





# Dupilumab demonstrated efficacy and was well tolerated regardless of prior use of swallowed topical corticosteroids in adolescent and adult patients with eosinophilic oesophagitis: a subgroup analysis of the phase 3 LIBERTY EoE TREET study

Albert J Bredenoord ,<sup>1</sup> Evan S Dellon,<sup>2</sup> Ikuo Hirano ,<sup>3</sup> Alfredo J Lucendo ,<sup>4</sup> Christoph Schlag,<sup>5</sup> Xian Sun,<sup>6</sup> Lila Glotfelty,<sup>7</sup> Leda Mannent,<sup>7</sup> Jennifer Maloney,<sup>6</sup> Elizabeth Laws,<sup>7</sup> Eric Mortensen,<sup>6</sup> Arsalan Shabbir<sup>6</sup>

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For numbered affiliations see end of article.

## Correspondence to

Dr Albert J Bredenoord, Amsterdam University Medical Centres, Amsterdam, The Netherlands; [a.j.bredenoord@amsterdamumc.nl](mailto:a.j.bredenoord@amsterdamumc.nl)

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## ABSTRACT

**Objective** To assess the effect of long-term dupilumab on histological, symptomatic and endoscopic aspects of eosinophilic oesophagitis (EoE) in adolescent and adult patients with and without prior use of swallowed topical corticosteroids (STC) or prior inadequate response, intolerance or contraindication to STC.

**Design** Pre-specified analysis of data from the phase 3 LIBERTY EoE TREET study on patients who received dupilumab 300 mg once a week or placebo for 24 weeks (W24) in parts A and B, and an additional 28 weeks (W52) in part C. Patients were categorised as with/without prior STC use and with/without inadequate/intolerance/contraindication to STC. The proportion of patients achieving  $\leq 6$  eosinophils per high-power field (eos/hpf), absolute change in Dysphagia Symptom Questionnaire (DSQ) score, mean change in Endoscopic Reference Score and Histologic Scoring System grade/stage scores were assessed for each subgroup.

**Results** Regardless of prior STC use, dupilumab increased the proportion of patients achieving  $\leq 6$  eos/hpf and improved DSQ score versus placebo at W24, with improvements maintained or improved at W52. The DSQ score and the proportion of patients achieving  $\leq 6$  eos/hpf after switching from placebo to dupilumab at W24 were similar to those observed in the dupilumab group at W24, regardless of prior STC use or inadequate/intolerance/contraindication to STC. Improvements in other outcomes with dupilumab were similar in patients with/without prior STC use or inadequate/intolerance/contraindication to STC.

**Conclusion** Dupilumab 300 mg once a week demonstrated efficacy and was well tolerated in patients with EoE regardless of prior STC use or inadequate response, intolerance and/or contraindication to STC.

**Trial registration number** NCT03633617.

## INTRODUCTION

Eosinophilic oesophagitis (EoE) is a chronic, progressive, type 2 inflammatory disease with substantial impact on quality of life and increasing incidence and prevalence.<sup>1–5</sup> Historically, there

## WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Swallowed topical corticosteroids (STC) are used for the treatment of eosinophilic oesophagitis (EoE), but inadequate or loss of response is common, and long-term use may be associated with side effects.
- ⇒ Once a week dupilumab improved histological outcomes and alleviated disease symptoms in adults and adolescents with active EoE.
- ⇒ Prior to the approval of dupilumab, there were few alternative treatment options for patients with EoE who fail to respond to or are intolerant of STC.

## WHAT THIS STUDY ADDS

- ⇒ The subgroup analysis of the LIBERTY EoE TREET randomised controlled trial demonstrated that dupilumab 300 mg once a week is a well-tolerated and efficacious treatment option for adult and adolescent patients with EoE, regardless of prior use of STC or inadequate response, intolerance and/or contraindication to STC.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ These results indicate that prior treatment history with STC does not affect dupilumab's efficacy for patients with EoE.

has been a lack of treatments approved for EoE, and options were non-specific, presented adherence challenges and offered suboptimal long-term disease control.<sup>6–9</sup> Swallowed topical corticosteroids (STC) are a current treatment option for EoE and a budesonide formulation is approved in most Western countries.<sup>10</sup> Several studies have demonstrated the short-term and long-term efficacy of STC in improving clinical and histological aspects of EoE, with the majority of patients achieving histological disease remission.<sup>6 11 12</sup> Notably, long-term treatment with budesonide orodispersible

**Table 1** Baseline and disease characteristics of patients with or without use of prior STC

	Part A		Part B		
	Placebo (n=39)	Dupilumab qw (n=42)	Placebo (n=79)	Dupilumab qw (n=80)	Dupilumab q2w (n=81)
Age (years), mean (SD)					
With prior STC use	28.2 (12.4)	29.3 (14.9)	28.5 (12.1)	28.2 (14.5)	27.6 (13.6)
Without prior STC use	31.3 (13.8)	44.1 (12.1)	26.3 (13.7)	29.6 (11.9)	28.5 (11.6)
Sex (female), n (%)					
With prior STC use	15 (38.5)	9 (21.4)	16 (20.3)	24 (30.0)	28 (34.6)
Without prior STC use	3 (7.7)	5 (11.9)	5 (6.3)	6 (7.5)	8 (9.9)
Duration of EoE (years), mean (SD)					
With prior STC use	5.5 (4.8)	5.6 (4.0)	6.3 (4.3)	6.6 (4.9)	6.6 (5.1)
Without prior STC use	2.1 (1.7)	4.4 (4.6)	1.4 (2.5)	4.4 (3.9)	3.2 (4.9)
History of prior swallowed topical corticosteroid use for EoE, n (%)					
With prior STC use	31 (79.5)	29 (69.0)	56 (70.9)	55 (68.8)	65 (80.2)
Without prior STC use	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Inadequate response, intolerant or contraindicated to swallowed topical corticosteroids, n (%)					
With prior STC use*	–	–	38 (48.1)	37 (46.3)	41 (50.6)
Without prior STC use*	–	–	1 (1.3)	1 (1.3)	0 (0.0)

