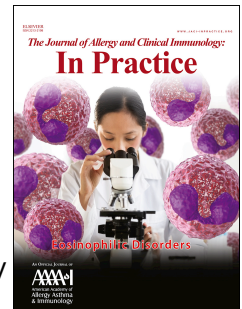


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Omalizumab in Asthma With Fixed Airway Obstruction: Post Hoc Analysis of EXTRA

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27 Conflict of interest

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35 Gupta, B. Yoo, and C.T.J. Holweg are employees of Genentech, Inc. N. Mumneh is an employee of
36 and stockholder in Novartis Pharmaceuticals Corporation. B.E. Chipps is an advisor, consultant, and
37 speaker bureau member for AstraZeneca, Boehringer Ingelheim, Circassia, Genentech, Inc., Novartis,
38 Regeneron, and Sanofi.

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ABSTRACT (249/250 words)

BACKGROUND: Although asthma is typically characterized by bronchodilator responsiveness (BDR), fixed airflow obstruction (FAO) occurs in ~50% of patients with severe asthma.

OBJECTIVE: Do FAO/BDR associate with efficacy of omalizumab, a monoclonal antibody that targets IgE?

METHODS: In EXTRA, patients aged 12-75 years with inadequately controlled severe allergic asthma despite high-dose inhaled corticosteroids plus long-acting β_2 -agonists were randomized to omalizumab (n = 427) or placebo (n = 423) for 48 weeks of treatment. In this post hoc analysis, high/low BDR were defined as $\geq 12\%$ / $< 12\%$ increases in baseline FEV₁ following bronchodilator administration, respectively. FAO presence (+)/absence (-) were defined as baseline postbronchodilator FEV₁/forced vital capacity $< 70\%$ / $\geq 70\%$, respectively. Poisson regression/analysis of covariance models were used to estimate exacerbation relative rate reductions (RRR)/least squares mean changes in FEV₁, respectively.

RESULTS: In patients with high BDR, omalizumab reduced exacerbations more than placebo over the 48-week treatment period regardless of FAO status (RRR [95% CI]: FAO+, 59.8% [17.7-80.4%]; FAO-, 44.3% [16.6-62.8%]). Omalizumab improved FEV₁ compared with placebo in the FAO-, high BDR subgroup (FEV₁ change from baseline [95% CI] for omalizumab vs placebo, 0.065 L [-0.071 to 0.201 L] to 0.236 L [0.112-0.359 L]) across 48 weeks. This was not observed in patients with low BDR, irrespective of FAO.

CONCLUSION: Omalizumab was more efficacious than placebo at reducing exacerbations in patients with high, but not low, BDR, regardless of presence of FAO. Lung function improvement primarily occurred in FAO-, high BDR patients, suggesting that asthma with low BDR may represent a difficult-to-treat phenotype.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov registration number NCT00314574 (<https://clinicaltrials.gov/ct2/show/NCT00314574>)

70 **Highlights (max. 35 words)**

What is already known about the topic?	Fixed airflow obstruction in patients with asthma has been associated with reduced responsiveness to asthma medications.
What does this article add to our knowledge?	Omalizumab reduced exacerbations in patients with high bronchodilator reversibility and fixed airflow obstruction and improved lung function in patients without fixed airflow obstruction and high bronchodilator reversibility.
How does this study impact current management guidelines?	Identifying patient characteristics associated with improved outcomes with omalizumab may help to define patient populations that are more likely to derive benefit from omalizumab.

71

72 **Key words:** *Asthma; Omalizumab; Airway obstruction*

73

74 **Abbreviations used**75 *+: Presence*76 *-: Absence*77 *BDR: Bronchodilator responsiveness*78 *FAO: Fixed airflow obstruction*79 *ICS: Inhaled corticosteroids*80 *LABA: Long-acting β_2 -agonist*81 *OCS: Oral corticosteroids*82 *RRR: Relative rate reduction*

