosal peak eosinophil count ≥ 24 per HPF) and had a stable PPI dose for at least 30 days prior to study enrolment. Antihistamines were permitted if the participant required them for a medical condition.

Endpoints

The primary endpoint was safety and tolerability of APT-1011, as assessed by treatment-emergent adverse events (TEAEs), morning serum cortisol and salivary cortisol levels, laboratory tests (haematology, serum chemistry, liver function tests, urinalysis, and urine chemistry), physical examination, and vital signs at Weeks 2, 4, 6, 8, and at follow-up.

Exploratory efficacy endpoints were also measured. At screening and at Week 8, participants underwent oesophagogastroduodenoscopy during which 2 to 4 biopsies from the distal, middle and/or the proximal oesophagus were taken. Oesophageal eosinophil counts per HPF in all parts of the oesophagus were assessed. Endoscopic appearance of the oesophagus was evaluated by a treatment-blinded endoscopist. The endoscopist graded the presence and severity of oedema (decreased vascular markings), rings, exudates, furrows, felinization, linear shearing, and stricture(s) in

accordance with the endoscopic reference score (EREFS) grading and classification system.[17] Total EREFS was calculated by summing the severity scores of the individual components (oedema 0-1, rings 0-3, exudates 0-2, furrows 0-2, strictures 0-1) assessed separately for both the proximal and distal oesophagus (ranges 0-18, with higher scores indicating more severe endoscopic findings).

Questionnaires developed for the Eosinophilic Esophagitis Activity Index (EEsAI) study were adapted for use in this clinical trial. The following were completed prospectively by the study participants and the physicians[18]: EREFS grading and classification system completed by the endoscopist at screening and at Week 8; Physician Global Assessment completed by the investigator at randomisation, Week 4, and Week 8; EEsAI patient-reported outcomes (PRO) instrument[18] with 7-day recall period, and Patient Global Assessment with 7-day recall period completed at randomisation, Week 4, and Week 8 by the patient; and Pathologist Questionnaire (querying presence of various histologic features in biopsies obtained in distal, proximal, and/or middle part of the oesophagus) completed at screening and at Week 8.

The Physician Global Assessment of the participant's overall EoE activity (Likert scale 0–10, where 0 signifies no EoE activity and 10 represents the most severe EoE activity) takes into account participant-reported symptoms, endoscopic findings, and histologic activity. Study participants provided the Patient Global Assessment of symptom severity and EEsAI PRO (score range 0–100, score increases with increasing symptom severity)[18] at randomisation, Week 4, and Week 8. Participants also completed the Mayo Dysphagia Questionnaire-30[19,20] and the Gastrointestinal Symptom Rating Scale Questionnaire[21] at randomisation, Week 4, and Week 8.

Statistical Analysis

All statistical analyses were performed using the statistical program R (version R3.3.1).

The sample size of 24 participants (8 per group) was expected to provide sufficient observation to assess safety and tolerability. As formal sample size calculations were not performed for the study, the analyses presented here can only be considered directional. All efficacy analyses are based on the intent-to-treat (ITT) population. All randomised participants received at least 1 dose of a study drug, had at least 1 efficacy measure, and were included in all safety and efficacy analyses.

TEAEs were summarised by treatment group, according to preferred term from the Medical Dictionary for Regulatory Activities (MedDRA, version 14.0).

As per protocol, the mean, median, min, and max values of distal and proximal eosinophil counts per HPF (for subjects in whom these values were available and stratified by participant treatment group) are reported at baseline and at Week 8. Change over time in the mean and median values of these counts also are presented. A participant was considered to show a response to treatment if the peak eosinophil count decreased from >24 to <15 eosinophils/HPF and a complete response if the peak eosinophil count decreased from >24 to 0 eosinophils/HPF at Week 8.

Additional exploratory post-hoc analyses were carried out in line with current reporting standards. Study participants were first categorized into 3 treatment groups: placebo, APT-1011 at 1.5 mg BID, and APT-1011 at 3.0 mg QD. We also categorized study participants into placebo and APT-1011–treated groups (the APT-1011 at 1.5 mg

BID and the APT-1011 at 3.0 mg QD groups combined). For each patient at each visit we calculated the mean and median value of the EREFS, the EEsAI PRO score (scoring system was published after protocol development and study completion), and the overall inflammatory burden by taking peak eosinophils/HPF value from proximal, middle, and distal oesophagus. Changes in EREFS, EEsAI PRO score, Patient Global Assessment, and maximum peak oesophageal eosinophils/HPF from baseline to Week 8 were calculated as the difference between the value observed at Week 8 and baseline. The variation in these changes was analysed using linear regression models that included the effect of treatment with APT-1011 (relative to placebo) and adjustment for the baseline value. We first investigated the effect of treatment on the change in these values by comparing the patients from the 3 treatment groups: placebo, APT-1011 at 1.5 mg BID, and APT-1011 at 3.0 mg QD. Additionally, we combined the patients from both APT-1011–treated groups. We compared the change in values in APT-1011–treated patients with those in placebo group. A *P*-value of <.05 was considered to be significant.

