



Original Research

Dupilumab efficacy in subgroups of type 2 asthma with high-dose inhaled corticosteroids at baseline

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ABSTRACT

Background and objective: Dupilumab blocks the shared receptor component for interleukin (IL)-4/IL-13, key and central drivers of type 2 inflammation in multiple diseases. In phase 3 QUEST (NCT02414854), add-on dupilumab 200 and 300 mg every 2 weeks reduced severe exacerbations, improved pre-bronchodilator forced expiratory volume in 1 s (FEV₁), and was generally well tolerated in patients with uncontrolled moderate-to-severe asthma. This post hoc analysis assessed dupilumab efficacy in subpopulations of patients with type 2 asthma and high-dose inhaled corticosteroids (ICS).

Methods: Adjusted annualized severe exacerbation rates over the treatment period, least squares (LS) mean change from baseline at Week 12 in pre-bronchodilator FEV₁, and LS mean change from baseline at Week 24 in 5-item Asthma Control Questionnaire (ACQ-5) scores were analyzed in subgroups of patients receiving high-dose (>500 µg) ICS with baseline blood eosinophils ≥150 cells/µL and/or fractional exhaled nitric oxide ≥25 ppb. Subgroups included allergic phenotype (with/without), comorbid chronic rhinosinusitis and/or nasal polyposis (with/without), pre-bronchodilator FEV₁/forced vital capacity (<70%/≥70%), blood eosinophil level, exacerbation history, median baseline pre-bronchodilator FEV₁, age at asthma onset (≤40/>40 years), median FEV₁ reversibility, body mass index (<30/≥30 kg/m²), and sex.

Results: Dupilumab vs placebo reduced exacerbations and improved pre-bronchodilator FEV₁ at Week 12 and ACQ-5 at Week 24 across subgroups of patients with type 2 asthma and high-dose ICS at baseline. Dupilumab was also effective in patients receiving medium-dose ICS.

Abbreviations: ACQ-5, asthma control questionnaire; BMI, body mass index; CRS/NP, chronic rhinosinusitis and/or nasal polyposis; FeNO, functional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroids; IL, interleukin; LS, least squares; MART, maintenance and reliever therapy; q2w, every 2 weeks.

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Conclusion: Dupilumab reduced severe exacerbations and improved lung function and asthma control in subgroups of patients with type 2 asthma and high-dose ICS at baseline.

Clinical trial registration number: NCT02414854.

1. Introduction

Asthma represents a heterogeneous group of disorders, with distinct endotypes and phenotypes that produce symptoms of wheezing, shortness of breath, and airflow obstruction to varying degrees [1]. Approximately 20% of patients with asthma have uncontrolled moderate-to-severe disease, characterized by persistent symptoms and recurrent exacerbations despite use of high- and medium-dose inhaled corticosteroids (ICS) and additional controller therapy [2,3]. Uncontrolled asthma may also impair quality of life, culminating in considerable healthcare resource use and costs [4]. While ICS remain the mainstay of treatment in adults with asthma, chronic use of medium- and high-dose ICS poses a significant risk of systemic adverse effects [5].

Add-on biologic therapies for patients with uncontrolled moderate-to-severe asthma can specifically target elements of type 2 inflammation [6,7]. Dupilumab, a fully human VelocImmune®-derived monoclonal antibody, blocks the shared receptor component for interleukin (IL)-4 and IL-13, cytokines that are key and central drivers of type 2 inflammation in multiple diseases, including asthma [8–11]. In phase 3 LIBERTY ASTHMA QUEST (NCT02414854), add-on dupilumab 200 mg and 300 mg every 2 weeks (q2w) vs placebo significantly reduced severe asthma exacerbations and improved pre-bronchodilator forced expiratory volume in 1 s (FEV₁) in the overall population of patients with uncontrolled, moderate-to-severe asthma. Treatment effects were greater in patients with elevated type 2 biomarkers at baseline (blood eosinophils ≥ 150 cells/ μ L or fractional exhaled nitric oxide [FeNO] ≥ 25 ppb). Dupilumab was generally well tolerated [12].

Given the heterogeneity of asthma, it is important to determine the effects of add-on biologic therapy in different subpopulations of patients with baseline characteristics more/less responsive to standard treatment. Dupilumab was shown to reduce severe exacerbations and improve lung function in a rapid and sustained manner in patients treated with high-dose ICS who had evidence of increased type 2 inflammation (baseline blood eosinophils ≥ 150 cells/ μ L and/or FeNO ≥ 25 ppb) in an analysis of QUEST and phase 2b study data [13]. To further characterize dupilumab efficacy in clinically relevant subgroups, we conducted a post hoc analysis of QUEST to assess clinical outcomes according to relevant patient- and disease-related factors among patients with a type 2 inflammatory asthma phenotype who were treated with high-dose ICS.