\*Data not collected for part A.  
EoE, eosinophilic oesophagitis; qw, once a week; q2w, every two weeks; STC, swallowed topical corticosteroids.

tablets showed maintenance of clinical and histological remission in most patients compared with placebo.<sup>13</sup> However, treatment adherence can be challenging,<sup>14</sup> and there is a high prevalence of disease recurrence should the treatment for EoE be stopped<sup>15</sup>; histological and symptomatic relapses (ie, loss of response) can also occur despite ongoing STC treatment.<sup>11–16</sup> Although rare, STC side effects include candida infections and adrenal insufficiency.<sup>17–18</sup>

Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for interleukin (IL)-4/IL-13, key and central drivers of type 2 inflammation in multiple diseases including EoE.<sup>19–21</sup> A phase 3 study of dupilumab 300 mg once a week (LIBERTY EoE TREET) demonstrated histological remission and improvements in symptoms, as well as consistent improvement in endoscopic and molecular aspects of the disease, in adults and adolescents with EoE up to 52 weeks.<sup>22–23</sup> Dupilumab is approved in the USA and EU for the treatment of EoE in adults and adolescents 12 years or older weighing at least 40 kg.<sup>24–25</sup> In some gastrointestinal diseases such as inflammatory bowel disease, failure on corticosteroids is an unfavourable prognostic characteristic associated with failure on subsequent treatments and increased occurrence of complications.<sup>26–27</sup> Therefore, an assessment of the efficacy of dupilumab on patients with previous use of glucocorticoids has been previously suggested.<sup>23</sup> The aim of the current subgroup analysis of the LIBERTY EoE TREET study was therefore to assess the efficacy and safety of dupilumab 300 mg versus placebo once a week for up to 52 weeks of treatment in patients according to previous use of STC, and inadequate response, intolerance and/or contraindication to STC.

## METHODS

### Study design

This was a pre-specified analysis of data collected during parts A, B and C of the phase 3, multicentre, randomised, double-blind, placebo-controlled LIBERTY EoE TREET study (NCT03633617), details of which have been previously published.<sup>22</sup> Briefly, patients with active EoE despite the use of high-dose proton pump inhibitors (PPIs) were randomised 1:1 to subcutaneous placebo or dupilumab 300 mg once a week (part

A) or 1:1:1 to subcutaneous placebo or dupilumab 300 mg once a week or dupilumab 300 mg every 2 weeks, for 24 weeks (part B). PPI use at baseline was maintained throughout the treatment period, while new initiation of PPI was prohibited. Prior use of STC was permitted, however use of STC was prohibited within 8 weeks prior to baseline and as a background therapy during the treatment period. Patients who completed parts A and B entered part C (parts A–C and B–C, respectively) for 28 weeks. Part A patients who continued to part C received dupilumab 300 mg once a week; part B patients who received dupilumab continued on the same regimen in part C and those who received placebo were re-randomised 1:1 to dupilumab 300 mg once a week or every 2 weeks. The current analysis included patients treated with dupilumab 300 mg once a week (the approved regimen) or placebo, unless otherwise stated.

### Patients

In the LIBERTY EoE TREET study, inclusion and exclusion criteria were identical for parts A and B as previously described.<sup>22</sup> Briefly, adolescents ( $\geq 12$  to  $< 18$  years) and adults ( $\geq 18$  years) with confirmed diagnosis of EoE (peak eosinophil count  $\geq 15$  eosinophils per high-power field (eos/hpf)) despite 8 weeks of high-dose PPI treatment and a Dysphagia Symptom Questionnaire (DSQ) score of  $\geq 10$  at randomisation were eligible. Patients were required to have an STC washout period of 8 weeks. At the screening visit, clinicians categorised patients according to their clinical history of STC. For parts A and B, patients who had previously used STC were categorised as ‘with prior STC use’ and patients with no previous use as ‘without prior STC use’. For part B only, (1) patients for whom STC use for the treatment of EoE was deemed ineffective in relieving EoE symptoms by the clinician were categorised as ‘with inadequate response to STC’, (2) patients who had to stop effective STC treatment for EoE due to concomitant medical concerns or contraindications or side effect(s) were categorised as ‘with intolerance to STC’, and (3) patients who never used STC for the treatment of EoE due to concomitant medical concerns, or contraindication (eg, diabetes, immunomodulating treatment) or potential side effect(s) from STC were categorised as ‘with contraindication to STC’; all together, these patients were categorised as with

**Table 2** Baseline and disease characteristics of patients with or without inadequate response, intolerance and/or contraindication to STC

	Part B		
	Placebo (n=79)	Dupilumab qw (n=80)	Dupilumab q2w (n=81)
Age (years), mean (SD)			
With prior inadequate response to STC	28.9 (11.0)	29.2 (15.7)	26.8 (12.7)
Without prior inadequate response to STC	26.9 (14.0)	28.2 (11.8)	28.9 (13.8)
Sex (female), n (%)			
With prior inadequate response to STC	14 (17.7)	16 (20.0)	19 (23.5)
Without prior inadequate response to STC	7 (8.9)	14 (17.5)	17 (21.0)
Duration of EoE (years), mean (SD)			
With prior inadequate response to STC	5.9 (4.3)	7.0 (5.2)	5.9 (5.0)
Without prior inadequate response to STC	3.9 (4.5)	4.9 (3.9)	5.9 (5.5)
History of prior swallowed topical corticosteroid use for EoE, n (%)			
With prior inadequate response to STC	38 (48.1)	37 (46.3)	41 (50.6)
Without prior inadequate response to STC	18 (22.8)	18 (22.5)	24 (29.6)
Inadequate response, intolerant or contraindicated to swallowed topical corticosteroids, n (%)			
With prior inadequate response to STC	39 (49.4)	38 (47.5)	41 (50.6)
Without prior inadequate response to STC	0 (0.0)	0 (0.0)	0 (0.0)

EoE, eosinophilic oesophagitis; qw, once a week; q2w, every 2 weeks; STC, swallowed topical corticosteroids.

or without ‘inadequate response, intolerance and/or contraindication to STC’. In this manuscript, an ‘inadequate response, intolerance and/or contraindication to treatment with STC’ will be stated as ‘STC inadequate/intolerance/contraindication’ to facilitate reading.