RESULTS

The study was performed between October 2011 and October 2012. Twenty-four participants were randomised, and 22 participants completed the study (Figure 1). Demographic and baseline characteristics were largely similar between the treatment groups (Table 1); however, there was a higher percentage of participants in the placebo group who experienced continuous dysphagia. More than half of the participants continued to use PPI therapy during the study.

Safety and Tolerability

There were no deaths, serious TEAEs, severe TEAEs, or discontinuations from the study related to a TEAE. A total of 41 TEAEs were reported by 18 participants: 12 participants receiving APT-1011 reported 26 TEAEs, and 6 participants receiving placebo reported 15 TEAEs. Two participants on placebo discontinued due to TEAEs. A total of 3 TEAEs were considered by a treatment-blinded investigator to be possibly related to the study drug: 2 participants receiving APT-1011 at 3.0 mg QD and 1 participant receiving placebo reported a TEAE of decreased blood cortisol (Table 2). Two participants had an adverse event of special interest, adrenal suppression: 1 participant receiving placebo and 1 participant receiving APT-1011 at 1.5 mg BID. In the participant receiving APT-1011 at 1.5 mg BID, serum cortisol levels were 27.7 µg/dL at baseline and 4.8 µg/dL at Day 27. The participant did not report any associated symptoms or signs of adrenal insufficiency, and results of a subsequent adrenocorticotropic hormone stimulation test were within normal limits. The adverse event was reported due to low cortisol value, but no adrenal insufficiency was present.

The participant receiving placebo who had adrenal suppression had used systemic steroid therapy, in violation of the study protocol, and had a serum cortisol of 2.6 µg/dL; this participant was diagnosed with adrenal insufficiency unrelated to study drug.

There were no reports of oral or oesophageal candidiasis in either APT-1011 treatment group or the placebo group. Besides the changes in cortisol levels described above, there were no clinically meaningful changes in laboratory values, vital signs, or findings of physical examination during the 8-week study.

Efficacy

Histology

Prespecified analyses

The mean/median eosinophil counts in the proximal and distal oesophagus and changes in these values from baseline to Week 8 in the ITT population are shown in Table 3. The median peak eosinophils/HPF in patients who received APT-1011 at 1.5 mg BID was reduced by 92% in the distal oesophagus and by 100% in the proximal oesophagus from screening to Week 8 (Distal eosinophils/HPF: screening = 39.0, Week 8 = 3.0; proximal eosinophils/HPF: screening = 47.0, Week 8 = 0). The median peak eosinophils/HPF in participants who received APT-1011 at 3.0 mg QD was reduced by 63% in the distal oesophagus and by 97% in the proximal oesophagus from screening to Week 8 (Distal eosinophils/HPF: screening = 65.5, Week 8 = 24.5; proximal eosinophils/HPF: screening = 29.5, Week 8 = 1.0). With placebo treatment, reductions in eosinophil counts over 8 weeks were less than in the active treatment groups (12% reduction in median eosinophils/HPF in the distal oesophagus and 0% reduction in the

proximal oesophagus). Histologic response rates based on a reduction from ≥24 eosinophils/HPF at screening to ≤15 eosinophils/HPF at Week 8 and a complete histologic response (0 eosinophils/HPF) at Week 8 are shown in Figure 2A.

Post-hoc Analyses

The maximal peak eosinophils/HPF in the oesophagus overall at baseline and Week 8 is shown in Figure 2B (baseline values are shown in Supplementary Table 1). When comparing each of the APT-1011–treated groups to placebo, differences in changes in maximal eosinophils/HPF from baseline to end of treatment were observed. Participants treated with APT-1011 at 1.5 mg BID had a greater reduction in eosinophils/HPF from baseline than placebo-treated participants (coefficient, -47.05; 95% confidence interval [CI]: -82.67, -1.02; *P* = .012). Participants treated with APT-1011 at 3.0 mg QD had a greater reduction in eosinophils/HPF from baseline than placebo-treated participants (coefficient, -38.2; 95% CI: -73.94, -1.02; *P* = .037).

The results of linear regression analyses for changes in maximal peak eosinophils/HPF in combined APT-1011–treated groups relative to the placebo-treated group are shown in Supplementary Table 2.