INTRODUCTION

Asthma is a chronic disease in which inflammation and bronchospasm of the respiratory tract lead to episodic airflow obstruction.¹ Most patients with asthma demonstrate bronchodilator responsiveness (BDR) of airflow obstruction following bronchodilator administration, generally defined and used for clinical trial enrollment as a >12% increase and ≥ 200 -mL increase in FEV₁.² However, a subgroup of patients with asthma have fixed airflow obstruction (FAO).³ FAO is typically defined as a postbronchodilator FEV₁/forced vital capacity <70%, and may be present in approximately half of patients with severe asthma.^{3,4}

FAO in asthma develops over many years, resulting from airway inflammation and continued remodeling that results in thickening of the airway walls and parenchymal lung damage, leading to loss of elastic recoil.^{5,6} These changes are associated with significant reductions in the size of the airway lumen and increased resistance to airflow.^{5,6} Thickening of the airway walls are at least in part due to changes to the bronchial smooth muscle cells, including smooth muscle cell hypertrophy and hyperplasia, and increased deposition of extracellular matrix.⁷⁻⁹ Early life factors, including *in utero* or postnatal viral infection, and exposure to air pollution or tobacco smoking, are also believed to be important contributors to these airway structural changes.¹⁰ Additional risk factors associated with FAO include increased age, African American race, male sex, smoking, long duration of asthma, high fraction of exhaled nitric oxide (FeNO), elevated levels of IgE, and ongoing eosinophilic inflammation.¹¹⁻¹³ The presence of FAO (FAO+) in patients with asthma is associated with increased exacerbation frequency, decreased lung function, and greater mortality compared with those without FAO (FAO-).^{14,15}

FAO is difficult to treat with current treatments.³ No prospective studies have investigated the differential effect of biologics in FAO+ patients with asthma compared with FAO- patients. Because FAO is associated with elevated IgE levels,¹⁶ we examined whether blocking IgE in FAO+ patients with asthma would be beneficial.

Omalizumab is a recombinant humanized monoclonal antibody that selectively binds to free IgE and subsequently inhibits IgE-dependent cellular events.¹⁷ In patients with moderate-to-severe asthma, omalizumab improves asthma symptoms and consistently and significantly reduces the frequency of exacerbations.¹⁸⁻²² Additionally, multiple studies have demonstrated modest improvements in lung function with omalizumab.^{20,21,23}

In this *post hoc* analysis of data from the EXTRA study,¹⁸ we examined the efficacy of omalizumab in terms of exacerbation reduction and lung function in patients with severe, uncontrolled asthma by FAO status. Patients were further analyzed using subgroups of BDR.

METHODS

Study design and patient population

Full details of the study design and patient population for EXTRA (NCT00314574) have been described previously.¹⁸ Briefly, patients were included if they were aged 12-75 years and had a history of severe, persistent allergic asthma for >1 year before screening. Patients were also required to have baseline prebronchodilator FEV₁ of 40-80% of predicted values, serum IgE level of 30-700 IU/mL, and body weight of 30-150 kg. BDR was not an inclusion criterion for EXTRA, allowing for enrollment of patients with high and low BDR. After a 2- to 4-week run-in period, eligible patients were randomized in a 1:1 ratio to receive omalizumab or placebo (in addition to high-dose inhaled corticosteroids [ICS] and long-acting β_2 -agonists [LABAs], with or without additional controller medications) for 48 weeks. To account for baseline asthma controller medication, the randomization included a single concomitant asthma medication stratification factor with 3 strata: M1 (ICS plus LABAs alone), M2 (ICS plus LABAs plus ≥ 1 additional asthma controller medication, but excluding oral corticosteroids [OCS]), and M3 (ICS plus LABAs plus OCS). Omalizumab dose and dosing regimen were determined based on serum total IgE level (IU/mL) and body weight (kg) at screening, according to the US omalizumab dosing table (ensuring a minimum dose of 0.008 mg/kg/IgE [IU/mL] every 2 weeks or 0.016 mg/kg/IgE [IU/mL] every 4 weeks). No modifications to the doses of omalizumab or concomitant asthma medications were allowed during the study.⁴

EXTRA was conducted according to US Food and Drug Administration regulations, International Conference on Harmonisation E6 Guidelines for Good Clinical Practice, the Declaration of Helsinki, and other national requirements. Institutional review board approval was obtained by all sites and all patients provided signed informed consent to receive treatment and for their medical data to be used in a study.