Analysis of prior STC use (with/without) included all patients; analysis with STC inadequate/intolerance/contraindication included only patients from parts B and B–C (as data related to this were not collected for part A).

### Outcomes and assessments

For parts A and B, the co-primary endpoints of LIBERTY EoE TREET were the proportion of participants achieving peak oesophageal intraepithelial eosinophil count of  $\leq 6$  eos/hpf<sup>28 29</sup> and the absolute change in DSQ score (range 0–84; higher scores indicate greater dysphagia-related symptom burden)<sup>30 31</sup> at week 24. The key secondary endpoints were the percentage change in peak oesophageal intraepithelial eosinophil count, the absolute changes in Histology Scoring System (HSS) mean grade and stage scores (range 0–3; higher scores indicate greater severity),<sup>32</sup> and the absolute change in the Endoscopic Reference Score (EREFS; range 0–18; higher scores indicate greater severity).<sup>33</sup> Other secondary endpoints included the proportion of patients achieving peak oesophageal intraepithelial eosinophil count of  $< 15$  eos/hpf and the percentage change in DSQ score at week 24. All above endpoints were assessed as secondary endpoints in part C.

All above endpoints were assessed in this analysis.

### Statistical analyses

#### Efficacy analysis in part A and part B

Efficacy analyses were performed using the full analysis set, which included all randomised patients, according to the treatment allocated by the Interactive Voice Response Systems/Interactive Web Response Systems at randomisation. Safety was assessed using the safety analysis set, which included all randomised patients who received at least 1 dose of study drug.

For binary variables, p-values were derived using the Cochran–Mantel–Haenszel test stratified by age group ( $\geq 12$  to  $< 18$  vs  $\leq 18$  years) and use of PPI at randomisation (yes vs no). For continuous variables, p-values were based on least squares

(LS) mean changes using an analysis of covariance model with baseline measurement as covariate and the treatment, age group ( $\geq 12$  to  $< 18$  vs  $\leq 18$  years) and PPI use at randomisation (yes vs no) strata as fixed factors. All calculated p-values are nominal.

For all endpoints, values after first rescue treatment used were set to missing (censored). Patients with missing peak oesophageal intraepithelial eosinophil count at week 24 were considered non-responders, unless the data were missing due to COVID-19, in which case multiple imputation was used. For the co-primary endpoint of change in DSQ score, missing values were imputed by multiple imputation. For all other endpoints, missing values were imputed by worst observation carried forward method if not due to COVID-19 and by multiple imputation if due to COVID-19.

#### Efficacy analysis in part A–C and part B–C

Endpoints at week 52 were analysed using descriptive statistics, without comparator. The summaries were based on all observed data from the part C safety analysis set, which included all patients who received at least one dose in part C.

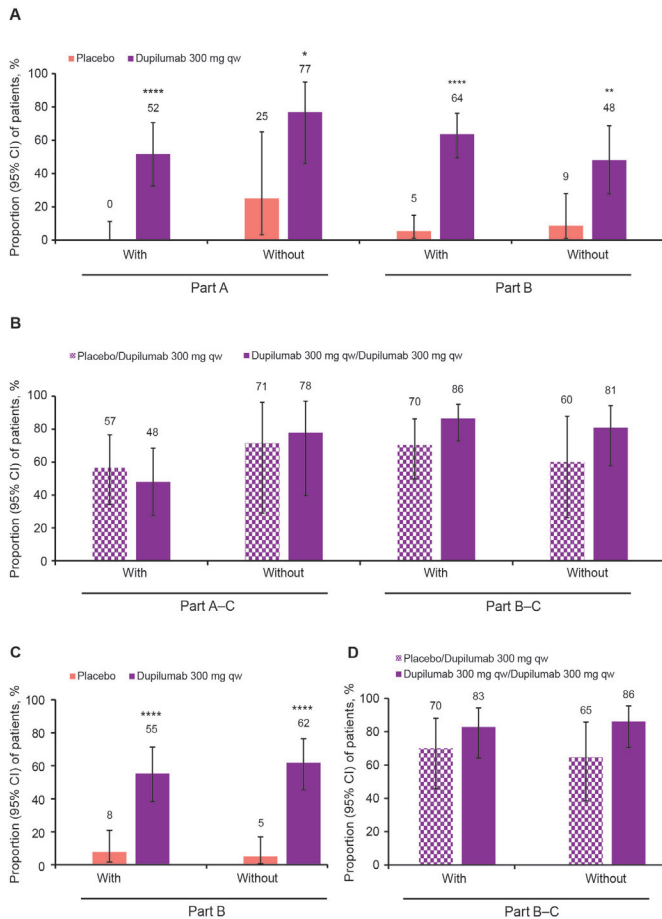
## RESULTS

### Patients

In part A, 42 patients were randomised to dupilumab once a week and 39 to placebo; in part B, 80 patients were randomised to dupilumab once a week, 81 to dupilumab every 2 weeks and 79 to placebo. Thirty-seven patients from part A switched from placebo to dupilumab and 40 continued dupilumab (part A–C); 37 patients from part B switched from placebo to dupilumab once a week and 37 to dupilumab every 2 weeks; 74 continued dupilumab once a week and 79 continued dupilumab every 2 weeks (part B–C).