2. Material and methods

2.1. Study design and patients

Phase 3 QUEST (NCT02414854) was a multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group study assessing efficacy and safety of dupilumab in patients with uncontrolled asthma treated with medium- or high-dose ICS plus up to two additional controllers. Medium- and high-dose ICS were classified as >250 – 500 μ g and >500 μ g inhaled fluticasone propionate or equipotent equivalent, respectively. Patients ≥ 12 years were randomized 2:2:1:1 to receive add-on subcutaneous dupilumab 200/300 mg q2w or volume-matched placebo over the 52-week treatment period. The study was open to all patients, irrespective of eosinophilic status or any other biomarker requirement. Full study methods have been reported previously [12].

The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guideline, and applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded

monitoring of patient safety data. The local institutional review board or ethics committee at each study center oversaw trial conduct and documentation. All patients, or their parents/guardians, provided written informed consent before trial initiation.

2.2. Study endpoints

Endpoints included the annualized severe exacerbation rate, defined as the number of severe exacerbations per patient-year over the 52-week treatment period, least squares (LS) mean change in pre-bronchodilator FEV₁ from baseline at Week 12 and over the treatment period, and LS mean change in the 5-item Asthma Control Questionnaire (ACQ-5) score from baseline at Week 24.

2.3. Subgroups

This post hoc analysis included QUEST patients with high-dose ICS and a type 2 inflammatory asthma phenotype (baseline blood eosinophils ≥ 150 cell/ μ L or FeNO ≥ 25 ppb). To further assess dupilumab efficacy across subpopulations, we examined each endpoint in the population subgroups presented above, defined by the following baseline characteristics: evidence of an allergic phenotype (defined by ≥ 1 perennial aeroallergen-specific IgE ≥ 0.35 IU/mL and total IgE ≥ 30 IU/mL [14,15], with/without); self-reported comorbid chronic rhinosinusitis and/or nasal polyposis (CRS/NP; with/without); pre-bronchodilator FEV₁/forced vital capacity (FVC) ratio ($<70\%$ and $\geq 70\%$); blood eosinophil levels (≥ 150 , ≥ 300 , and ≥ 500 cells/ μ L); number of exacerbations in the year prior to QUEST ($\geq 1/\geq 2/\geq 3/\geq 4$); pre-bronchodilator FEV₁ ($</\geq$ median value [1.66 L for high-dose ICS, 1.81 L for medium-dose ICS]); age at asthma onset ($\leq 40/>40$ years); FEV₁ reversibility ($</\geq$ median value [22.32% for high-dose ICS, 21.04% for medium-dose ICS]); body mass index (BMI; <30 kg/m²/ ≥ 30 kg/m²); and sex (male/female). The analysis was also performed in patients with baseline eosinophils ≥ 150 cells/ μ L or FeNO ≥ 25 ppb receiving medium-dose ICS at baseline. Results are presented separately for each dupilumab dose and volume-matched placebo and for dupilumab and placebo combined groups.

2.4. Statistical analysis

Annualized rate of severe asthma exacerbations was analyzed using a negative binomial regression model, with number of events from randomization up to Visit 18 or last contact date (whichever comes earlier) as the response variable, and with treatment, age, geographic region (pooled country), baseline eosinophil strata, and number of severe exacerbation events in the previous year as covariates. LS mean change from baseline in pre-bronchodilator FEV₁ and ACQ-5 score were analyzed using linear mixed-effects models with repeated measures. Covariates for pre-bronchodilator FEV₁ included treatment, age, sex, baseline height, geographic region (pooled country), baseline eosinophil strata, visit, intervention-by-visit interaction, baseline pre-bronchodilator FEV₁, and baseline-by-visit interaction. Covariates for ACQ-5 included treatment, age, geographic region (pooled country), baseline eosinophil strata, visit, treatment-by-visit interaction, baseline ACQ-5, and baseline-by-visit interaction. If a subgroup was based on pre-defined covariates, then that covariate was dropped from the corresponding model.