Assessments

In this *post hoc* analysis, the efficacy of omalizumab was evaluated in FAO+ and FAO- patients and in those who did or did not show reversibility after bronchodilator administration. FAO+ and FAO- were defined as baseline postbronchodilator FEV₁/forced vital capacity <70% and ≥70%, respectively. High and low BDR were defined as changes of ≥12% and <12% in baseline FEV₁ following albuterol administration, respectively.

The endpoints evaluated in this analysis were the rate of exacerbations and change from baseline in prebronchodilator FEV₁ over the 48-week study period. Protocol-defined asthma exacerbations were defined as worsening asthma symptoms requiring treatment with systemic corticosteroids for ≥3 days, or for patients receiving long-term OCS, an ≥20-mg increase in the average daily dose of oral prednisone (or a comparable dose of another systemic corticosteroid). Prebronchodilator FEV₁ was measured every 4 weeks from weeks 0-48.

Statistical analyses

Adjusted relative rate reductions (RRR) in exacerbations for omalizumab versus placebo, and 95% CIs, were examined using Poisson regression analysis for all patients and by FAO status (+/-) and BDR (high/low). The model included the following covariates: treatment (omalizumab, placebo), dosing schedule (every 2 weeks, every 4 weeks), concomitant medication (M1, M2, and M3 groups), and number of exacerbations in the past year. Data were normalized by patient-time on study at risk.

Analysis of covariance models were used to calculate the least squares mean treatment differences (omalizumab vs placebo) and 95% CIs for absolute FEV₁ change from baseline at each postbaseline study week. The analysis of covariance models included baseline FEV₁, treatment (omalizumab, placebo), and their interaction as covariates.

RESULTS

Of the 848 modified intention-to-treat patients in the EXTRA study, 813 patients were included in this subgroup analysis. Thirty-five patients were excluded from this subgroup-specific analysis due to missing baseline FAO and/or BDR data. Baseline demographic and clinical characteristics of patients by FAO and BDR status are presented in Table I. Notably, 279/813 (34%) patients met the criteria for FAO+ and 513/813 (63%) had low BDR. The FAO+ subgroup had more male patients, and on average, FAO+ patients were older, had a longer history of asthma, and worse prebronchodilator FEV₁ compared with FAO- patients. History of exacerbations, blood eosinophil counts, and total IgE levels were similar between subgroups.

Asthma exacerbation rate

In the overall sample, exacerbation RRR (95% CI) for omalizumab versus placebo was 24.8% (7.9-38.6%; Figure 1). For both the FAO+ and FAO- subgroups, exacerbation RRRs were greater in those with high BDR (59.8% [17.7-80.4%] and 44.3% [16.6-62.8%], respectively) than in those with low BDR (6.0% [-46.8% to 39.8%] and 17.4% [-13.3% to 39.8%], respectively).

Lung function change

In the overall sample, omalizumab showed benefit over placebo in lung function (FEV₁) improvements as early as week 4, which was maintained across the entire 48 weeks of treatment (Figure 2A). Distinct benefits in lung function improvement with omalizumab compared with placebo were only observed in the FAO- subgroup with high BDR. In this subgroup, least squares mean difference (95% CI) in FEV₁ change from baseline for omalizumab versus placebo ranged from 0.065 L (-0.071 to 0.201 L) to 0.236 L (0.112-0.359 L) across 48 weeks (Figure 2E). No lung function improvement was observed in patients who were FAO- with low BDR (Figure 2D) or for FAO+ patients, irrespective of BDR status (Figure 2B-C). Placebo patients with low BDR showed no change from baseline in either the FAO+ or FAO- groups, whereas there was an improvement in lung

190 function in placebo-treated patients that was similar to patients treated with omalizumab in FAO+
191 patients with high BDR.

DISCUSSION

In this *post hoc* analysis of data from the EXTRA study, omalizumab was associated with lower exacerbation rates and larger improvements in FEV₁ throughout the study when compared with placebo. Improvements in lung function were observed as early as week 4. Examination of omalizumab effectiveness in FAO+ and FAO- patients with high or low BDR demonstrated that omalizumab was more efficacious than placebo in reducing exacerbations in patients with high BDR, irrespective of FAO status, but was no more efficacious than placebo in patients with low BDR. Lung function improvement was primarily seen in FAO- patients with high BDR. Neither omalizumab-treated nor placebo-treated patients with low BDR, regardless of FAO status, showed improvement in FEV₁.

