Budesonide Oral Suspension Significantly Improves Eosinophilic Esophagitis Histology Scoring System Results

Analyses From a 12-Week, Phase 2, Randomized, Placebo-controlled Trial

Margaret H. Collins, MD,* Evan S. Dellon, MD,† David A. Katzka, MD,‡ Ikuo Hirano, MD,§ James Williams, MD,∥ and Lan Lan, PhD

Abstract: Budesonide oral suspension (BOS) is a novel topical corticosteroid, which has been shown to improve symptoms and endoscopic appearance, and reduce peak eosinophil counts in patients with eosinophilic esophagitis (EoE). This trial evaluated the effect of BOS or placebo on the severity (grade) and extent (stage) of 8 histopathologic features observed in EoE, using the validated eosinophilic esophagitis histologic scoring system (EoE HSS). Patients with EoE aged 11 to 40 years with dysphagia were randomized to receive either BOS (2.0 mg twice daily) or placebo for 12 weeks. Mean (SD) EoE HSS grade and stage total scores at baseline for placebo and BOS groups were: grade, 0.42 (0.16) and 0.49 (0.14), respectively; stage: 0.38 (0.14) and 0.46 (0.11), respectively. These scores significantly decreased (improved) from baseline for patients receiving BOS versus placebo (grade: least squares mean change [SE]: placebo vs. BOS, −0.04 [0.03] vs. −0.24 [0.02]; P < 0.0001; stage: −0.01 [0.02] vs. −0.19 [0.02]; P < 0.0001). EoE HSS total scores improved for 6 of the 8 and 5 of the 8 histopathologic features for grade and stage, respectively, versus placebo. Change in EoE HSS total scores correlated moderately but significantly with change in endoscopic severity (endoscopic reference score; grade: R = 0.5349; stage: R = 0.5416; both P < 0.0001). Change in EoE HSS stage total score correlated weakly with change in Dysphagia Symptom Questionnaire scores (grade: R = 0.1925; P = 0.0740; stage: R = 0.2135; P = 0.0471). These data demonstrate that the EoE HSS is a valuable endpoint of treatment response in randomized clinical trials and should be considered for future trials for EoE.

Key Words: budesonide oral suspension, topical corticosteroid, eosinophilic esophagitis, histology, peak eosinophil count

(Am J Surg Pathol 2019;43:1501–1509)
Eosinophilic esophagitis (EoE) is an immune-mediated, chronic disease characterized by esophageal eosinophilia, defined as at least 15 eosinophils in at least 1 eos/HPF and symptoms of esophageal dysfunction, which can include solid-food dysphagia, chest pain, food impaction, and upper abdominal pain. The prevalence and incidence of EoE have steadily increased over the past 30 years. In the United States, medical resource utilization costs are increased in patients with EoE compared with healthy individuals, with estimated total health care-related costs ranging from $503 million to $1.36 billion per year. Topical corticosteroids are one of the first-line pharmacologic treatments for patients with EoE. However, these are primarily used off-label and include aerosolized asthma preparations that are swallowed rather than inhaled, or formulations that are swallowed as slurries.

Budesonide oral suspension (BOS) is a novel topical corticosteroid formulation that is muco-adherent and designed specifically for the treatment of patients with EoE. BOS (2.0 mg twice daily [bid]) is generally well tolerated and induces histologic response in children with EoE. More recently, BOS has been shown to improve symptoms and endoscopic features, as well as decrease peak eosinophil counts in adolescents and adults with EoE during a 12-week, randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov identifier: NCT01642212). Although the peak eosinophil count is considered the gold standard for pathologic diagnosis of EoE and is frequently used as an outcome measure in clinical trials for this disease, other important histopathologic features are commonly observed in patients with EoE. In light of this, an eosinophilic esophagitis histologic scoring system (EoE HSS) was recently developed and validated to encompass a more comprehensive range of the histopathologic features observed in EoE. Histopathologic features of the EoE HSS that evaluate aspects of eosinophil infiltration are eosinophil inflammation (EI), eosinophil abscess (EA), eosinophil surface layering (SL), and surface epithelial alteration (SEA); features that do not include eosinophils in their definition are basal zone hyperplasia (BZH), dilated intercellular spaces (DIS), dyskeratotic epithelial cells (DEC), and lamina propria fibrosis (LPF) (Table 1 and Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/PAS/A838). The EoE HSS examines the severity (grade) and extent (stage) of these abnormalities using a 4-point scale (0 = the feature is not present in a biopsy and 1 to 3 = the severity or extent of the histopathologic feature if present, with 3 indicating the maximum possible severity or extent). The EoE HSS has been shown to outperform peak eosinophil counts alone for the diagnosis and monitoring of EoE.