3. Results

3.1. Baseline characteristics

In QUEST, 785 patients with type 2 inflammation received high-dose ICS at baseline (dupilumab: 504, placebo: 281; [Table 1](#)). 720 patients with type 2 inflammation received medium-dose ICS at baseline (dupilumab: 478, placebo: 242; [Table S1](#) in Supporting Information). Patients receiving high-dose ICS at baseline had worse lung function and asthma control and more prior exacerbations than patients taking medium-dose ICS, indicating greater disease severity and need for higher controller medication dose.

3.2. Annualized rate of severe asthma exacerbations by subgroup

In patients with type 2 asthma who received high-dose ICS at baseline, dupilumab consistently reduced the annualized rate of severe asthma exacerbations across subgroups ([Fig. 1](#); [Figs. S1–S11](#) in Supporting Information). Although no minimum clinically important reduction in exacerbations has been identified and validated, for individual patients it is clinically relevant to prevent even one severe exacerbation episode [16]. Here, a negative rate ratio, indicating a favorable reduction in severe exacerbations, was observed with 200 and 300 mg dupilumab doses ([Figs. S11A and S11B](#)), as well as combined doses ([Fig. 1](#)). Dupilumab vs placebo reduced exacerbations to a greater extent in patients with features of greater type 2 inflammation, such as comorbid CRS/NP and elevated blood eosinophils. Dupilumab 200 and 300 mg vs matched placebo reduced exacerbations by 74% and 56%, respectively, in patients with comorbid CRS/NP, and by 43% and 41% in patients without comorbid CRS/NP. In both dose groups, dupilumab efficacy appeared to be greater in subgroups with increasing baseline blood eosinophils, reducing exacerbations by 55%, 59%, 69% (200 mg) and 53%, 66%, and 72% (300 mg) in patients with baseline blood eosinophils ≥ 150 , ≥ 300 , and ≥ 500 cells/ μ L. Dupilumab 200 and 300 mg reduced exacerbations by 53% and 48% in patients with ≥ 1 exacerbation in the year prior to QUEST, with greatest efficacy observed in patients with ≥ 4 exacerbations (73% and 58%). In patients subdivided by baseline lung function parameters (pre-bronchodilator FEV₁, FEV₁/FVC, and FEV₁ reversibility) cut-offs, dupilumab consistently reduced exacerbation rates vs placebo across subgroups.

Similar results were observed in patients with type 2 asthma treated with medium-dose ICS at baseline ([Figs. S12–S21](#) in Supporting Information).

3.3. Change in pre-bronchodilator FEV₁ by subgroup

Patients with type 2 asthma receiving high-dose ICS at baseline experienced improvements in pre-bronchodilator FEV₁ at Week 12 in most subgroups when treated with dupilumab 200 mg ([Fig. S22A](#)), 300 mg ([Fig. S22B](#)), and combined doses ([Fig. 2](#)) vs matched placebo. FEV₁ changes $\geq 20\%$ in the short term (i.e. weeks of duration) and changes $\geq 15\%$ in the longer term (i.e. ≥ 1 year) are considered clinically meaningful [16,17]. In patients with/without comorbid CRS/NP, dupilumab vs placebo improved pre-bronchodilator FEV₁ (LS mean difference, 200 mg: 0.19 L/0.13 L; 300 mg: 0.18 L/0.13 L, respectively). Dupilumab vs placebo also consistently improved lung function in patients with elevated baseline blood eosinophil levels, with the greatest benefit observed in patients with ≥ 500 eosinophils/ μ L (LS mean difference vs placebo [95% CI], 200 mg: 0.23 L [0.08–0.38], 300 mg: 0.28 L [0.14–0.43]). Dupilumab improved pre-bronchodilator FEV₁ in all patients regardless of baseline exacerbation history, except in the small subgroup with a history of ≥ 4 exacerbations in the year prior to QUEST treated with dupilumab 200 mg vs matched placebo. In patient subgroups defined by lung function parameter cut-offs, dupilumab improved pre-bronchodilator FEV₁, with the most consistent effects observed in patients analyzed by combined dupilumab vs matched

placebo.

Changes from baseline in pre-bronchodilator FEV₁ over time are shown in [Figs. S23–S32](#) in Supporting Information. Generally similar results were observed in patients with a type 2 inflammatory asthma phenotype who were treated with medium-dose ICS ([Figs. S33–S42](#) in Supporting Information).