The proportions of patients with a history of prior STC use were 74% in part A and 70% in part B. Demographics and disease characteristics of patients with and without prior STC use are shown in [table 1](#) and online supplemental table 1 and were generally similar between subgroups.

In total, 48% of patients in part B were categorised as having a history of prior STC inadequate/intolerance/contraindication. Demographics and disease characteristics of patients with and without STC inadequate/intolerance/contraindication for part B



**Figure 1** Proportion of patients with peak oesophageal intraepithelial eosinophil count  $\leq 6$  eos/hpf with or without use of prior STC at (A) week 24 and (B) week 52, and with or without inadequate response, intolerance and/or contraindication to STC at (C) week 24 and (D) week 52. \*\*\*\* $p < 0.0001$ , \*\* $p < 0.01$ , \* $p < 0.05$  versus placebo. eos/hpf, eosinophils per high-power field; qw, once a week; STC, swallowed topical corticosteroids.

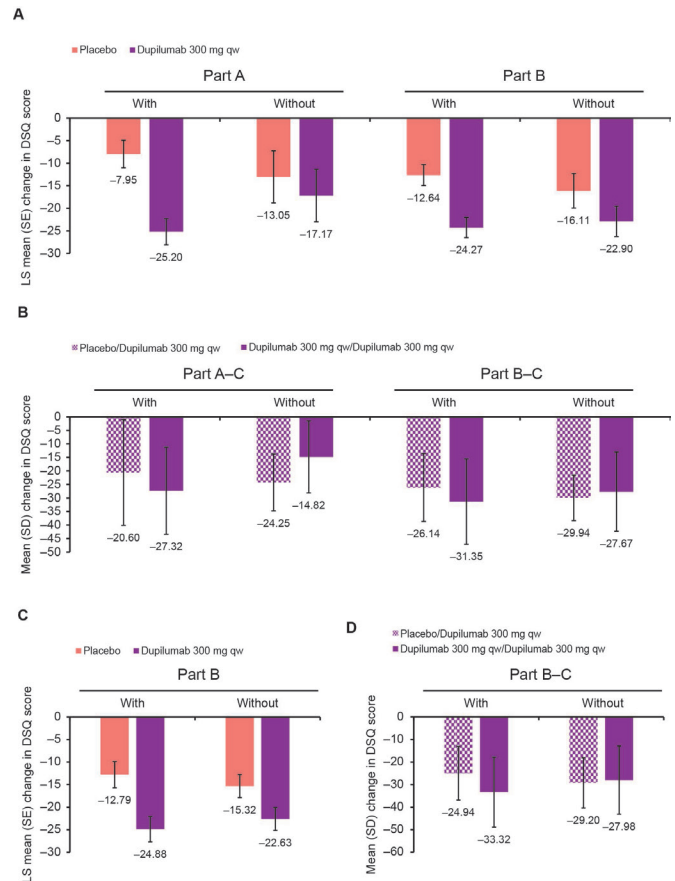
are shown in [table 2](#) and online supplemental table 2 and were generally similar between subgroups.

### Primary endpoints

#### With/without prior STC use

Dupilumab increased the proportion of patients achieving peak oesophageal intraepithelial eosinophil count  $\leq 6$  eos/hpf versus placebo at week 24 in both patients with prior STC use (52% dupilumab vs 0% placebo,  $p < 0.0001$ , and 64% vs 5%,  $p < 0.0001$  in parts A and B, respectively) and patients without prior STC use (77% vs 25%,  $p < 0.05$  and 48% vs 9%,  $p < 0.01$ , respectively) ([figure 1A](#)). In both subgroups, after the 28-week extension period (week 52) the proportion of patients achieving peak oesophageal intraepithelial eosinophil count  $\leq 6$  eos/hpf was either maintained (part A–C) or further increased (part B–C) from week 24 in patients receiving continuous dupilumab and increased for the patients who switched from placebo to dupilumab at week 24 ([figure 1B](#)). Similar results were observed with dupilumab every 2 weeks treatment (online supplemental figure 1A).

The DSQ scores of dupilumab-treated patients improved (decreased) versus those receiving placebo through week 24 in the subgroup with prior STC use ([figure 2A](#) and online supplemental figure 2A and 3A,B) (LS mean difference (95% CI) dupilumab vs placebo part A  $-17.25$  ( $-25.15$  to  $-9.35$ ), part B  $-11.63$  ( $-17.64$