The aim of this analysis was to use the EoE HSS to assess the effect of BOS (2.0 mg bid) and placebo over 12 weeks on the severity and extent of histopathologic features commonly found in patients with EoE. Several post hoc analyses were also performed to assess correlations between the change in EoE HSS, and endoscopic and symptomatic outcomes.

### METHODS

**Study Design and Participants**

The MPI 101-06 trial (ClinicalTrials.gov identifier: NCT01642212) was a multicenter, randomized, double-blind, placebo-controlled, phase 2 trial of BOS in adolescents and adults with EoE. The trial consisted of a 6-week screening period, a 4-week, single-blind, placebo run-in period, and a 12-week double-blind phase, during which patients were randomized 1:1 to receive either BOS (2.0 mg bid) or placebo (Supplementary Fig. 1, Supplemental Digital Content 1, http://links.lww.com/PAS/A838). Patients were aged 11 to 40 years, had at least 15 eos/HPF after receiving 8 weeks of a high-dose proton pump inhibitor, had at least 15 eos/HPF from at least 2 levels of the esophagus on screening esophagogastroduodenoscopy (EGD), and had at least 4 days of dysphagia in any 2 of the first 3 weeks of screening as well as 2 weeks before randomization, and with at least 70% completion of days using the daily Dysphagia Symptom Questionnaire (DSQ) during the first 3 weeks of screening and within 2 weeks of randomization. Patients who completed treatment were eligible to enter a 24-week open-label extension (Supplementary Fig. 1, Supplemental Digital Content 1, http://links.lww.com/PAS/A838), which is discussed elsewhere.

Key exclusion criteria included the presence of other gastrointestinal diseases, esophageal stricture precluding passage of an adult upper endoscope (insertion tube diameter, ~9.0 mm), and the use of topical or systemic corticosteroids 4 weeks before the screening EGD. A full list of inclusion and exclusion criteria has been published previously.

### EGD and Biopsy Collection

For study entry, patients were required to undergo an EGD before or during the screening period, but within

### TABLE 1. Definitions of Histologic Features Comprising the EoE HSS Scoring System

| Histologic Features | Abbreviation | Definition |
|---------------------|--------------|-----------|
| Eosinophilic inflammation | EI | Intraepithelial eosinophil density |
| Basal zone hyperplasia | BZH | Basal zone exceeds 15% of the total epithelial thickness |
| Eosinophilic abscess | EA | An aggregate of eosinophils that disrupts the underlying epithelial architecture |
| Eosinophilic surface layering | SL | Eosinophils align in a linear fashion in the superficial portion of the epithelium |
| Dilated intercellular spaces | DIS | Periepithelial cell spaces in which intercellular bridges are visible |
| Surface epithelial alteration | SEA | Surface epithelial cells have cytoplasm that is more intensely pink than normal |
| Dyskeratotic epithelial cells | DEC | Epithelial cells with small hyperchromatic nuclei and cytoplasm that is more intensely pink than normal |
| Lamina propria fibrosis | LPF | Thickened lamina propria fibers |

DIS indicates dilated intercellular spaces.
10 weeks of the placebo run-in period. A final EGD (with esophageal biopsy) was performed at the 12-week evaluation or early termination. The screening EGD was performed by either the physician at the study center or the referring physician. At least 2 biopsies were collected from each of the 3 regions of the esophagus: proximal, 3 cm below the cricopharyngeus muscle; middle level, midpoint between the cricopharyngeus muscle and the gastroesophageal junction; and distal, 3 cm above the gastroesophageal junction. Endoscopy evaluated the proximal and distal regions of the esophagus only.

Biopsies were processed at the facility where the EGD was performed. Biopsy slides, either those used for clinical reports or recut slides, were sent to an independent, central pathologist (M.H.C.) for examination who was blinded to treatment allocation. Histopathologic features of the EoE HSS and gross endoscopic findings were evaluated for each screening EGD and the 12-week/early termination EGD.

**Histopathologic Evaluation**

The central review pathologist evaluated the following 8 histologic features at each level of the esophagus (proximal, mid, and distal): EA, DEC, BZH, DIS, EI, LPF, SEA, and eosinophil SL, as described previously. LPF was examined if the biopsy contained sufficient lamina propria for evaluation. The grade score assessed the degree of severity for each histologic feature present in the biopsy, whereas the stage score assessed how much of the tissue (< 33%, 33% to 66%, or > 66%) was affected by the feature (Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/PAS/A838). The change from baseline in EoE HSS total scores (grade and stage) was a secondary efficacy endpoint of this study (NCT01642212).