In this analysis of EXTRA data, we examined response to omalizumab by FAO status. Interestingly, improvements in exacerbations occurred in patients with high BDR irrespective of FAO status, whereas lung function improvements over placebo were only observed in the FAO- subgroup with high BDR. This disparity in response for exacerbation reduction and lung function improvements can possibly be explained by the underlying mechanisms. For instance, acute exacerbations are thought to be related to an acute inflammatory response owing to the increase in inflammatory markers preceding the exacerbation²⁴ and reductions in exacerbations following reductions in inflammatory cells.²⁵ However, previous studies by Tonga et al suggest that FAO may relate to structural changes in the lung.⁶ Additionally, the numbers in some of the groups were small and may have influenced the ability to observe a difference between omalizumab and placebo.

The current analysis was unique in being able to assess the effectiveness of omalizumab in patients with asthma based on BDR subgroups because most placebo-controlled trials for omalizumab have only included patients who demonstrate high BDR (typically $\geq 12\%$).²⁰⁻²² In this analysis, lung function improvement with omalizumab compared with placebo was only demonstrated in FAO- patients with high BDR. These findings concur with previous studies demonstrating larger improvements following ICS initiation in patients with asthma²⁶ with a

reversible phenotype. Larger lung function improvements are thought to be due to patients with high BDR having lower baseline lung function, which allows for greater improvements in FEV₁ with treatment. In this study, patients with high BDR had lower mean baseline percent predicted FEV₁ than their respective low BDR subgroups, supporting this observation. However, it should be noted that BDR and response to treatment remains a controversial topic, with limited available data in patients with asthma. It should also be noted that the improvements in FEV₁ with omalizumab compared with placebo in the FAO- patients with high BDR were small (0.065 to 0.236 L) and may not be clinically important, if a minimal clinically important difference of 0.23 L is used.²⁷

Another interesting observation in this analysis was that placebo-treated patients with high BDR demonstrated large improvements from baseline in FEV₁ (0.2-0.3 L) over the course of the study. The improvements were similar to those achieved by omalizumab-treated FAO+ patients, but were substantially lower than those achieved by omalizumab-treated FAO- patients. It is possible that these improvements reflect improved adherence to and/or an optimized dose of ICS that was initiated during the run-in period of EXTRA; however, dose optimization was accounted for because patients were already on high-dose corticosteroids before enrollment.²⁸ Furthermore, the response was confined to patient populations with high BDR, suggesting that it may be due to inherent characteristics related to bronchomotor tone. It is also the case that FEV₁ was measured before bronchodilator use; if postbronchodilator FEV₁ had been used, this placebo effect may not have been observed.

In a recent study of benralizumab in patients with severe asthma by FAO status, larger placebo-corrected lung function improvements were observed in FAO+ patients (159 mL) than in FAO- patients (103 mL), suggesting that reducing inflammation may positively affect lung function in FAO+ patients.²⁹ Although both omalizumab and benralizumab target aspects of the type 2 inflammatory pathway, comparisons between the results of the 2 studies are difficult because different patient populations were enrolled in each of the studies, leading to substantial differences in baseline characteristics in treated patients. For example, all of the patients in the benralizumab

study had high BDR, the association of BDR and benralizumab was not studied, and the population was enriched for eosinophilic asthma.²⁹ Indeed, baseline median eosinophil counts in the benralizumab analysis were higher (510 cells/ μ L for FAO+ patients and 490 cell/ μ L for FAO- patients)²⁹ than in the current study (230-370 cells/ μ L for FAO+ patients and 240-310 cells/ μ L for FAO- patients). However, the lower eosinophil counts in this present analysis may not have affected response to therapy, because the STELLAIR and PROSPERO studies demonstrated that omalizumab efficacy does not vary with pretreatment blood eosinophil count in patients with allergic asthma.^{19,30} It would have been interesting to analyze responses in the FAO-/+ and high or low BDR groups by baseline type 2 biomarkers in this study, but the subgroups would have become too small to draw meaningful conclusions.