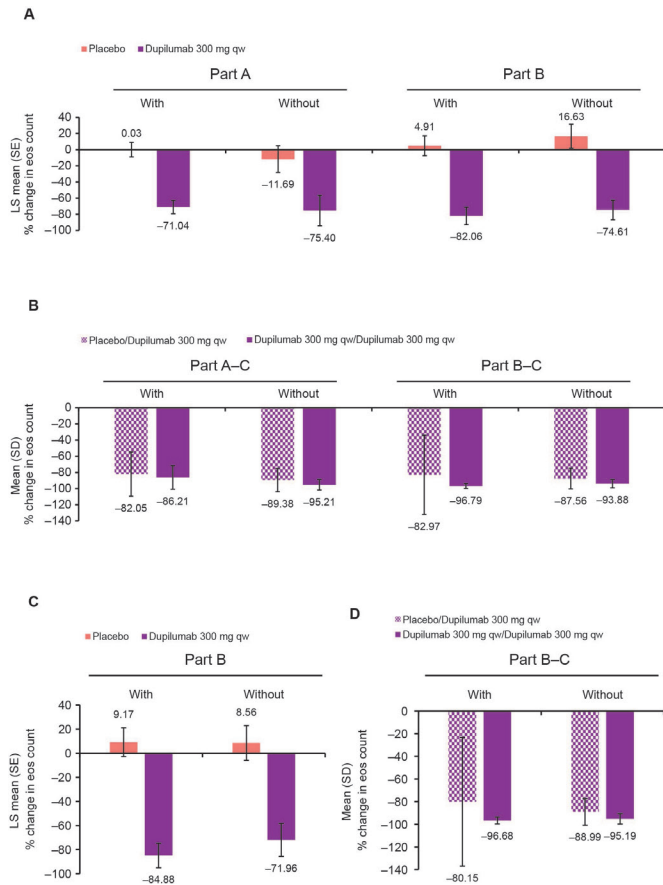


**Figure 2** Change from baseline part A or B in DSQ score for patients with or without use of prior STC at (A) week 24 and (B) week 52, and with or without inadequate response, intolerance and/or contraindication to STC at (C) week 24 and (D) week 52. DSQ, Dysphagia Symptom Questionnaire; LS, least squares; qw, once a week; STC, swallowed topical corticosteroids.

to  $-5.62$ )). In the subgroup without prior STC use, DSQ score was also improved vs placebo ( $-4.11$  ( $-16.18$  to  $7.96$ ) in part A,  $-6.79$  ( $-15.78$  to  $2.20$ ) in part B), although compared with patients with prior STC use, the differences between the placebo and dupilumab groups were smaller due to the larger improvement in DSQ score in the placebo group. In both subgroups, the DSQ scores were maintained (part A–C) or improved (part B–C) between week 24 and week 52 for the patients receiving continuous dupilumab and improved for the patients who switched from placebo to dupilumab at week 24 ([figure 3B](#) and online supplemental figure 2B and 4A,B). The DSQ scores of patients treated with dupilumab every 2 weeks did not improve versus those receiving placebo at week 24 or to the same extent as those receiving dupilumab once a week through week 52 (online supplemental figures 5A, 6A and 7).

#### With/without prior STC inadequate/intolerance/contraindication

Treatment with dupilumab increased the proportion of patients achieving peak oesophageal intraepithelial eosinophil count  $\leq 6$  eos/hpf versus placebo both in patients with (55% vs 8%,  $p < 0.0001$ ) and in patients without (62% vs 5%,  $p < 0.0001$ ) STC inadequate/intolerance/contraindication at week 24 ([figure 1C](#)). In both subgroups, the proportion of patients achieving peak oesophageal intraepithelial eosinophil count  $\leq 6$  eos/hpf further increased between week 24 and week 52 for the patients receiving continuous dupilumab treatment (83% with and 86% without) and increased in patients who switched from placebo



**Figure 3** Per cent change from baseline part A or B in peak oesophageal intraepithelial eos count in patients with or without use of prior STC at (A) week 24 and (B) week 52, and with or without inadequate response, intolerance and/or contraindication to STC at (C) week 24 and (D) week 52. eos, eosinophils; LS, least squares; qw, once a week; STC, swallowed topical corticosteroids.

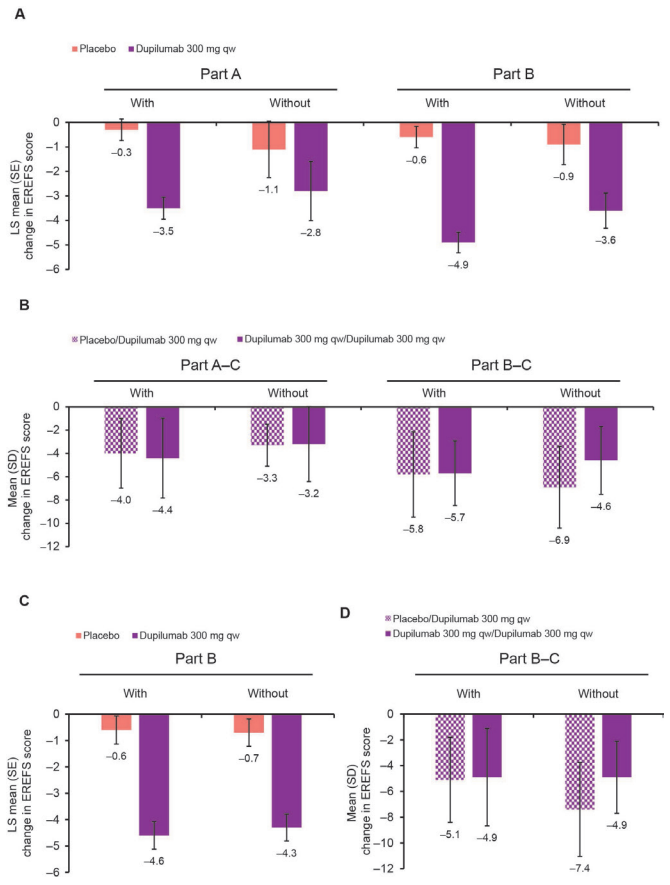
to dupilumab at week 24 (70% with and 65% without). Similar results were observed with dupilumab every 2 weeks treatment (online supplemental figure 1B).

Dupilumab treatment also improved the DSQ scores versus treatment with placebo through week 24 both in patients with (-12.10 (-19.66 to -4.53)) and in patients without (-7.31 (-13.90 to -0.73)) prior STC inadequate/intolerance/contraindication (figure 2C and online supplemental figure 2C,3C). In both subgroups, the DSQ score further improved between week 24 and week 52 for the patients receiving continuous dupilumab (absolute change (SD) change with -33.32 (15.55), without -27.98 (15.12)) and improved in patients who switched from placebo to dupilumab (with -24.94 (11.88), without -29.20 (11.18)) (figure 2D and online supplemental figure 2D,4C). Similar to patients with and without prior STC use, the DSQ scores of patients treated with dupilumab every 2 weeks did not improve versus those receiving placebo at week 24 or to the same extent as those receiving dupilumab once a week through week 52 (online supplemental figures 5B, 6B and 8).