Endoscopic Appearance

Prespecified analyses

Endoscopic features reflecting acute inflammation (including oedema, exudates, and furrowing) demonstrated the greatest differences between placebo- and APT-1011–treated participants, as shown in Supplementary Table 3. Whereas oedema and furrowing were unchanged from baseline to Week 8 in the placebo-treated participants,

these endoscopic features were less likely to be present among APT-1011–treated participants at Week 8 compared to baseline. Study participants were less likely to have white exudates at week 8 compared to baseline; white exudates were absent in APT-1011–treated participants at Week 8.

Post-hoc analyses

Median EREFS values observed in the different groups and at different visits are presented in Figure 2C (baseline values are shown in Supplementary Table 1). When comparing each of the APT-1011–treated groups to placebo, differences in EREFS from baseline to end of treatment were observed (on average, a decrease of 2.92 points [95% CI: -4.68, -0.88] in the APT-1011 at 1.5 mg BID group relative to placebo [*P* = .002] and a decrease of 2.74 points [95% CI: -4.5, -0.88] in the APT-1011 at 3.0 mg QD group relative to placebo [*P* = .004]). The results of linear regression analysis for changes in EREFS in the combined APT-1011–treated group relative to the placebo-treated group are shown in Supplementary Table 2.

Symptoms

Prespecified analyses

Dysphagia was not a required symptom for entry into the study (patients were eligible if they had at least one of the following symptoms: chest pain or discomfort [58%], dysphagia [84%], or food impaction [33%]) at baseline. The data on participants' symptoms, as measured by the Patient Global Assessment of EoE symptom severity, are shown in Figure 3A (baseline values are shown in Supplementary Table 1).

Post-hoc analyses

When comparing each of the APT-1011–treated groups to placebo, differences in changes in Patient Global Assessment of EoE symptom severity from baseline to end of treatment were observed (on average, a decrease of 2.4 points [95% CI: -4.04, -1.21] in the APT-1011 at 1.5 mg BID group relative to placebo [*P* = .006] and a decrease of 1.55 points [95% CI: -3.17, -1.21] in the APT-1011 at 3.0 mg QD group relative to placebo [*P* = .061]).

EEsAI PRO symptom scores were calculated in 23 patients (1 placebo patient was missing frequency of dysphagia information at end of treatment) (baseline values are shown in Supplementary Table 1). Trends toward significant changes in EEsAI PRO in the drug-treated group relative to the placebo group were observed (on average, a decrease of 15.13 points [95% CI: -33.5, -1.07] in the APT-1011 at 1.5 mg BID group relative to placebo [*P* = .1] and a decrease of 13.27 points [95% CI: -29.87, -1.07] in the APT-1011 at 3.0 mg QD group relative to placebo [*P* = .11]).

The data on the percentage of patients in clinical remission (based on EEsAI PRO <20) and patients free of dysphagia over the last 7 days are shown in Figures 3B and 3C. Compared to baseline, an additional 4 patients in the APT-1011 at 1.5 mg BID group (in addition to 3 patients with no dysphagia at baseline) and 2 patients in the APT-1011 at 3.0 mg QD group (in addition to 1 patient with no dysphagia at baseline) were free of dysphagia in the 7 days prior to the endoscopy visit. No patient had complete resolution of dysphagia as assessed by EEsAI PRO in the placebo group (1 patient had no dysphagia at baseline) compared to 6 patients in the APT-1011–treated

groups. Although the percentage of participants without trouble swallowing during the week prior to the end of treatment was greater in participants treated with APT-1011, these data should be interpreted with caution given the variability in dysphagia frequency/symptoms severity between the different groups at baseline.

Data from the Gastrointestinal Symptom Rating Scale Questionnaire and Mayo Dysphagia Questionnaire did not demonstrate any meaningful changes (data not shown).

DISCUSSION

Prior studies of fluticasone in EoE have relied on oral administration of preparations that are designed for airway delivery in the treatment of asthma. Despite the length of time from completion to its publication, this phase 1b/2a, double-blind, placebo-controlled, proof-of-concept trial represents a novel evaluation of an orally disintegrating tablet formulation of fluticasone, called APT-1011, which was specifically designed for the treatment of EoE. As the primary endpoint of this proof-of-concept study, there were no safety issues noted with either dose of APT-1011 compared to placebo. Additionally, 75% and 63% of participants receiving APT-1011 at 1.5 mg BID and APT-1011 at 3.0 mg QD, respectively, achieved a reduction in inflammation to <15 eosinophils/HPF compared to only 13% of participants treated with placebo. We observed a greater improvement in maximal oesophageal eosinophilia, EREFS, Patient Global Assessment, and EEsAI PRO (trend) in APT-1011 treatment groups compared to placebo. No participants had complete resolution of dysphagia as assessed by EEsAI PRO in the placebo group, whereas 6 participants (38%) in APT-1011–treated groups

achieved complete resolution of dysphagia symptoms. Given the small sample size and imbalances in symptom severity at baseline, particularly as some subjects experienced no dysphagia at randomisation, the data on clinical remission should be interpreted with caution.