3.4. Change in ACQ-5 score by subgroup

Mean changes in ACQ-5 asthma control scores were consistently improved with dupilumab vs placebo in patients with type 2 asthma treated with high-dose ICS at baseline ([Fig. 3](#)). For all versions of the ACQ in adults and children, a change in score is considered clinically important if it exceeds approximately 0.5;¹⁶ LS mean differences vs placebo were observed across all subgroups, except for patients with BMI ≥ 30 kg/m² receiving dupilumab 300 mg vs matched placebo ([Fig. S43B](#)). Dupilumab improved ACQ-5 scores patients with comorbid CRS/NP (LS mean difference vs placebo [95% CI], 200 mg: −0.54 [−0.99, −0.09]; 300 mg: −0.61 [−1.08, −0.14]) and in patients without comorbid CRS/NP (200 mg: −0.22 [−0.48, 0.03]; 300 mg: −0.09 [−0.35, 0.16]). The impact of dupilumab on ACQ-5 score appeared to be greater in patients with higher baseline eosinophil counts (LS mean difference vs placebo [95%CI] 200 mg, ≥ 500 cells/ μ L: −0.54 [−0.95, −0.13], ≥ 150 cells/ μ L: −0.34 [−0.58, −0.11]; 300 mg, ≥ 500 cells/ μ L: −0.59 [−0.98, −0.19], ≥ 150 cells/ μ L: −0.25 [−0.48, −0.01]). Dupilumab improved asthma control regardless of exacerbation history. In combined dupilumab vs combined placebo, the effect on asthma control scores was highest in patients with ≥ 4 exacerbations in the year prior to QUEST (−0.56 [−0.98, −0.15]). Dupilumab vs placebo improved asthma control in patient subgroups defined by lung function parameter cut-offs.

Results in patients treated with medium-dose ICS at baseline were generally consistent with results in the high-dose ICS group ([Fig. S44](#) in Supporting Information).

4. Discussion

In this post hoc analysis evaluating dupilumab efficacy in patients from the LIBERTY ASTHMA QUEST study with type 2 inflammation, dupilumab vs placebo reduced severe asthma exacerbation rates and improved pre-bronchodilator FEV₁ in patients on high- or medium-dose ICS further subdivided by baseline patient characteristics. Dupilumab was effective across subgroups representative of asthma with varying severity, including patients with/without features of enhanced type 2 signature (comorbid CRS/NP, elevated baseline blood eosinophil levels), varying disease severity as assessed by exacerbation history, and measures of baseline lung function parameters, as well as various baseline demographic and disease characteristics (evidence of allergic phenotype, comorbid obesity, age of disease onset, and sex). These findings complement a previous efficacy analysis of add-on dupilumab in the intention-to-treat population of patients treated with high- or medium-dose ICS at baseline [13]. Dupilumab appeared to perform worse than placebo in patients with ≥ 4 exacerbations in the year prior to QUEST treated with 200 mg dupilumab (pre-bronchodilator FEV₁) and in patients with BMI ≥ 30 kg/m² treated with 300 mg dupilumab (ACQ-5). These results could be attributed to the small sample sizes, since dupilumab demonstrated consistent efficacy across subgroups when combined dupilumab 200 and 300 mg treatment groups compared with combined placebo was analyzed.

Consistent with previous findings, the magnitude of dupilumab efficacy was greater in patients with a higher type 2 signature [12,13,18]. Approximately 50% of patients with asthma have increased levels of type 2 airway inflammation [19]. Although some patients with type 2 asthma respond to ICS with a reduction in type 2 biomarker expression [20], for others asthma remains uncontrolled despite ICS treatment [19]. This post hoc analysis supports the use of dupilumab in patients with elevated blood eosinophils or FeNO despite treatment with

Table 1

Baseline demographic and disease characteristics in patients with type 2 inflammation on high-dose ICS at baseline.