**Secondary endpoints**

**Peak oesophageal intraepithelial eosinophil count**

Dupilumab treatment resulted in a greater percentage decrease from baseline in peak oesophageal intraepithelial eosinophil count at week 24 versus placebo (figure 3A) in both patients with and patients without prior STC use. Regardless of prior



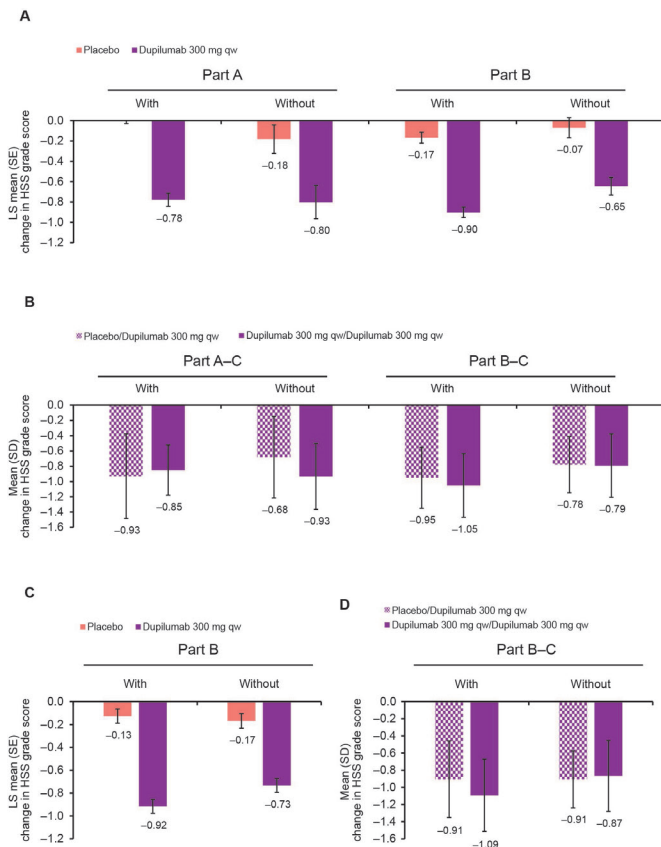
**Figure 4** Absolute change in EREFS total score from baseline part A or B with or without use of prior STC at (A) week 24 and (B) week 52, and with or without inadequate response, intolerance and/or contraindication to STC to (C) week 24 and (D) week 52. EREFS, Endoscopic Reference Score; LS, least squares; qw, once a week; STC, swallowed topical corticosteroids.

STC use, at week 52 (figure 3B), the percentage change from baseline (parts A or B) in peak oesophageal intraepithelial eosinophil count of patients continuously on dupilumab further increased from week 24 and increased in patients who switched from placebo to dupilumab to levels similar to those observed for patients continuously on dupilumab. Similar results were observed in patients treated with dupilumab every 2 weeks (online supplemental figure 9A).

The percentage change from baseline in peak oesophageal intraepithelial eosinophil count at week 24 improved (decreased) with dupilumab versus placebo both in patients with STC inadequate/intolerance/contraindication and those without STC inadequate/intolerance/contraindication (figure 3C). At week 52, continuous dupilumab treatment further improved the percentage change in peak oesophageal intraepithelial eosinophil count from week 24, and switch from placebo to dupilumab at week 24 improved the percentage change in peak oesophageal intraepithelial eosinophil count to levels similar to patients who received dupilumab continuously, regardless of prior inadequate response to STC (figure 3D). Similar results were observed in patients treated with dupilumab every 2 weeks (online supplemental figure 9B).

**Endoscopic severity (EREFS)**

At week 24, dupilumab-treated patients (figure 4A) had lower EREFS score versus placebo regardless of prior STC use in both



**Figure 5** Absolute change in HSS grade score from baseline part A or B with or without use of prior STC at (A) week 24 and (B) week 52, and with or without inadequate response, intolerance and/or contraindication to STC to (C) week 24 and (D) week 52. HSS, Histology Scoring System; LS, least squares; qw, once a week; STC, swallowed topical corticosteroids.

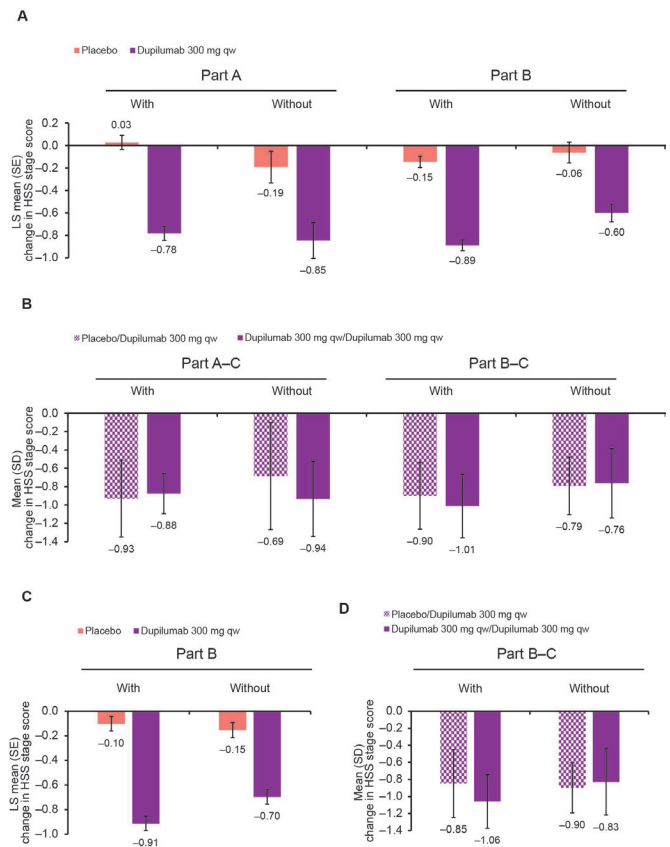
parts A and B. From week 24 to week 52 (figure 4B), EREFS scores further improved (decreased) in patients who continued dupilumab and improved in patients who switched from placebo to dupilumab at week 24, regardless of prior STC use. Similar results were observed in patients treated with dupilumab every 2 weeks (online supplemental figure 10A).