Although the safety of omalizumab was not analyzed for these subgroups, the overall safety results from the EXTRA study have been published previously, demonstrating no difference between omalizumab and placebo in terms of the incidence of adverse events and serious adverse events.¹⁸ Furthermore, omalizumab has a good safety and tolerability profile across clinical trials and in extensive postmarketing surveillance.¹⁷

EXTRA was a large study that did not have inclusion requirements based on BDR, which enabled the current analysis of the efficacy of omalizumab in both high and low subgroups. This allowed for novel insights into the efficacy of omalizumab in FAO+ and FAO- patients who had high or low BDR. A limitation of the current analysis is that it was *post hoc* and, thus, the analysis was not prespecified and is considered hypothesis generating. Also applicable to this study was the inherent limitation that high BDR is not stable over time.³¹ Likewise, the classification of FAO and high BDR were based on a single assessment at baseline, and variability over time may occur.^{32,33} Consequently, because there is considerable heterogeneity reported between lung function tests, which can also be affected by intrinsic and extrinsic factors, there is potential for misclassification in these data.³⁴ In addition, subgroups were small, which may have precluded the observation of meaningful differences. Similarly, it would have been interesting to evaluate the responses in the

FAO-/+ and high or low BDR groups by concomitant medication status (M1, M2, and M3), however, due to the small number of patients in each subgroup, it would have been difficult to draw any meaningful conclusions.

Interpretation

In conclusion, omalizumab was more efficacious than placebo at reducing exacerbations in high BDR subgroups, regardless of the presence of FAO, but was not in low BDR subgroups. Lung function improvement primarily occurred in FAO- patients with high BDR, which suggests that asthma with low BDR may represent a more difficult-to-treat phenotype.

279 Data sharing statement

280 Qualified researchers may request access to individual patient level data through the clinical
281 study data request platform (<https://vivli.org/>). Further details on Roche's criteria for eligible studies
282 are available here (<https://vivli.org/members/ourmembers/>). For further details on Roche's Global
283 Policy on the Sharing of Clinical Information and how to request access to related clinical study
284 documents, see here
285 ([https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/o](https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm)
286 [ur_commitment_to_data_sharing.htm](https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm)).

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FIGURE LEGENDS

FIGURE 1. Exacerbation rate (mean/year) in placebo- and omalizumab-treated patients subgrouped by FAO+ or FAO- and high or low BDR. +, Presence; -, absence; *BDR*, bronchodilator responsiveness; *FAO*, fixed airflow obstruction; *RRR*, relative rate reduction.

FIGURE 2. Lung function change (LSM changes in FEV₁) in (A) the overall sample, and patients with (B) FAO+, low BDR, (C) FAO+, high BDR, (D) FAO-, low BDR, and (E) FAO-, high BDR. +, Presence; -, absence; *BDR*, bronchodilator responsiveness; *FAO*, fixed airflow obstruction; *LSM*, least squares mean.