Histopathologic features were scored for grade and stage (0 to 3 points for each feature), and the points summed to generate a total score for grade and a total score for stage for each biopsy. The maximum total score possible was 24 (maximum grade or stage score of 3 × 8 features = 24), representing the most severe grade or stage for each esophageal biopsy collected (proximal, mid, and distal regions) if all 8 features were evaluated. If one of the features was not evaluable for a biopsy, the maximum possible score was reduced by 3 for that biopsy (i.e., the maximum total score was 21 for 7 features). To account for missing features, scores were normalized by dividing the observed total score by the maximal possible score for that biopsy to result in a “total score ratio” that is designated as “total score” in the results below; for example, if there were no missing features and all the features had the maximum possible total score, the grade or stage total score ratio would be 1 (24/24 = 1). However, for a biopsy with 7 evaluable features and an observed grade or stage score of 12, the grade or stage total score ratio would be 0.571 (12/21 = 0.571). The mean of the total score ratios for each endoscopy was then calculated using the following equation:

\[
\text{Proximal total score ratio} + \text{mid total score ratio} + \text{distal total score ratio} / 3. 
\]

The mean of the total score ratios was then calculated for patients by treatment group. Peak eosinophil counts were assessed as previously described, a HPF area of ∼0.3 mm² was used.

**Symptom and Endoscopy Evaluation**

Symptoms of dysphagia were assessed using the DSQ, a validated patient-reported outcome measure, described elsewhere. Endoscopic features were assessed using the validated endoscopic reference (EREFS) score system (exudate, rings, edema, furrows, and strictures), as previously described. For this study, the EREFS total score was calculated by summing the severity scores of the individual endoscopic findings assessed for both the proximal and distal regions of the esophagus. The score could, therefore, range from 0 to 20 (proximal, 0 to 10; distal, 0 to 10), with higher scores indicating more severe endoscopic findings.

**Statistical Analysis**

It is common practice in studies of pharmaceutical products to evaluate efficacy by comparing the change in values from baseline, as opposed to comparing the observed posttherapy values in the treatment groups. Therefore, an analysis of covariance model was used to compare the changes in EoE HSS from baseline to the end of the double-blind treatment phase (week 12) between BOS and placebo groups adjusting for baseline EoE HSS total score. An analysis of covariance model was performed for change in LPF for patients who had evaluable lamina propria layer present in their biopsies at baseline and at week 12. Post hoc correlation analyses of change in EoE HSS total score with change in DSQ score, and with change in total EREFS score were performed to further assess relationships between the EoE HSS and endoscopic and symptomatic measures of EoE. These correlation analyses were then also performed for individual EoE HSS features and EREFS features. In these analyses, EoE HSS scores used the mean of the scores from the proximal, mid, and distal regions of the esophagus, and the EREFS scores included the sum of scores from the proximal and distal regions of the esophagus instead. The Pearson or Spearman correlation coefficient analyses and associated P values were reported. The following limits and descriptors were used for the correlation coefficients: very weak, 0.00 to 0.19; weak, 0.20 to 0.39; moderate, 0.40 to 0.59; strong, 0.60 to 0.79; very strong, 0.80 to 1.00.

**RESULTS**

**Patient Demographics and Baseline Characteristics**

Patient demographics and baseline characteristics for this trial have been previously reported. Mean (SD) EoE HSS grade total scores at baseline were 0.42 (0.16) and 0.49 (0.14) for patients receiving placebo (n = 38) and BOS (n = 49), respectively. Mean (SD) EoE HSS stage total scores at baseline were 0.38 (0.14) and 0.46 (0.11) for patients receiving placebo (n = 38) and BOS (n = 49), respectively. The proportion of patients with each of the 8 histopathologic features on the EoE HSS at baseline is...
shown in Supplementary Figure 2 (Supplemental Digital Content 1, http://links.lww.com/PAS/A838).