Dupilumab decreased the EREFS scores versus placebo both in patients with and in patients without a history of inadequate response to STC at week 24 (figure 4C). From week 24 to week 52 (figure 4D), patients who switched from placebo to dupilumab at week 24 improved their EREFS scores to levels close to those of patients who were continuously on dupilumab, regardless of STC inadequate/intolerance/contraindication. Similar results were observed in patients treated with dupilumab every 2 weeks (online supplemental figure 10B).

#### Histological severity (EoE HSS)

Dupilumab also improved the histological severity of the disease versus placebo as reflected by reduction in HSS grade scores, regardless of the patient history of STC use at week 24 (figure 5A) in both parts A and B. At week 52 (figure 5B), HSS grade scores further improved from week 24 in patients who were continuously on dupilumab and improved in patients who switched from placebo to dupilumab at week 24.

For patients with and without STC inadequate/intolerance/contraindication, HSS grade scores were improved with dupilumab versus placebo at week 24 in both subgroups (figure 5C).



**Figure 6** Absolute change in HSS stage score from baseline part A or B with or without use of prior STC at (A) week 24 and (B) week 52, and with or without inadequate response, intolerance and/or contraindication to STC to (C) week 24 and (D) week 52. HSS, Histology Scoring System; LS, least squares; qw, once a week; STC, swallowed topical corticosteroids.

From week 24 to week 52, HSS grade scores further improved in patients continuously on dupilumab and improved in patients switching from placebo to dupilumab at week 24 to levels close to patients continuously on dupilumab at Week 24 (figure 5D).

HSS stage score was improved in a similar way as the HSS grade scores, regardless of prior STC use or STC inadequate/intolerance/contraindication at week 24 and week 52 (figure 6). Similar results were observed in patients treated with dupilumab every 2 weeks (online supplemental figures 11,12).

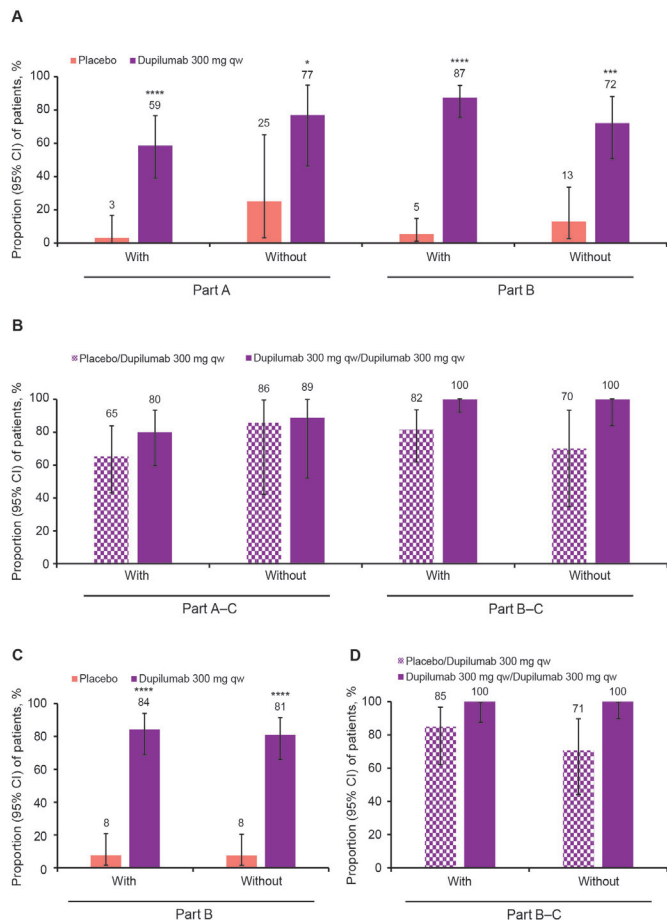
#### Peak oesophageal intraepithelial eosinophil <15 eos/hpf

Finally, dupilumab treatment increased the proportions of patients reaching peak oesophageal intraepithelial eosinophil <15 eos/hpf at week 24 (figure 7A,B) versus placebo in both patients with and patients without prior STC use. Similar results were observed in patients with and without STC inadequate/intolerance/contraindication and in patients treated with dupilumab every 2 weeks (online supplemental figure 13).

Notably, regardless of prior STC use or STC inadequate/intolerance/contraindication, 100% of patients continuously on dupilumab reached peak oesophageal intraepithelial eosinophil <15 eos/hpf at week 52 (figure 7C,D).

#### Safety

The safety profile of dupilumab was consistent with that reported previously, with no major differences in the incidence or type



**Figure 7** Proportion of patients with peak oesophageal intraepithelial eosinophil count <15 eos/hpf with or without use of prior STC at (A) week 24 and (B) week 52, and with or without inadequate response, intolerance and/or contraindication to STC at (C) week 24 and (D) week 52. \*\*\*\*p<0.0001, \*\*\*p<0.001, \*p<0.05 versus placebo. eos/hpf, eosinophils per high-power field; qw, once a week; STC, swallowed topical corticosteroids.

of adverse events, including serious adverse events, across the subgroups (online supplemental tables 3 and 4).