	Placebo 1.14 mL (n = 140)	Dupilumab 200 mg q2w (n = 247)	Placebo 2 mL (n = 141)	Dupilumab 300 mg q2w (n = 257)
Age (years), mean (SD)	48.8 (14.4)	49.3 (13.7)	49.0 (13.4)	48.9 (14.6)
Female sex, n (%)	85 (60.7)	150 (60.7)	99 (70.2)	168 (65.4)
BMI (kg/m ²), mean (SD)	30.5 (7.0)	29.8 (6.2)	29.6 (6.8)	29.5 (6.4)
With ongoing atopic medical condition, ^a n (%)	121 (86.4)	201 (81.4)	117 (83.0)	212 (82.5)
Severe asthma exacerbations ^b experienced in the past year, mean (SD)	2.21 (1.67)	2.15 (1.74)	2.62 (2.42)	2.24 (1.75)
Pre-bronchodilator FEV ₁ (L), mean (SD)	1.75 (0.58)	1.68 (0.55)	1.65 (0.47)	1.69 (0.58)
Pre-bronchodilator % predicted (%), mean (SD)	57.96 (12.68)	56.09 (13.59)	56.18 (12.62)	56.70 (13.73)
FEV ₁ reversibility (%), mean (SD)	24.25 (16.37)	26.97 (21.49)	27.75 (15.98)	28.75 (23.84)
ACQ-5 score, mean (SD)	2.83 (0.73)	2.92 (0.91)	2.90 (0.84)	2.89 (0.81)
AQLQ (range 1–7), mean (SD)	4.15 (1.04)	4.18 (1.12)	4.11 (1.03)	4.09 (1.02)
Blood eosinophil count (cells/ μ L), median (IQR),	335.00 (220.00–550.00)	300.00 (190.00–560.00)	370.00 (210.00–585.00)	320.00 (200.00–520.00)
Total IgE (IU/mL), median (IQR)	245.00 (70.00–464.00)	181.50 (64.00–562.00)	202.50 (77.50–442.00)	200.00 (71.00–520.00)

^aA patient is considered to have ongoing atopic medical condition if he/she has any of the following ongoing conditions: atopic dermatitis, allergic conjunctivitis or rhinitis, eosinophilic esophagitis, food allergy, hives; or has baseline total IgE ≥ 100 IU/mL and at least one aeroallergen specific IgE is positive (≥ 0.35 IU/mL) at baseline.

^bSevere asthma exacerbation prior to the study is defined as any treatment with 1 systemic (oral or parenteral) steroid bursts or more for worsening asthma or hospitalization or an emergency/urgent medical care visit for worsening asthma.