**Mean Peak Eosinophil Counts, DSQ, and EREFS Scores**

Results for peak eosinophil counts (eos/HPF), DSQ, and EREFS scores have been previously reported for this study.¹⁴

**Grade and Stage Total EoE HSS Scores**

EoE HSS grade total scores decreased (improved) from baseline to week 12 in patients receiving BOS compared with patients receiving placebo (least squares [LS] mean change [SE]: placebo vs. BOS, −0.04 [0.03] vs. −0.24 [0.02]; P < 0.0001; Fig. 1A). Similar findings were observed for EoE HSS stage scores (LS mean change [SE]: placebo vs. BOS, −0.01 [0.02] vs. −0.19 [0.02]; P < 0.0001; Fig. 1B). Box plots presenting EoE HSS grade and stage total scores for all patients (in each arm of the study) at baseline and week 12 are shown in Supplementary Figure 3 (Supplemental Digital Content 1, http://links.lww.com/PAS/A838). Representative histology images for patients receiving BOS (2.0 mg bid) or placebo at baseline and after 12 weeks of treatment are presented (Figs. 2A–D).

**Grade and Stage Scores For Each Histopathologic Feature on the EoE HSS**

Improvements in EoE HSS grade scores from baseline to week 12 were significantly greater in patients receiving BOS than in patients receiving placebo for 6 of the 8 features (Table 2). The 6 histopathologic features were: EI, BZH, EA, SL, DIS, and LPF. The difference in change from baseline between placebo and BOS was largest for EI and BZH (LS mean difference [95% confidence interval]: EI, −1.14 [−1.55, −0.73]; BZH, −1.19 [−1.57, −0.82]; P < 0.0001). Similarly, for changes in EoE HSS stage scores from baseline to week 12, improvements were significantly greater in patients receiving BOS than in patients receiving placebo for 5 of the 8 histopathologic features (Table 3). The 5 features were EI, BZH, EA, SL, and SEA. The largest difference between the placebo and BOS groups was again seen for EI and BZH: EI, −1.26 (−1.68, −0.83); P < 0.0001 and BZH, −1.04 (−1.48, −0.61); P < 0.0001. Box plots for EoE HSS grade and stage scores for the 8 histopathologic features for all patients (in each arm of the study) at baseline and week 12 are presented in Supplementary Figure 4 (Supplemental Digital Content 1, http://links.lww.com/PAS/A838) and Supplementary Figure 5 (Supplemental Digital Content 1, http://links.lww.com/PAS/A838), respectively.

Overall, 37% (14/38) and 43% (21/49) of patients receiving placebo and BOS, respectively, had biopsies in which the lamina propria could be evaluated. Additional analyses examined EoE HSS grade and stage scores for LPF for patients who had this layer present in biopsies at baseline and at week 12 (Supplementary Table 2, Supplemental Digital Content 1, http://links.lww.com/PAS/A838). As with the LS mean changes in EoE HSS grade and stage scores shown earlier (Tables 2, 3, respectively), improvements in EoE HSS grade and stage scores for LPF from baseline to week 12 were greater in patients receiving BOS than those receiving placebo for patients with nonmissing data (evaluable lamina propria; Supplementary Table 2, Supplemental Digital Content 1, http://links.lww.com/PAS/A838). These findings were statistically significant for LPF grade scores (placebo vs. BOS, −0.3 [0.29] vs. −1.1 [0.24]; P = 0.0474) but not for LPF stage scores (Supplementary Table 2, Supplemental Digital Content 1, http://links.lww.com/PAS/A838).

**Correlation of Microscopic Pathology Measured by the EoE HSS With Endoscopic Severity Measured by EREFS**

The change in EoE HSS total scores (grade and stage) from baseline to week 12 correlated moderately and significantly with change in EREFS scores over the same period (grade, R = 0.5349; stage, R = 0.5416; both P < 0.0001; Table 4). Change in the majority of individual EoE HSS histopathologic feature scores correlated with change in EREFS scores (Table 4). The change in EoE HSS total scores (grade and stage) from baseline to week 12 correlated weakly to moderately and significantly with change in EREFS scores irrespective of esophageal region.

**FIGURE 1.** LS mean (SE) change in (A) EoE HSS grade and (B) stage total score from baseline to week 12 for patients receiving placebo or BOS (2.0 mg bid). LS mean (SE) values were determined using an analysis of covariance model, including treatment group and baseline value as a covariate. Total number of patients assessed: placebo, n = 38; BOS, n = 49. CI indicates confidence interval.
The additional post hoc analysis examined correlations between change in EREFS inflammatory features (exudates, furrows, and edema), both combined and individually, and change in EoE HSS grade and stage total scores from baseline (Supplementary Material; Supplementary Table 3, Supplemental Digital Content 1, http://links.lww.com/PAS/A838).