**DISCUSSION**

STCs are used as a standard-of-care treatment for EoE and although they may be effective, they can fail to induce histological remission in some patients.<sup>34</sup> Relapses or loss of response are common,<sup>34 35</sup> and adherence to treatment can be challenging.<sup>14</sup> Additional treatment options currently include PPIs and dietary elimination therapy, but up to half of patients may not respond.<sup>36</sup> Consistent with this, all patients enrolled in the LIBERTY EoE TREET study had failed PPIs, many had a lack of response to STC (73% in part A and 59% in part B) or had previously been on a food elimination diet (57% and 58%, respectively). This highlights the value of treatment options that address the underlying inflammatory processes and prevent or control disease.

In this subgroup analysis of the phase 3 LIBERTY EoE TREET study, taking into account the current lack of standardised definition for refractory EoE,<sup>36</sup> patients with STC inadequate/intolerance/contraindication were defined at baseline by clinicians based on whether STC treatment was ineffective or presented side effects, or whether STC treatment was overall contraindicated. The results demonstrated that, regardless of a patient’s

prior STC use or STC inadequate/intolerance/contraindication, dupilumab 300 mg once a week reduced the peak oesophageal intraepithelial eosinophil count versus placebo. Notably, 100% of patients receiving dupilumab treatment for 52 weeks in part B–C of the study had an intraepithelial eosinophil count <15 eos/hpf, which is the histological diagnostic threshold for EoE. While some studies noted reduction in eosinophil count without improvement in symptoms, we found that dupilumab 300 mg once a week improved patient-reported symptoms versus placebo, as demonstrated by decreases in DSQ total score and percentage change from baseline to week 24 regardless of prior STC use or STC inadequate/intolerance/contraindication, with scores at least maintained when dupilumab treatment was extended for 28 weeks. Dupilumab weekly treatment also improved EREFS, HSS grade and stage scores versus placebo at week 24, and at least maintained this improvement when dupilumab treatment was extended up to 52 weeks, regardless of prior STC use or STC inadequate/intolerance/contraindication.

Dupilumab biweekly treatment led to similar results in histological, endoscopic and molecular outcomes to weekly treatment, except for symptoms (as measured by DSQ scores), which did not improve versus placebo at week 24 or to the same degree as patients receiving weekly dupilumab through week 52. These results confirm those previously observed in the overall TREET population where dupilumab biweekly treatment improved histological, endoscopic and molecular outcomes but not DSQ, EoE impact or symptom questionnaire scores.<sup>22</sup> This emphasises the efficacy of dupilumab 300 mg once a week, which is the approved dosage.

STC treatment regimens for EoE are not standardised and can include different active ingredients, doses, modes of administration and variable durations, resulting in inconsistent outcomes. While patients with EoE in Europe, Australia and Canada are more likely to be prescribed orodispersible budesonide as it is approved in these regions,<sup>10 37 38</sup> STCs are not FDA approved for EoE in the USA. While a majority of patients respond to STC treatment,<sup>39</sup> less than half of those who do not respond to this first-line therapy achieve a response in other second-line therapy,<sup>40</sup> highlighting the lack of treatment options for patients not responding to STC. Dupilumab is approved in the USA and EU for the treatment of EoE,<sup>24 25</sup> and the results of the current analysis indicate that it provides similar efficacy regardless of prior therapy, suggesting that it may be a reliable therapeutic option for patients with EoE who did not respond to first-line treatment. Dupilumab was also well tolerated, with safety in subgroups similar to overall safety profile reported previously.<sup>22</sup>

Limitations of the current analysis include the lack of standardised definition for inadequate response, intolerance or contraindication to STC, which in this study relied on clinician judgement. There is also no information on the STC inadequate/intolerance/contraindication for patients from part A of the study. Despite this, there was a reasonable number of patients for analysis in both subgroups in parts B and B–C and these patients were representative of the wider population of patients with EoE. Finally, although the number of patients in the subgroups without prior STC use in part A was small (placebo n=8 and dupilumab n=13), numerical improvements were observed.

**CONCLUSION**

The results of this pre-specified analysis show that prior treatment with STC does not negatively affect responsiveness to subsequent treatment with dupilumab 300 mg once a week. In addition, patients with an inadequate response, intolerance and/

or contraindication to STC also demonstrated improvements with dupilumab 300 mg once a week compared with placebo.

#### Author affiliations

<sup>1</sup>Department of Gastroenterology and Hepatology, Amsterdam University Medical Centers, Amsterdam, The Netherlands

<sup>2</sup>Department of Medicine, Division of Gastroenterology and Hepatology, The University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, North Carolina, USA

<sup>3</sup>Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

<sup>4</sup>Instituto de Investigación Sanitaria Princesa, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, Instituto de Investigación Sanitaria de Castilla-La Mancha (IDISCAM), Hospital General Tomelloso, Tomelloso, Spain

<sup>5</sup>Klinik und Poliklinik für Innere Medizin II, Klinikum rechts der Isar der Technischen Universität München, Munich, Germany

<sup>6</sup>Regeneron Pharmaceuticals Inc, Tarrytown, New York, USA

<sup>7</sup>Sanofi, Bridgewater, New Jersey, USA

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#### ORCID iDs

Albert J Bredenoord <http://orcid.org/0000-0001-5918-2062>

Ikuo Hirano <http://orcid.org/0000-0001-7688-9377>

Alfredo J Lucendo <http://orcid.org/0000-0003-1183-1072>

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