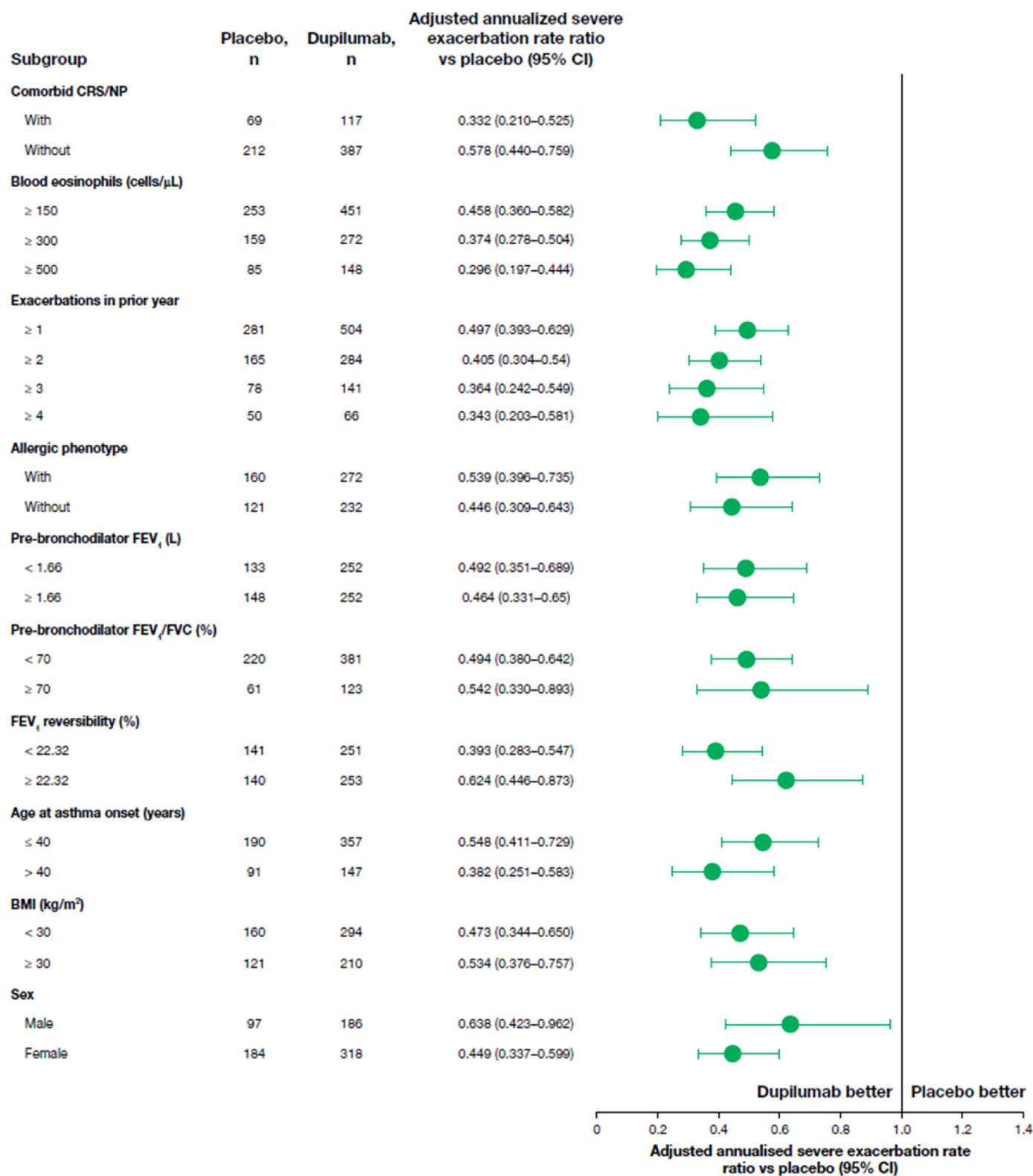


Fig. 1. Forest plot of annualized rate of severe exacerbations. Divided by subgroup for patients treated with dupilumab combined doses vs matching placebo. All patients had type 2 asthma and were treated with high-dose ICS at baseline. BMI: -body mass index; CRS/NP: chronic rhinosinusitis and/or nasal polyposis; FEV₁: forced expiratory volume in 1 s.

high-dose ICS. Similar efficacy outcomes in patients with type 2 inflammation have also been shown in randomized controlled trials of other biologics targeting underlying type 2 inflammatory processes: benralizumab [21,22], reslizumab [23,24], mepolizumab [25–27],

omalizumab [28], and tezepelumab [29]. However, those trials did not include subgroup analyses.

Asthma is often associated with comorbidities, including CRSwNP and allergic rhinitis [30]. CRSwNP is a significant, independent risk