Further post hoc analysis examined correlations between change in rings and strictures with change in BZH and LPF scores from baseline (Supplementary Material; Supplementary Table 5, Supplemental Digital Content 1, http://links.lww.com/PAS/A838).

**Correlation of EoE HSS With DSQ Scores**

The change in EoE HSS grade total score from baseline to week 12 did not correlate significantly with change in DSQ scores ($R = 0.1925$; $P = 0.0740$), but the change in the EoE HSS total stage score correlated weakly but significantly ($R = 0.2135$; $P = 0.0471$) with a change in DSQ scores (Table 4). Among the individual EoE HSS features, change in EI (grade) and SL (grade and stage) correlated significantly with change in DSQ scores (Table 4). In an additional post hoc analysis, very few significant correlations were found between change in EoE HSS features and change in DSQ score when stratified by presence of stricture (Supplementary Table 6, Supplemental Digital Content 1, http://links.lww.com/PAS/A838) or presence of rings (severity score, $\geq 2$) (Supplementary Table 7, Supplemental Digital Content 1, http://links.lww.com/PAS/A838). However, a very strong significant correlation was observed between change in grade LPF score and change in DSQ score ($R = 0.9000$; $P = 0.0374$) in patients with esophageal strictures ($n = 5$) (Supplementary Table 6, Supplemental Digital Content 1, http://links.lww.com/PAS/A838).

**DISCUSSION**

To our knowledge, this study represents the most complete analysis of EoE histopathology before and after...
TABLE 2. Mean (SD) Grade Scores For Each EoE HSS Histopathologic Feature at Baseline and at Week 12 For Patients Receiving BOS (2.0 mg bid) and Placebo

| EoE HSS Histopathologic Feature | Placebo (n = 38) | BOS (2.0 mg bid) (n = 49) | P |
|----------------------------------|-----------------|---------------------------|---|
| EI                              |                 |                           |   |
| Baseline                        | 2.3 (0.57)      | 2.6 (0.44)                |   |
| Week 12                         | 2.2 (0.86)      | 1.1 (1.00)                |   |
| LS mean (SE) change from baseline | −0.3 (0.15)    | −1.4 (0.14)               | <0.0001 |
| DIS                             |                 |                           |   |
| Baseline                        | 2.2 (0.84)      | 2.4 (0.59)                |   |
| Week 12                         | 2.2 (0.84)      | 1.1 (0.93)                |   |
| LS mean (SE) change from baseline | −0.1 (0.14)    | −1.3 (0.12)               | <0.0001 |
| EA                              |                 |                           |   |
| Baseline                        | 0.4 (0.53)      | 0.6 (0.67)                |   |
| Week 12                         | 0.4 (0.61)      | 0.1 (0.21)                |   |
| LS mean (SE) change from baseline | −0.0 (0.07)    | −0.4 (0.06)               | <0.0001 |
| SL                              |                 |                           |   |
| Baseline                        | 0.4 (0.59)      | 0.6 (0.72)                |   |
| Week 12                         | 0.6 (0.80)      | 0.1 (0.27)                |   |
| LS mean (SE) change from baseline | 0.1 (0.09)    | −0.4 (0.08)               | 0.0001 |
| DIS                             |                 |                           |   |
| Baseline                        | 2.5 (0.77)      | 2.6 (0.62)                |   |
| Week 12                         | 2.3 (0.75)      | 1.8 (0.71)                |   |
| LS mean (SE) change from baseline | −0.3 (0.12)    | −0.8 (0.10)               | 0.0006 |
| SEA                             |                 |                           |   |
| Baseline                        | 0.7 (0.93)      | 1.0 (1.03)                |   |
| Week 12                         | 0.6 (0.82)      | 0.4 (0.65)                |   |
| LS mean (SE) change from baseline | −0.3 (0.12)    | −0.5 (0.10)               | 0.1495 |
| DEC                             |                 |                           |   |
| Baseline                        | 0.1 (0.21)      | 0.1 (0.22)                |   |
| Week 12                         | 0.1 (0.16)      | 0.1 (0.17)                |   |
| LS mean (SE) change from baseline | −0.0 (0.03)    | −0.0 (0.02)               | 0.9470 |
| LPF                             |                 |                           |   |
| Baseline*                       | 1.6 (1.13)      | 2.4 (0.64)                |   |
| Week 12†                        | 1.7 (1.19)      | 1.3 (1.11)                |   |
| LS mean (SE) change from baseline | −0.3 (0.29)    | −1.1 (0.24)               | 0.0474 |

LS mean (SE) change from baseline is also shown for each feature.