APT-1011 was well tolerated, without demonstrable safety concerns with dosing at 1.5 mg BID and 3.0 mg QD for 8 weeks in adolescents and adults with EoE. Specifically, no participant who received active drug developed clinical manifestations of adrenal suppression or oral/oesophageal candidiasis in this small phase 1b/2a study. This safety profile is particularly relevant as the dose of fluticasone studied is higher than those currently used in clinical practice for EoE with swallowed asthma formulations of fluticasone (440 µg to 880 µg BID).[22] Measurable systemic side effects of oral fluticasone propionate therapy are not expected, because the absolute systemic bioavailability of orally administered fluticasone propionate is negligible (<1%) compared to inhaled fluticasone propionate (16.6%).[23,24] Ongoing clinical trials of swallowed topical corticosteroids are examining multiple aspects of safety, including adrenal function, in the context of long-term maintenance therapy.

Swallowed topical corticosteroids are the most commonly used medical therapy for the management of children and adults with EoE. Previous double-blind, placebo-controlled trials have demonstrated histologic improvement in oesophageal mucosal eosinophil density.[3,4,25] Three trials evaluated fluticasone using an inhaler formulation of fluticasone propionate designed for asthma, and 2 trials were performed in children with EoE. One trial of fluticasone in adults identified a significant reduction in eosinophil inflammation, but not in symptom improvement, compared with placebo over a 6-week

treatment period.[26] Recently, use of fluticasone powder extracted from the diskus formation of fluticasone for asthma was reported as an effective alternative to the metered-dose formulation in an uncontrolled study of 40 adults with EoE.[27] While topical corticosteroid preparations have not yet been approved by the US FDA, budesonide in an orally disintegrating tablet formulation was recently approved by the European Medicines Agency for the treatment of EoE.[28]

Disparate histologic definitions of therapeutic response were reported in prior studies of topical corticosteroids. On the basis of a histologic threshold of <15 eosinophils/HPF, response rates were highly variable, ranging from 50% to 90% of participants.[26,29] Reasons for this variation are being studied, but they may be related to differences in the phenotypic severity of EoE, use of concomitant medications, different doses of corticosteroids, or use of corticosteroid formulations that are optimised for oesophageal delivery. Potential genetic variation in corticosteroid metabolism and patient adherence are additional factors that may impact efficacy. In the current study, APT-1011 achieved a histologic response <15 eosinophils/HPF in 75% of participants, which supports the effectiveness of the novel delivery system, especially when combined with the observed improvement in endoscopic outcomes.

Although a small number of participants were recruited in this proof-of-concept study to assess the short-term safety of APT-1011, study results show improvements in histology and endoscopy outcomes. The results should be interpreted with a number of considerations in mind. The diagnostic threshold of 24 eosinophils/HPF used in the study exceeded the guideline-based criteria of ≥15 eosinophils/HPF. At the time of this trial, uniform inclusion criteria for EoE trials had not been established. Higher-than-

diagnostic-threshold criteria were followed in this trial to reduce the chance of including patients with borderline EoE activity. While we excluded patients with PPI-responsive oesophageal eosinophilia (PPI-REE), a large percentage of patients (66.7%) continued PPIs. The continued use of PPIs in this group of patients may have reflected the presence of concomitant gastro-oesophageal reflux disease. The role of dual therapy is still unclear in the management of EoE and is an area of active investigation. Dysphagia was not a required symptom for the purposes of study inclusion. For entry into this trial, no validated PRO instrument for assessment of EoE symptoms in adolescents and adults was used, as no such instrument was available when the trial was designed. The EEsAI PRO instrument used in this study was in an early stage of development for adult use. One participant in the placebo group violated the study protocol by taking exogenous corticosteroids for lumbar disc disease; this participant exhibited a profound decrease in oesophageal eosinophilia and severity of endoscopic findings from baseline to end of treatment. Finally, patients with PPI-REE were excluded based on 2007 and 2011 consensus guidelines for the diagnosis of EoE.[30,31] The recently published AGREE (A Working Group on PPI-REE) statement removed the PPI response criterion for EoE diagnosis, making PPI-REE part of the EoE spectrum.[4] It remains unclear whether the revised criteria will alter the therapeutic efficacy of medical therapies, as prior trials have excluded patients with PPI-REE.