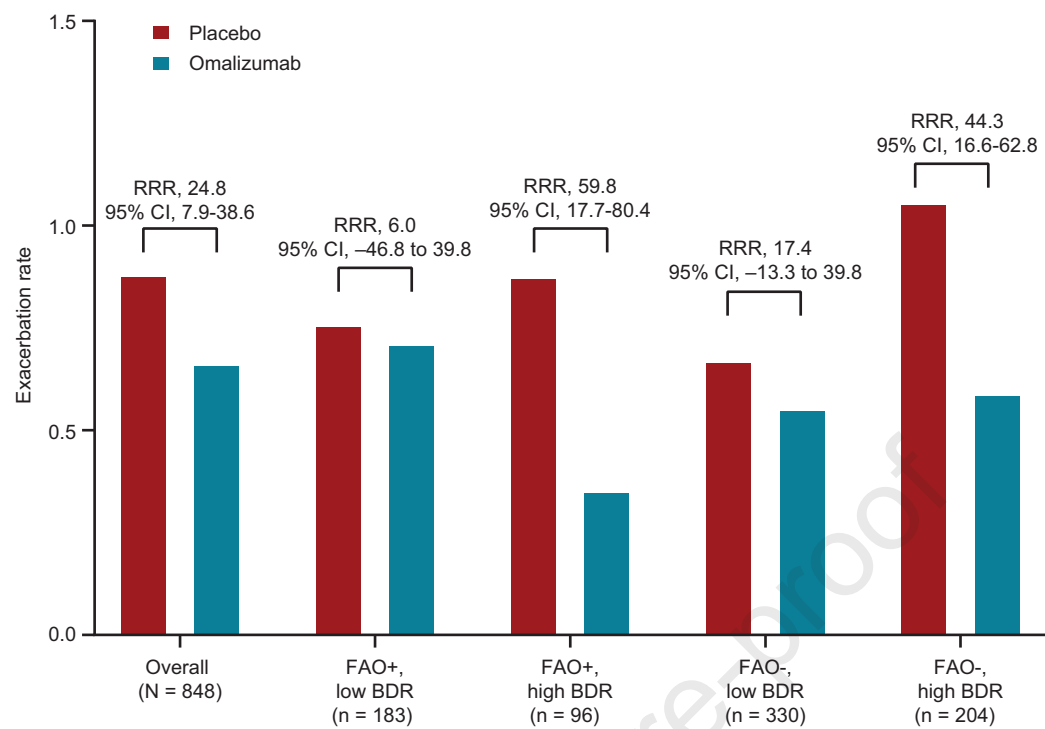
397 **TABLES**398 **TABLE I.** Baseline demographic and clinical characteristics of patients in EXTRA by FAO and BDR status