Data are presented as mean (SD) for placebo or BOS for each histopathologic feature unless otherwise stated. LS mean (SE) values were determined using an analysis of covariance model, including treatment group and baseline value as a covariate.

DIS indicates dilated intercellular spaces.

*Placebo, n = 26; BOS, n = 31.
†Placebo, n = 17; BOS, n = 30.
‡Placebo, n = 14; BOS, n = 21.

TABLE 3. Mean (SD) Stage Scores For Each EoE HSS Histopathologic Feature at Baseline and at Week 12 For Patients Receiving BOS (2.0 mg bid) and Placebo

| EoE HSS Histopathologic Feature | Placebo (n = 38) | BOS (2.0 mg bid) (n = 49) | P |
|----------------------------------|-----------------|---------------------------|---|
| EI                              |                 |                           |   |
| Baseline                        | 1.9 (0.88)      | 2.3 (0.63)                |   |
| Week 12                         | 1.8 (1.11)      | 0.8 (0.97)                |   |
| LS mean (SE) change from baseline | −0.2 (0.16)    | −1.5 (0.14)               | <0.0001 |
| BZH                             |                 |                           |   |
| Baseline                        | 2.3 (0.82)      | 2.6 (0.50)                |   |
| Week 12                         | 2.3 (0.85)      | 1.4 (1.15)                |   |
| LS mean (SE) change from baseline | −0.0 (0.16)    | −1.1 (0.14)               | <0.0001 |
| EA                              |                 |                           |   |
| Baseline                        | 0.3 (0.34)      | 0.4 (0.44)                |   |
| Week 12                         | 0.3 (0.44)      | 0.1 (0.19)                |   |
| LS mean (SE) change from baseline | 0.0 (0.05)    | −0.3 (0.05)               | 0.0001 |
| SL                              |                 |                           |   |
| Baseline                        | 0.3 (0.46)      | 0.5 (0.56)                |   |
| Week 12                         | 0.3 (0.46)      | 0.1 (0.22)                |   |
| LS mean (SE) change from baseline | −0.0 (0.06)    | −0.3 (0.05)               | 0.0006 |
| DIS                             |                 |                           |   |
| Baseline                        | 2.5 (0.81)      | 2.6 (0.65)                |   |
| Week 12                         | 2.7 (0.83)      | 2.4 (0.90)                |   |
| LS mean (SE) change from baseline | 0.1 (0.14)    | −0.2 (0.12)               | 0.0593 |
| SEA                             |                 |                           |   |
| Baseline                        | 0.4 (0.45)      | 0.7 (0.74)                |   |
| Week 12                         | 0.6 (0.86)      | 0.3 (0.44)                |   |
| LS mean (SE) change from baseline | 0.0 (0.11)    | −0.3 (0.10)               | 0.0469 |
| DEC                             |                 |                           |   |
| Baseline                        | 0.1 (0.20)      | 0.1 (0.22)                |   |
| Week 12                         | 0.1 (0.16)      | 0.1 (0.17)                |   |
| LS mean (SE) change from baseline | −0.0 (0.03)    | −0.0 (0.02)               | 0.7731 |
| LPF                             |                 |                           |   |
| Baseline*                       | 2.1 (1.27)      | 2.8 (0.42)                |   |
| Week 12†                        | 2.0 (1.16)      | 1.8 (1.39)                |   |
| LS mean (SE) change from baseline | −0.6 (0.34)    | −0.8 (0.28)               | 0.6020 |

LS mean (SE) change from baseline is also shown for each feature.

Data are presented as mean (SD) for placebo or BOS for each histopathologic feature unless otherwise stated. LS mean (SE) values were determined using an analysis of covariance model, including treatment group and baseline value as a covariate.

DIS indicates dilated intercellular spaces.

*Placebo, n = 26; BOS, n = 31.
†Placebo, n = 17; BOS, n = 30.
‡Placebo, n = 14; BOS, n = 21.