In conclusion, APT-1011, a novel, orally disintegrating tablet formulation of fluticasone, was safe and well tolerated in adolescents and adults with EoE. Exploratory efficacy outcomes demonstrated improvement in both endoscopic and histologic

findings as well as symptoms. The results of this study support the continued development of APT-1011 for the treatment of EoE.

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TABLES

Table 1. Demographic and Baseline Characteristics, ITT Population

	Placebo (n=8)	APT-1011 1.5 mg BID (n=8)	APT-1011 3.0 mg QD (n=8)
Age (years), mean (SD)	29.8 (13.9)	23.4 (11.3)	24.6 (10.6)
Adolescent, n	2	3	3
Adult	6	5	5
Male, n (%)	5 (62.5)	4 (50.0)	6 (75.0)
BMI (kg/m^2), mean (SD)	23.5 (3.2)	18.8 (2.7)	24.0 (5.6)
PPI use, n (%)			
Current	6 (75)	5 (62.5)	5 (62.5)
Prior	2 (25)	3 (37.5)	3 (37.5)
Chest pain/discomfort, n			
None	3	5	2
Intermittent	5	3	6
Continuous	0	0	0
Dysphagia, n			
None	2	1	1
Intermittent	3	7	6
Continuous	3	0	1
Food impaction, n			
None	4	4	8
Intermittent	3	4	0
Continuous	1	0	0

Abbreviations: BID, twice daily; BMI, body mass index; ITT, intent-to-treat; PPI, proton pump inhibitor; QD, once daily; SD, standard deviation.

Table 2. Treatment-Emergent Adverse Events Occurring in ≥2 Participants in Any Treatment Group, Safety Population

n (%)	Placebo (n=8)	APT-1011 1.5 mg BID (n=8)	APT-1011 3.0 mg QD (n=8)
Any TEAE	6 (75)	6 (75)	6 (75)
Blood cortisol decreased	2 (25)	3 (37.5)	1 (12.5)
Diarrhoea	0	0	2 (25)
Nasopharyngitis	0	1 (12.5)	1 (12.5)

Abbreviations: BID, twice daily; ITT, intent-to-treat; QD, once daily; TEAE, treatment-emergent adverse event.

Table 3. Eosinophil Counts per High-Power Field (400×; 0.275 mm radius) in the Distal and Proximal Oesophagus

	Placebo	APT-1011 1.5 mg BID	APT-1011 3.0 mg QD
Distal Oesophagus			
Number of patients with oesophageal biopsies	8	8	8
Baseline			
mean eos/HPF	73.1	39.4	66.1
min-max eos/HPF	28-140	0-96	30-148
median eos/HPF	55.5	39.0	65.5
Week 8/end of treatment			
mean change	-14.3	-32.0	-46.6
mean % change	-20%	-81%	-70%
median change	-6.5	-36.0	-41.0
median % change	-12%	-92%	-63%
Proximal Oesophagus			
Number patients with oesophageal biopsies	5	5	4
Baseline			
mean eos/HPF	54.6	63.8	34.5
min-max eos/HPF	0-98	28-107	11-68
median eos/HPF	72	47.0	29.5
Week 8/end of treatment			
mean change	-14.8	-63.8	-34.0
mean % change	-27%	-100%	-99%
median change	0.0	-47.0	-28.5
median % change	0%	-100%	-97%

Abbreviations: BID, twice daily; eos/HPF, eosinophils per high-power field; QD, once daily.

FIGURE LEGENDS

Figure 1. Study flow diagram.

Abbreviations: BID, twice daily; QD, once daily.

Figure 2. Percent of participants with treatment response from >24 to <15 eosinophils/HPF and >24 to 0 eosinophilic per HPF (A), median maximum peak oesophageal eosinophils/HPF in the oesophagus overall (B), and median total EREFS in patients treated with placebo, APT-1011 at 1.5 mg BID, and APT-1011 at 3.0 mg QD (C).

Abbreviations: BID, twice daily; HPF, high-power field; QD, once daily.

Figure 3. Patient Global Assessment of Symptom Severity (A), percentage of patients in remission based on EEsAI PRO <20 (B), and percentage of patients free of dysphagia in the past 7 days (C).