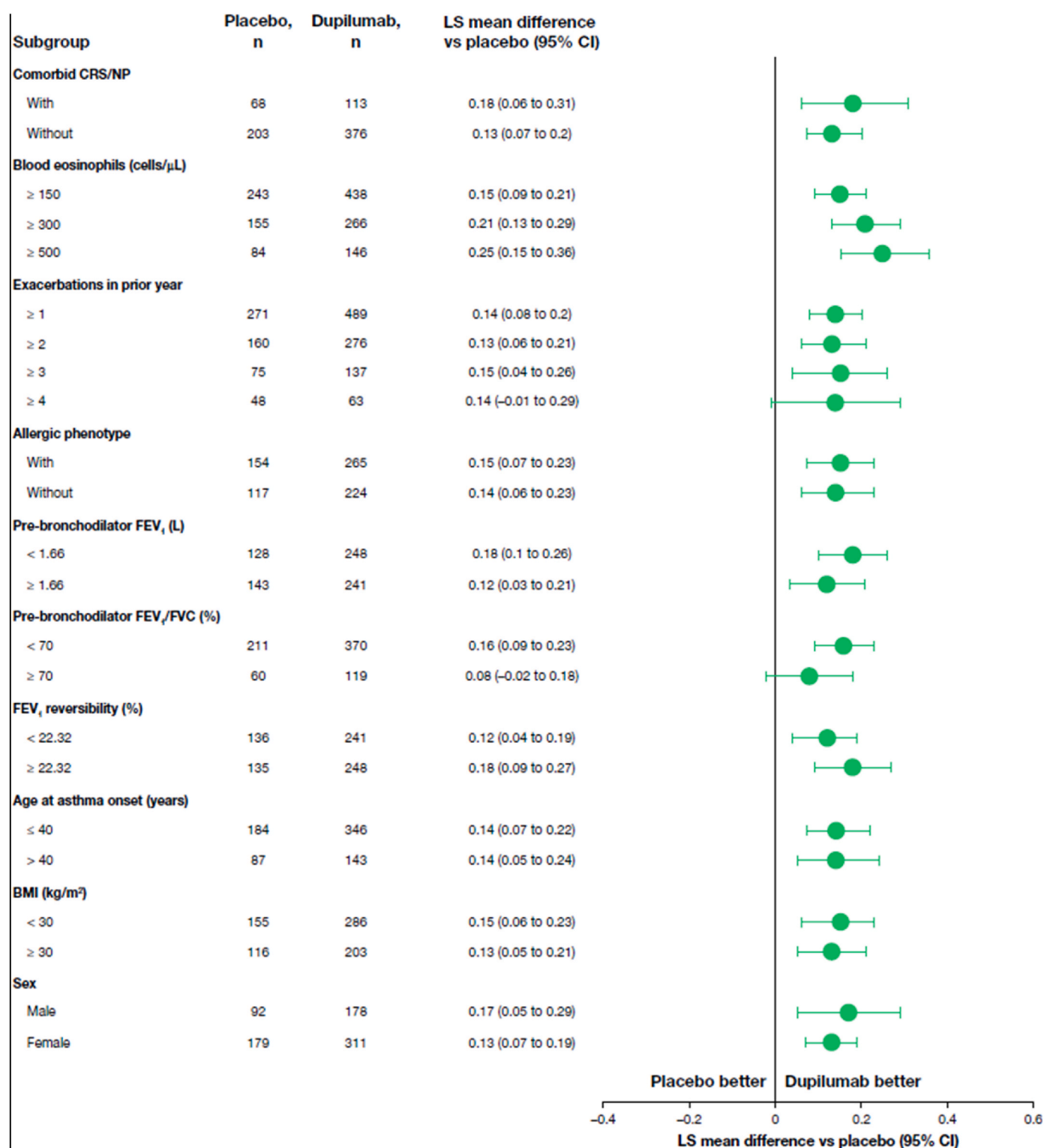


Fig. 2. Forest plot of change from baseline at Week 12 in FEV₁. Divided by subgroup for patients treated with dupilumab combined doses vs matching placebo. All patients had type 2 asthma and were treated with high-dose ICS at baseline. BMI: body mass index; CRS/NP: chronic rhinosinusitis and/or nasal polyposis; FEV₁: forced expiratory volume in 1 s.

factor for frequent asthma exacerbations [30–32] and elevated levels of type 2 cytokines are observed in patients with this comorbidity [33,34]. The presence of comorbid CRSwNP is associated with more severe disease in patients with type 2 asthma [35,36]. In this analysis, dupilumab reduced exacerbation rates and improved lung function and asthma control in patients with/without CRS/NP, though patients with CRS/NP

experienced the greatest benefit. Obesity is another common asthma comorbidity that worsens disease severity [37]. In patients with obesity and asthma that is poorly controlled with medium- or high-dose ICS, add-on dupilumab reduced the annualized exacerbation rate and improved lung function.