Treatment in a randomized controlled trial of a single therapy; other EoE clinical trials using the EoE HSS have only reported aggregate data.21 Previous studies have shown that treatment with BOS (2.0 mg bid) resulted in statistically significant improvements in symptoms, endoscopy, and peak eosinophil counts in patients with EoE compared with placebo over 12 weeks.14 In addition to the improvement in mean peak, eosinophil counts previously reported,14 this analysis showed that treatment with BOS (2.0 mg bid) significantly improved the extent and severity of a range of other histopathologic features over 12 weeks, using the validated EoE HSS for total scores and individual feature scores.12 First, significantly greater improvements were observed in total scores for grade (extent) and stage (severity) of EoE in patients receiving BOS compared with patients receiving placebo. Second, significantly greater improvements in grade scores were observed for 6 of the 8 individually assessed histopathologic features in patients receiving BOS compared with patients receiving placebo. Similar findings were observed for stage scores; 5 of the 8 individually assessed histopathologic features had significantly greater improvements in patients.
receiving BOS compared with patients receiving placebo. However, it should be noted that grade and stage total scores for some histopathologic features, such as DEC, were very low at baseline, making treatment effect difficult to interpret. Overall, these findings demonstrate that BOS (2.0 mg bid) for 12 weeks not only reduced peak eosinophil counts in children and adults with EoE, showed that changes in EoE HSS LPF grade and stage scores from baseline to week 12 were greater in patients receiving BOS than those receiving placebo; however, this was only statistically significant for grade scores. This finding supports the potential improvement of fibrosis in adolescents and adults with EoE treated with BOS (2.0 mg bid) for 12 weeks. A number of other studies have also reported this reversibility of fibrosis after topical corticosteroid or dietary therapy in EoE.26–28 In contrast, a prospective study of fluticasone propionate in adults with EoE demonstrated a nonsignificant reduction in subepithelial fibrosis after 1 year of treatment. However, fibrosis scores in treated patients with EoE were still higher than those observed in healthy controls,29 demonstrating that further studies are needed to assess the reversibility of fibrosis in children, adolescents, and adults with EoE.

A strength of this analysis is that it was performed as part of a rigorously conducted phase 2 randomized, double-blind trial of BOS and provides the most complete histopathologic analysis of EoE, to our knowledge, by standardized central review by a pathologist masked to treatment allocation to date. Furthermore, this study used a range of validated outcome measures to assess histologic, symptomatic, and endoscopic features of adolescents and adults with EoE (the EoE HSS, DSQ, and EREFS, respectively).15,18,19 This is important considering the recent finding that clinical trials for EoE lack uniform definitions for histologic, endoscopic, and patient-reported outcomes.30 In this study, statistically significant correlations were found between the instruments used to evaluate changes in endoscopic pathology (ERefs) and microscopic pathology (EoE HSS) with treatment. These instruments were developed independently by a gastroenterologist (I.H.) and a pathologist (M.H.C.) with extensive experience in EoE. The positive correlations provide reassurance of the pertinence of the features measured by each instrument and indicate that the outcome measures used here should be employed in future clinical trials of patients with EoE.

The findings from this placebo-controlled, double-blind, randomized clinical trial have also highlighted several considerations that might impact daily practice for pathologists. First, changes in several histopathologic features evaluated here correlated significantly with changes in dysphagia (as measured by the DSQ), a common symptom among adult patients with EoE. Second, this study has shown that the extent (grade) and severity (stage) of pathology may be important to evaluate because of the correlation with EREFS and, to a lesser extent, dysphagia symptoms. This study provides evidence that reporting more than peak eosinophil counts may have additional clinical import and that clinical use of the EoE HSS should be

### TABLE 4. Correlation Analysis Between Change in Mean EoE HSS Grade and Stage Scores (Total Score and Individual Scores For Each EoE HSS Histopathologic Feature) Compared With Change in DSQ Score, and Change in EREFS Score From Baseline to Week 12 For All Patients (Irrespective of Treatment Allocation)*

| Change in EoE HSS Total Score or Individual Feature | Change in EREFS Score | Change in DSQ Score |
|-----------------------------------------------------|-----------------------|---------------------|
|                                                      | Pearson Correlation   | Pearson Correlation |
|                                                      | Coefficient $P$       | Coefficient $P$     |
| Grade: total score                                   | 0.5349 $< 0.0001$     | 0.1925 0.0740       |
| EI                                                   | 0.5605 $< 0.0001$     | 0.2496 0.0197       |
| BZH                                                 | 0.3192 $< 0.0001$     | 0.1070 0.3238       |
| EA                                                   | 0.2982 0.0050         | 0.0784 0.4705       |
| SL                                                   | 0.4279 $< 0.0001$     | 0.2185 0.0420       |
| DIS                                                 | 0.2686 0.0119         | 0.1290 0.2338       |
| SEA                                                  | 0.2451 0.0221         | 0.0558 0.6080       |
| DEC                                                 | $-0.0625 0.5654$      | 0.0802 0.4604       |
| LPF†                                                 | 0.2383 0.1680         | 0.2342 0.1757       |
| Stage: total score                                   | 0.5416 $< 0.0001$     | 0.2135 0.0471       |
| EI                                                   | 0.5718 $< 0.0001$     | 0.1839 0.0882       |
| BZH                                                 | 0.4623 $< 0.0001$     | 0.1773 0.1005       |
| EA                                                   | 0.3322 0.0017         | 0.0807 0.4574       |
| SL                                                   | 0.4328 $< 0.0001$     | 0.2110 0.0498       |
| DIS                                                 | 0.2400 0.0251         | 0.1271 0.2408       |
| SEA                                                  | 0.3168 0.0028         | 0.1563 0.1482       |
| DEC                                                 | $-0.6025 0.5654$      | 0.0802 0.4604       |
| LPF†                                                 | 0.1155 0.5087         | 0.1380 0.4292       |