Abbreviations: BID, twice daily; EEsAI PRO, Eosinophilic Esophagitis Activity Index patient-reported outcomes; QD, once daily.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	6
	2b	Specific objectives or hypotheses	7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	8
	4b	Settings and locations where the data were collected	8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	12
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	12
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	12
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	9
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	9

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	9
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	12
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	14
	13b	For each group, losses and exclusions after randomisation, together with reasons	14
Recruitment	14a	Dates defining the periods of recruitment and follow-up	14
	14b	Why the trial ended or was stopped	14
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	27
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	27
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	15-16
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	30
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	18
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	28
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	21
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	22
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	21
Other information			
Registration	23	Registration number and name of trial registry	8
Protocol	24	Where the full trial protocol can be accessed, if available	8
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	8

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Figure 1

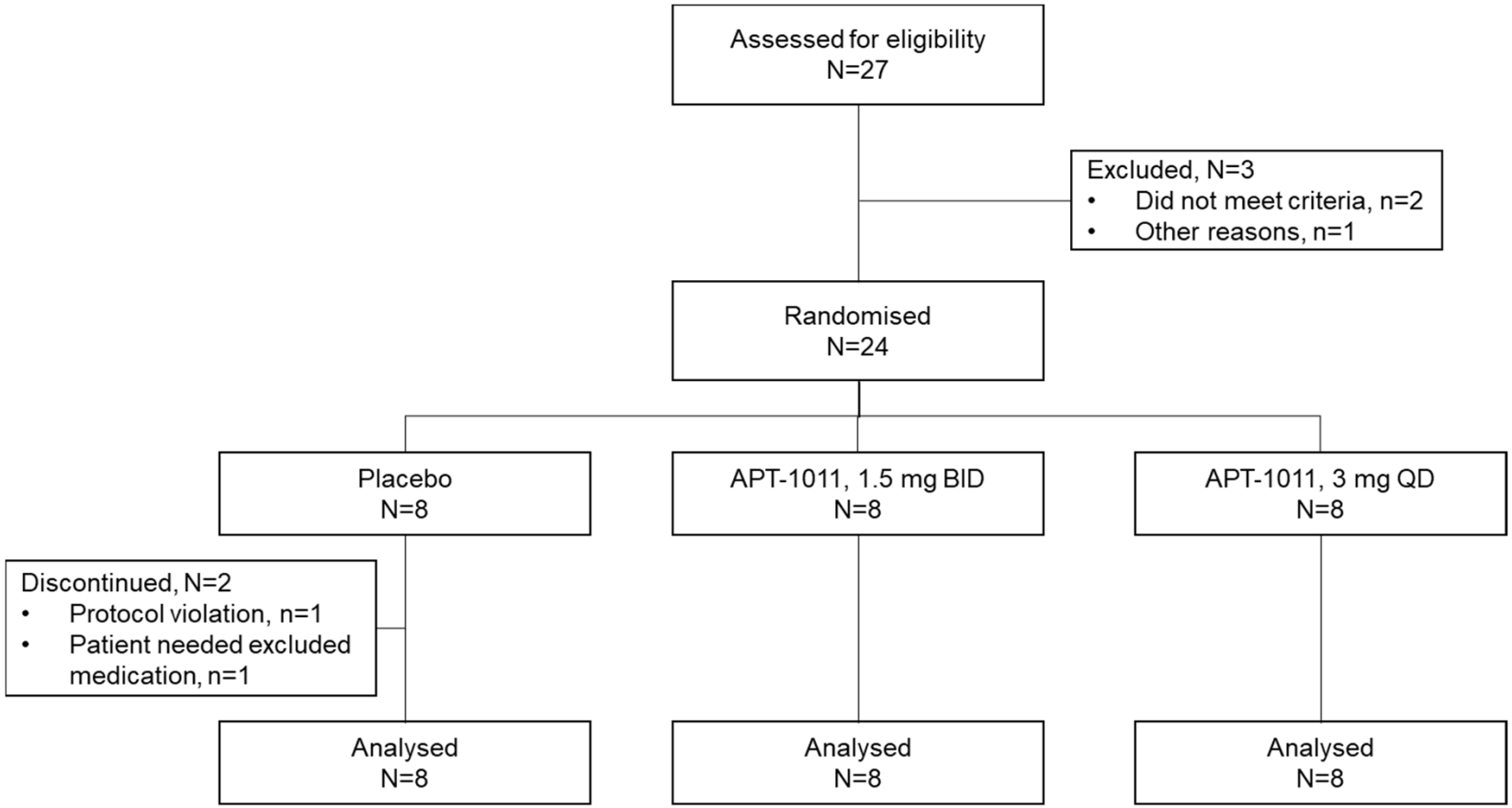

Assessed for eligibility
N=27
Excluded, N=3
• Did not meet criteria, n=2
• Other reasons, n=1
Randomised
N=24
Placebo
N=8
APT-1011, 1.5 mg BID
N=8
APT-1011, 3 mg QD
N=8
Discontinued, N=2
• Protocol violation, n=1
• Patient needed excluded medication, n=1
Analysed
N=8
Analysed
N=8
Analysed
N=8