The impact of dupilumab was generally similar across subgroups,

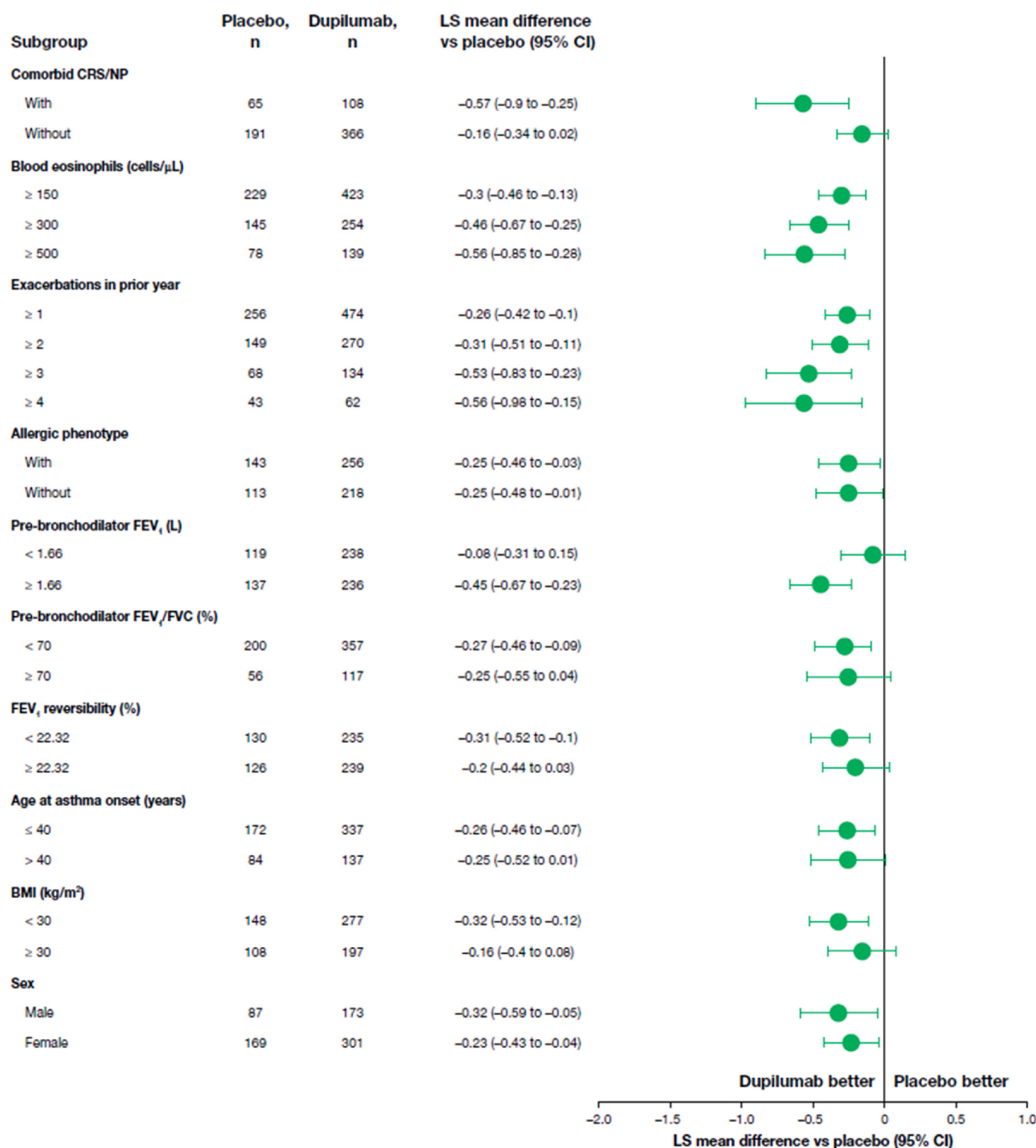


Fig. 3. Forest plot for change from baseline at Week 24 in ACQ-5 score. Divided by subgroup for patients treated with combined dupilumab doses vs matching placebo. All patients had type 2 asthma and were treated with high-dose ICS at baseline. ACQ-5: 5-item Asthma Control Questionnaire; BMI: body mass index; CRS/NP: chronic rhinosinusitis and/or nasal polyposis.

regardless of whether patients were treated with medium- or high-dose ICS. As study patients had uncontrolled asthma despite treatment with medium- or high-dose ICS, these analyses support dupilumab treatment of refractory type 2 inflammation [38] across patient subgroups that reflect varying disease severity.

Strengths of this analysis include the randomized, double-blind

design, the large study population size, and the wide range of baseline demographic and disease characteristics evaluated. A major limitation is the small sample size of certain subgroups, including patients with $\geq 3/\geq 4$ exacerbations in the year prior to QUEST and those with baseline eosinophil levels $\geq 300/\geq 500$ cells/ μ L. Subgroups were not defined *a priori* and the study was therefore not powered specifically to investigate

differences between patients with high- and medium-dose ICS at baseline in these specific subpopulations. Other limitations include a lack of information on patient adherence to ICS and the self-reported diagnosis of comorbid CRS/NP. Due to the small sample sizes, safety could not be reliably assessed in all subgroups; dupilumab was generally well tolerated by patients participating in the QUEST parent study [12].

5. Conclusion

This analysis shows that dupilumab reduces annualized severe asthma exacerbation rates and improves lung function and asthma control in subgroups of patients with type 2 asthma receiving high-dose ICS at baseline. Similar efficacy was observed in subgroups of patients with type 2 asthma receiving baseline medium-dose ICS. While dupilumab demonstrated efficacy across a broad range of demographic and disease characteristics, the magnitude of effect tended to be greater in patients who had higher type 2 inflammatory signatures and features of more severe disease.

Author Contributions

MD, BO, JAJ, YD, and PJR contributed to project concept, study design, and study implementation; AB, AP, NLL, PB, and MA contributed to data collection; ND contributed to data and statistical analysis; all authors, including JCV, DMGH, and RG, contributed to data analysis and interpretation, and manuscript editing; all authors critically reviewed and approved the final version of the manuscript.

Data statement

Qualified researchers may request access to patient level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient level data will be anonymized, and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: <https://www.vivli.org/>

Declaration of competing interest

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Appendix A. Supplementary data

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