DIS indicates dilated intercellular spaces.

*Total number of patients assessed: N = 87 (placebo, n = 38; BOS, n = 49).
†Total number of patients assessed for LPF: N = 35 (placebo, n = 14; BOS, n = 21).

endoscopically, especially the muscularis propria, may contribute to symptomatology.

A limitation of this study was that LPF could not be assessed in a substantial proportion of samples, decreasing the number of data points available. This low yield is typical of endoscopic forceps used in the United States, compared with a type that is used in Europe that can provide a higher yield.25 Despite this, further analysis showed that improvements in EoE HSS LPF grade and stage scores from baseline to week 12 were greater in patients receiving BOS than those receiving placebo; however, this was only statistically significant for grade scores. This finding supports the potential improvement of fibrosis in adolescents and adults with EoE treated with BOS (2.0 mg bid) for 12 weeks. A number of other studies have also reported this reversibility of fibrosis after topical corticosteroid or dietary therapy in EoE.26–28...
considered by surgical pathologists. In fact, the EoE HSS has been reported to be reliable by pathologists who were not involved in its development.31 Warners et al31 reported almost perfect interobserver agreement scores for EoE HSS grade and stage total scores (intraclass coefficients of 0.84 and 0.88, respectively). Most individual histopathologic feature grade and stage scores were also rated above the benchmarks for moderate interobserver agreement.31 Although more data on the utility of the EoE HSS are needed, including an assessment of the frequency and relative levels of importance of the 8 histopathologic features examined, pathologists should consider our findings that changes in eosinophil SL scores, both severity and extent, correlate with changes in DSQ scores. Furthermore, in patients who have strictures, changes in EA scores, both grade and stage, and change in LPF severity correlate with change in DSQ scores. In addition to our findings, EoE HSS features have been shown to correlate positively with symptoms and negatively with health-related quality of life scores in pediatric and adult patients with EoE in a large observational study.32 These data collectively suggest that including evaluation of these features in surgical pathology reports may provide clinically meaningful treatment endpoints.

Several post hoc analyses were performed that demonstrated consistent correlations between change in inflammatory EREFS features and change in EoE HSS (grade and stage scores) in the proximal and distal esophagus, providing validation of both measures. These analyses also highlighted a very strong correlation between change in LPF and change in DSQ scores in patients who had strictures; however, there were only 5 patients who could be included in this analysis. Larger studies would, therefore, be required to confirm or refute these suggestive data.

In conclusion, this study represents, to our knowledge, the most comprehensive analysis of EoE histopathology before and after treatment with a single therapy. It also demonstrates that patients receiving BOS (2.0 mg bid) experience significant improvements not only in peak eosinophil counts,14 but also in a range of other histopathologic features associated with histologic severity and active disease in EoE, compared with placebo. In addition, the changes in EoE HSS total scores (and individual feature scores) correlate moderately with a change in EREFS scores (and to a lesser extent change in DSQ scores). These data also demonstrate that the EoE HSS, used collectively and with selective histologic features, is responsive and suitable for use as a valuable endpoint of treatment response in randomized clinical trials and should be considered for future trials for EoE.

ACKNOWLEDGMENTS

The authors thank all MPI 101-06 investigators (listed in the Supplementary Materials Supplemental Digital Content 1, http://links.lww.com/PASI/A838) and participants for their contribution to this study and associated manuscripts.14,17 They also thank Luci Witcomb, PhD, of PharmaGenesis London, London, United Kingdom, for providing medical writing support funded by Shire International GmbH, a member of the Takeda Group of Companies.

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