Figure 2

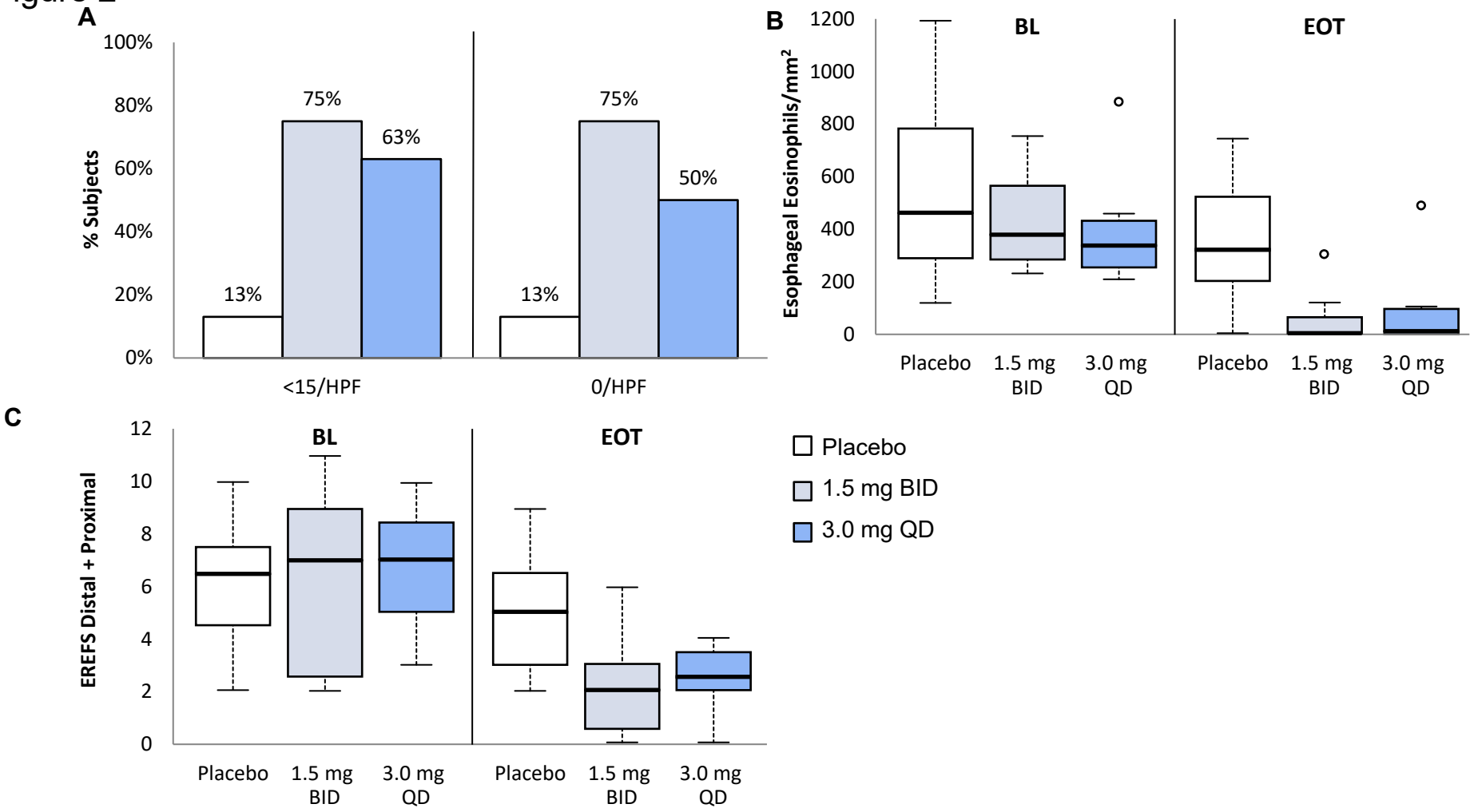
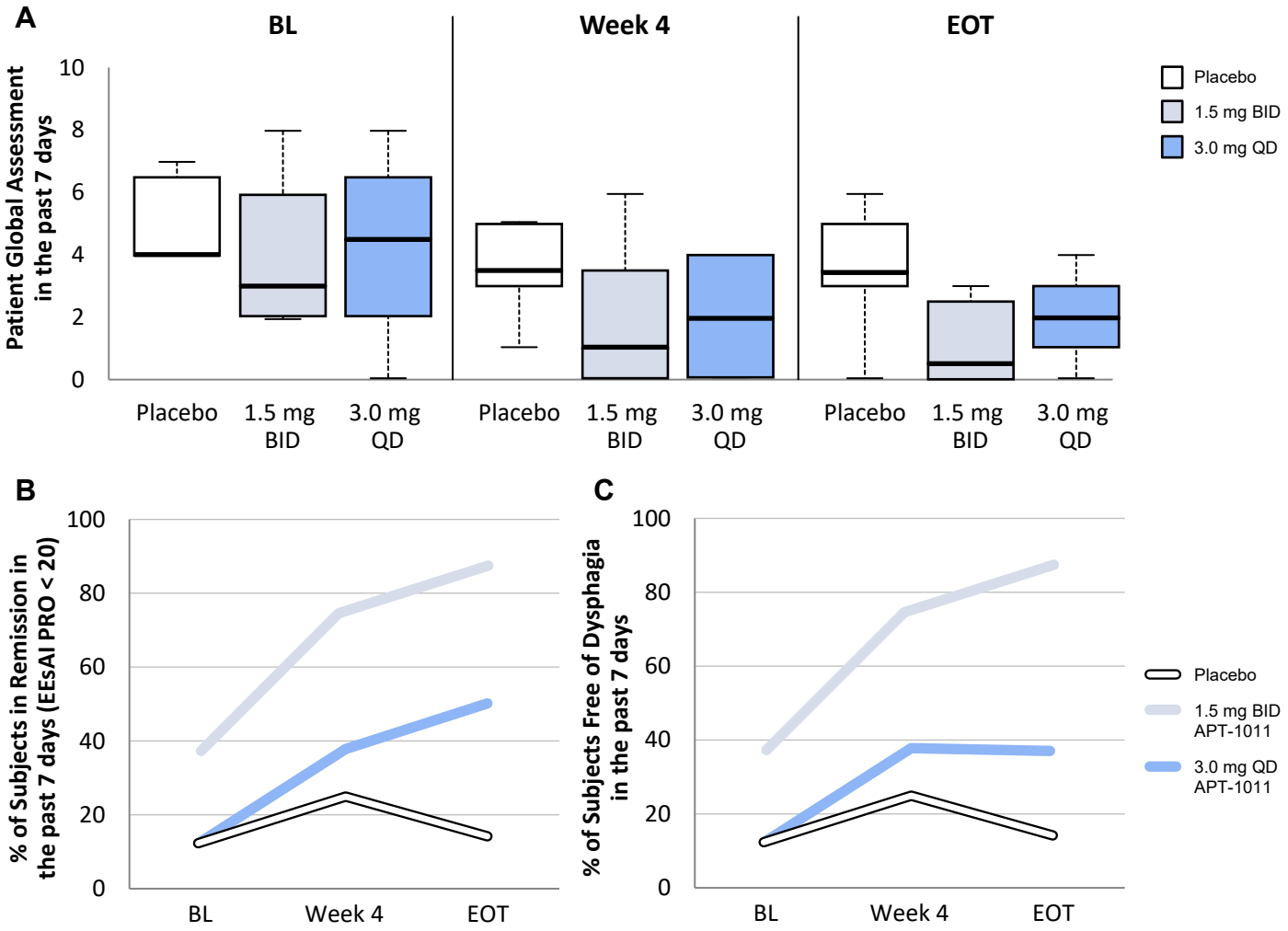