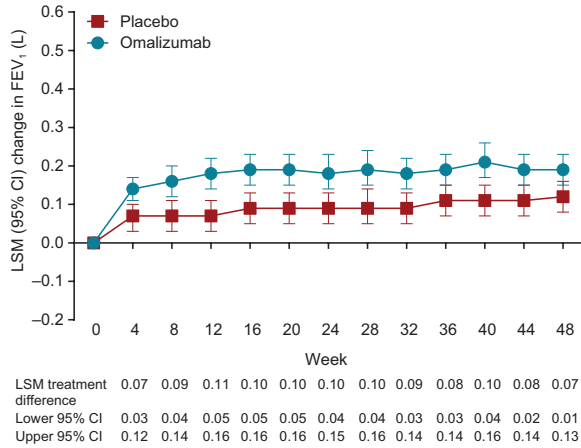
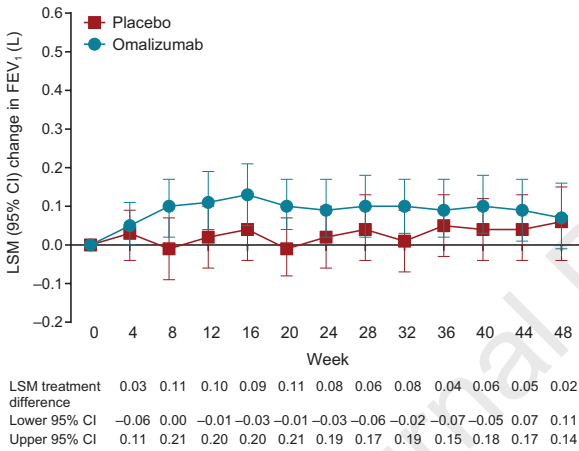
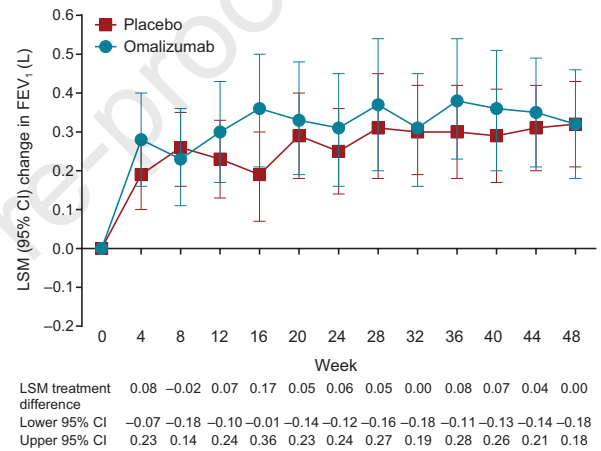
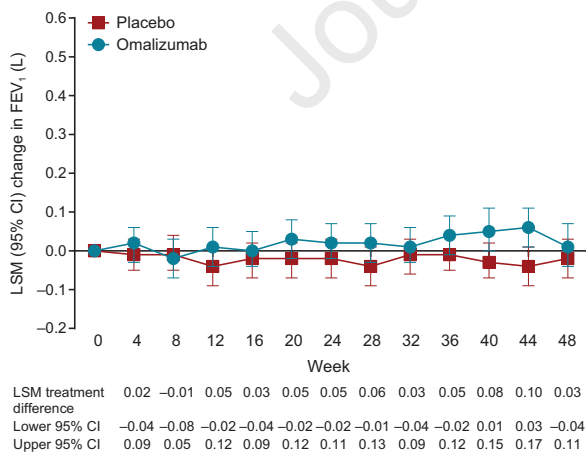
	FAO+, low BDR		FAO+, high BDR		FAO-, low BDR		FAO-, high BDR	
	Placebo	Omalizumab	Placebo	Omalizumab	Placebo	Omalizumab	Placebo	Omalizumab
Characteristic	(n = 84)	(n = 99)	(n = 60)	(n = 36)	(n = 171)	(n = 159)	(n = 90)	(n = 114)
Age (y), mean (SD)	49.1 (14.0)	48.5 (13.8)	47.2 (13.0)	49.5 (10.0)	45.1 (13.5)	43.0 (13.4)	40.7 (14.1)	38.8 (15.8)
Female, n (%)	52 (61.9)	51 (51.5)	39 (65.0)	20 (55.6)	123 (71.9)	104 (65.4)	71 (78.9)	77 (67.5)
Duration of asthma (y), mean (SD)	27.6 (18.0)	26.0 (16.9)	29.2 (15.4)	28.8 (14.0)	23.9 (15.3)	21.8 (15.7)	21.5 (14.2)	19.6 (13.5)
Prebronchodilator % predicted FEV ₁ , mean (SD)	59.4 (11.7)	58.6 (13.3)	50.5 (10.3)	51.7 (13.8)	72.1 (12.0)	73.5 (12.6)	64.5 (10.8)	64.2 (14.7)
FAO (%), mean (SD)	61.1 (6.3)	61.2 (7.1)	61.5 (6.6)	61.6 (7.9)	79.7 (5.8)	79.5 (6.7)	80.8 (6.8)	82.3 (11.8)
Bronchodilator response in FEV ₁ (%), mean (SD)	3.6 (5.5)	3.9 (5.6)	25.4 (16.8)	24.4 (19.0)	3.1 (6.6)	3.2 (5.6)	26.6 (15.4)	28.8 (17.1)

No. of exacerbation treatments in previous year, mean (SD)	2.1 (1.3)	2.0 (1.5)	1.9 (1.6)	2.2 (1.5)	1.8 (1.4)	2.0 (1.6)	2.0 (1.6)	2.1 (3.5)
Baseline total IgE (IU/mL), median (IQR)	142.0 (182.5)	149.0 (160.0)	189.0 (160.0)	121.5 (146.5)	111.1 (156.0)	128.0 (182.0)	140.0 (200.0)	151.5 (195.0)
Baseline total eosinophils (cells/ μ L), median (IQR)	230 (310.0)	300 (230.0)	370 (370.0)	275 (310.0)	240 (250.0)	265 (275.0)	310 (300.0)	245 (235.0)

+, Presence; -, absence; *BDR*, bronchodilator responsiveness; *FAO*, fixed airflow obstruction.

FAO+ and *FAO*- were defined as postbronchodilator FEV₁/forced vital capacity <70% and $\geq$ 70% at baseline, respectively. High and low *BDR* were defined as changes of $\geq$ 12% and <12% in FEV₁ following albuterol administration, respectively.



(A) Overall population (N = 842)**(B) FAO+, low BDR (n = 183)****(C) FAO+, high BDR (n = 96)****(D) FAO-, low BDR (n = 330)****(E) FAO-, high BDR (n = 204)**