A
100%
80%
60%
40%
20%
0%
% Subjects
75%
63%
13%
75%
50%
13%
<15/HPF
0/HPF
B
1200
1000
800
600
400
200
0
Esophageal Eosinophils/mm²
BL
EOT
Placebo
1.5 mg BID
3.0 mg QD
Placebo
1.5 mg BID
3.0 mg QD
C
12
10
8
6
4
2
0
EREFS Distal + Proximal
BL
EOT
Placebo
1.5 mg BID
3.0 mg QD
Placebo
1.5 mg BID
3.0 mg QD
Placebo
1.5 mg BID
3.0 mg QD

Figure 3


A
BL
Week 4
EOT
Patient Global Assessment in the past 7 days
10
8
6
4
2
0
Placebo
1.5 mg BID
3.0 mg QD
Placebo
1.5 mg BID
3.0 mg QD
Placebo
1.5 mg BID
3.0 mg QD
Placebo
1.5 mg BID
3.0 mg QD
B
% of Subjects in Remission in the past 7 days (EEsAI PRO < 20)
100
80
60
40
20
0
BL
Week 4
EOT
C
% of Subjects Free of Dysphagia in the past 7 days
100
80
60
40
20
0
BL
Week 4
EOT
Placebo
1.5 mg BID APT-1011
3.0 mg QD APT-1011